

**TOXICOLOGICAL PROFILE FOR
ALDRIN/DIELDRIN**

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

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UPDATE STATEMENT

A toxicological profile for aldrin/dieldrin was released in 1993. An updated draft for public comment version was released on October 17, 2000. This edition supersedes any previously released draft or final profile.

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:

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FOREWORD

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

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

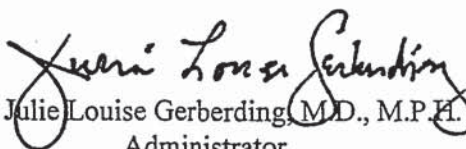
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels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

Each profile includes the following:

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

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

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


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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99–499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to 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.

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 *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), 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 (Aldrin/Dieldrin) Affect Children?
Section 1.7	How Can Families Reduce the Risk of Exposure to (Aldrin/Dieldrin)?
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 **Internet:** <http://www.atsdr.cdc.gov>

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

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

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

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

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: <http://occ-env-med.mc.duke.edu/oem/aoec.htm>.

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.

PEER REVIEW

A peer review panel was assembled for aldrin/dieldrin. The panel consisted of the following members:

1. Dr. William B. Buck, Private Consultant, Consul-Tox, Inc., Tolono, Illinois.
2. Dr. Samuel Epstein, Professor of Environmental and Occupational Medicine, School of Public Health, University of Illinois Medical Center, Chicago, Illinois.
3. Dr. Syed Ghiasuddin, Toxicologist, Office of Water Management, Indiana Department of Environmental Management, Indianapolis, Indiana.
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6. Dr. Peter Lacouture, Associate Director, Clinical Research, The Purdue Frederick Company, Norwalk, Connecticut.
7. Dr. Fumio Matsumura, Assistant Director, Toxic Substances Program, LEHR Facility, University of California, Davis, California.
8. Dr. Edward Morgan, Assistant Professor, Department of Pharmacology, Emory University, Atlanta, Georgia.
9. Dr. Raghubir Prasad Sharma, Fred C. Davison Distinguished Chair in Toxicology, College of Veterinary Medicine, The University of Georgia, Athens, Georgia.

These experts collectively have knowledge of aldrin/dieldrin'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 aldrin and dieldrin and the effects of exposure to these chemicals.

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. Aldrin has been found in at least 207 of the 1,613 current or former NPL sites, and dieldrin has been found in at least 287 of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at which aldrin and dieldrin are found may increase. This information is important because exposure to these substances 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 aldrin or dieldrin, 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 them. 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 ARE ALDRIN AND DIELDRIN?

Aldrin and dieldrin are the common names of two structurally similar compounds that were once used as insecticides. They are chemicals that are made in the laboratory and do not occur naturally in the environment. The scientific name for aldrin is 1,2,3,4,10,10-hexachloro-1,4,4 α ,5,8,8 α -hexahydro-1,4-endo,exo-5,8-dimethanonaphthalene. The abbreviation for the scientific name of aldrin is HHDN. Technical-grade aldrin contains not less than 85.5% aldrin.

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The trade names used for aldrin include Aldrec, Aldrex, Drinox, Octalene, Seedrin, and Compound 118. The scientific name for dieldrin is 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4 α ,5,6,7,8,8 α -octahydro-1,4-endo,exo-5,8-dimethanonaphthalene. The abbreviation for the scientific name for dieldrin is HEOD. Technical-grade dieldrin contains not less than 85% dieldrin. The trade names used for dieldrin include Alvit, Dielatrix, Octalox, Quintox, and Red Shield.

Pure aldrin and dieldrin are white powders, while technical-grade aldrin and dieldrin are tan powders. Aldrin and dieldrin slowly evaporate in the air. Aldrin evaporates more readily than dieldrin. Both aldrin and dieldrin have mild chemical odors. You might find aldrin and dieldrin in the soil, in water, or in homes where these compounds were used to kill termites. You might also find aldrin and dieldrin in plants and animals near hazardous waste sites.

Aldrin and dieldrin are no longer produced or used. From the 1950s until 1970, aldrin and dieldrin were used extensively as insecticides on crops such as corn and cotton. The U.S. Department of Agriculture canceled all uses of aldrin and dieldrin in 1970. In 1972, however, EPA approved aldrin and dieldrin for killing termites. Use of aldrin and dieldrin to control termites continued until 1987. In 1987, the manufacturer voluntarily canceled the registration for use in controlling termites.

In this profile, the two chemicals are discussed together because aldrin readily changes into dieldrin once it enters either the environment or your body. More information on the chemical and physical properties of aldrin and dieldrin is found in Chapter 4. More information on the production and use of aldrin and dieldrin is found in Chapter 5.

1. PUBLIC HEALTH STATEMENT

1.2 WHAT HAPPENS TO ALDRIN AND DIELDRIN WHEN THEY ENTER THE ENVIRONMENT?

Aldrin and dieldrin can enter the environment from accidental spills or leaks from storage containers at waste sites. In the past, aldrin and dieldrin entered the environment when farmers used these compounds to kill pests on crops and when exterminators used them to kill termites. Aldrin and dieldrin are still present in the environment from these past uses. Sunlight and bacteria in the environment can change aldrin to dieldrin. Therefore, you can find dieldrin in places where aldrin was originally released. Dieldrin in soil or water breaks down (degrades) very slowly. Dieldrin sticks to soil and may stay there unchanged for many years. Water does not easily wash dieldrin off soil. Dieldrin does not dissolve in water very well and is therefore not found in water at high concentrations. Most dieldrin in the environment attaches to soil and to sediments at the bottoms of lakes, ponds, and streams. Dieldrin can travel large distances by attaching to dust particles, which can then be transported great distances by the wind. Dieldrin can evaporate slowly from surface water or soil. In the air, dieldrin changes to photodieldrin within a few days. Plants can take up dieldrin from the soil and store it in their leaves and roots. Fish or animals that eat dieldrin-contaminated materials store a large amount of the dieldrin in their fat. Animals or fish that eat other animals have levels of dieldrin in their fat many times higher than animals or fish that eat plants. For more information, see Chapters 5 and 6.

1.3 HOW MIGHT I BE EXPOSED TO ALDRIN AND DIELDRIN?

For most people, exposure to aldrin and dieldrin occurs when they eat foods contaminated with either chemical. Contaminated foods might include fish or shellfish from contaminated lakes or streams, root crops, dairy products, and meats. Exposure to aldrin and dieldrin also occurs when you drink water, breathe air, or come into contact with contaminated soil at hazardous waste sites. Skin contact and breathing of aldrin and dieldrin by workers who used these chemicals to kill insects were at one time common. However, aldrin and dieldrin are no longer produced and no longer used. People with the greatest potential for exposure include those who live in homes that were once treated for termites using aldrin or dieldrin. Studies indicate that people can be exposed to aldrin and dieldrin years after they were applied in a home.

1. PUBLIC HEALTH STATEMENT

Exposure to aldrin is generally limited because aldrin is changed quickly to dieldrin in the environment. Dieldrin remains in the environment for a long time and is usually detected in soil, sediment, and animal fat. Levels of both aldrin and dieldrin have decreased over the years since they are no longer produced or used. The levels of aldrin and dieldrin in air and water are typically very low. For more information on human exposure to aldrin and dieldrin, see Chapter 6.

1.4 HOW CAN ALDRIN/DIELDRIN ENTER AND LEAVE MY BODY?

Aldrin can enter your bloodstream through your lungs when you breathe air, through your stomach after eating food or drinking water containing it, or through your skin. Exposure to aldrin or dieldrin around hazardous waste sites can mainly occur by breathing contaminated air or touching contaminated soil. Exposure near hazardous waste sites can also occur by eating contaminated food or drinking contaminated water. Exposure of the general population most likely occurs through eating food contaminated with aldrin or dieldrin. Exposure of some infants occurs by drinking mother's milk containing aldrin or dieldrin. Studies in animals show that both aldrin and dieldrin enter the body quickly after exposure. Once aldrin is inside your body, it quickly changes to dieldrin. Dieldrin then stays in your fat for a long time. Dieldrin can change to other products. Most dieldrin and its breakdown products leave your body in the feces. Some breakdown products can also leave in the urine. It can take many weeks or years for all of the compound to leave your body. Chapter 3 contains more information on how aldrin and dieldrin enter and leave the body.

1. PUBLIC HEALTH STATEMENT

1.5 HOW CAN ALDRIN/DIELDRIN AFFECT MY HEALTH?

Aldrin and dieldrin affect your health in similar ways. Symptoms of aldrin and dieldrin poisoning have been seen in people who were exposed to very large amounts of these pesticides during their manufacture. Symptoms of poisoning have also been seen in people who intentionally or accidentally ate or drank large amounts of aldrin or dieldrin. Most of these people experienced convulsions or other nervous system effects, and some had kidney damage. Some people who intentionally ate or drank large amounts of aldrin or dieldrin died. Health effects in people exposed to smaller amounts of aldrin or dieldrin occur because levels of the chemicals build up in the body over time. Exposure to moderate levels of aldrin or dieldrin for a long time causes headaches, dizziness, irritability, vomiting, or uncontrollable muscle movements. Some sensitive people seem to develop a condition in which aldrin or dieldrin causes the body to destroy its own blood cells. We do not know whether aldrin or dieldrin affects the ability of people to fight diseases. We also do not know whether aldrin or dieldrin affects the ability of men to father children, or causes birth defects or cancer in people. The International Agency for Research on Cancer has determined that aldrin and dieldrin are not classifiable as to their carcinogenicity to humans. Based on studies in animals, the EPA has determined that aldrin and dieldrin are probable human carcinogens.

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.

Results from animal studies show that high levels of aldrin and dieldrin cause effects on the nervous system and on the kidneys similar to those seen in people. Results from animal studies also show additional effects of aldrin and dieldrin after exposure to lower levels for longer

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periods. We do not know whether these effects also occur in people. These other health effects of aldrin and dieldrin in animals include changes in the liver and reduced ability to fight infections. In addition, animals born to mothers who have eaten large amounts of aldrin or dieldrin do not live very long. This results, in part, from the newly born animals being poisoned by aldrin or dieldrin in the mother's milk. Studies in animals give conflicting information about whether aldrin and dieldrin cause birth defects. Studies in animals also give conflicting information about whether aldrin and dieldrin make it more difficult for male animals to reproduce. Some studies show that aldrin and dieldrin may damage sperm. Aldrin and dieldrin have been shown to cause liver cancer in mice, but not in other species of animals.

Additional information regarding the health effects of aldrin and dieldrin can be found in Chapter 3.

1.6 HOW CAN ALDRIN/DIELDRIN AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children can be exposed to aldrin or dieldrin in the same ways as adults, mainly by eating food contaminated with aldrin or dieldrin, or by exposure in homes treated for termites using aldrin or dieldrin. Children can also be exposed by coming into contact with aldrin- or dieldrin-contaminated water, air, or soil near hazardous waste sites. There are no known unique exposure pathways for children. We do not know if children's intake of aldrin or dieldrin per kilogram of body weight is different than that of adults.

Adults and children who swallowed (either by accident or on purpose) amounts of aldrin or dieldrin that were much greater than those found in the environment suffered convulsions, and some died. We do not know whether children differ from adults in their susceptibility to health effects from aldrin or dieldrin exposure.

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We do not know whether aldrin or dieldrin affect the ability of people to have children or whether they cause birth defects in children. Some studies in animals show that females given aldrin or dieldrin by mouth have smaller numbers of babies. Some other studies show that large amounts of aldrin damage the testes, but it is unknown whether such large amounts affect the ability of animals to reproduce. Pregnant animals given aldrin or dieldrin by mouth had some babies with low birth weights and some with skeletal variations. Because these effects occurred in animals, they might also occur in humans. Aldrin and dieldrin can cross the placenta. Dieldrin has been found in human breast milk. More information on this topic can be found in Sections 3.7 and 6.6.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ALDRIN OR DIELDRIN?

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

Since aldrin and dieldrin are no longer produced or used, exposure to these compounds will occur from past usage. Families with the greatest risk of exposure to aldrin and dieldrin are those living in homes that were once treated with either chemical for termite protection. Aldrin and dieldrin were usually applied to the basement level of homes to protect the foundation from termites. Studies indicate that detectable levels of both chemicals can exist in a home for up to 10 years after the first application. Before buying a home, families should investigate what, if any, pesticides have been used within the home.

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1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ALDRIN/DIELDRIN?

Aldrin is quickly changed to dieldrin in the body, and dieldrin can be measured in your blood, urine, and body tissues if you have been exposed to a large amount. Tests to measure aldrin or dieldrin in such bodily tissues or fluids are not usually available at a doctor's office because special equipment is needed. However, a sample taken in the doctor's office can be properly packed and shipped to a special laboratory, if necessary. Because aldrin changes to dieldrin fairly quickly in the body, these methods are useful for finding aldrin only within a few days after you are exposed to aldrin. Since dieldrin can stay in the body for months, measurements of dieldrin can be made for much longer after you are exposed to either aldrin or dieldrin. The test results cannot be used to predict if you will have any adverse health effects. Exposure to other chemicals at the same time as exposure to aldrin and/or dieldrin could cause some confusion in understanding test results for aldrin and/or dieldrin. More information about tests to find dieldrin in the body is presented in 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

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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 aldrin and dieldrin include the following:

The federal government has developed regulatory standards and guidelines to protect people from the harmful health effects of aldrin and dieldrin. In 1974, EPA banned all uses of aldrin or dieldrin except as a termite killer. In 1981, EPA required labeling changes to warn against applying these chemicals near water supplies, heating ducts, or crawl spaces. They also warned against applying them too frequently.

EPA advises lifetime drinking water exposure concentration limits (DWELs, see Table 8-1) for aldrin and dieldrin of 0.001 and 0.002 mg/L, respectively, for protection against adverse non-cancer health effects, that assume all of the exposure to the contaminant is from drinking water. Regarding cancer risk, EPA advises a lower drinking water exposure concentration limit of 0.0002 mg/L for aldrin and dieldrin that would, in theory, limit the lifetime risk for developing cancer from exposure to each compound to 1 in 10,000.

The FDA regulates the residues of aldrin and dieldrin in raw foods. The allowable range for residues is from 0 to 0.1 ppm depending on the type of food product. This limits the intake of aldrin and dieldrin in food to levels considered to be safe.

EPA has named aldrin and dieldrin as hazardous solid waste materials. If quantities greater than 1 pound enter the environment, the National Response Center of the federal government must be told immediately.

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OSHA recommended a maximum average amount of aldrin and dieldrin in the air in the workplace to protect workers. This amount is 250 micrograms in a cubic meter of air ($\mu\text{g}/\text{m}^3$) for an 8-hour workday over a 40-hour workweek. NIOSH recommended the same limit ($250 \mu\text{g}/\text{m}^3$) for both compounds for up to a 10-hour workday over a 40-hour workweek. For more information, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

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: 1-800-553-6847 or 1-703-605-6000

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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ALDRIN AND DIELDRIN IN THE UNITED STATES

Aldrin ($C_{12}H_8Cl_6$) and dieldrin ($C_{12}H_8Cl_6O$) are two organochlorine insecticides that were used for agricultural and public health purposes from the early 1950s until 1989, when their manufacture in the United States was discontinued. Aldrin and dieldrin were popular pesticides for corn and cotton crops, and were used as a prophylactic and for treatment of timber against termite infestation. Consistent with their intended use on insects in soil, aldrin and dieldrin are not very water soluble, but readily bind to sediment and are rarely leached into deeper soil layers and groundwater. As they take decades to break down in the environment, past agricultural uses of aldrin and dieldrin have resulted in persisting soil residues and uptake in a wide range of crops. In biological systems of soils, plants, and animals, aldrin converts rapidly to dieldrin by a microsomal oxidation reaction (epoxidation). The half-life of dieldrin in temperate soils is about 5 years, while it disappears more quickly (up to 90% in 1 month) from tropical soils. Organochlorine pesticides, including dieldrin, continue to enter streams in the United States from atmospheric deposition and erosion of soils contaminated from past use. Aldrin and dieldrin may be volatilized from sediment and redistributed by air currents, contaminating areas far from their sources. Nationally, levels of aldrin and dieldrin have declined since their agricultural uses were discontinued. Aldrin bioconcentrates in mollusks and fish, and high levels of dieldrin have been found concentrated in fish, snails, and lake trout. Detectable dieldrin concentrations in fish have shown a strong association with corn production acreage.

Exposure to aldrin or dieldrin at hazardous waste sites is possible via inhalation, oral, or dermal routes. The Henry's law constants of aldrin and dieldrin indicate that volatilization from moist soil surfaces will occur. Both compounds also bind strongly to soil particles and are often associated with dust particles in the atmosphere. Exposure to these pesticides can therefore occur through inhalation and dermal contact with vapor and particulate phase aldrin and dieldrin. Populations residing near hazardous waste disposal sites may be subject to higher levels of aldrin and dieldrin in environmental media (i.e., air, soil) than those experienced by the general population. Aldrin has been identified in at least 207 of the 1,613 hazardous waste sites while dieldrin has been identified in at least 287 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of NPL sites evaluated for aldrin and dieldrin is not known. As more sites are evaluated, the number of sites where aldrin and/or dieldrin has been detected may increase.

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Exposure of the general population to aldrin and dieldrin may occur through ingestion of contaminated food (including fish and shellfish) or water, through inhalation of contaminated air, especially in homes that have been treated with either pesticide, and through dermal contact with contaminated soil or water. The dietary contribution is likely the most significant route of human exposure. Oral exposure may occur through consumption of foods that are contaminated with aldrin or dieldrin. These foods would include those obtained from plants grown on contaminated lands or from animals living in contaminated areas, as well as commercial food products high in animal fat, such as dairy, fish, and meat products. This is the result of previous widespread use, biomagnification, and persistence in the environment. Because of aldrin's rapid conversion to dieldrin, most of the dietary intake is in the form of dieldrin. During the period of 1965–1970, U.S. dietary intake was reported to be • 40 ng aldrin/kg/day and • 80 ng dieldrin/kg/day. Since 1970, the use of aldrin and dieldrin on food has been cancelled, and dietary intake has decreased. In 1988, on the basis of total diet analyses, daily intake of dieldrin in adults in the United States was estimated at • 5 ng/kg/day; a slightly higher daily intake of • 11 ng/kg/day was estimated for infants. High levels of dietary exposures to dieldrin in adults were estimated to be primarily due to frequent consumption of summer and winter squash grown on contaminated lands. Dieldrin was found in Food and Drug Administration (FDA) Total Diet study foods during the period of 1991–1999, with maximum levels in squash. Aldrin currently appears to be below the FDA limit of detection in food. Oral exposure to aldrin or dieldrin could also occur through ingestion of contaminated water. Studies indicate, however, that levels of aldrin and dieldrin in drinking water are extremely low.

Regarding exposure of the general population through inhalation of contaminated air, air samples from several states collected in 1970–1972 revealed mean ambient concentrations of 0.4 ng/m³ for aldrin and 1.6 ng/m³ for dieldrin. In 1972, the estimated U.S. average daily intake of aldrin plus dieldrin from the atmosphere was about 0.6 ng/kg body weight. Another source of exposure not related to living near a hazardous waste site is residue from the past use of aldrin or dieldrin for termite extermination. Although use for this application was voluntarily canceled by the manufacturer in 1987, aldrin and dieldrin levels in treated homes have been shown to decline slowly, with detectable levels present as many as 10 years after treatment. Dieldrin has been detected in human placenta, amniotic fluid, fetal blood, and breast milk, and breast milk levels appear to be correlated to dwelling dieldrin treatment for termite control. Dieldrin tends to be stored in high-fat tissues within the body, but can be mobilized during lactation or starvation.

See Chapter 6 for more detailed information regarding concentrations of aldrin and dieldrin in environmental media.

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2.2 SUMMARY OF HEALTH EFFECTS

Data regarding the health effects of aldrin or dieldrin in humans come from either epidemiological reports of occupational exposure or case reports of accidental or intentional poisonings. As precise levels of exposure are not known, these studies are inadequate for quantitative assessment of the health effects of aldrin or dieldrin. The main and best documented effect of acute high-level exposure to aldrin or dieldrin in humans is central nervous system excitation culminating in convulsions. Central nervous system stimulation is the cause of death in acute poisoning. Longer-term exposure of humans in occupational settings has also been associated with central nervous system intoxication, but other toxic effects in workers routinely exposed to these pesticides have not been conclusively established. A few case reports have attributed liver and kidney toxicity and hemolytic anemia to oral exposure to aldrin or dieldrin, but these effects were not observed in larger occupational studies, suggesting that they are likely to be quite rare.

Studies in animals have mainly involved oral exposure. Oral data in animals are consistent with the findings in humans that the central nervous system is an important target of toxicity, but further show that other effects may also be associated with exposure to aldrin or dieldrin, including liver and kidney toxicity, immunosuppression, fetal toxicity and increased postnatal mortality, neurodevelopmental effects, and decreased reproductive function. No studies were located regarding developmental effects in humans and conflicting results exist in animals. Fetuses may be affected through transplacental exposure. The liver is the critical target of chronic toxicity in several species based on available long-term oral studies, although data on other end points known to be sensitive from shorter-duration studies (e.g., immunosuppression, subtle neurological effects) are insufficient. The mechanism for aldrin and dieldrin toxicity is not equally well understood for all target organs.

Aldrin and dieldrin are carcinogenic in animals, but this effect appears to be specific to the mouse liver. The International Agency for Research on Cancer has categorized aldrin and dieldrin as Group 3 (unclassifiable as to human carcinogenic potential) chemicals. Based on the finding of liver tumors in mice, EPA classified both aldrin and dieldrin as B2, probable human carcinogens; however, current mechanistic data suggest that the mouse carcinogenicity data may not be highly relevant to humans. The preponderance of evidence appears to indicate that aldrin and dieldrin induce a carcinogenic response through nongenotoxic mechanisms (i.e., not acting directly on the DNA).

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Limited reports of adverse effects in aldrin- or dieldrin-exposed children (indicate similar signs and symptoms to those in adults. Limited animal data indicate that dose-response may change with age. The principal health effects are discussed in the following sections.

Hepatic Effects. While adverse hepatic effects have not generally been observed in workers employed in the manufacture or application of aldrin or dieldrin, the liver was the most sensitive target of aldrin and dieldrin toxicity in chronic-duration animal studies. Serum liver enzyme activities (alkaline phosphatase, alanine and aspartate aminotransferases) were normal in volunteers who ingested low doses of dieldrin (0.14–3 g/kg/day) for 18 months; however, slight increases in alanine and aspartate aminotransferase activities have been correlated with increased serum levels of dieldrin in pesticide-exposed workers. Liver injury was observed in a child who drank an unknown quantity of a 5% dieldrin solution. However, the dieldrin solution most likely contained a substantial amount of solvent, and it is unclear whether the hepatic toxicity was directly due to the dieldrin or the solvent. The injury appeared to be reversible to some extent; however, the child was not followed for a sufficient period to determine whether the injury was completely reversible. Exposure of animals to 0.025 mg/kg/day of aldrin or dieldrin over intermediate-to-chronic periods has also been reported to cause adverse effects such as elevated serum enzyme levels, decreased serum proteins, hyperplasia, bile duct proliferation, focal degeneration, and areas of necrosis in the liver.

These degenerative effects are distinct from the adaptive changes observed in livers of a number of animal species in response to exposure to aldrin, dieldrin, or other chlorinated hydrocarbon pesticides. Such adaptive changes occur as a result of the induction of microsomal enzymes by aldrin or dieldrin and include increases in liver weight and/or size, liver cell enlargement, cytoplasmic eosinophilia, an increase in the smooth endoplasmic reticulum, an increase in microsomal protein, an increase in cytochrome P-450 content, and/or an increase in microsomal enzyme activity. Studies of workers employed in the manufacture or application of aldrin or dieldrin have not shown evidence of microsomal enzyme induction. Studies have shown, however, that species differences exist with respect to the magnitude of these changes. The most prolific changes have been observed in rats, with dogs, mice, and monkeys experiencing progressively lesser changes. It might be expected, based on the close evolutionary relationship between Rhesus monkeys and humans, that limited enzyme induction might also occur in humans.

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Neurological Effects. Central nervous system excitation is the primary adverse effect observed in humans in cases of aldrin or dieldrin intoxication. In cases of acute intoxication, in which a large amount of these pesticides is ingested over a short period of time, convulsions occur within several minutes after ingestion. In cases of longer-term exposures, where a slow rate of elimination from the body results in a gradual buildup of these agents in the blood to toxic levels, convulsions may also be produced. During such longer-term exposures, however, other less-serious symptoms of central nervous system toxicity may also be observed including headaches, dizziness, hyperirritability, general malaise, nausea, vomiting, muscle twitching, or myoclonic jerking.

Both acute- and longer-duration studies in animals support these findings. For example, acute-duration oral exposure to aldrin caused subtle neurological changes as indicated by altered electroconvulsive shock threshold in the offspring of mice exposed during gestation. Operant behavior was disrupted in rats following single doses of dieldrin ranging from 0.5 to 16.7 mg/kg, whereas convulsions resulted at higher doses ranging from 40 to 50 mg/kg. When aldrin or dieldrin was administered to rats for 3 days, convulsions were observed at a dose of 10 mg/kg/day.

In intermediate-duration animal studies, impaired learning was found at 0.1 dieldrin/kg/day, physical signs of neurotoxicity (tremors) occurred at aldrin or dieldrin doses as low as 0.5 mg/kg/day, and histopathological degenerative changes in the brain were found at doses as low as 0.7 mg/kg/day.

In chronic studies, serious neurological effects including convulsions and/or tremors developed in rats and dogs administered dieldrin at doses as low as 0.5 mg/kg/day and in rats administered 2.1 mg aldrin/kg/day. Central nervous system histopathological changes were noted at lower doses. Slight neuronal degeneration in dogs was reported following 1 year of exposure to aldrin or dieldrin at 0.2 mg/kg/day, and cerebral edema and small foci of degeneration were reported in rats exposed to dieldrin at 0.016 mg/kg/day for 2 years; however, these effects were reported in studies limited by the small number of animals examined.

It is highly unlikely that high enough levels of aldrin or dieldrin could be absorbed acutely by persons living near hazardous waste sites to cause convulsions, although exposure to sufficiently high levels may cause some of the less adverse central nervous system effects.

It is generally believed that the central nervous system excitation observed in animals results from a generalized activation of synaptic activity throughout the central nervous system; however, it has not been

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established whether aldrin and dieldrin act at the nerve terminal to facilitate neurotransmitter release or whether these agents cause excitation by depressing activity of inhibitory neurotransmitters within the central nervous system. Experimental evidence appears to indicate a blocking action on the GABA_A receptor-chloride channel complex. Additional information on mechanisms of neurotoxicity of aldrin and dieldrin is included in Section 3.5.

Reproductive Effects. Studies in humans have not addressed whether adverse reproductive effects occur as a result of exposure to aldrin or dieldrin. However, decreased fertility was observed in several (but not all) studies at doses as low as 0.63 mg aldrin/kg/day or 0.125 mg dieldrin/kg/day administered to maternal or paternal animals by the oral route. In additional animal studies of reproductive toxicity following intraperitoneal injection of aldrin, investigators have observed several adverse effects of this agent on the male reproductive system. These findings include decreased sperm count, degeneration of germ cells, decreased weights of seminal vesicles and prostate and coagulating glands, decreased seminiferous tubule diameter, decreased plasma and testicular testosterone, decreased prostatic fructose content and acid phosphatase activity, and decreased plasma luteinizing hormone and follicular stimulating hormone. Also, *in vitro* studies conducted using rat prostate tissue have shown that dieldrin blocks binding of the androgen, 5 α -dihydrotestosterone, to a protein fraction of the prostate. These findings may provide clues regarding the mechanism of the decreased fertility in males. Based on the findings reported in these studies, an adverse effect of exposure to sufficiently high levels of aldrin or dieldrin on male fertility cannot be excluded.

Developmental Effects. Studies in humans have not addressed whether adverse developmental effects occur as a result of exposure to aldrin or dieldrin. External malformations have been observed in a study in mice and hamsters at doses of 15 and 30 mg dieldrin/kg/day, respectively, but at doses 10 times lower, conflicting results regarding these types of effects were reported. Decreased postnatal survival following *in utero* exposure to dieldrin has been observed in a number of studies in laboratory animals. This decrease in survival does not appear to be dependent on exposure to this agent postnatally via the mothers' milk or to effects of dieldrin on maternal behavior, although these factors appear to contribute to the postnatal mortality. However, the mechanism for the neonate lethality at present is not known. In addition, subtle changes in neurological function, such as changes in the electroconvulsive shock threshold, have been observed in offspring of mice treated with aldrin during pregnancy.

See Chapter 3 for more detailed information regarding the health effects of aldrin and dieldrin.

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

Information regarding inhalation toxicity of aldrin and dieldrin in humans is mainly available from studies of workers involved in the manufacture or use of the chemicals (de Jong 1991; Hunter et al. 1972; Jager 1970; Kazantzis et al. 1964; Morgan and Lin 1978; Morgan and Roan 1974; Morgan et al. 1980; Patel and Rao 1958; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). Limitations associated with these reports include lack of quantitative exposure data, lack of data on duration of exposure, the possibility of multiple routes of exposure (i.e., dermal as well as inhalation), and concurrent exposure to other chemicals. The human occupational data therefore essentially provide only qualitative data on health effects associated with inhalation exposures to aldrin and dieldrin and are unsuitable for MRL derivation. Extremely limited animal inhalation toxicity data are available for aldrin and dieldrin in several species (Treon et al. 1957b), but limitations of these studies, particularly lack of exposure levels and sublimation of the chemicals that may have generated thermal decomposition products and/or other volatile contaminants, also preclude derivation of inhalation MRLs.

Oral MRLs***Acute-duration Oral MRLs******Aldrin***

- An MRL of 0.002 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to aldrin.

The acute-duration oral MRL for aldrin was derived based on observations of 18% decreased body weight and a significantly increased electroconvulsive shock brain seizure threshold in the offspring of mice gavaged with 2 or 4 mg/kg/day for 5–7 days during the third trimester of pregnancy (Al-Hachim 1971). There was no effect on the acquisition of a conditioned avoidance response in the offspring. Another acute-duration oral developmental toxicity study of aldrin showed developmental toxicity at higher doses of aldrin in both mice and hamsters (Ottolenghi et al. 1974). Administration of aldrin by gavage caused an increase in the incidence of webbed feet in mice following 25 mg/kg on gestation day (Gd) 9 and

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increased fetal mortality in hamsters following 50 mg/kg/day on Gd 7, 8, or 9. These results support the developmental toxicity of aldrin. Additionally, the neurodevelopmental effect is consistent with evidence showing that the central nervous system is a well-documented target of aldrin and dieldrin toxicity in adult animals. Because the end points measured in the current study may be more sensitive indicators of fetal toxicity than overt neonatal neurological effects and fetal death or malformations, the lowest tested dose is considered to be a lowest-observed-adverse-effect level (LOAEL) for developmental toxicity. The acute-duration MRL of 0.002 mg/kg/day was derived by dividing the 2 mg/kg/day LOAEL by an uncertainty factor of 1,000 (10 for extrapolating from a LOAEL to a NOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

Dieldrin

An acute-duration oral MRL was not derived for dieldrin. Severe signs of neurotoxicity were reported in humans accidentally or intentionally ingesting relatively large doses of dieldrin (Black 1974; Garrettson and Curley 1969). Convulsions were observed in rats given dieldrin in single oral doses ranging from 10 to 50 mg/kg (Mehrotra et al. 1989; Wagner and Greene 1978; Woolley et al. 1985). Other studies in rats reported disruption of operant behavior (Burt 1975) and impaired responses in an inescapable foot shock stress paradigm (Carlson and Rosellini 1987) following acute oral administration of dieldrin at doses of 2.5 and 0.5 mg/kg, respectively. Monkeys orally administered 0.1 mg dieldrin/kg/day for 55 days showed signs of impaired learning <15 days after the initiation of treatment (Smith et al. 1976). This study identified a no-observed-adverse-effect level (NOAEL) of 0.01 mg/kg/day for impaired learning in monkeys treated for up to 55 days; the NOAEL was used as the basis for derivation of an intermediate-duration oral MRL for dieldrin. Adverse effects were also observed in the immune system of mice following acute oral exposure to dieldrin levels as low as 0.065 mg/kg (Loose et al. 1981), indicating that the immune system may be the most sensitive target of dieldrin-induced toxicity in animals. However, due to the lack of data to suggest that the immune system may be a target of toxicity in humans following ingestion of dieldrin, an acute-duration oral MRL for dieldrin based on immunotoxicity was not derived.

Intermediate-duration Oral MRLs***Aldrin***

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An intermediate-duration oral MRL was not derived for aldrin due to lack of appropriate effect levels. In intermediate-duration oral studies, the lowest NOAEL of 0.63 mg/kg/day was identified for decreased body weight in rats consuming aldrin for 27 weeks (Treon et al. 1953b). The associated LOAEL of 1.25 mg/kg/day, which was also a NOAEL for other systemic effects (liver and kidney weight), was within the range of 0.89–1.78 mg/kg/day reported in dogs exposed for 9 months for frank signs of neurotoxicity that included tremors, convulsions, labored respiration, and vomiting (Treon et al. 1951b). NOAELs for these neurotoxic effects were not identified. The neurotoxic effects are considered by ATSDR to be serious effects, and MRLs are not derived using LOAELs for serious end points. An intermediate-duration MRL was not derived based on the NOAEL of 0.63 mg/kg/day for decreased body weight because of its proximity (within a factor of 10) to the LOAELs for serious end points.

Dieldrin

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

The intermediate-duration oral MRL for dieldrin was derived based on observations of impaired learning of a successive discrimination reversal task in squirrel monkeys fed 0.1 mg dieldrin/kg/day for 55 days, whereas the 0.01 mg/kg/day dose level had no apparent effect on learning (Smith et al. 1976). The study by Burt (1975) provides supporting evidence of neurotoxicity in rats fed dieldrin in the diet for 60–120 days. A concentration of 5 ppm (a calculated dose level of 0.25 mg/kg/day, using reference values from EPA (1986m) resulted in significantly impaired maze training; no adverse effects were seen in rats exposed for 60 days to a concentration resulting in a dose level of 0.025 mg/kg/day. The intermediate-duration oral MRL of 0.0001 mg/kg/day was calculated by dividing the 0.01 mg/kg/day NOAEL by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

Chronic-duration Oral MRLs***Aldrin***

- An MRL of 0.00003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to aldrin.

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The liver was the most sensitive target of aldrin toxicity in chronic-duration studies. Rats exposed to aldrin at doses as low as 0.025 mg/kg/day for 2 years had increases in relative liver weight and hepatic histopathological changes similar to those induced by other chlorinated insecticides (Fitzhugh et al. 1964). The hepatic lesions that were seen at 0.025 mg/kg/day were characterized by hypertrophy of centrilobular hepatocytes, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferations. Liver changes were marked at 2.5 mg/kg/day and included an increase in the severity of hepatic cell vacuolation; this is consistent with evidence for dose-related progression of hepatotoxicity in other studies (Deichmann et al. 1967; Harr et al. 1970; Thorpe and Walker 1973; Treon et al. 1955b).

Several of the liver cell changes that were observed at 0.025 mg/kg/day were considered to be consistent with marked adaptation. Modifications occurring in the mixed function oxidase system consequent to the adaptive response may result in its functional enhancement or neutralization. This in turn has the consequence of potentiating or inhibiting toxic responses to other exogenous substances. Even though the mechanism of aldrin-mediated hepatotoxicity has not been elucidated, the potential significance of the marked adaptive response in cell injury cannot be dismissed. The extreme magnitude of cellular adaption that results from aldrin toxicity creates a liver that potentially has a tremendously heightened state of metabolic activity which correspondingly may have a similarly heightened capacity to toxify or detoxify upon continued exposure to aldrin (or other substance that may be present at NPL sites).

Particularly in considering that the liver is a major target organ for aldrin toxicity, and the marked adaptive response and other histopathologic lesions (cytoplasmic vacuolation and bile duct proliferation) observed in the Fitzhugh et al. study, a chronic-duration oral MRL for aldrin of 0.00003 mg/kg/day was derived by dividing the LOAEL of 0.025 mg/kg/day by 1,000 (10 for extrapolating from a LOAEL to a NOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

Dieldrin

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

The liver was the most sensitive target of dieldrin toxicity in chronic-duration studies. Rats that were exposed to 0.005, 0.05, or 0.5 mg/kg/day dieldrin in the diet for 2 years had increased relative liver weight at 0.05 mg/kg/day and liver parenchymal cell changes characteristic of organochlorine exposure,

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as well as indications of focal hyperplasia, at 0.5 mg/kg/day (Walker et al. 1969). There were no indications of dieldrin-related changes in serum alkaline phosphatase or SGPT, histology of non-liver tissues, or body weight in any of the exposed groups, although signs of dieldrin neurotoxicity (irritability, tremors, and occasional convulsions) occurred at 0.5 mg/kg/day. These behavioral changes usually occurred during handling, did not progress after 3 months of exposure, and did not affect well-being. Based on the 0.005 mg/kg/day NOAEL for liver effects and considering the evidence for dose-related progression of hepatotoxicity, the chronic oral MRL of 0.00005 mg/kg/day was calculated for dieldrin using an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

The main source of general population oral exposure to aldrin and dieldrin is through the diet (see Section 6.5). In an FDA Total Diet study conducted in 1982–1984, mean dietary intake of dieldrin in the United States was 0.5 µg/day (0.007 µg/kg/day assuming a 70-kg body weight) (Gunderson 1988; Lombardo 1986), which is approximately 7 times lower than the dieldrin chronic oral MRL. In the same study, aldrin intake was <0.001 µg/kg/day, which is approximately 30 times lower than the aldrin chronic oral MRL.

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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 aldrin/dieldrin. 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.

Aldrin and dieldrin are structurally similar pesticides. The only difference between the structures of aldrin and dieldrin is the presence, in dieldrin, of an epoxied ring at the site of one of the carbon-carbon double bonds in aldrin (see Chapter 4). Because aldrin is rapidly metabolized to dieldrin in the body and converted to dieldrin in the environment, these two compounds are discussed together throughout Chapter 3 and the rest of this document.

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

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insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) 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 aldrin and dieldrin are indicated in Tables 3-1 and 3-2, respectively, and Figures 3-1 and 3-2, respectively. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-2 also show 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 aldrin and dieldrin. 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 1990d), 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

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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.

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

Virtually all of the studies presented in this section on inhalation exposure are either epidemiological reports of occupational exposure or case reports of either accidental or intentional poisonings. Extremely limited information was located regarding the effects of inhalation exposures of animals to aldrin or dieldrin. In many of the human and animal studies, inhalation exposure may occur simultaneously with dermal exposure. Thus, many of the effects reported in this section may be due, in part, to dermal exposure to aldrin or dieldrin. Furthermore, in occupational studies and case reports of poisonings, precise levels of exposure are not known. Thus, the results in this section are not presented in an LSE table and figure.

No studies were located regarding cardiovascular, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after inhalation exposure to aldrin/dieldrin.

3.2.1.1 Death

No increase in mortality from any cause was reported in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, and/or telodrin at a facility in the Netherlands for >4 years (cohort=233 workers) (van Raalte 1977; Versteeg and Jager 1973). Furthermore, in a 20-year follow-up of this population and expansion of the cohort to include workers exposed for at least 1 year between 1954 and 1970 (cohort=570 workers), a lower than expected overall incidence of mortality was observed (de Jong 1991). Although the workers described by de Jong represented a unique population because they had been under observation for an average of 25.86 years, all of the studies described above are limited because of the small number of subjects used (• 570 workers), uncertainty regarding exposure levels, and the potential exposure of the subjects to more than one of these pesticides and/or to other chemicals at the chemical manufacturing complex. Several of these studies have attempted to estimate

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exposures using blood levels. However, blood levels were not obtained for approximately 10 years (during what is expected to have been the period of heaviest exposures) and extrapolations were based on data obtained in a study using constant daily low-level oral dosing (Hunter and Robinson 1967). It is unclear whether such extrapolations accurately reflect exposure levels in the occupational situation. Only two case studies were located regarding deaths that may have been attributable to occupational exposure to aldrin or dieldrin (Muirhead et al. 1959; Pick et al. 1965). One of these studies concerned a farmer with multiple exposures to insecticides that contained dieldrin. The farmer died in hemolytic crisis after developing immunohemolytic anemia (Muirhead et al. 1959). Immunologic testing revealed a strong antigenic response to red blood cells coated with dieldrin. The other study concerned a worker from an orange grove who developed aplastic anemia and died following repeated exposures to aldrin during spraying (Pick et al. 1965). In the latter study, the relationship between aldrin exposure and the aplastic anemia is considerably more tenuous, being linked only in that the onset of symptoms corresponded with spraying and the condition deteriorated upon subsequent exposure.

Only very limited data were located regarding death in animals following inhalation exposure to aldrin or dieldrin. Cats, guinea pigs, rats, rabbits, and mice were exposed to aldrin vapors and particles generated by sublimating aldrin at 200 °C (Treon et al. 1957b). Aldrin levels of 108 mg/m³ for 1 hour resulted in death in 9 out of 10 rats, 3 out of 4 rabbits, and 2 out of 10 mice. Cats and guinea pigs were less sensitive. One out of 1 cat and no guinea pigs died following exposure to 215 mg/m³ for 4 hours. Interpretation of the results of this study are limited in that sublimation may have resulted in the generation of atmospheres containing a higher proportion of volatile contaminants and thermal decomposition products than would be expected in atmospheres typical of most occupational exposures.

3.2.1.2 Systemic Effects

Respiratory Effects. Extremely limited information is available regarding the respiratory effects of aldrin and dieldrin in humans after inhalation exposure. A study of workers with at least 4 years of employment in the manufacture of aldrin, dieldrin, endrin, or telodrin found no new pulmonary disease or deterioration of existing pulmonary disease (Jager 1970). Similarly, no increase in mortality from respiratory diseases was noted in workers employed for at least 1 year at the same plant during 1954–1970 when these workers were followed for at least 20 years (de Jong 1991). In contrast, in another study that examined workers involved in the manufacture of aldrin, dieldrin, and/or endrin for at least a year, a significantly increased incidence of pneumonia and other pulmonary diseases was found when compared to the incidence in U.S. white males (Ditraglia et al. 1981). However, all of these studies

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are limited by small sample size and the possible exposure of the workers to other chemicals and/or pesticides.

Extremely limited data were located regarding respiratory effects in animals after inhalation exposure to aldrin or dieldrin. Cats, guinea pigs, rats, rabbits, and mice exposed to aldrin vapors and particles generated by sublimating aldrin at 200 •C were reported to have exhibited symptoms indicative of mucous membrane irritation (Treon et al. 1957b). However, the exposure levels associated with these effects were not reported, and the contribution of thermal decomposition products or other volatile contaminants other than aldrin cannot be eliminated.

Cardiovascular Effects. Very limited information is available regarding the cardiovascular effects of aldrin and dieldrin in humans after inhalation exposure. Suggestive evidence of an association between dieldrin and hypertension was obtained in a study examining disease incidence in patients with elevated fat levels of dieldrin (Radomski et al. 1968). However, the number of patients with hypertension in this study was low (eight cases), and elevated fat levels of other pesticide residues also correlated with hypertension. Furthermore, other studies did not support the correlation of hypertension with dieldrin exposure. For example, a study examining disease incidence in 2,620 pesticide-exposed workers reported no increase in the incidence of hypertension in workers with elevated serum dieldrin (Morgan et al. 1980). Also, workers involved in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years had normal blood pressure (Jager 1970). Similarly, no increased mortality from circulatory system diseases was observed in the mortality study by de Jong (1991). All of these studies are limited because the subjects were exposed to a variety of other chemicals.

A slight, but significant, increase in serum cholesterol was observed in pesticide-exposed workers with elevated serum dieldrin (Morgan and Lin 1978). However, this study was limited in that the workers were occupationally exposed to a number of different pesticides and other chemicals including hydrocarbon solvents.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to aldrin or dieldrin.

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Gastrointestinal Effects. No increased mortality from digestive system causes was observed in a mortality study of workers employed in the manufacture of aldrin and dieldrin for at least 1 year between 1954 and 1970 (de Jong 1991).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to aldrin or dieldrin.

Hematological Effects. No abnormal values for hemoglobin, white blood cells, or erythrocyte sedimentation rate were found in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years (Jager 1970). Similarly, no increase in blood diseases was observed in a morbidity study of workers employed at the plant described by Jager (1970) over the period of 1979–1990 (de Jong 1991). Also, workers who had been involved in either the manufacture or application of pesticides and who had elevated blood levels of dieldrin, had no hematological effects of clinical significance (Morgan and Lin 1978; Warnick and Carter 1972). These studies are limited by either potential exposure to other chemicals (de Jong 1991; Jager 1970; Morgan and Lin 1978) or by known exposure to other pesticides as demonstrated by elevated blood levels of "β-benzine [sic] hexachloride" (β-benzene hexachloride), heptachlor epoxied, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p'*-DDT), 1,1,1-trichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (*o,p'*-DDT), and 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethene (*p,p'*-DDE) (Warnick and Carter 1972).

A case of immunohemolytic anemia attributable to multiple dieldrin exposures was reported (Muirhead et al. 1959). Also, a worker from a grove where aldrin was sprayed developed aplastic anemia (Pick et al. 1965) and one person employed in the manufacture of aldrin and dieldrin between 1954 and 1970 died from aplastic anemia (de Jong 1991). However, it is unclear whether these cases of aplastic anemia were directly due to aldrin or dieldrin exposures because exposure to a variety of other chemicals was possible. Also, three cases of pancytopenia and one case of thrombocytopenia associated with exposure to dieldrin were reported during 1961 (AMA 1962). However, no assessment of whether dieldrin was the causative agent was provided in the report.

No studies were located regarding hematologic effects in animals after inhalation exposure to aldrin or dieldrin.

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Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to aldrin or dieldrin.

Hepatic Effects. Although a slight increase in serum hepatic enzymes (serum alanine aminotransferase [ALT] and serum aspartate aminotransferase [AST]) has been observed to correlate with serum dieldrin levels in one study of pesticide-exposed workers (Morgan and Lin 1978), no evidence of any hepatic effects of aldrin or dieldrin exposure have been observed in other studies of workers involved in either the manufacture (de Jong 1991; Hoogendam et al. 1965; Hunter et al. 1972; Jager 1970; van Sittert and de Jong 1987) or the manufacture or application (Morgan and Roan 1974; Warnick and Carter 1972) of these pesticides. Parameters that have been examined in the negative studies include serum hepatic enzyme activity (Hoogendam et al. 1965; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987; Warnick and Carter 1972), hepatic enlargement (Jager 1970), and tests intended to detect microsomal enzyme induction (Hunter et al. 1972; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987). All of the studies are limited by the potential exposure of the workers to other chemicals and/or organochlorine pesticides.

No studies were located regarding hepatic effects in animals after inhalation exposure to aldrin or dieldrin.

Renal Effects. No evidence of renal damage was seen in workers employed for four or more years in the manufacture of aldrin or dieldrin (Jager 1970). This study is limited by the potential exposure of the workers to other chemicals.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to aldrin or dieldrin.

Dermal Effects. No evidence of dermatitis was seen in workers employed for four or more years in the manufacture of aldrin, dieldrin, endrin, or telodrin (Jager 1970). This study is limited by the possible exposure of the workers to other chemicals.

Extremely limited data were located regarding dermal/ocular effects in animals after inhalation exposure to aldrin or dieldrin. Cats, guinea pigs, rats, rabbits, and mice exposed to aldrin vapors and particles generated by sublimating aldrin at 200 •C were reported to have exhibited symptoms indicative of mucous membrane irritation (Treon et al. 1957b). However, the exposure levels associated with these

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effects were not reported and the contribution of thermal decomposition products or other volatile contaminants other than aldrin cannot be eliminated.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after inhalation exposure to aldrin or dieldrin.

3.2.1.3 Immunological and Lymphoreticular Effects

Limited information is available regarding the immunological effects of aldrin or dieldrin in humans after inhalation exposure. A case report was located concerning a pesticide sprayer who developed immunohemolytic anemia after multiple exposures to dieldrin, heptachlor, and toxaphene (Muirhead et al. 1959). Antibodies for dieldrin-coated or heptachlor-coated red blood cells were found in the subject's serum. However, this study is limited because of the exposure of the subject to other pesticides.

No studies were located regarding immunological effects in animals after inhalation exposure to aldrin or dieldrin.

3.2.1.4 Neurological Effects

Central nervous system excitation culminating in convulsions was the principal adverse effect noted in occupational studies of workers employed in either the application or manufacture of aldrin or dieldrin. In many cases, convulsions appeared suddenly and without prodromal signs (Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958). Electroencephalograms (EEGs) taken shortly after the convulsions revealed bilateral irregular alpha rhythms interrupted by spike and wave patterns (Avar and Czegledi-Janko 1970; Kazantzis et al. 1964). In one case study of dieldrin sprayers who developed convulsions, the convulsive episodes did not follow known accidental overexposures (Patel and Rao 1958). Rather, the convulsions developed anywhere from 14 to 154 days after the first exposure to dieldrin. The time to onset was more rapid for those sprayers using the more concentrated spray. An accumulative type of intoxication was also reported in workers involved in the manufacture of aldrin, dieldrin, telodrin, or endrin (Jager 1970). In this report, convulsions were believed to have been caused by either accumulating levels of dieldrin in the blood or modest overexposures in the presence of subconvulsive accumulations of dieldrin.

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Other central nervous system symptoms reported by workers involved in the manufacture or application of aldrin and/or dieldrin included headaches (Jager 1970; Patel and Rao 1958), dizziness (Jager 1970), hyperirritability (Jager 1970; Kazantzis et al. 1964), general malaise (Jager 1970), nausea and vomiting (Jager 1970; Kazantzis et al. 1964), anorexia (Jager 1970), muscle twitching (Jager 1970; Patel and Rao 1958), and myoclonic jerking (Jager 1970; Kazantzis et al. 1964). The more severe symptoms were accompanied by EEG patterns with bilateral spike and wave complexes and multiple spike and wave discharges in the alpha region (Jager 1970; Kazantzis et al. 1964). Less severe symptoms were accompanied by bilateral theta (Jager 1970; Kazantzis et al. 1964) and/or delta (Kazantzis et al. 1964) wave discharges.

In all cases in which follow-up of the subjects was reported, removal from the source of exposure caused a rapid physical recovery and a slower recovery of the EEG activity (within a year) to normal levels (Avar and Czegledi-Janko 1970; Hoogendam et al. 1962, 1965; Jager 1970; Kazantzis et al. 1964).

A morbidity study of workers employed in the manufacture of aldrin and dieldrin between 1979 and 1990 noted no degenerative disorders of the nervous system (de Jong 1991). However, this study reported significant increases in mental diseases among those <30 years old and in those 46–50 years old. The diseases were classified as stress reactions, short-term depression, or sleep disorders. It is unclear whether these effects were the result of aldrin/dieldrin exposure.

Results from a comprehensive neurological workup of 27 workers involved in either the manufacture or application of dieldrin were compared to those of a group of unexposed workers (Sandifer et al. 1981). Scores on five psychological tests were significantly different from those of the unexposed controls; however, the importance of the results was questioned by the authors because of differences in the degree of literacy between the two groups. Also, three exposed workers had abnormal electromyograms (EMGs) suggesting a peripheral neuropathy. However, EMGs were not obtained in the control group; thus, the significance of these results is unknown.

No studies were located regarding neurological effects in animals after inhalation exposure to aldrin or dieldrin.

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3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to aldrin or dieldrin.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to aldrin or dieldrin.

3.2.1.7 Cancer

Selected Mortality Studies. Aldrin and dieldrin were manufactured at two sites worldwide in plants at the Rocky Mountain Arsenal in Denver, Colorado, and at Pernis in the Netherlands. Workers from these plants have been included in two series of retrospective cohort mortality studies which have been updated several times. Exposure to dibromochloropropane (DBCP) and several organophosphates may also have occurred in the Denver plant. Cancer mortality findings of the studies at the Denver plant (Amoateng-Adjepong et al. 1995; Brown 1992; Ditraglia et al. 1981; Ribbens 1985) and the Pernis plant (de Jong 1991; de Jong et al. 1997; Jager 1970; Ribbens 1985; van Raalte 1977) are inconclusive, as summarized below.

The first study of the Denver plant found no significant increase in cancer mortality, but concluded that additional follow-up was necessary due to a small number of deaths (173) and the relatively short period of observation (Ditraglia et al. 1981). In the follow-up by Brown (1992), 1,158 workers who were employed for at least 6 months prior to 1965 and were followed through 1987 were investigated. Cause-specific mortality analysis of 337 deaths showed an increase in liver and biliary tract cancer (five cases observed) that was statistically significant when compared to state and local rates (Standardized mortality ratios [SMRs] of 5.10 and 4.86, respectively), but not the national rate (SMR=3.93). All of these five deaths (three from biliary tract/bile duct cancer, one from gall bladder cancer, and one from hepatoma) occurred after 15 years of latency (SMR=4.85). The cohort in the most recent study of the Denver plant (Amoateng-Adjepong et al. 1995) was expanded to 2,384 subjects and followed through 1990 (median 29 years). The median age at hiring was 26 years and the median tenure was 2 years. The increase in hepatobiliary cancer was of a lower magnitude than in the previous study and was no longer statistically significant, although no additional cases had occurred (5 cases observed/2.0 expected based on state rates,

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SMR=249). Based on this information and findings that the cancers were not limited to any particular production unit, did not display duration-response trends, and essentially occurred in the biliary tract or gall bladder (rather than liver), the investigators concluded that the hepatobiliary cancer excess was not due to occupational exposures at the plant.

No indications of a carcinogenic effect were found in the early mortality studies of the Dutch (Pernis) workers (Jager 1970; Ribbens 1985; van Raalte 1977). Similarly, in the follow-up study by de Jong (1991), there were no increases in cause-specific mortality among 76 deaths in 570 workers who were employed for at least 1 year between 1954 and 1970 and followed-up until 1987. Follow-up of this cohort until 1993 (118 deaths) showed a significant increase in mortality from rectal cancer (6 deaths observed versus 1.5 expected compared to Netherlands national rates, SMR=390.4) and an insignificant increase in liver cancer deaths (2 observed versus 0.9 expected, SMR=225.0) (de Jong et al. 1997). Stratification by dose level (low, moderate, or high exposure based on blood levels of dieldrin) did not disclose any indications of a dose-response relation for either of these causes of death.

Equivocal evidence exists for an association between dieldrin and breast cancer risk from three human epidemiologic studies (Dorgan et al. 1999; Høyer et al. 1998, 2000). In these studies, while dieldrin exposure was verified through blood sampling, and exposure by inhalation, as well as by ingestion and dermal contact, was possible, no specific route of exposure was identified or estimated with any certainty.

The potential of dieldrin to affect breast cancer risk was evaluated in a prospective nested case control study of women in Denmark (Høyer et al. 1998). Serum samples were obtained from 7,712 women from 1976 to 1978. In 1996–1997, serum samples from 240 women who had developed invasive breast cancer and 477 matched breast cancer-free controls were analyzed for levels of dieldrin and 17 other organochlorine pesticides or metabolites and 28 PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Irrespective of breast cancer status, dieldrin was detected in 78% of the women enrolled in the study, with median levels at 24.4 ng/g lipid. Dieldrin was the only organochlorine compound of those tested associated with a significant increase in breast cancer risk. Women in the highest quartile of the serum dieldrin range had double the risk of breast cancer compared to women in the lowest quartile (odds ratio [OR] 2.25, 95% confidence interval [CI] 1.32–3.84, p trend=0.003). Relative risk (RR) did not change significantly when adjusted for potential confounders of weight and number of full-term pregnancies (OR 2.05, 95% CI 1.17–3.57, p trend=0.01).

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A subsequent study using the same cohort of Danish women investigated whether breast cancer survival was affected by past exposure to dieldrin (Høyer et al. 2000). Dieldrin, at blood concentrations >57.6 ng/g, representative of the highest quartile, was found to have a significant adverse effect on overall survival and breast cancer specific survival compared to the lowest quartile levels of <12 ng/g lipid (RR 2.78, 95% CI 1.38–5.59, p trend <0.01 ; RR 2.61, 95% CI 0.97–7.01, p trend <0.01) in this case-control study of Danish women between 20 and 80 years of age. A total of 195 breast cancer cases, who each provided two blood samples that were taken in 1976–1978 and 1981–1983, respectively, were included in the survival analysis. The median duration of follow-up with regard to death was 86 months after the first examination (1976–1978) and 79 months after the second examination (1981–1983). Relative risk was adjusted for number of positive lymph nodes and tumor size and grade. When the analysis was performed using an average of the blood concentrations from the two collections, the association was even stronger, with a 5-fold higher risk of death in women from the highest quartile compared to the lowest quartile (RR 5.76, 95% CI 1.86–17.92, p trend <0.01) and a clear dose-response relationship. Potential confounders as body mass index, age at menopause, and hormone replacement therapy did not influence the results. This study was limited by small size, 6–39 women per quartile.

A cohort study of women from Missouri failed to find an association between serum dieldrin levels and breast cancer risk (Dorgan et al. 1999). Blood samples were collected from 7,224 women from 1977 to 1987. During the 9.5-year follow-up period, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum in 56.2% of the cases and 61.8% of the controls. The relative risk of cancer in the highest dieldrin serum concentration range quartile was moderately lower compared to the lowest quartile (RR 0.7, 95% CI 0.3–1.3, $p=0.44$).

Animal Cancer Studies. No studies were located regarding cancer in animals after inhalation exposure to aldrin or dieldrin. As summarized in Section 3.2.2.7, EPA derived carcinogenic potency estimates for oral exposure to aldrin and dieldrin using liver tumor responses in mice. Based on the oral data, unit risk estimates for inhalation exposures (the excess cancer risk associated with lifetime exposure to $1\mu\text{g}/\text{m}^3$) of 4.9×10^{-3} and 4.6×10^{-3} were calculated for aldrin and dieldrin, respectively (EPA 1986; IRIS 2002a, 2002b). Based on these unit risk values, aldrin and dieldrin cancer risk levels of 10^{-4} , 10^{-5} , 10^{-6} , and 10^{-7} correspond to 70 years of continuous exposure to 0.02, 0.002, 0.0002, and 2.0×10^{-5} $\mu\text{g}/\text{m}^3$, respectively (1.3 , 1.3×10^{-1} , 1.3×10^{-2} , and 1.3×10^{-3} ppt). The predicted cancer risks are considered conservative upper estimates. The actual risk of cancer is unlikely to be higher and may be substantially lower.

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3.2.2 Oral Exposure**3.2.2.1 Death**

A 2-year-old child died a short time after consuming an unknown quantity of a 5% solution of dieldrin (Garrettson and Curley 1969). It is unclear from this report whether the child died during the severe convulsions produced by the dieldrin or during the postictal period (the period immediately following a seizure that is characterized by central nervous system depression). This child's 4-year-old brother, who also consumed an unknown quantity of the 5% dieldrin solution, experienced severe convulsions but recovered completely.

Of several persons who consumed wheat that had been mixed with aldrin and lindane for a period of 6–12 months, an infant female child died within a few hours after experiencing a severe generalized convulsion (Gupta 1975).

The doses at which aldrin is acutely lethal in experimental animals are quite similar to lethal dieldrin doses. Oral LD₅₀ values for single doses of aldrin in rats ranged from 39 to 64 mg/kg (Gaines 1960; Treon et al. 1952). Oral LD₅₀ values for single doses of dieldrin in adult rats ranged from 37 to 46 mg/kg/day (Gaines 1960; Lu et al. 1965; Treon et al. 1952). Aldrin was lethal in females at a slightly lower dose when it was administered in solution in oil (LD₅₀=48 mg/kg) than when it was administered in a kerosene vehicle (LD₅₀=64 mg/kg) (Treon et al. 1952).

The age of the animals appeared to influence the acute toxicity of a single administration of dieldrin. Newborn rats had a relatively high LD₅₀ (168 mg/kg) (Lu et al. 1965); whereas 2-week-old rats had an LD₅₀ of 25 mg/kg, which is somewhat lower than the adult LD₅₀ value (Lu et al. 1965). When aldrin was widely used as an insecticide, several incidents were reported in which livestock died as the result of accidental mixing of unspecified amounts of aldrin with livestock feed (Buck and Van Note 1968). In an incident in which both calves and adult cattle were exposed, mortality occurred exclusively among the calves.

Decreased survival in animals consuming aldrin and/or dieldrin over longer periods was seen at lower doses. All rats consuming 15 mg/kg/day aldrin or dieldrin in the diet died by the end of the second week of exposure (Treon et al. 1951a). Rats exposed to aldrin or dieldrin for 6 weeks exhibited increased mortality at estimated doses of 8 and 16 mg/kg/day, respectively (NCI 1978a). When exposed for 2 years

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or more, rats exhibited decreased survival at doses of 0.5–2.5 mg/kg/day aldrin or dieldrin (Deichmann et al. 1970; Fitzhugh et al. 1964; Harr et al. 1970; NCI 1978a).

In intermediate- and chronic-duration studies, dogs and mice appeared to have a sensitivity to the lethal effects of aldrin and/or dieldrin that is similar to that of rats. All dogs given aldrin at doses of 0.89–1.78 mg/kg/day or dieldrin at doses of 1.95–4.24 mg/kg/day died or were killed in a moribund condition in a 9-month dietary study (Treon et al. 1951b). Dogs appeared to survive for longer periods if the dog was larger or older at the start of the study. Decreased survival in dogs exposed for 25 months was also observed at 1 mg/kg/day aldrin or 0.5 mg/kg/day of dieldrin (Fitzhugh et al. 1964). In mice, decreased survival was seen at 1.3 mg/kg/day dieldrin (Thorpe and Walker 1973; Walker et al. 1972). In contrast, hamsters appeared to be less sensitive to dieldrin. Exposure to 14.9 mg/kg/day dieldrin for 120 weeks had no effect on hamster survival (Cabral et al. 1979).

The highest NOAEL values, all LD₅₀ values, and all reliable LOAEL values for death in each species and duration category are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding dermal/ocular effects in humans or animals after oral exposure to aldrin or dieldrin.

The highest NOAEL values and all reliable LOAEL values for each study for each end point for dieldrin are recorded in Table 3-2 and plotted in Figure 3-2.

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Table 3-1. Levels of Significant Exposure to Aldrin - Oral

Key to figure ^a	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat	1 x (GO)				39 ^d (LD ₅₀ male) 60 (LD ₅₀ female)	Gaines 1960
2	Rat	2 wk ad lib (F)				15 (10/10 died)	Treon et al. 1951a
3	Rat	1 d (G)				63.6 (LD ₅₀)	Treon et al. 1952
4	Rat	1 d (GO)				48.3 (LD ₅₀)	Treon et al. 1952
Neurological							
5	Rat	3 d 1x/d (GO)		5		10 (convulsions)	Mehrotra et al. 1979
Reproductive							
6	Mouse	5 d 1x/d (G)		1.0			Epstein et al. 1977
Developmental							
7	Mouse	5-7 d (GO)			2 ^b (decreased body weight and increased seizure threshold in offspring)		Al-Hachim 1971

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Table 3-1. Levels of Significant Exposure to Aldrin - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
8	Mouse	1 x Gd 9 (GO)				25 (webbed feet)	Ottolenghi et al. 1974
9	Hamster	1 x Gd 7, 8, or 9 (GO)				50 (increased fetal mortality)	Ottolenghi et al. 1974

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Table 3-1. Levels of Significant Exposure to Aldrin - Oral (continued)

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
10	Rat	6 wk ad lib (F)				8 (2/10 died)	NCI 1978a
11	Mouse	6 wk ad lib (F)				2.6 (2/10 died)	NCI 1978a
12	Dog	9 mo ad lib (F)				0.89-1.78 (2/2 died)	Treon et al. 1951b
13	Dog	5 wk 5d/wk (C)				1.5 (3/3 pre-weanlings died)	Treon et al. 1955b
Systemic							
14	Rat	27 wk ad lib (F)	Hepatic Renal Bd Wt	1.25 1.25 0.63	1.25 (decreased body weight gain)		Treon et al. 1953b
15	Dog	9 mo ad lib (F)	Gastro Hepatic	0.89- 1.78 0.89- 1.78	(vomiting) (moderate hepatocellular degeneration)		Treon et al. 1951b

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Table 3-1. Levels of Significant Exposure to Aldrin - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	
Neurological						
16	Dog	9 mo ad lib (F)			0.89- 1.78	(hypersensitivity; tremors; convulsions; neuronal degeneration) Treon et al. 1951b

Table 3-1. Levels of Significant Exposure to Aldrin - Oral (continued)

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Death							
17	Rat	31 mo 7d/wk (F)				2.5 (33% reduced survival in females)	Deichmann et al. 1970
18	Rat	2 yr ad lib (F)				2.5 (58% reduced survival)	Fitzhugh et al. 1964
19	Mouse	80 wk ad lib (F)				0.78 (34% reduced survival)	NCI 1978a
Systemic							
20	Rat	25 mo ad lib (F)	Hemato Hepatic Renal	0.25	0.25 (slight liver degeneration) 0.25 (hyaline casts)		Deichmann et al. 1967
21	Rat	2 yr ad lib (F)	Hepatic		0.025 ^c (hepatocellular enlargement and vacuolation, bile duct proliferation)		Fitzhugh et al. 1964 Reuber 1980
22	Dog	15.7 mo 7 d/wk 1-3x/d (F)	Renal Hepatic Renal	0.1 0.04-0.09	0.5 (nephritis) 0.12-0.25 (hyaline droplet degeneration) 0.04-0.09 (vacuolation of renal tubules)	2.5 (bladder distension and hemorrhages)	Treon et al. 1955b

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Table 3-1. Levels of Significant Exposure to Aldrin - Oral (continued)

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
23	Rat	74-80 wk ad lib (F)				1.5 (convulsions)	NCI 1978a
24	Mouse	80 wk ad lib (F)			0.39 (hyperexcitability)		NCI 1978a
Reproductive							
25	Rat	3 gen ad lib (F)				0.63 (decreased number of litters)	Treon et al. 1954a
Developmental							
26	Rat	3 gen ad lib (F)				0.125 (increased mortality of offspring)	Treon et al. 1954a
Cancer							
27	Rat	74-80 wk ad lib (F)				1.5 (CEL - thyroid)	NCI 1978a
28	Mouse	2 yr 7d/wk (F)				1.3 (CEL - liver)	Davis and Fitzhug 1962

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Table 3-1. Levels of Significant Exposure to Aldrin - Oral (continued)

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
29	Mouse	80 wk ad lib (F)				0.52 (CEL - liver)	NCI 1978a

^aThe number corresponds to entries in Figure 3-1.

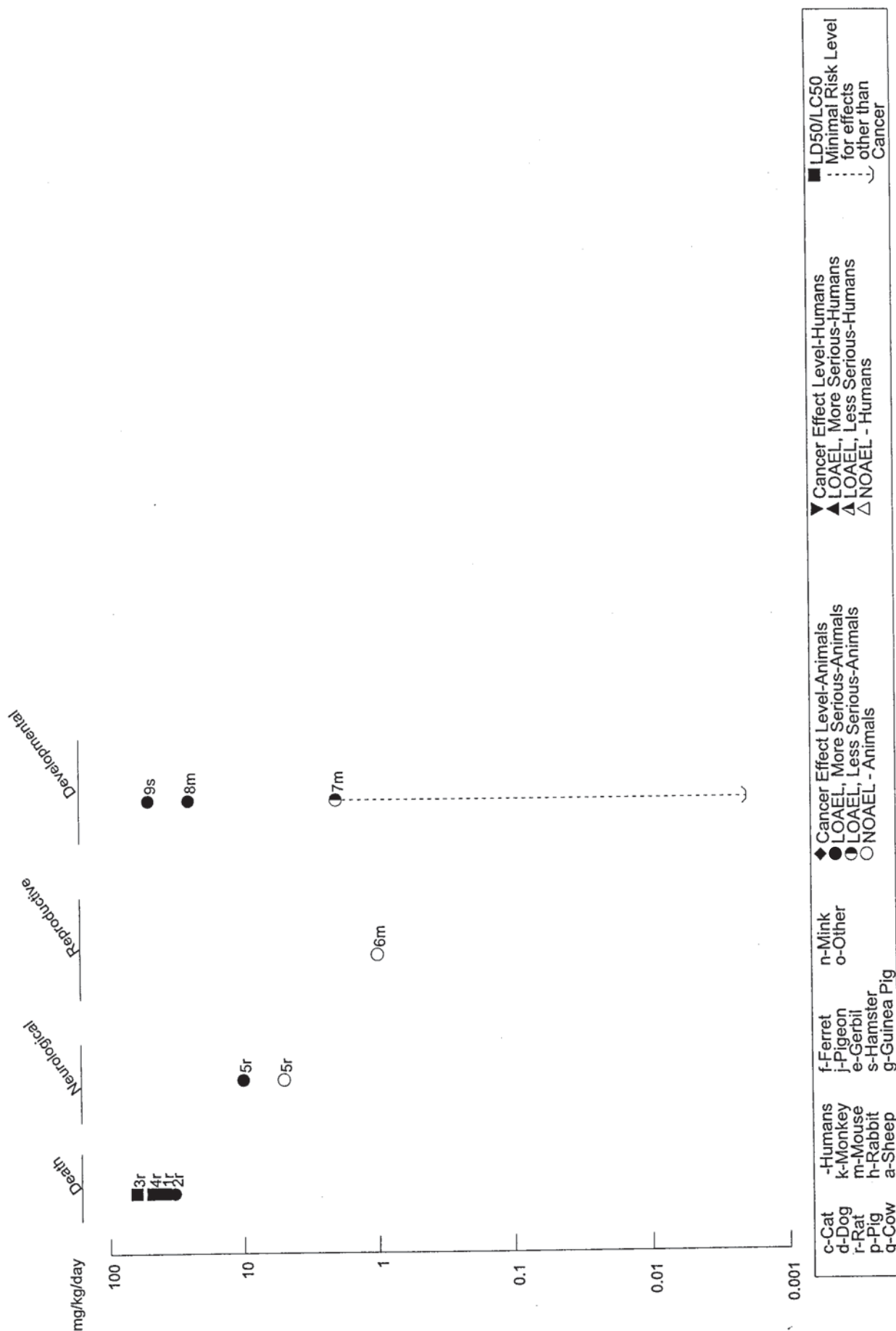
^bUsed to derive an acute oral Minimal Risk Level (MRL) of 0.002 mg/kg/day; LOAEL (2 mg/kg/day) divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

^cUsed to derive a chronic oral Minimal Risk Level (MRL) of 0.00003 mg/kg/day; LOAEL (0.025 mg/kg/day) divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

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

ad lib = ad libitum; (C) = capsule; CEL = cancer effect level; d = day(s); (F) = feed; (G) = gavage (not specified); Gastro = gastrointestinal; Gd = gestation day(s); gen = generation(s); (GO) = gavage (oil); LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

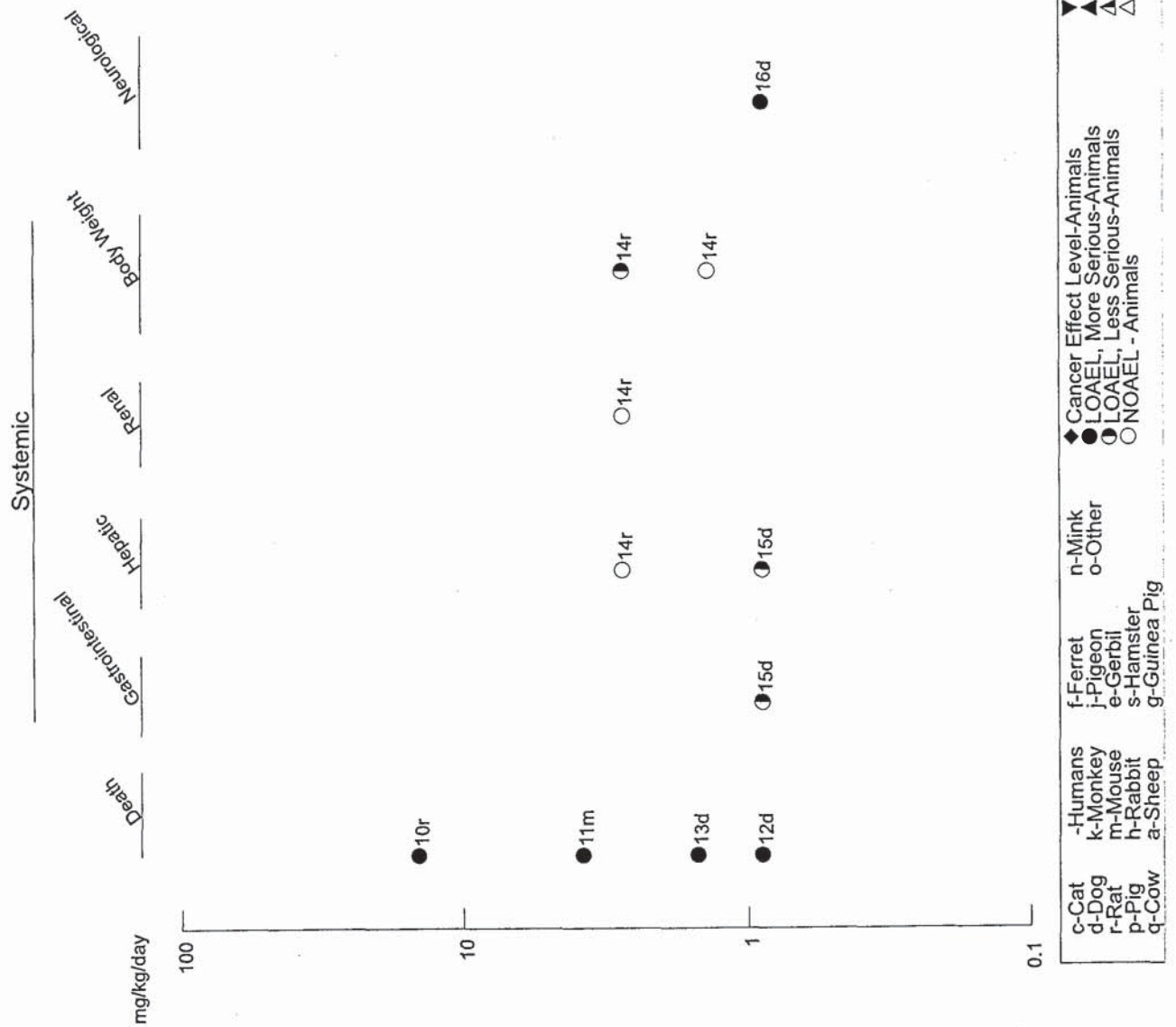
Figure 3-1. Levels of Significant Exposure to Aldrin - Oral
Acute (≤ 14 days)



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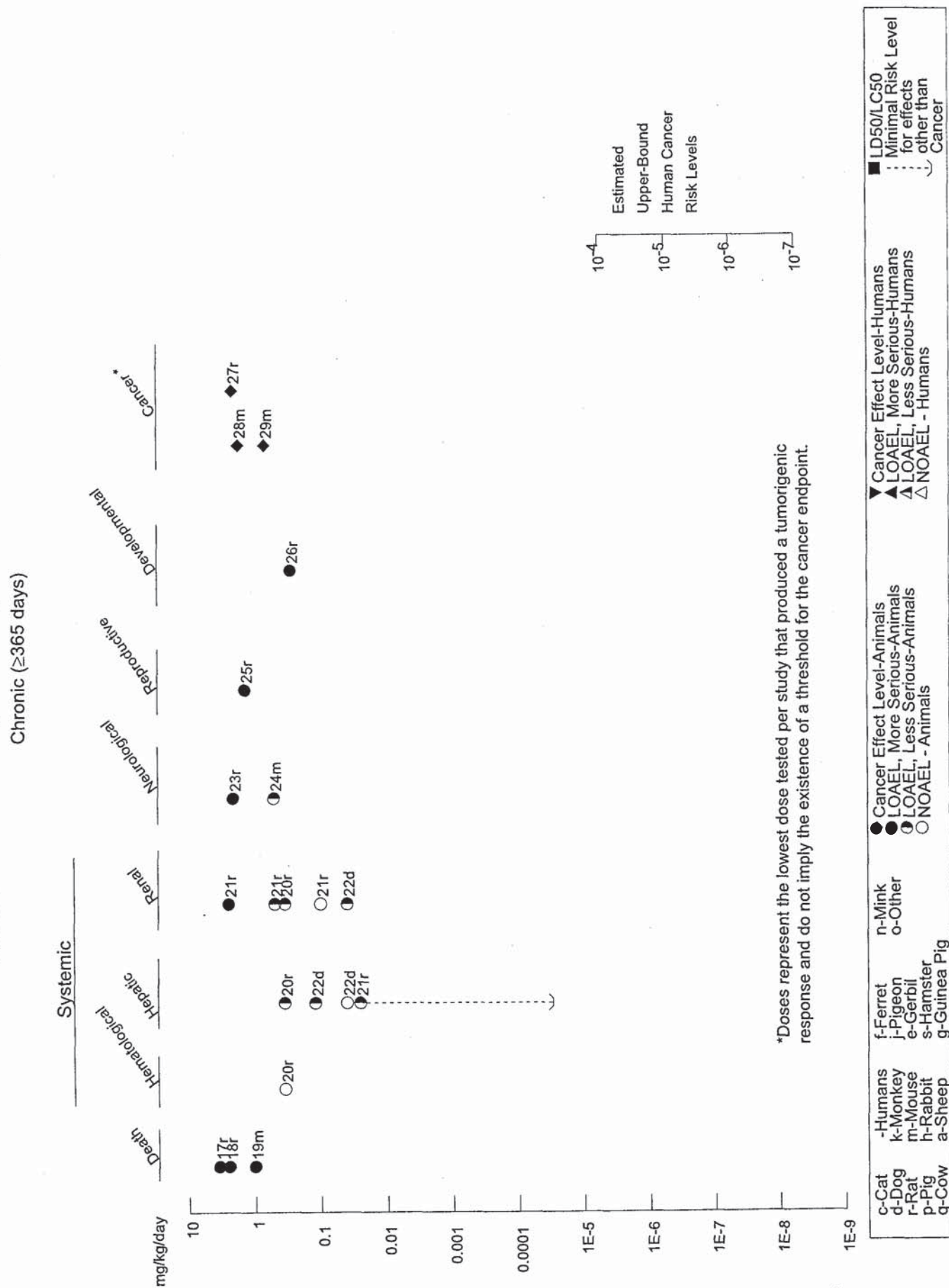
Figure 3-1. Levels of Significant Exposure to Aldrin - Oral (*Continued*)

Intermediate (15-364 days)



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Figure 3-1. Levels of Significant Exposure to Aldrin - Oral (Continued)



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

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat	10 d 1x/d Gd7-16 (GO)		3		6 (13/32 dams died)	Chernoff et al. 1975
2	Rat	1 x (GO)				46 (LD ₅₀)	Gaines 1960
3	Rat	1 x (GO)				168 (LD ₅₀ , newborn)	Lu et al. 1965
4	Rat	1 x (GO)				37 (LD ₅₀ , young adult)	Lu et al. 1965
5	Rat	4 d 1 x (GO)				9 (LD ₅₀ , 14-16 day old)	Lu et al. 1965
6	Rat	1 x (GO)				25 (LD ₅₀ , 14-16 day old)	Lu et al. 1965
7	Rat	4 d 1x/d (GO)				54.8 (LD ₅₀ , young adult)	Lu et al. 1965
8	Rat Carworth (F)	2 wk ad lib (F)				15 (10/10 died)	Treon et al. 1951a
9	Rat	1 d (GO)				38.8 (LD ₅₀)	Treon et al. 1952

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

Key to ^a Species figure (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic						
10 Rat	1 x (GO)	Hepatic		26 (increased lipid peroxidation)		Goel et al. 1988
11 Rat	1 x (GO)	Hepatic		30 (decreased lipid peroxidation)		Kohli et al. 1977
12 Rat	3 d 1x/d (GO)	Cardio	10			Mehrotra et al. 1989
13 Mouse	1-2 wk ad lib (F)	Hepatic	1.6			Wright et al. 1972
Immunological/Lymphoreticular						
14 Mouse	2 x (GO)			16.6 (impaired T-cell activity)		Fournier et al. 1988
15 Mouse	1 x (GO)		12		18 (increased lethality following viral infection)	Krzyszniak et al. 1985
16 Mouse	2 wk ad lib (F)			0.065 (impaired antigen processing by macrophages)		Loose et al. 1981
Neurological						
17 Rat	1 x (GO)		8.4		16.7 (disrupted operant behavior)	Burt 1975
18 Rat	1 x (GO)				2.5 (disrupted operant behavior)	Burt 1975

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

Key to ^a Species figure (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
			NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
19 Rat	1 x (GO)				0.5 (impaired behavior)	Carlson and Rosellini 1987
20 Rat	1 x (GO)			40 (hypothermia)	50 (convulsions)	Wagner and Greene 1978
21 Rat	1 x (GO)				25 (increased evoked potentials)	Woolley et al. 1985
22 Sheep	4 d (C)				20 (impaired operant behavior; EEG changes)	Sandler et al. 1969
Developmental						
23 Rat	10 d 1x/d Gd7-16 (GO)		6			Chernoff et al. 1975
24 Mouse	10 d 1x/d Gd7-16 (GO)		1.5		3 (supernumerary ribs)	Chernoff et al. 1975
25 Mouse	13 d Gd6-18 (GO)			2 (low blood glucose level in neonates)		Costella and Virgo 1980
26 Mouse	1 x (GO)				15 (webbed foot; cleft palate)	Ottolenghi et al. 1974
27 Hamster	1 x Gd 7, 8, or 9 (GO)				30 (open eye; webbed foot; cleft palate; increased resorptions; increased fetal mortality)	Ottolenghi et al. 1974

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

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
28	Rat	6 wk ad lib (F)				16 (7/10 died)	NCI 1978a
29	Mouse	6 wk ad lib (F)				2.6 (7/10 died)	NCI 1978a
30	Mouse	74 d ad lib (F)				2.6 (17% increased mortality)	Virgo and Bellward 1975
31	Mouse	40 wk (F)				7.5 (4/4 died)	Wright et al. 1972
32	Dog	9 mo ad lib (F)				1.95- 4.24 (3/3 died)	Treon et al. 1951b
Systemic							
33	Rat	6 mo ad lib (F)	Hepatic Renal		10 (hepatocellular necrosis) 10 (epithelial cell degeneration)		Ahmed et al. 1986a
34	Rat	15 d (GO)	Hepatic Renal		5 (diffuse necrosis) 5 (glomerulonephritis; renal tubular nephrosis)		Bandyopadhyay et al. 1982b
35	Rat (Fischer- 344)	90d (F)	Hepatic	0.5			Kolaja et al. 1996a

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

Key to figure ^a	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
36	Rat	1-6 mo (F)	Hepatic		2	(decreased hepatic protein; areas of necrosis)	Shakoori et al. 1982
37	Rat	27 wk ad lib (F)	Hepatic Renal	1.25 1.25			Treon et al. 1953b
38	Mouse (B6C3F1)	90d (F)	Hepatic	1.3			Kolaja et al. 1996a
39	Mouse (B6C3F1)	28d (F)	Hepatic	1.3			Stevenson et al. 1995a
40	Mouse	40 wk (F)	Hepatic	1.6			Wright et al. 1972
41	Dog	9 mo ad lib (F)	Gastro Hepatic	0.73- 1.85	1.95- 4.24 0.73- 1.85	(vomiting) (moderate hepatocellular degeneration)	Treon et al. 1951b
Immunological/Lymphoreticular							
42	Mouse	10 wk ad lib (F)				0.13 (increased lethality following protozoan infection)	Loose 1982
43	Mouse	3, 6, 18 wk, 7d/wk, 1x/d (F)				0.13 (increased lethality following tumor implant)	Loose et al. 1981

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

Key to ^a Species figure (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological						
44 Monkey	55-109 d 1x/d (F)		0.01 ^b		0.1 (learning deficit)	Smith et al. 1976
45 Rat	6-120 d (F)		0.025		0.25 (disrupted operant behavior)	Burt 1975
46 Rat	60 d ad lib (GO)				0.5 (tremors)	Mehrotra et al. 1989
47 Dog	9 mo ad lib (F)				0.73-1.85 (neuronal degeneration convulsions)	Treon et al. 1951b
Reproductive						
48 Mouse	120 d 1x/d (F)				0.65 (decreased litter size)	Good and Ware 1969
49 Mouse	74 d ad lib (F)		0.65		1.3 (decreased fertility)	Virgo and Bellward 1975
50 Mouse	74 d ad lib (F)		0.65	1.3 (long latency to nursing)		Virgo and Bellward 1975
Developmental						
51 Mouse	74 d ad lib (F)		0.325		0.65 (increased pup mortality)	Virgo and Bellward 1975

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

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Death							
52	Rat	31 mo (F)				1.5 (11% reduced survival in females)	Deichmann et al. 1970
53	Rat	2 yr ad lib (F)				2.5 (58% reduced survival)	Fitzhugh et al. 1964
54	Mouse	80 wk ad lib (F)				0.65 (10% increased mortality)	NCI 1978a
55	Mouse	132 wk 1x/d (F)				1.3 (50% mortality reached at 15 months versus 20-24 months in controls)	Walker et al. 1972
Systemic							
56	Human	18 mo (C)	Hemato	0.003			Hunter and Robinson 1967
			Hepatic	0.003			
57	Monkey	69 mo 1x/d (F)	Hepatic	0.1			Wright et al. 1978
58	Rat	2 yr ad lib (F)	Hepatic		0.025 (hepatocellular enlargement and vacuolation, bile duct proliferation)		Fitzhugh et al. 1964; Reuber 1980
			Renal	0.5	2.5 (nephritis)	5 (bladder distension and hemorrhages)	

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

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
59	Rat	2 yr ad lib (F)	Resp	0.5			Walker et al. 1969
			Cardio	0.5			
			Gastro	0.5			
			Hemato	0.5			
			Musc/skel	0.5			
			Hepatic	0.005 ^c F	0.05 F (increased liver weight with parenchymal cell changes including focal hyperplasia at a higher dose)		
60	Mouse	92 wk 7d/wk ad lib (F)	Renal	0.5			Tennekes et al. 1981
			Endocr	0.5			
			Dermal	0.5			
			Bd Wt	0.5			
			Hepatic	1.3			
61	Mouse	2 yr (F)	Hepatic		1.3 (liver hyperplasia)		Thorpe and Walker 1973
62	Dog	15.7 mo 7 d/wk 1-3x/d (F)	Hepatic	0.14- 0.26			Treon et al. 1955b
			Renal		0.14- 0.26 (vacuolation of renal tubules)		

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

Key to figure ^a	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
63	Dog	2 yr 1x/d (C)	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Endocr Dermal Ocular Bd Wt	0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05			Walker et al. 1969
Neurological							
64	Human	18 mo (C)		0.003			Hunter and Robinson 1967
65	Rat	59-80 wk ad lib (F)			1.45 (hyperexcitability)		NCI 1978a
66	Rat	104-105 wk ad lib (F)		0.5		2.5 (convulsions)	NCI 1978b
67	Rat	2 yr ad lib (F)		0.05		0.5 (tremors and occasional convulsions)	Walker et al. 1969
68	Mouse	80 wk ad lib (F)				0.33 (tremors)	NCI 1978a

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

Key to figure ^a	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
69	Dog	2 yr 1x/d (C)		0.05			Walker et al. 1969
Reproductive							
70	Rat	3 gen ad lib (F)				0.125 (decreased number of litters)	Treon et al. 1954a
Developmental							
71	Rat	3 gen ad lib (F)				0.125 (increased mortality of offspring)	Treon et al. 1954a
Cancer							
72	Mouse	2 yr 7d/wk (F)				1.3 (CEL - liver)	Davis and Fitzhugh 1962
73	Mouse	75 wk ad lib (F)				1.3 (CEL - liver)	Lipsky et al. 1989
74	Mouse	85 wk ad lib (F)				1.3 (CEL - liver)	Meierhenry et al. 1983
75	Mouse	80 wk ad lib (F)				0.65 (CEL - liver)	NCI 1978a

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

Key to ^a figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
76	Mouse	92 wk 7d/wk ad lib (F)				1.3 (CEL - liver)	Tennekes et al. 1981
77	Mouse	132 wk 1x/d (F)				1.3 (CEL - liver)	Walker et al. 1972
78	Mouse	128 wk 1x/d (F)				0.33 (CEL - liver)	Walker et al. 1972

^aThe number corresponds to entries in Figure 3-2.

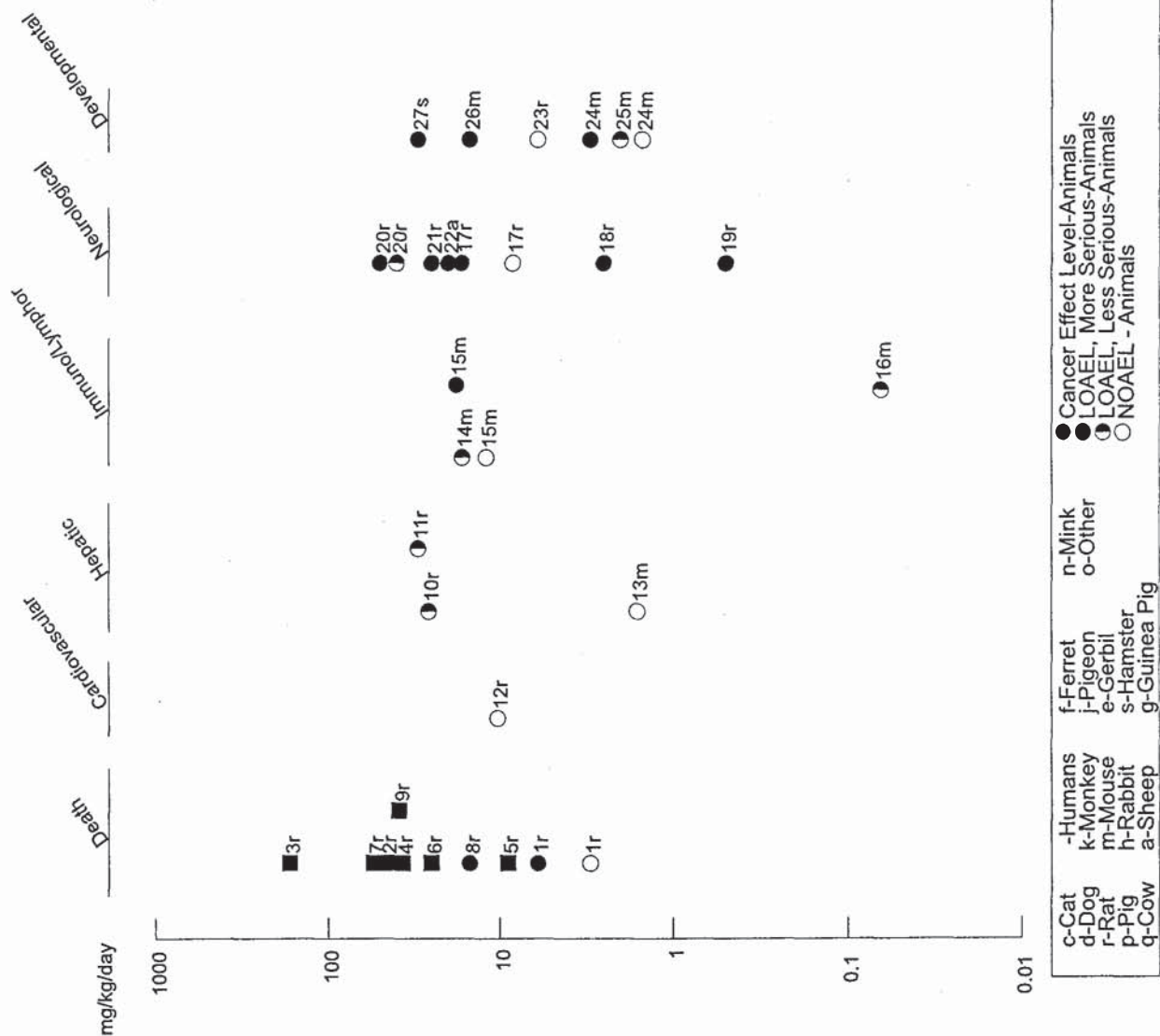
^bUsed to derive an intermediate oral Minimal Risk Level (MRL) of 0.0001 mg/kg/d; NOAEL (0.01 mg/kg/day) divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

^cUsed to derive a chronic oral Minimal Risk Level (MRL) of 0.00005 mg/kg/d; NOAEL (0.005 mg/kg/day) divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); EEG = electroencephalogram; (F) = feed; Gastro = gastrointestinal; Gd = gestation day(s); gen = generation(s); (GO) = gavage oil; Hemato = hematological; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

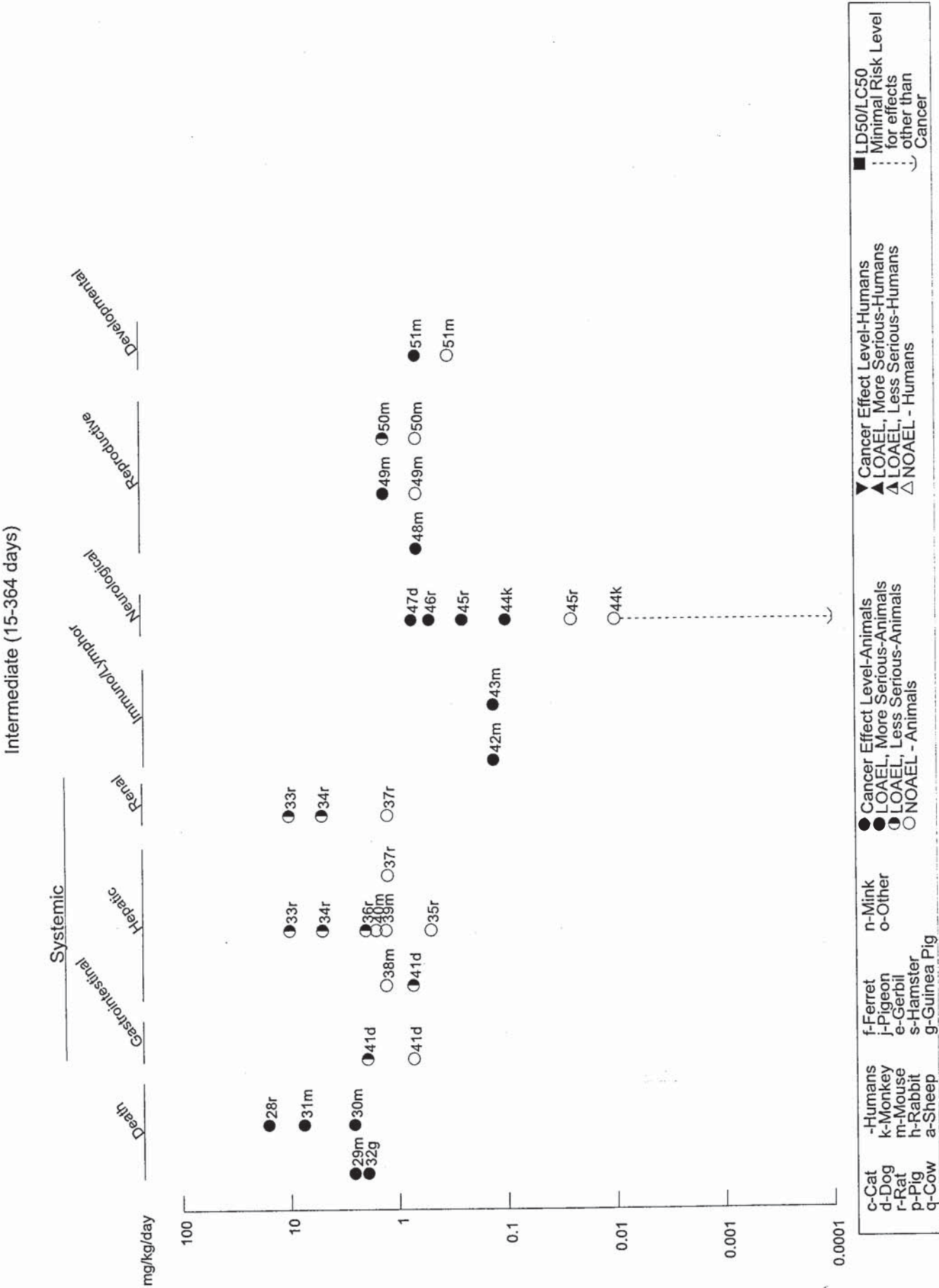
3. HEALTH EFFECTS

Figure 3-2. Levels of Significant Exposure to Dieldrin - Oral

Acute (≤ 14 days)

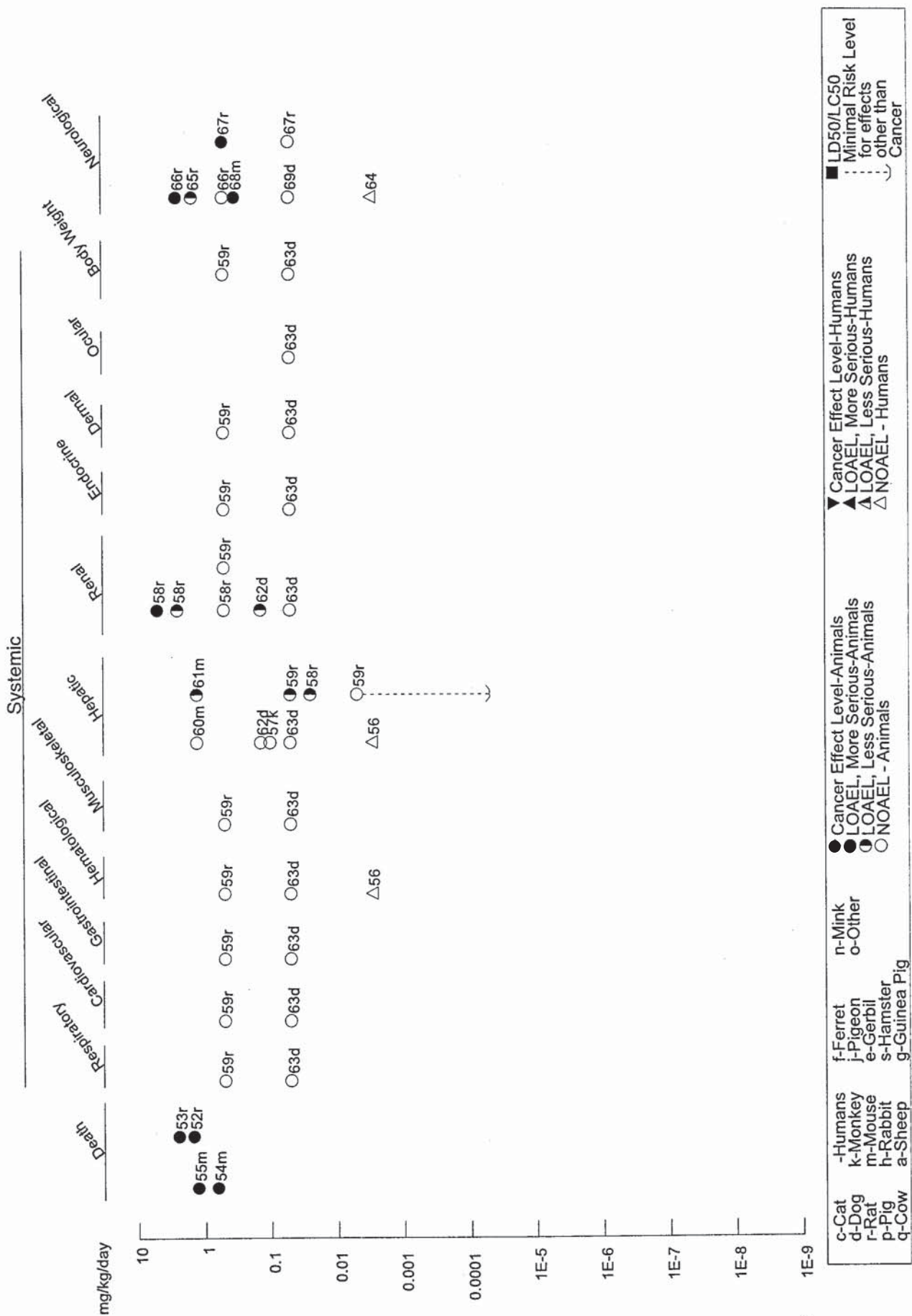
3. HEALTH EFFECTS

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



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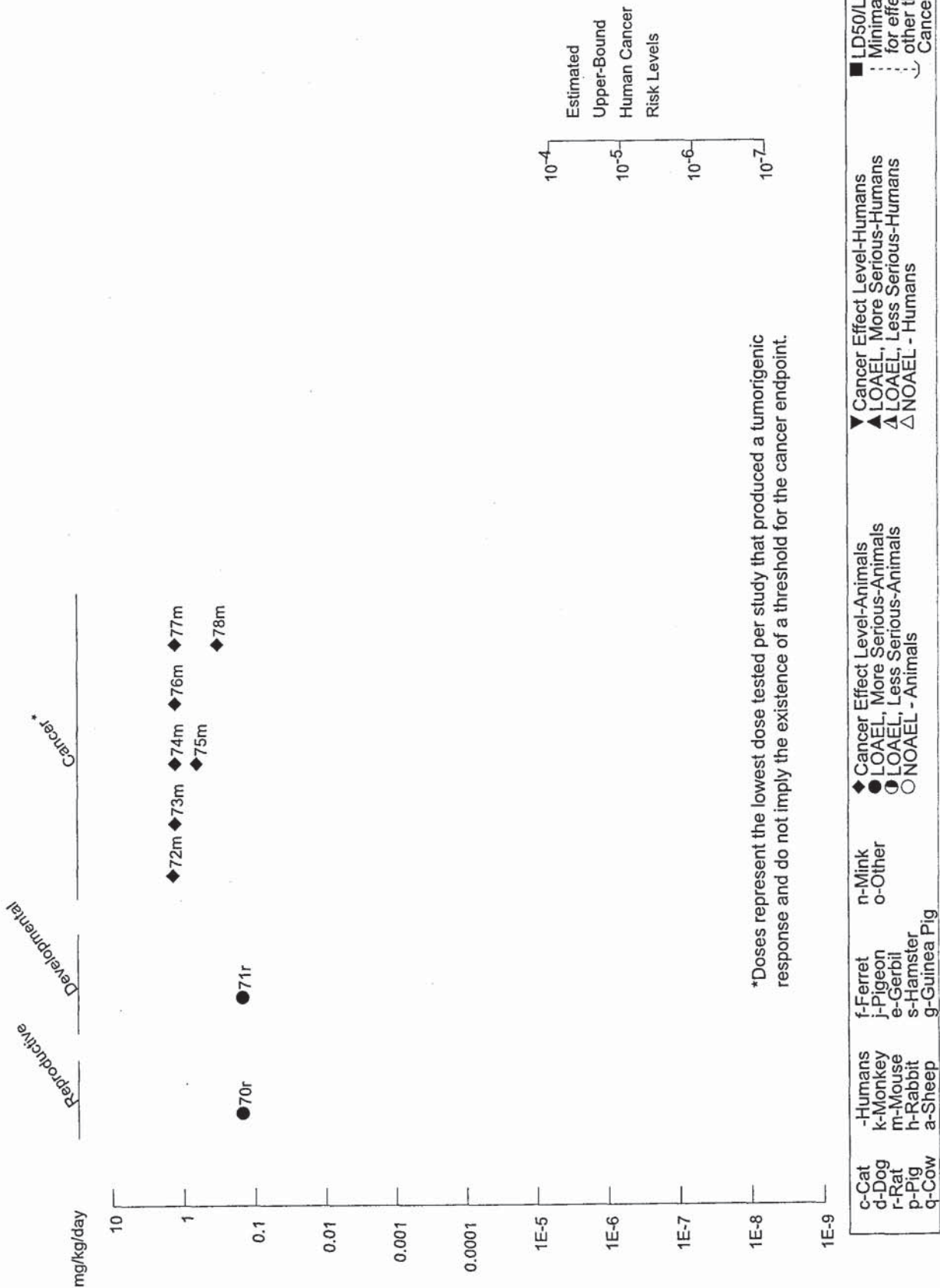
Figure 3-2. Levels of Significant Exposure to Dieldrin - Oral (Continued)

Chronic (≥ 365 days)

3. HEALTH EFFECTS

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

Chronic (≥365 days)



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Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to aldrin or dieldrin.

Routine gross and microscopic examinations showed no adverse effects in the lungs of rats exposed to • 3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), • 3 mg/kg/day aldrin or • 3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a, 1978b), or • 0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to • 1.04 mg/kg/day aldrin or • 0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to • 0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Cardiovascular Effects. A young man who attempted suicide by consuming approximately 25.6 mg/kg of aldrin had extremely labile blood pressure upon admission to the hospital (Spiotta 1951). His electrocardiogram was normal. Another man who ingested 120 mg/kg of dieldrin had tachycardia and elevated blood pressure at the time of his admission to the hospital (Black 1974). Both men were suffering from convulsions at the time that these effects were observed; thus, it is possible that these cardiovascular effects may have been the result of altered activity in the central nervous system. In the case of the man who ingested 120 mg/kg of dieldrin, the cardiovascular effects were controlled with β -adrenergic blocking drugs, suggesting that the effects were due to increased sympathetic output (Black 1974).

A correlation between adipose tissue levels of dieldrin and the incidence of hypertension was reported in a study of terminal hospital patients (Radomski et al. 1968). However, interpretation of these results is limited by the small number of cases of hypertension (eight cases) and the observation that the levels of a number of other pesticides in adipose tissues also correlated with the incidence of hypertension.

Acute oral administration of aldrin and dieldrin inhibited Ca^{2+} -pump activity in the heart (and brain) of rats (Mehrortra et al. 1989). Treatment by gavage for 3 days caused significantly decreased cardiac calmodulin levels at doses as low as 1 mg/kg/day dieldrin and 5 mg/kg/day aldrin, and significant inhibition of Ca^{2+} ATPase activity in heart sarcoplasmic reticulum at 10 mg/kg/day aldrin or dieldrin. The authors suggested that such changes could adversely affect cardiac contractility by altering calmodulin-regulated Ca^{2+} -pump activity in neurons, but no measurement of cardiac function were performed to support this hypothesis.

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Routine gross and microscopic examinations showed no adverse effects in the heart of rats exposed to • 3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), • 3 mg/kg/day aldrin or • 3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or • 0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to • 1.04 mg/kg/day aldrin or • 0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to • 0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969). Examination of the vascular system does not appear to have been performed in these studies.

Chronic exposure of rats to dieldrin at dietary doses as low as 0.016 mg/kg/day was reported to cause fibrinoid degeneration, inflammation, endothelial proliferation, and perivascular edema in small-to-medium-size arteries (Harr et al. 1970). However, this condition is known to occur spontaneously, no dose-response information was provided, and statistical analyses of these data were not presented. Also, the study by Harr et al. (1970) utilized a semisynthetic diet rather than standard rodent chow, and it is unclear whether such a diet may have affected the outcome of this study. Thus, the significance of this finding is unknown.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to aldrin or dieldrin.

Dogs that ingested lethal doses of aldrin (as low as 0.89–1.78 mg/kg/day over a period of 5–6 months) or dieldrin (as low as 1.95–4.24 mg/kg/day over a period of 11 days–1.3 months) during a 9-month study vomited and became emaciated several days prior to death (Treon et al. 1951b). It is unclear whether the vomiting was directly due to gastrointestinal irritation. Routine gross and microscopic examinations showed no adverse effects in the stomach or intestines of rats exposed to • 3 mg/kg/day aldrin or • 3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or • 0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to • 1.04 mg/kg/day aldrin or • 0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to • 0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Hematological Effects. Limited information is available on hematological effects in orally-exposed humans. Groups of 3–4 volunteers who consumed dieldrin in capsules at doses as high as 0.003 mg/kg/day over a period of 18 months experienced no adverse effects on cellular components of the blood (hemoglobin, packed cell volume, total and differential white blood cell count) or plasma proteins (Hunter and Robinson 1967). Blood coagulation tests were normal in the case of a man who ingested 120 mg/kg of dieldrin followed by repeated stomach lavage in an effort to limit absorption (Black 1974).

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One case of immunohemolytic anemia attributable to ingestion of dieldrin was reported (Hamilton et al. 1978). Three cases of pancytopenia and one case of thrombocytopenia have also been associated with exposure to dieldrin, but no assessment regarding whether dieldrin was the causative agent was provided in the report (AMA 1962).

Routinely-examined hematological indices were normal in dietary studies of rats exposed to 0.25 mg/kg/day aldrin for up to 25 months (Deichmann et al. 1967), rats exposed to • 0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969), and dogs exposed to • 0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969). Some histological changes in blood-forming tissues of exposed animals have been reported. The rats that were exposed to 0.25 mg/kg/day aldrin for 25 months had moderate to marked congestion of the red pulp with slight hemolysis in the spleen (Deichmann et al. 1967), but the significance of these findings is unclear due to a lack of incidence data and the normal hematology indices. Dogs given doses as low as 1 mg/kg/day of either aldrin or dieldrin for 25 months had a reduced number of mature granulocytes and erythroid cells in the bone marrow (Fitzhugh et al. 1964), but these data are limited by small numbers of animals (1–2 males and 1–2 females per dose).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to aldrin or dieldrin.

Muscular lesions, including focal edema, coagulative necrosis, and chronic myositis (inflammation), were observed in rats that were fed aldrin in doses of 0.016 mg/kg/day for 750 days or 0.032 mg/kg/day for 546 days (Harr et al. 1970). Although these effects were not observed in controls, interpretation of the findings is complicated by study limitations, which include small numbers of animals (two per sex per dose), lack of incidence data, and use of a semisynthetic diet rather than standard rodent chow.

Additionally, no gross or histopathological changes in muscle were reported in other studies at higher oral doses, including rats exposed to • 3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), • 3 mg/kg/day aldrin or • 3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or • 0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969), mice exposed to • 1.04 mg/kg/day aldrin or • 0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or dogs exposed to • 0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Treatment of rats with 1.25 mg/kg/day of dieldrin for 60 days was reported to impair the performance of rats who had been trained to pull a weight up an inclined plane in order to receive food (Khairy 1960). Although the author attributed the impaired performance to a decrease in muscular efficiency, no attempt

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was made to determine whether the effect was neurological or muscular in origin. Thus, this effect cannot be established as a musculoskeletal effect.

Hepatic Effects. Healthy male subjects who consumed up to 0.003 mg/kg/day of dieldrin in capsules for 18 months showed no clinical signs and had no adverse hepatic effects as indicated by normal serum levels of liver enzymes (alanine and aspartate aminotransferases, and alkaline phosphatase); however, no liver function tests or biopsies were performed (Hunter and Robinson 1967). However, a child who drank an unknown quantity of a 5% dieldrin solution and who experienced severe convulsions had evidence of liver dysfunction (Garrettson and Curley 1969). The half-life of phenobarbital in the child was greatly increased shortly after the initial intoxication, indicating a decreased ability of the liver to metabolize phenobarbital. Six months later, the phenobarbital half-life had returned to normal levels. However, serum alkaline phosphatase and thymol turbidity test results were elevated above normal levels. Evidence of liver damage (elevated serum aminotransferases) was also observed in a man 5 days after ingesting 120 mg/kg of dieldrin despite vigorous intervention to limit absorption (Black 1974). In the study by Black (1974), the dieldrin was a 15% solution in toluene. It is likely that the solution ingested by the child described by Garrettson and Curley (1969) also contained solvents and possibly emulsifiers. It is possible that the other ingredients in the dieldrin solutions contributed to the hepatic toxicity that was observed.

A number of adaptive changes characteristically produced by halogenated hydrocarbon pesticides were observed in livers of dogs, mice, and rats exposed to aldrin and/or dieldrin. These changes include an increase in liver weight and/or size (Bandyopadhyay et al. 1982b; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; Kohli et al. 1977; Olson et al. 1980; Tennekes et al. 1981; Treon et al. 1951a, 1953b, 1955b; Walker et al. 1969; Walton et al. 1971; Wright et al. 1972), liver cell enlargement (Olson et al. 1980; Treon et al. 1951a, 1954b; Walker et al. 1972), cytoplasmic eosinophilia with migration of basophilic granules (Fitzhugh et al. 1964; Treon et al. 1951a, 1954b; Walker et al. 1969, 1972), an increase in the smooth endoplasmic reticulum (Wright et al. 1972), an increase in microsomal protein (Wright et al. 1972), an increase in cytochrome P-450 content (Walton et al. 1971; Wright et al. 1972, 1978), and/or an increase in microsomal enzyme activity (Den Tonkelaar and van Esch 1974; Kohli et al. 1977; Tennekes et al. 1981; Walton et al. 1971; Wright et al. 1972, 1978).

Within 1 week, alterations of liver cell ultrastructure (an increase in cytoplasmic vacuoles and smooth endoplasmic reticulum) and increased microsomal protein and mixed-function oxidase activity were observed in rats exposed to 8 mg/kg/day or mice exposed to 1.6 mg/kg/day of dieldrin (Wright et al.

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1972). After 4 weeks of exposure to 2 mg/kg/day of dieldrin, similar effects were observed in dogs. In addition, liver cell enlargement and increased levels of cytochrome P-450 were apparent in rats and mice 4 weeks after exposure to 8 and 1.6 mg/kg/day, respectively (Wright et al. 1972). Cessation of dosing with dieldrin allowed the reversal of these changes in these animals (Wright et al. 1972). The lowest dose at which an increase in liver-to-body-weight ratio was observed in rats was 0.00035 mg/kg/day of dieldrin for 85 days (Olson et al. 1980). However, this study was limited in that only one dose of dieldrin was tested and animals received limited rations during the last 15 days of the study to maintain their body weights below normal. Monkeys exposed to dieldrin for between 5 and 6 years had a more limited response than dogs, mice, or rats. Exposure to concentrations as high as 0.1 mg/kg/day of dieldrin produced increased mixed-function oxidase activity and cytochrome P-450 content in livers but no histologic changes in the liver that were observable by light or electron microscopy (Wright et al. 1972, 1978). In virtually all of these studies no other evidence of hepatic toxicity was reported; thus, these adaptive changes were not considered to be adverse.

Mixed results regarding changes in hepatic lipid peroxidation have been observed. A single oral dose of 30 mg/kg was reported to decrease hepatic lipid peroxidation in male rats (Kohli et al. 1977). In contrast, a single oral dose of 26 mg/kg was reported to increase hepatic lipid peroxidation in female rats (Goel et al. 1988). It is unclear whether the contrasting results of these two studies are attributable to sex-related differences in metabolism.

Limited evidence for adverse hepatic effects has been observed in rats in intermediate-duration studies following 1–6 months of exposure to 2 mg/kg/day of dieldrin (Shakoori et al. 1982) or 6 months of exposure to 10 mg/kg/day of dieldrin (Ahmed et al. 1986a). At 2 mg/kg/day dieldrin, adverse effects were limited to decreased hepatic protein and some instances of necrosis (Shakoori et al. 1982). At 10 mg/kg/day, there was an increase in serum hepatic enzyme activity (alkaline phosphatase and/or alanine aminotransferase) with decreases in hepatic protein and areas of necrosis (Ahmed et al. 1986a). The statistical significance of the incidence of necrotic areas was not presented. Both of these studies are limited because only one dose of dieldrin was used. No histopathological changes were observed in the livers of rats exposed to 3.75 mg/kg/day aldrin or dieldrin for 6 months, although small numbers of animals were examined (Treon et al. 1951a). Dogs that ingested doses as low as 0.89–1.78 mg/kg/day of aldrin or 0.73–1.85 mg/kg/day of dieldrin for 9 months had moderate parenchymatous degeneration (Treon et al. 1955b). Although the degeneration appeared to increase in severity with dose, this study is limited by a small number of animals.

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Evidence for adverse hepatic effects has also been observed in chronic studies. Hyaline droplet degeneration was observed in the livers of dogs that ingested 0.12–0.25 mg/kg/day of aldrin for 15.7 months (Treon et al. 1955b). Similar effects were not observed in dogs that ingested 0.14–0.26 mg/kg/day of dieldrin over the same period. In dogs exposed to 1 mg/kg/day of aldrin or dieldrin for 25 months, slight-to-moderate fatty degeneration was observed (Fitzhugh et al. 1964). Also, in dogs given doses as low as 0.2 mg/kg/day of dieldrin for up to 1 year, degeneration was observed (Kitselman 1953). The degree of necrosis increased with dose. However, these studies are limited in that too few animals were tested (Fitzhugh et al. 1964; Kitselman 1953; Treon et al. 1955b). Both male and female dogs exposed to 0.05 mg/kg/day of dieldrin for 2 years had elevated serum alkaline phosphatase levels, and males at this dose had decreased serum proteins (Walker et al. 1969). The origin of the increased serum alkaline phosphatase activity was unknown, but not believed to be due to bone disorders or biliary obstruction (i.e., the usual clinical interpretation of elevated serum alkaline phosphatase in dogs [Cornelius 1970; Walker et al. 1969]). The decrease in total serum proteins was slight and considered to have no clinical or toxicological significance since the electrophoretic pattern of the proteins was unchanged. The possibility that increased serum alkaline phosphatase may not necessarily represent hepatic damage in dogs was also raised by El-Aharaf et al. (1972), who showed that dogs exposed to 0.05–0.20 mg/kg/day of dieldrin for 1 year had increased serum alkaline phosphatase of hepatic origin but no increase in serum levels of 5'-nucleotidase (a hepatic membrane enzyme that should be elevated in the serum as a result of hepatic damage). Because hepatic levels of alkaline phosphatase increased in parallel with serum levels of alkaline phosphatase, these authors suggested that alkaline phosphatase may be transferred directly from the hepatocyte to the sinusoidal blood.

Rats exposed to doses of dieldrin ranging from 0.016 to 0.063 mg/kg/day throughout their lifetime were reported to have developed hepatic lesions consisting of centrilobular degeneration and peripheral hyperplasia (Harr et al. 1970). Pyknosis of hepatocellular nuclei was also reported; however, no statistics, dose-response data, or incidence data were presented to support this conclusion. Also, the rats in this study received dieldrin in a semisynthetic diet, and it is unclear whether such a diet may have affected the study outcome.

Rats exposed via their diets to aldrin or dieldrin for 2 years at doses as low as 0.025 mg/kg/day had increases in liver-to-body-weight ratio and hepatic histopathological changes consistent with exposure to chlorinated hydrocarbons (Fitzhugh et al. 1964). At 2.5 mg/kg/day, gross enlargement of the liver was observed, and the histopathological changes were considered to be marked and included an increase in the severity of hepatic cell vacuolation. The hepatic lesions that were seen at the aldrin dose of

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0.025 mg/kg/day were characterized by hypertrophy of centrilobular hepatocytes, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation, changes consistent with a marked hepatic adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. No NOAEL for liver effects of chronic aldrin exposure was identified. Based on the LOAEL of 0.025 mg/kg/day (Fitzhugh et al. 1964) and considering the evidence for dose-related progression of hepatotoxicity in this and other studies, a chronic oral MRL of 3.0×10^{-5} mg/kg/day was calculated for aldrin as described in the footnote in Table 3-1.

Rats that were exposed to 0.005, 0.05, or 0.5 mg/kg/day dieldrin in the diet for 2 years similarly had increased absolute and relative liver weights at • 0.05 mg/kg/day, and at the highest dose of 0.5 mg/kg/day, liver parenchymal cell changes characteristic of organochlorine exposure, as well as indications of focal hyperplasia (Walker et al. 1969). Based on the 0.005 mg/kg/day NOAEL for liver effects (Walker et al. 1969) and considering the evidence for dose-related progression of hepatotoxicity, a chronic oral MRL of 5.0×10^{-5} mg/kg/day was calculated for dieldrin as described in the footnote in Table 3-2.

Mice exposed to 1.3 mg/kg/day dieldrin for 2 years had livers with occasional necrotic areas (Thorpe and Walker 1973); however, this study is limited because it is unclear whether the necrotic areas were secondary to tumor development, the incidence of these areas was not reported, and only one dose of dieldrin was tested. Routine histological examinations in other chronic studies showed no nonneoplastic liver changes in mice exposed to • 1.04 mg/kg/day aldrin for 80 weeks (NCI 1978a), • 0.65 mg/kg/day dieldrin for 80 weeks (NCI 1978a), or 1.3 mg/kg/day dieldrin for 92 weeks (Tennekes et al. 1981), although the emphasis in these studies was on detection of carcinogenicity.

Renal Effects. A man who attempted suicide by consuming approximately 25.6 mg/kg of aldrin had elevated blood urea nitrogen, gross hematuria, and albuminuria upon admission to the hospital (Spiotta 1951). By 17 days after admission, levels of nitrogen, blood, and protein in the urine had returned to normal. Six weeks after the suicide attempt, the ability to concentrate the urine was determined to be poor. In contrast, a man who ingested 120 mg/kg of dieldrin had no evidence of renal damage (Black 1974). In both of these case reports, the actual dose available for absorption was unknown because efforts were made to limit absorption of the chemicals from the gastrointestinal tract.

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Adverse effects on the kidneys have been observed following exposure of rats and dogs to aldrin and/or dieldrin. Exposure of rats to 5 mg/kg/day of dieldrin for 15 days resulted in membranous glomerulonephritis, nephrosis in the proximal convoluted tubules, vacuolated cytoplasm, necrotic cells in the tubular lumen, and large intertubular spaces (Bandyopadhyay et al. 1982b). Similarly, exposure of rats to 10 mg/kg/day of dieldrin for 6 months in a single-dose level study resulted in degenerative changes in the epithelial cells of the kidney and lymphocyte and macrophage infiltration (Ahmed et al. 1986a). Rats exposed to 0.25 mg/kg/day of dieldrin for 25 months in a single-dose level study showed slight lymphocyte infiltration, vascular congestion in the renal cortex, and hyaline casts in the renal tubules (Deichmann et al. 1967). Increases in the incidence and severity of nephritis were also observed in male rats exposed to doses as low as 0.5 mg/kg/day of aldrin or 0.125 mg/kg/day of dieldrin for 2 years (Fitzhugh et al. 1964; Harr et al. 1970; Reuber 1980). However, these studies are limited because no statistical analyses were presented to support these conclusions. Dogs exposed to doses of aldrin or dieldrin as low as 0.2 mg/kg/day also had degeneration of the renal tubules (Fitzhugh et al. 1964; Kitselman 1953), but these studies are limited by the absence of sufficient experimental detail, the lack of histopathological data on many of the animals, and the small number of animals tested. In the study by Fitzhugh et al. (1964), only one or two males and females were used per dose; in the study by Kitselman (1953), three dogs were used per dose. Slight vacuolation of the renal tubules was also reported in dogs exposed to doses as low as 0.14–0.26 mg/kg/day of dieldrin or 0.04–0.09 mg/kg/day of aldrin for 15.7 months, but this study was also limited by the small number of dogs used (Treon et al. 1955b). Routine gross and microscopic examinations showed no adverse effects in the kidneys of rats exposed to • 3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), • 3 mg/kg/day aldrin or • 3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a, 1978b), or • 0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to • 4.04 mg/kg/day aldrin or • 0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to • 0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Endocrine Effects. No information was located regarding effects of aldrin or dieldrin on the endocrine system in humans following oral exposure.

Histological examination of nonreproductive endocrine tissues in intermediate- and chronic-duration studies showed no aldrin- or dieldrin-related non-neoplastic changes in animals. Tissues that were examined in these studies included adrenal, thyroid, parathyroid, pancreas, and/or pituitary in rats exposed to • 3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), rats exposed to • 3.75 mg/kg/day aldrin for up to 80 weeks (NCI 1978a), mice exposed to • 4.04 mg/kg/day aldrin for up

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to 80 weeks (NCI 1978a), rats exposed to •0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969), rats exposed to •3.25 mg/kg/day dieldrin for 80–104 weeks (NCI 1978a), mice exposed to •0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), and dogs exposed to •0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969). Animal fertility studies indicate that the testis is a target of aldrin and dieldrin in males (see Section 3.2.2.5, Reproductive Effects).

The ability of chlorinated hydrocarbons to disrupt estrogen homeostasis, by up-regulating selected gene transcription, has been hypothesized to be responsible for their oncogenic effects. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 µmol/kg/day, 5 days/week, for 9 months, when administered with toxaphene (30 µmol toxaphene/kg/day and 7.5 µmol/kg/day), bone mass density was significantly increased (Syversen et al. 2000). A single dose of dieldrin (37 mg/kg) administered to female rats by gavage significantly increased expression of cytochrome P450 CYP1A1, CYP1A2, and CYP1B1, which are involved in estrogen metabolism, in the liver, kidney, and mammary tissues (Badawi et al. 2000).

Dermal Effects. Routine histological examinations showed no adverse effects in the skin of rats exposed to •3 mg/kg/day aldrin or •3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or •0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to •1.04 mg/kg/day aldrin or •0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to •0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Ocular Effects. Routine histological examinations showed no adverse effects in the eyes of rats exposed to •3 mg/kg/day aldrin or •3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or •0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to •1.04 mg/kg/day aldrin or •0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to •0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

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3.2.2.3 Immunological and Lymphoreticular Effects

Limited information was located regarding immunological effects in humans after oral exposure to aldrin or dieldrin. A case report was located concerning a man who developed immunohemolytic anemia after eating fish that contained high levels of dieldrin (Hamilton et al. 1978). Testing of the patient's serum revealed a positive antibody test for dieldrin-coated red blood cells.

An epidemiological study of 98 breast-fed and 73 bottle-fed Inuit infants from Nunavik (Arctic Quebec, Canada) indicated that the RR of experiencing otitis media (three or more episodes) over the first year of life increased with prenatal exposure to dieldrin (Dewailly et al. 2000). The RR for 4–7-month-old infants in the highest exposure group ($>43 \mu\text{g/kg}$ dieldrin in maternal breast milk) as compared to infants in the lowest exposure group ($<21 \mu\text{g/kg}$) was 1.75 (95% CI 1.05–2.91). The RR of infants experiencing three or more episodes of otitis media over the first year of life was 3.5 (95% CI 0.95–12.97). No clinically relevant differences were noted between breast-fed and bottle-fed infants with regard to immunologic parameters, nor were any of the immunologic parameters associated with prenatal dieldrin exposure.

Immunosuppression by dieldrin has been reported in a number of studies in mice. An increase in lethality of mouse hepatitis virus three and a decrease in the antigenic response to the virus were observed in mice given a single oral dose of dieldrin (48 mg/kg) (Krzystyniak et al. 1985). Similarly, an increase in lethality of infections with the malaria parasite, *Plasmodium berghei*, or *Leishmania tropica* in mice was produced by treatment of the mice with dieldrin in the diet at doses as low as 0.13 mg/kg/day for 10 weeks (Loose 1982). Also, a decrease in tumor cell killing in mice was observed after dieldrin treatment with doses as low as 0.13 mg/kg/day for 3, 6, or 18 weeks (Loose et al. 1981).

Since resistance to intracellular organisms and tumor cell killing require induction of cell-mediated immunity through thymus-derived lymphocyte (T-lymphocyte) interactions with macrophages, the effects of dieldrin consumption on the activity of these components of the response were tested. A decrease in antigen processing by alveolar macrophages was observed in mice following consumption of dieldrin for 2 weeks (Loose et al. 1981). Macrophages that ingested sheep red blood cell antigen manifested a significantly impaired ability to transfer an adequate immunogen to naive control mice. Splenic and alveolar macrophages were the most sensitive cell types as the decrease occurred following exposure to dieldrin doses as low as 0.065 mg/kg/day (lowest tested dose). Peritoneal macrophage antigen processing was significantly depressed at 0.65 mg/kg/day , and Kupffer cell antigen processing was depressed at

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6.5 mg/kg/day. This effect was observed in the absence of effects on macrophage respiration, phagocytic activity or capacity, or microbicidal activity. In addition, macrophages from dieldrin-treated (0.65 mg/kg/day for 10 weeks) mice were found to produce a soluble factor that induced T-lymphocyte suppressor cells (Loose 1982). Inhibition of lymphocyte proliferation was also seen in a mixed lymphocyte reaction test in which splenic cells from mice treated twice with 16.6 mg/kg dieldrin were combined with stimulator cells from control animals (Fournier et al. 1988). However, this study is limited because only one dose level of dieldrin was tested.

All reliable LOAEL values for immunologic effects of dieldrin in mice in acute- and intermediate-duration studies are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Case reports regarding accidental poisonings or suicide attempts provide the majority of the information on the neurological effects of aldrin and dieldrin by the oral route. Two children who consumed an unknown amount of a 5% dieldrin solution began to salivate heavily and developed convulsions within 15 minutes (Garrettson and Curley 1969). In the surviving child, the seizure episode lasted for 7.5 hours before being controlled by phenobarbital. EEG recordings taken from this child showed bursts of synchronous high-voltage slow waves. Both the child's condition and the EEG recordings returned to normal with time. Convulsions also developed rapidly in a man who attempted suicide by consuming an estimated 25.6 mg/kg of aldrin (Spiotta 1951) and in a man who ingested 120 mg/kg of dieldrin (Black 1974). Anticonvulsants were given to control the seizures, but one man exhibited motor hyperexcitability and restlessness for several days (Spiotta 1951), and the other required muscle paralysis to sufficiently control the convulsions to allow artificial respiration (Black 1974). EEGs taken a few days after admission showed epileptiform activity, but the EEGs returned toward normal with time.

A small group of persons who consumed wheat that had been mixed with aldrin and lindane over a period of 6–12 months developed a variety of central nervous system symptoms (Gupta 1975). These included bilateral myoclonic jerks, generalized seizures, auditory and visual auras, hyperexcitability, and irritability. In some cases, the onset of symptoms was abrupt. EEGs showed spike and wave activity and abnormal bursts of slow delta-wave discharges. After exposure was discontinued, the symptoms slowly improved. However, 1 year after exposure, infrequent myoclonic jerks were observed in several of the subjects. One subject also complained of memory loss and irritability, and a 7-year-old child was believed to have developed mild mental retardation as a result of the exposure. Although both aldrin and

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lindane had been mixed with the wheat, the author concluded that the effects observed were due to the aldrin exposure because in previous years wheat had been routinely mixed with lindane and consumed with no apparent adverse effects. Persistent headaches, irritability, and short-term memory loss were also reported following recovery from convulsions in a man who ingested 120 mg/kg of dieldrin (Black 1974).

Dieldrin administered to volunteers daily for 18 months at doses as high as 0.003 mg/kg/day had no effect on central nervous system activity (as measured by EEG), peripheral nerve activity, or muscle activity (Hunter and Robinson 1967).

Ingestion of aldrin and dieldrin most likely was not a significant route of exposure and therefore probably did not contribute significantly to the neurological effects observed in many of the occupational studies presented in Section 3.2.1.4. However, in the study by Patel and Rao (1958), the authors could not eliminate oral exposure by dieldrin since workers reportedly mixed the dieldrin solutions with their bare hands and some time later consumed food using their hands.

Convulsions were also observed in rats given single doses of dieldrin ranging from 40 to 50 mg/kg (Wagner and Greene 1978; Woolley et al. 1985). When aldrin or dieldrin was administered to rats for 3 days, convulsions were observed at a dose of 10 mg/kg/day (Mehrotra et al. 1989). Transient hypothermia and anorexia were also observed following a single dose of 40 mg/kg (Woolley et al. 1985). Long-term potentiation of limbic evoked potentials was observed following a single dose of 25 mg/kg, and subthreshold limbic stimulation caused convulsions following a single dose of 40 mg/kg (Woolley et al. 1985). Neurotoxic signs observed in cattle poisoned with unspecified dietary concentrations of aldrin included tremors, running, hyperirritability, and seizures (Buck and Van Note 1968).

Operant behavior was disrupted in rats following single doses of dieldrin ranging from 0.5 to 16.7 mg/kg. The simpler paradigms of fixed interval responding and maze training were both impaired at doses as low as 16.7 mg/kg, whereas differential responding to low rates of reinforcement was impaired at 2.5 mg/kg (Burt 1975). Responses in an inescapable foot shock stress paradigm were impaired at doses as low as 0.5 mg/kg (Carlson and Rosellini 1987). In sheep, operant responding was decreased 38–76% during a 4-day treatment with 20 mg/kg/day dieldrin (Sandler et al. 1969). EEGs obtained during exposure showed high-voltage, slow wave activity.

In studies of intermediate duration, operant behavior was disrupted at somewhat lower doses of dieldrin. Following 60–120 days of exposure of rats to 0.25 mg/kg/day, dieldrin significantly impaired maze

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training (Burt 1975). In a study which was used as the basis for an intermediate-duration oral MRL (Smith et al. 1976), monkeys orally administered 0.1 mg dieldrin/kg/day for 55 days demonstrated impaired learning (difficulty learning a successive discrimination reversal task); this effect was not seen in monkeys administered 0.01 mg/kg/day, a dose considered to be a NOAEL for impaired learning. No effect on operant behavior in rats was observed following 0.025 mg/kg/day for 60–120 days. Sheep appeared to be somewhat less sensitive to the effects of dieldrin on behavior, although a small number of animals was used in these studies (Van Gelder 1975). The lowest dose at which sheep had impaired operant behavior was 2.5 mg/kg/day for 12 weeks. This was determined using an auditory signal detection test. Visual discrimination was not impaired until doses of 10 mg/kg/day were administered, and maze training and extinction of a conditioned avoidance response were not impaired at 15 mg/kg/day (Van Gelder 1975).

Physical signs of neurotoxicity were observed in two single-dose level, intermediate-duration studies in rats. Tremors were observed in rats at a dose of 0.5 mg/kg/day for 60 days (Mehrotra et al. 1988) and hyperexcitability was observed at 2.5 mg/kg/day in an 8-week study (Wagner and Greene 1978). Exposure to 1.25 mg/kg/day aldrin or dieldrin for 6 months caused degenerative histological changes in brain cells of rats (Treon et al. 1951a). Dogs given aldrin at 0.89–1.78 mg/kg/day or dieldrin at 0.73–1.85 mg/kg/day for up to 9 months experienced neuronal degeneration in the cerebral cortex and convulsions (Treon et al. 1951b). At this dose, aldrin-treated dogs also exhibited hypersensitivity to stimulation, twitching, and tremors. At higher doses, the basal ganglia and cerebellum also exhibited degenerative changes.

Irritability, tremors, and/or convulsions were observed in rats exposed to aldrin or dieldrin in doses ranging from 0.65 to 3.25 mg/kg/day, but not at 0.05 mg/kg/day, for 1.5–2 years (NCI 1978a, 1978b; Walker et al. 1969). Mice experienced hyperexcitability, fighting and/or tremors at 0.39 mg/kg/day aldrin or 0.33 mg/kg/day dieldrin in 80-week bioassays (NCI 1978a).

EEGs taken from dogs exposed to 0.05 mg/kg/day for 2 years were normal (Walker et al. 1969). However, dogs were reported to develop convulsions when given 0.5 mg/kg/day for 25 months (Fitzhugh et al. 1964), and slight neuronal degeneration was reported following 1 year of exposure to aldrin or dieldrin at 0.2 mg/kg/day (Kitselman 1953). However, both of these studies are limited by the small number of animals tested. The only other study that noted histopathological evidence of central nervous system damage was a 2-year study of the effects of dieldrin in rats (Harr et al. 1970). Cerebral edema and small foci of degeneration were reported in rats exposed to dieldrin at 0.016 mg/kg/day, but no statistical

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analysis of these results was presented. Also, the study by Harr et al. (1970) used a semisynthetic diet, and it is unclear whether the use of such a diet may have affected the study outcome.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

3.2.2.5 Reproductive Effects

Aldrin levels in blood and placental tissues of women who had premature labor or spontaneous abortions were significantly higher than in women with normal deliveries (Saxena et al. 1980). However, interpretation of this study is limited because levels of six other organochlorine pesticides were also significantly elevated and because other potential distinctions between the two groups that might have contributed to premature labor or abortion, such as smoking or alcohol consumption, were not addressed. Nevertheless, this observation suggests that aldrin can pass through the human placenta and accumulate in the developing fetus. Similarly, accumulation of dieldrin in the amniotic fluid and in the developing fetus has been reported by Polishuk et al. (1977b).

Acute exposure of male mice to aldrin or dieldrin produced no adverse effects on reproduction. Male mice treated with doses of aldrin up to 1 mg/kg/day for a period of 5 days showed no significant effects in a dominant lethal study (Epstein et al. 1972). Similarly, single oral doses of dieldrin ranging from 12.5 to 50 mg/kg had no significant effect on the number of pregnancies produced by male mice in a dominant lethal assay (Dean et al. 1975).

A significant but slight decrease in fertility was observed in female mice exposed to 1.3 or 1.95 mg/kg/day of dieldrin from 4 weeks prior to mating through weaning (Virgo and Bellward 1975). In this study, males were exposed to test material only during the 2-week mating period. Similarly, male and female rats receiving diet containing aldrin or dieldrin at doses of aldrin as low as 0.63 mg/kg/day and dieldrin as low as 0.125 mg/kg/day from the time they were 28 days old had decreased fertility (decreased number of litters) during the first mating of the parental generation in a three-generation reproduction study (Treon et al. 1954a). A subsequent mating of the parental rats receiving aldrin showed no reproductive effects, and those receiving dieldrin failed to show a consistent dose-related effect on fertility. At matings of the offspring, no effect on fertility (number of litters) was observed at 0.125 mg/kg/day; however, effects on fertility due to higher doses were difficult to assess because few

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offspring survived to be mated. In contrast, no consistent effect of doses of dieldrin as high as 2 mg/kg/day was found on the conception rate of male and female rats exposed from the time they were 28 days old through the period of mating (initiated when the rats were 146 days old) (Harr et al. 1970). These results are limited in that no statistical analysis of the data was presented. In addition, male and female mice exposed to 0.65 mg/kg/day of dieldrin for 30 days prior to mating and then for 90 days thereafter experienced no adverse effects on fertility, fecundity, or the length of gestation (Good and Ware 1969). The only adverse reproductive effect observed in this study was a slight decrease in litter size. However, this study is limited in that only one dose level of dieldrin was tested.

A number of adverse reproductive effects were observed in dogs following exposure of males and females to 0.15 or 0.30 mg/kg/day for 14 months prior to mating (Deichmann et al. 1971). These included delayed estrus, reduced libido, lack of mammary function and development, and an increased number of stillbirths. However, this study is limited by the small number of animals tested.

Maternal behavior was adversely affected by dieldrin when mice were treated from 4 weeks prior to delivery until weaning. At 1.3 mg/kg/day, Virgo and Bellward (1975) observed a delay in the time before mice nursed their pups. Also, at doses of 1.95 mg/kg/day and above, some dieldrin-treated maternal animals violently shook the pups, ultimately killing them, and others neglected their litters (Virgo and Bellward 1975). At doses of dieldrin above 1.95 mg/kg/day, high maternal mortality was also observed in this study.

The highest NOAEL for dieldrin and all reliable LOAEL values for reproductive effects in animals after oral exposure to aldrin or dieldrin are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

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3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to aldrin or dieldrin. However, a study of dieldrin levels in women and their fetuses during labor revealed detectable levels of dieldrin in the placenta, amniotic fluid, and fetal blood (Polishuk et al. 1977b). These results suggest that dieldrin can pass through the human placenta and accumulate in the developing fetus.

Conflicting results have been obtained in animal studies examining the ability of aldrin and dieldrin to cause external malformations or skeletal anomalies. Such effects have been observed in mice and hamsters following a single very large dose of aldrin or dieldrin in mid-gestation (Ottolenghi et al. 1974). Significant increases in cleft palate and webbed foot were observed in mice following a dose of 15 mg/kg of dieldrin or 25 mg/kg of aldrin on gestation day 9. Significant increases in cleft palate, open eye, and webbed foot were seen following a dose of 30 mg/kg of dieldrin or 50 mg/kg of aldrin on gestation days 7, 8, and/or 9 in hamsters. Fetal mortality was also significantly increased, and fetal weight was significantly decreased in hamsters. No information was provided regarding the health of maternal animals in this study. Also, this study is limited in that only a single dose of aldrin and dieldrin was tested. A significant increase in supernumerary ribs was observed in mice from dams exposed to 3 or 6 mg/kg/day dieldrin on gestation days 7–16 (Chernoff et al. 1975). In this study, these doses of dieldrin also caused an increase in the maternal liver-to-body-weight ratio. However, other studies examining developmental effects of aldrin and/or dieldrin have failed to observe similar malformations or anomalies. No developmental defects were observed in rats exposed to concentrations of dieldrin as high as 6 mg/kg/day from gestation day 7 to 16 (Chernoff et al. 1975). Also, no significant developmental effects were observed in mice exposed to doses of dieldrin as high as 4 mg/kg/day from gestation day 6 to 14 (Dix et al. 1977), although the number of litters tested in this study was somewhat low.

Offspring of mice treated for 5–7 days during the third trimester of pregnancy with 2 or 4 mg/kg/day of aldrin had 18% decreased body weight and a significantly increased electroconvulsive shock brain seizure threshold, although there was no disruption of the acquisition of a conditioned avoidance response (Al-Hachim 1971). Based on the 2 mg/kg/day LOAEL for developmental effects, an acute oral MRL of 0.002 mg/kg/day was calculated for aldrin as described in the footnote in Table 3-1. Rat pups that were exposed to 0.00035 mg/kg/day dieldrin from gestation day 5 until the pups were 70 days old showed a significant improvement in swimming and maze running performance (Olson et al. 1980). This dose of dieldrin is several orders of magnitude below any other dose at which developmental effects have been

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observed. Interpretation of these results is difficult because the significance of improved performance in behavioral paradigms is unknown, and the study is limited because only one dose of dieldrin was tested.

Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin. Mice exposed to dieldrin in the diet at doses as low as 1 mg/kg/day from 4 weeks prior to mating through weaning had significantly decreased pup survival (Virgo and Bellward 1975). Maternal mortality was unaffected in this study at doses below 2.6 mg/kg/day. A similar decrease in postnatal survival has been observed in rats and dogs exposed to aldrin and/or dieldrin by the oral route. Increased mortality of offspring during the first 5 days of life was observed at 0.125 mg/kg/day of either aldrin and dieldrin in the first mating of a three-generation reproduction study in rats (Treon et al. 1954a). Maternal mortality was unaffected at doses as high as 1.25 mg/kg/day of either aldrin or dieldrin. Similarly, rats exposed to dieldrin from the time that they were 28 days old to when they were mated at 146 days old had decreased postnatal pup survival at doses as low as 0.125 mg/kg/day (Harr et al. 1970). Maternal mortality in this study was unaffected at doses below 0.5 mg/kg/day. This study is limited, however, in that no statistical analysis of the data was presented to confirm this assertion. Also, the rats in this study received a semisynthetic diet, and it is unclear whether such a diet may have affected the study outcome. Dogs exposed to doses of aldrin as low as 0.2 mg/kg/day or dieldrin at doses as low as 0.6 mg/kg/day for up to 1 year had poor litter survival (Kitselman 1953). In some instances, apparently normal puppies were born but died after a few days of nursing. Although maternal toxicity was not specifically addressed in this study, dogs receiving similar doses of aldrin and dieldrin had histopathological evidence of hepatic and renal toxicity. This study is also limited because too few dogs were tested, pregnancies were incidental to the study protocol, and thus adequate controls were not used. Dogs mated 2 weeks to 9 months after a 14-month exposure to doses of aldrin as low as 0.15 mg/kg/day also had high mortality among the offspring (Deichmann et al. 1971). However, this study was also limited by the small number of animals tested.

A number of studies have been undertaken to assess the cause of the decreased pup survival. To test whether the decrease in pup survival was dependent on maternal postnatal care, a cross-fostering experiment was performed (Virgo and Bellward 1977). Mice born to dieldrin-exposed dams were nursed by untreated dams. Significantly decreased pup survival was also observed in this study at 1 mg/kg/day irrespective of whether pups were nursed by birth or foster maternal animals. In a single-dose level study of mice that were exposed to 2 mg/kg/day dieldrin between 6 and 18 days of gestation, pups that were examined at varying times after birth had a rapid decrease in blood glucose and depletion of tissue glycogen stores that were significant when compared to controls (Costella and Virgo 1980). These

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decreases occurred despite apparently normal gluconeogenesis. Cardiac failure, secondary to cardiac glycogen depletion, has been proposed as the cause of death (Costella and Virgo 1980).

Histopathological examination of pups born to treated maternal animals was performed in two studies. Rat pups born to dams treated with dieldrin at doses as low as 0.004–0.008 mg/kg/day had neural lesions consisting of cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration. Hepatic degeneration was seen in the pups of dams fed doses of dieldrin as low as 0.016 mg/kg/day (Harr et al. 1970). However, no information regarding the dose-dependency of these effects or the relative numbers of animals affected was reported. Also, the rats in this study received a semisynthetic diet, and it is unclear whether such a diet may have affected the study outcome. Offspring from dogs that had been treated with doses of aldrin as low as 0.2 mg/kg/day or dieldrin as low as 0.6 mg/kg/day had degeneration of hepatic and renal tissues (Kitselman 1953). Both of these studies are limited by the lack of supporting clinical chemistry data and the absence of statistical analyses of the histopathological data. Furthermore, in the study by Kitselman (1953), not all offspring were examined histopathologically.

The highest NOAEL values and all reliable LOAEL values for developmental effects in animals after acute- or intermediate-duration exposure to dieldrin are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

A few epidemiological studies have examined cancer mortality in workers employed in the manufacture of aldrin and dieldrin. The results of these studies may be found in Sections 3.2.1.7 and 3.2.3.7. However, although possible, ingestion of aldrin or dieldrin is not thought to have been a significant source of exposure in these studies because manufacturing practices limit such exposures (Jager 1970).

Equivocal evidence exists for an association between dieldrin and breast cancer risk from three human epidemiologic studies (Dorgan et al. 1999; Høyer et al. 1998, 2000). In these studies, while dieldrin exposure was verified through blood sampling, and exposure by ingestion, as well as by inhalation and dermal contact, was possible, no specific route of exposure was identified or estimated with any certainty.

The potential of dieldrin to affect breast cancer risk was evaluated in a prospective nested case control study of women in Denmark (Høyer et al. 1998). Serum samples were obtained from 7,712 women from 1976 to 1978. In 1996–1997, serum samples from 240 women who had developed invasive breast cancer

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and 477 matched breast cancer-free controls were analyzed for levels of dieldrin and 17 other organochlorine pesticides or metabolites and 28 PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Irrespective of breast cancer status, dieldrin was detected in 78% of the women enrolled in the study, with median levels at 24.4 ng/g lipid. Dieldrin was the only organochlorine compound of those tested associated with a significant increase in breast cancer risk. Women in the highest quartile of the serum dieldrin range had double the risk of breast cancer compared to women in the lowest quartile (OR 2.25, 95% CI 1.32–3.84, p trend=0.003). Relative risk did not change significantly when adjusted for potential confounders of weight and number of full-term pregnancies (OR 2.05, 95% CI 1.17–3.57, p trend=0.01).

A subsequent study using the same cohort of Danish women investigated whether breast cancer survival was affected by past exposure to dieldrin (Høyer et al. 2000). Dieldrin at blood concentrations >57.6 ng/g, representative of the highest quartile, was found to have a significant adverse effect on overall survival and breast cancer specific survival compared to the lowest quartile levels of <12 ng/g lipid (RR 2.78, 95% CI 1.38–5.59, p trend<0.01; RR 2.61, 95% CI 0.97–7.01, p trend<0.01) in this case-control study of Danish women between 20 and 80 years of age. A total of 195 breast cancer cases, who each provided two blood samples that were taken in 1976–1978 and 1981–1983, respectively, were included in the survival analysis. The median duration of follow-up with regard to death was 86 months after the first examination (1976–1978) and 79 months after the second examination (1981–1983). Relative risk was adjusted for number of positive lymph nodes and tumor size and grade. When the analysis was performed using an average of the blood concentrations from the two collections, the association was even stronger, with a 5-fold higher risk of death in women from the highest quartile compared to the lowest quartile (RR 5.76, 95% CI 1.86–17.92, p trend<0.01) and a clear dose-response relationship. Potential confounders as body mass index, age at menopause, and hormone replacement therapy did not influence the results. This study was limited by small size, 6–39 women per quartile.

A cohort study of women from Missouri failed to find an association between serum dieldrin levels and breast cancer risk (Dorgan et al. 1999). Blood samples were collected from 7,224 women from 1977 to 1987. During the 9.5-year follow-up period, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum in 56.2% of the cases and 61.8% of the controls. The relative risk of cancer in the highest dieldrin serum concentration range quartile was moderately lower compared to the lowest quartile (RR 0.7, 95% CI 0.3–1.3, p =0.44).

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Several bioassays indicate that the response in mice to prolonged ingestion of aldrin or dieldrin differs from that in other species in that a generalized hepatomegaly observed in several species (rat [Cleveland 1966; Fitzhugh et al. 1964; Hodge et al. 1967; Treon and Cleveland 1955; Walker et al. 1969], dog [Fitzhugh et al. 1964; Hodge et al. 1967; Walker et al. 1969], and mouse [Davis and Fitzhugh 1962; Walker et al. 1972]) appears to be uniquely followed in mice, after about 1 year with threshold levels of aldrin or dieldrin in the diet, by an increase in liver tumors. With respect to aldrin, studies in two strains of mice (C3HeB/Fe and B6C3F₁) show an increase in hepatic tumors with chronic exposure (Davis and Fitzhugh 1962; NCI 1978a). A significant increase in the incidence of hepatocellular carcinoma was reported in males receiving 0.52 mg/kg/day of aldrin for 80 weeks (NCI 1978a). An increase in the incidence of hepatic cell adenomas at 1.3 mg/kg/day was also reported in a 2-year study by Davis and Fitzhugh (1962). Reevaluation of the histopathology data by Reuber (1980) and other pathologists indicated that most tumors classified by Davis and Fitzhugh (1962) as hepatic cell adenomas were hepatocellular carcinomas (Epstein 1975).

With respect to dieldrin, bioassays in Balb/c, CF₁, B6C3F₁, C3HeB/Fe, C3H/He, and C57BL/6J mice have also shown an increase in the incidence of hepatocellular adenoma and/or carcinomas with chronic exposure. A study in B6C3F₁ mice by NCI (1978a) showed a significant increase in the incidence of hepatocellular carcinoma with exposure of males to 0.65 mg/kg/day for 80 weeks. Increased incidences of hepatocellular carcinomas were also reported in male C3H/He, B6C3F₁, and C57BL/6J mice exposed to 1.3 mg dieldrin/kg/day for 85 weeks (Meierhenry et al. 1983) and in male CF₁ mice exposed to 1.3 mg dieldrin/kg/day for 92 weeks (Tennekes et al. 1981). An increase in both hepatocellular adenomas (Type A tumors) and hepatocellular carcinomas (Type B tumors) in CF₁ mice that ingested 1.3 mg/kg/day for 2 years was identified by Thorpe and Walker (1973). Similarly, a significant increase was observed in the incidence of hepatocellular carcinomas and combined incidence of both hepatocellular adenomas and carcinomas in a 132-week study at 1.3 mg/kg/day and of combined incidence of both hepatocellular adenomas and carcinomas in a 128-week study at 0.33 mg/kg/day in CF₁ mice (Walker et al. 1972). In a 75-week study in Balb/c mice (Lipsky et al. 1989) and a 2-year study in C3HeB/Fe mice, (Davis and Fitzhugh 1962) increases in the incidence of hepatic cell adenoma were observed at 1.3 mg/kg/day. However, reexamination of the histopathology data by Reuber (1980) and other pathologists showed an increase in the incidence of hepatocellular carcinomas (Epstein 1975). Although reanalysis of the data presented in the Walker et al. (1972) study by Reuber also indicated a significant increase in pulmonary adenomas and carcinomas in female mice at 0.013 and 0.13 mg/kg/day and a significant increase in lymphoid and other tumors in female mice at 0.13 mg/kg/day (Epstein 1975), these conclusions were

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based on errors in the reporting of the number of females examined at 0.013 and 0.13 mg/kg/day (Hunt et al. 1975).

In addition to producing an increase in the incidence of hepatocellular carcinomas in mice, dieldrin was also shown to significantly decrease the time to tumor development in mice at doses as low as 0.013 mg/kg/day in females and 0.13 mg/kg/day in males (Tennekes et al. 1982).

Carcinogenicity studies of aldrin and/or dieldrin in rats and hamsters have produced mostly negative results (Cabral et al. 1979; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; NCI 1978b; Walker et al. 1969). However, several of these studies have been determined to be flawed based on limited microscopic examination of animals (Fitzhugh et al. 1964; Walker et al. 1969), too few animals being used (Fitzhugh et al. 1964; NCI 1978b), and/or high levels of early mortality with insufficient numbers of animals surviving until termination of the study (Deichmann et al. 1970; Fitzhugh et al. 1964). Furthermore, reanalysis of the data from the study by Fitzhugh et al. (1964) revealed a significant increase in multiple-site tumors when doses of aldrin and dieldrin at or below 0.5 mg/kg/day were combined and an increased incidence of liver carcinomas at 5 mg/kg/day when data from both sexes were combined (Epstein 1975).

A carcinogenic response was also observed in rats exposed to 1.5 mg/kg/day of aldrin for 80 weeks (NCI 1978a). These animals had a significantly increased incidence of follicular cell adenoma and carcinoma of the thyroid. Also, a significant increase in adrenal cortical adenomas was seen in female rats at this dose. However, these effects were not dose-dependent. Similarly, a significant increase in the combined incidence of adrenal cortical adenomas and carcinomas was observed in females given 1.5 mg/kg/day for 59 weeks but not at 3 mg/kg/day (NCI 1978a). This result was, however, discounted by the study authors because of the historical variability of this result in control animals.

There is evidence that dieldrin can act as a liver tumor promoter in mice, but not in rats (Kolaja et al. 1996c). Preneoplastic focal hepatic lesions were initiated by intraperitoneal treatments with diethylnitrosamine (two injections separated by two weeks in male F344 rats, two injections per week for 8 weeks in male B6C3F1 mice). After the preneoplastic lesions developed, dieldrin was administered in the diet for 7, 30, or 60 days at estimated doses of 0.05, 0.15 or 0.5 mg/kg/day in the rats and 0.013, 0.13, or 1.3 mg/kg/day in the mice. Dieldrin induced significant increases in the number, volume, and deoxyribonucleic acid (DNA) labeling index of the DEN-induced preneoplastic foci in mice at the highest dose after 30 and 60 days. The lower doses (• 0.13 mg/kg/day) did not produce these promotional effects

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at any time point. The results of this study are consistent with findings of other studies of generally similar design by the same investigators (Kolaja et al. 1995a, 1995b, 1998).

The lowest dose that produced a tumorigenic response (Cancer Effect Levels, CELs) for each species and duration category of exposure to aldrin and dieldrin are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

The EPA reviewed the carcinogenicity data on aldrin and dieldrin and calculated human potency estimates using liver tumor responses in mice (EPA 1986l; IRIS 2002a, 2002b). The potency estimates (q_1^*) represent a 95% upper confidence limit of the extra lifetime human risks. Using potency estimates calculated from three data sets in two mouse strains and both sexes (Davis 1965; Epstein 1975; NCI 1978a), a geometric mean of $17 \text{ (mg/kg/day)}^{-1}$ was chosen for the oral cancer risk estimate for aldrin (IRIS 2002a). The unit risk estimate for drinking water exposures (the excess cancer risk associated with lifetime exposure to $1 \text{ } \mu\text{g/L}$) is 4.9×10^{-4} . Using potency estimates calculated from 13 data sets in five mouse strains and both sexes (Davis 1965; Epstein 1975; Meierhenry et al. 1983; NCI 1978a, 1978b; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1972), a geometric mean of $16 \text{ (mg/kg/day)}^{-1}$ was chosen for the oral cancer risk estimate for dieldrin (IRIS 2002b). The unit risk estimate for drinking water exposures to dieldrin is 4.6×10^{-4} . Based on the unit risk values for aldrin and dieldrin, cancer risk levels of 10^{-4} , 10^{-5} , 10^{-6} , and 10^{-7} correspond to 70 years of continuous drinking water exposure to 0.2, 0.02, 0.002, and 0.0002 $\mu\text{g/L}$, respectively (0.006, 0.0006, 6.0×10^{-5} , and $6.0 \times 10^{-6} \text{ } \mu\text{g/kg/day}$). The predicted cancer risks are considered conservative upper estimates. The actual risk of cancer is unlikely to be higher and may be substantially lower. These values are recorded in Figures 3-1 and 3-2.

3.2.3 Dermal Exposure

As indicated in the section on inhalation exposure, it is often difficult to clearly separate dermal from inhalation exposures in many occupational studies. Thus, many of the findings described in the section on inhalation exposure are repeated here.

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3.2.3.1 Death

No increase in mortality from any cause was found in studies of workers who had been employed in the manufacture of aldrin, dieldrin, endrin, and/or telodrin at a facility in the Netherlands for >4 years (cohort=233 workers) (van Raalte 1977; Versteeg and Jager 1973). Furthermore, in a 20-year follow-up of this population and expansion of the cohort to include workers employed for at least 1 year during 1954–1970 (cohort=570 workers), a lower than expected overall mortality was observed (de Jong 1991). Although the group of workers described by de Jong (1991) represents a unique population because they have been under medical supervision for an average of 25.86 years, all of the studies described above are limited because of the small number of subjects used (• 570 workers) and the potential exposure of the subjects to more than one of these pesticides and/or to other chemicals at the chemical manufacturing complex. Several of these studies have attempted to estimate exposure levels using blood levels. However, blood levels were not obtained for approximately 10 years (during what is expected to have been the period of heaviest exposure) and extrapolations were based on data obtained in a study using constant daily low-level oral dosing (Hunter and Robinson 1967). It is unclear whether such extrapolations accurately reflect exposure levels in the occupational situation. Only two case studies were located regarding deaths that may have been attributable to occupational exposure to aldrin or dieldrin (Muirhead et al. 1959; Pick et al. 1965). One concerned a farmer with multiple exposures to insecticide containing dieldrin. The farmer died in hemolytic crisis after developing immunohemolytic anemia (Muirhead et al. 1959). Immunologic testing revealed a strong antigenic response of blood cells coated with dieldrin. The other concerned a worker from an orange grove who developed aplastic anemia and died following repeated exposures to aldrin during spraying (Pick et al. 1965). In the latter study, the relationship between aldrin exposure and the aplastic anemia is considerably more tenuous, being linked only in that the onset of symptoms corresponded with spraying and the condition deteriorated upon subsequent exposure.

In rats, a single dermal application of aldrin in xylene was reported to produce death in 50% of the animals tested at 98 mg/kg/day (Gaines 1960). Dieldrin in xylene produced an LD₅₀ value of 60 mg/kg/day in female rats and 90 mg/kg/day in male rats (Gaines 1960). However, this study is limited because the rats were not restrained, oral intake could not be eliminated, and the xylene vehicle has intrinsic dermal toxicity. A single 24-hour dermal exposure of rabbits to dry crystallized aldrin or dieldrin resulted in LD₅₀ values between 600 and 1,250 mg/kg for both chemicals (Treon et al. 1953a). Similar results were obtained when these chemicals were prepared as oil solutions and maintained in contact with the skin for 24 hours. Also, sheep dipped in a solution of 200 mg/L of dieldrin (twice the

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recommended dose) experienced an 11% mortality rate within the 1st month following exposure (Glastonbury et al. 1987). This study is limited because the preparation of dieldrin used was unsuitable for use in emulsions and may have been stripped from the bath during the dipping of the first sheep resulting in much higher doses for some animals than others. In addition, wool biting was observed among these sheep; this type of oral exposure may have contributed to the lethal effects.

Dermal exposure of rabbits to aldrin or dieldrin (2 hours/day, 5 days/week, for 10 weeks) resulted in slightly greater lethality when these chemicals were prepared as solutions in oil and much greater lethality when the chemicals were administered as suspensions in kerosene than when crystallized material was placed directly in contact with the skin (Treon et al. 1953a). In the case of aldrin, three out of three rabbits survived exposure to average doses of 34–39 mg/kg/day during the 10-week period; one out of three died after exposure to 19–26 mg/kg/day in oil; and three out of three died after exposure to 19–27 mg/kg/day in kerosene. Crystallized dieldrin exposures of 39–41 mg/kg/day were survived by three out of three rabbits; but all rabbits died at 43–57 mg/kg/day in oil and 24–26 mg/kg/day in kerosene. The greater lethality of the kerosene suspensions may have been associated with greater absorption as a result of skin damage caused by the kerosene.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded for aldrin in Table 3-3 and for dieldrin in Table 3-4.

3.2.3.2 Systemic Effects

The highest NOAEL values for each study for dermal/ocular effects are recorded for aldrin in Table 3-3 and for dieldrin in Table 3-4.

Respiratory Effects. Conflicting reports were located regarding the respiratory effects of aldrin and dieldrin in humans after dermal exposure. In a study of workers with at least 4 years of employment in the manufacture of aldrin, dieldrin, endrin, or telodrin, no new pulmonary disease or deterioration of existing pulmonary disease were observed (Jager 1970). Similarly, no increase in mortality from respiratory diseases was noted in workers employed for at least 1 year at the same facility during 1954–1970 when these workers were followed for at least 20 years (de Jong 1991). In contrast, however, in another study that examined workers involved in the manufacture of aldrin, dieldrin, and/or endrin for

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Table 3-3. Levels of Significant Exposure to Aldrin - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	LOAEL			Reference
			NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
Rabbit	1 d 24hr/d			1250	(4/4 died)	Treon et al. 1953a
INTERMEDIATE EXPOSURE						
Death						
Rabbit	10 wk 5d/wk 2hr/d			120-125 19-26 4-5	(2/3 died-dry) (1/3 died-oil solution) (2/4 died-kerosene suspension)	Treon et al. 1953a
Systemic						
Rabbit	10 wk 5d/wk 2hr/d	Dermal	221- 320			Treon et al. 1953a

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

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Table 3-4. Levels of Significant Exposure to Dieldrin - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	LOAEL			Reference
			NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
Rabbit	1 d 24hr/d				360 600 (1/4 died - dry) (1/4 died - oil solution)	Treon et al. 1953a
Systemic						
Human	4 d 24hr/d	Dermal	0.5%			Suskind 1959
Immunological/Lymphoreticular						
Human	4 d 24hr/d		0.5%			Suskind 1959
INTERMEDIATE EXPOSURE						
Death						
Rabbit	10 wk 5d/wk 2hr/d				97-174 43-57 4-5 (3/3 died-dry) (3/3 died-oil solution) (2/3 died-kerosene suspension)	Treon et al. 1953a
Systemic						
Rabbit	10 wk 5d/wk 2hr/d	Dermal	97-174			Treon et al. 1953a
Neurological						
Human	180 d 5.5d/wk 6hr/d		1.8			Fletcher et al. 1959

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

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at least a year, a significantly increased incidence of pneumonia and other pulmonary diseases was observed when the incidence in the exposed workers was compared to the incidence in U.S. white males (Ditraglia et al. 1981). Both studies are limited by the small sample size and the possible exposure of the workers to other chemicals and/or pesticides. In addition, inhalation exposure may have contributed to the production of these effects since exposures by both inhalation and dermal absorption are likely in these populations of workers.

No effects on lung weight or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

Cardiovascular Effects. Limited information was available regarding the cardiovascular effects of aldrin or dieldrin in humans after dermal exposure. Suggestive evidence of an association between dieldrin and hypertension was obtained in a study examining the incidence of certain diseases in patients with elevated fat levels of dieldrin (Radomski et al. 1968). However, elevated fat levels of other pesticide residues also correlated with hypertension in this study. Furthermore, a study examining disease incidence in 2,620 workers exposed to a number of pesticides reported no increase in the incidence of hypertension in workers with elevated serum dieldrin (Morgan et al. 1980). The lack of a correlation between hypertension and aldrin or dieldrin exposure is also supported by the observation that workers involved in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years had normal blood pressure (Jager 1970). Similarly, no increase in mortality from circulatory system diseases was observed in a mortality study by de Jong (1991). All of these studies are limited because the subjects were exposed to a variety of other chemicals.

A slight, but significant, increase in serum cholesterol was observed in pesticide-exposed workers with elevated serum dieldrin (Morgan and Lin 1978). However, this study was limited in that the workers were occupationally exposed to a number of different pesticides and other chemicals including hydrocarbon solvents.

No effects on heart weight or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

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Gastrointestinal Effects. No increased mortality from digestive system causes was observed in a mortality study of workers employed in the manufacture of aldrin and dieldrin for at least 1 year between 1954 and 1970 (de Jong 1991).

No studies were located regarding gastrointestinal effects in animals after dermal exposure to aldrin or dieldrin.

Hematological Effects. No abnormal values for hemoglobin, white blood cells, or erythrocyte sedimentation rate were found in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years (Jager 1970). Similarly, no increase in blood diseases was observed in a morbidity study of workers employed at the same facility for at least 1 year (de Jong 1991). Also, workers who had been involved in either the manufacture or application of pesticides and who had significantly elevated blood levels of dieldrin compared to controls not employed in pesticide-related jobs had no hematological effects of clinical significance (Warnick and Carter 1972). These studies are limited by either potential exposure to other chemicals (Jager 1970) or by known exposure to other pesticides as demonstrated by elevated blood levels of β -benzine [sic] hexachloride (β -benzene hexachloride), heptachlor epoxied, *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE (Warnick and Carter 1972).

A case of immunohemolytic anemia attributable to dieldrin exposure was reported (Muirhead et al. 1959). Also, a worker from a grove where aldrin was sprayed developed aplastic anemia (Pick et al. 1965), and one person employed in the manufacture of aldrin and dieldrin between 1954 and 1970 died from aplastic anemia (de Jong 1991). However, it is unclear whether these cases of aplastic anemia were directly due to aldrin or dieldrin exposures because exposure to a variety of other chemicals was possible. Three cases of pancytopenia and one case of thrombocytopenia associated with exposure to dieldrin were reported during 1961 (AMA 1962). However, no assessment regarding whether dieldrin was the causative agent was provided in the report.

No studies were located regarding hematologic effects in animals after dermal exposure to aldrin or dieldrin.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to aldrin or dieldrin.

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Hepatic Effects. Although a slight increase in serum hepatic enzymes (alanine and aspartate aminotransferases) has been observed to correlate with serum dieldrin levels in pesticide-exposed workers (Morgan and Lin 1978), no evidence of any hepatic effects of aldrin or dieldrin exposure have been observed in other studies of workers involved in either the manufacture (de Jong 1991; Hoogendam et al. 1965; Hunter et al. 1972; Jager 1970; van Sittert and de Jong 1987) or the manufacture or application (Morgan and Roan 1974; Warnick and Carter 1972) of these pesticides. Parameters that have been examined in the negative studies include serum hepatic enzyme activity (Hoogendam et al. 1965; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987; Warnick and Carter 1972), hepatic enlargement (Jager 1970), and tests intended to detect microsomal enzyme induction (Hunter et al. 1972; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987). All of the studies are limited by the potential exposure of the workers to other chemicals and/or organochlorine pesticides.

No effects on liver weight, serum proteins, thymol turbidity, serum alkaline phosphatase, or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

Renal Effects. No evidence of renal damage was seen in workers employed for four or more years in the manufacture of aldrin, dieldrin, endrin, or telodrin (Jager 1970). However, this study is limited by the potential exposure of these workers to other chemicals.

No studies were located regarding renal effects in animals after dermal exposure to aldrin or dieldrin.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals after dermal exposure to aldrin or dieldrin.

Dermal Effects. Contact dermatitis was observed in police recruits wearing socks that had been moth-proofed with a solution containing dieldrin (Ross 1964). Several recruits had a positive patch test when tested against the moth-proofing agent. The outbreak of the dermatitis appeared to have been exacerbated by the presence of the particular dye used in the socks and by the fact that the recruits' feet had sweated heavily. In contrast, no evidence of dermatitis was seen in volunteers who wore patches of cotton broadcloth or wool flannel impregnated with up to 0.5% dieldrin by weight for 4 days (Suskind 1959) or in workers employed for four or more years in the manufacture of aldrin, dieldrin, endrin, or telodrin.

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(Jager 1970). The study by Jager (1970) is limited by the potential exposure of these workers to other chemicals.

Application of up to 6,000 mg/kg of aldrin or 3,600 mg/kg of dieldrin as either the crystalline material or as a solution in oil to the skin of rabbits for 24 hours was reported to result in occasional very slight erythema, but the lowest doses associated with this effect were not reported (Treon et al. 1953a). In contrast, no irritation was observed following application of 221–320 mg/kg/day aldrin or 97–174 mg/kg/day of dieldrin to the skin of rabbits for 2 hours/day, 5 days/week, for up to 10 weeks (Treon et al. 1953a). Also, no treatment-related effects were observed after microscopic examination of the skin of rabbits wrapped with wool fabric containing up to 0.04% dieldrin by weight for 52 weeks (Witherup et al. 1961).

Ocular Effects. No studies were located regarding ocular effects in humans or animals after dermal exposure to aldrin or dieldrin.

3.2.3.3 Immunological and Lymphoreticular Effects

Limited information is available regarding the immunological effects of aldrin and dieldrin in humans after dermal exposure. No sensitization was observed in volunteers who were reexposed to fabric containing up to 0.5% dieldrin 2 weeks following a 4-day exposure (Suskind 1959). However, a case report was located concerning a man who developed immunohemolytic anemia after multiple exposures to dieldrin, heptachlor, and toxaphene while spraying cotton fields (Muirhead et al. 1959). Antibodies for dieldrin-coated or heptachlor-coated red blood cells were found in the subject's serum. However, this study is limited because of the exposure of the subject to other pesticides.

No studies were located regarding immunological effects in animals after dermal exposure to aldrin or dieldrin.

All reliable LOAEL values for immunologic effects of dieldrin in humans in acute-duration dermal studies are recorded in Table 3-4.

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3.2.3.4 Neurological Effects

Central nervous system excitation culminating in convulsions was the principal toxic effect noted in occupational studies of workers employed in either the manufacture or application of aldrin or dieldrin. In many cases, convulsions appeared suddenly and without prodromal signs (Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958). EEGs taken shortly after the convulsions revealed bilateral irregular alpha rhythms interrupted by spike and wave patterns (Avar and Czegledi-Janko 1970; Kazantzis et al. 1964). In the case of dieldrin sprayers who developed convulsions, the convulsive episodes did not follow known accidental overexposures (Patel and Rao 1958). Rather, the convulsions developed anywhere from 14 to 154 days after the first exposure to dieldrin. The time to onset was more rapid for sprayers using the more concentrated spray. An accumulative type of poisoning was also reported in workers involved in the manufacture of aldrin, dieldrin, telodrin, or endrin (Jager 1970). In this report, convulsions were believed to have been caused by either accumulating levels of dieldrin in the blood or modest overexposures in the presence of subconvulsive accumulations of dieldrin. Other central nervous system symptoms reported by workers involved in the manufacturer or application of aldrin and/or dieldrin included headaches (Jager 1970; Patel and Rao 1958), dizziness (Jager 1970), hyperirritability (Jager 1970; Kazantzis et al. 1964), general malaise (Jager 1970), nausea and vomiting (Jager 1970; Kazantzis et al. 1964), anorexia (Jager 1970), muscle twitching (Jager 1970; Patel and Rao 1958), and myoclonic jerking (Jager 1970; Jenkins and Toole 1964; Kazantzis et al. 1964). The more severe symptoms were accompanied by EEG patterns with bilateral spike and wave complexes and multiple spike and wave discharges in the alpha region (Jager 1970; Kazantzis et al. 1964). Less severe symptoms were accompanied by bilateral theta (Jager 1970; Kazantzis et al. 1964) and/or delta (Kazantzis et al. 1964) wave discharges.

In all cases in which follow-up of the subjects was reported, removal from the source of exposure caused a rapid physical recovery and a slower recovery (within a year) of the EEG activity to normal levels (Avar and Czegledi-Janko 1970; Hoogendam et al. 1962, 1965; Jager 1970; Jenkins and Toole 1964; Kazantzis et al. 1964).

No symptoms of poisoning were observed in workers who were exposed to an estimated 1.8 mg/kg/day for 6 months at 6 hours/day for 5.5 days/week based on accumulation of dieldrin on absorbent pads that were attached to various surfaces on the workers (Fletcher et al. 1959).

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A morbidity study of workers employed in the manufacture of aldrin and dieldrin between 1979 and 1990 noted no degenerative disorders of the nervous system (de Jong 1991). However, this study reported significant increases in mental disorders among those <30 years old and in those 46–50 years old. The diseases were classified as stress reactions, short-term depression, or sleep disorders. It is unclear whether these effects were directly the result of aldrin or dieldrin exposure or may have had some other cause.

Results of a comprehensive neurological work-up of 27 workers involved in either the manufacture or application of dieldrin were compared to those of unexposed workers (Sandifer et al. 1981). Scores on five psychological tests were significantly different from those of the unexposed controls; however, the importance of the results was questioned by the authors because of a lack of equality in the level of literacy of the two groups. Also, three exposed workers had abnormal EMGs suggesting a peripheral neuropathy. However, EMGs were not obtained in the control group; thus, the significance of these results is unknown.

Tremors and convulsions were reported in a study examining the effects of acute dermal exposure to aldrin or dieldrin in rabbits (Treon et al. 1953a). However, the doses associated with these effects were not reported. Neurological symptoms including salivation, grinding of the teeth, and spasms were observed in rabbits that were dipped into an emulsion of dieldrin, xylene, Triton X-155[®], and water, at doses as low as 70 mg/kg once a week until death or termination of the experiment (Bundren et al. 1952). This study is limited in that no vehicle control was used and some dose levels were tested on a single animal.

The highest NOAEL for neurological effects in humans in an intermediate-duration study is recorded in Table 3-4.

3.2.3.5 Reproductive Effects

No studies were located regarding reproduction effects in humans or animals after dermal exposure to aldrin or dieldrin.

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3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to aldrin or dieldrin.

The only study located that referred to developmental effects following dermal exposure was a case report of a number of lambs that died either prior to or during parturition (Glastonbury et al. 1987). Ewes had been dipped in an aqueous emulsion of 210 mg/L of dieldrin on one occasion up to 4 months prior to giving birth. External appearance of the lambs was normal, but the lambs were small. Also, the brains of these lambs had an abnormal cerebellar structure. It is unclear whether these effects can be attributed entirely to dieldrin exposure since vitamin A deficiency was also observed in these sheep and vitamin A deficiency is known to cause fetal mortality.

3.2.3.7 Cancer

Aldrin and dieldrin were manufactured at two sites worldwide in plants at the Rocky Mountain Arsenal in Denver, Colorado, and at Pernis in the Netherlands. Workers from these plants have been included in two series of retrospective cohort mortality studies which have been updated several times. Exposure to DBCP and several organophosphates may also have occurred in the Denver plant. Cancer mortality findings of the studies at the Denver plant (Amoateng-Adjepong et al. 1995; Brown 1992; Ditraglia et al. 1981; Ribbens 1985) and the Pernis plant (de Jong 1991; de Jong et al. 1997; Jager 1970; Ribbens 1985; van Raalte 1977) are inconclusive, as summarized below.

The first study of the Denver plant found no significant increase in cancer mortality, but concluded that additional follow-up was necessary due to a small number of deaths (173) and relatively short period of observation (Ditraglia et al. 1981). In the follow-up by Brown (1992), 1,158 workers who were employed for at least 6 months prior to 1965 and were followed through 1987 were investigated. Cause-specific mortality analysis of 337 deaths showed an increase in liver and biliary tract cancer (five cases observed) that was statistically significant when compared to state and local rates (SMRs of 5.10 and 4.86, respectively), but not the national rate (SMR 3.93). All of these five deaths (three from biliary tract/bile duct cancer, one from gall bladder cancer, and one from hepatoma) occurred after 15 years of latency (SMR=4.85). The cohort in the most recent study of the Denver plant (Amoateng-Adjepong et al. 1995) was expanded to 2,384 subjects and followed through 1990 (median 29 years). The median age at hiring was 26 years and the median tenure was 2 years. The increase in hepatobiliary cancer was of a lower

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magnitude than in the previous study and was no longer statistically significant, although no additional cases had occurred (five cases observed/2.0 expected based on state rates, SMR=249). Based on this information and findings that the cancers were not limited to any particular production unit, did not display duration-response trends, and essentially occurred in the biliary tract or gall bladder (rather than liver), the investigators concluded that the hepatobiliary cancer excess was not due to occupational exposures at the plant.

No indications of a carcinogenic effect were found in the early mortality studies of the Dutch (Pernis) workers (Jager 1970; Ribbens 1985; van Raalte 1977). Similarly, in the follow-up study by de Jong (1991), there were no increases in cause-specific mortality among 76 deaths in 570 workers who were employed for at least 1 year between 1954 and 1970 and followed-up until 1987. Follow-up of this cohort until 1993 (118 deaths) showed a significant increase in mortality from rectal cancer (6 deaths observed versus 1.5 expected compared to Netherlands national rates, SMR=390.4) and an insignificant increase in liver cancer deaths (two observed versus 0.9 expected, SMR=225.0) (de Jong et al. 1997). Stratification by dose level (low, moderate, or high exposure based on blood levels of dieldrin) did not disclose any indications for a dose-response relation for either of these causes of death.

Equivocal evidence exists for an association between dieldrin and breast cancer risk from three human epidemiologic studies (Dorgan et al. 1999; Høyer et al. 1998, 2000). In these studies, while dieldrin exposure was verified through blood sampling, and exposure by dermal contact, as well as by inhalation and ingestion, was possible, no specific route of exposure was identified or estimated with any certainty.

The potential of dieldrin to affect breast cancer risk was evaluated in a prospective nested case control study of women in Denmark (Høyer et al. 1998). Serum samples were obtained from 7,712 women from 1976 to 1978. In 1996–1997, serum samples from 240 women who had developed invasive breast cancer and 477 matched breast cancer-free controls were analyzed for levels of dieldrin and 17 other organochlorine pesticides or metabolites and 28 PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Irrespective of breast cancer status, dieldrin was detected in 78% of the women enrolled in the study, with median levels at 24.4 ng/g lipid. Dieldrin was the only organochlorine compound of those tested associated with a significant increase in breast cancer risk. Women in the highest quartile of the serum dieldrin range had double the risk of breast cancer compared to women in the lowest quartile (OR 2.25, 95% CI 1.32–3.84, *p* trend=0.003). Relative risk did not change significantly when adjusted for potential confounders of weight and number of full-term pregnancies (OR 2.05, 95% CI 1.17–3.57, *p* trend=0.01).

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A subsequent study using the same cohort of Danish women investigated whether breast cancer survival was affected by past exposure to dieldrin (Høyer et al. 2000). Dieldrin at blood concentrations >57.6 ng/g, representative of the highest quartile, was found to have a significant adverse effect on overall survival and breast cancer specific survival compared to the lowest quartile levels of <12 ng/g lipid (RR 2.78, 95% CI 1.38–5.59, *p* trend<0.01; RR 2.61, 95% CI 0.97–7.01, *p* trend<0.01) in this case-control study of Danish women between 20 and 80 years of age. A total of 195 breast cancer cases, who each provided two blood samples that were taken in 1976–1978 and 1981–1983, respectively, were included in the survival analysis. The median duration of follow-up with regard to death was 86 months after the first examination (1976–1978) and 79 months after the second examination (1981–1983). Relative risk was adjusted for number of positive lymph nodes and tumor size and grade. When the analysis was performed using an average of the blood concentrations from the two collections, the association was even stronger, with a 5-fold higher risk of death in women from the highest quartile compared to the lowest quartile (RR 5.76, 95% CI 1.86–17.92, *p* trend<0.01) and a clear dose-response relationship. Potential confounders as body mass index, age at menopause, and hormone replacement therapy did not influence the results. This study was limited by small size, 6–39 women per quartile.

A cohort study of women from Missouri failed to find an association between serum dieldrin levels and breast cancer risk (Dorgan et al. 1999). Blood samples were collected from 7,224 women from 1977 to 1987. During the 9.5-year follow-up period, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum in 56.2% of the cases and 61.8% of the controls. The relative risk of cancer in the highest dieldrin serum concentration range quartile was moderately lower compared to the lowest quartile (RR 0.7, 95% CI 0.3–1.3, *p*=0.44).

No studies were located regarding cancer in animals after dermal exposure to aldrin or dieldrin.

3.2.4 Other Routes of Exposure

Dieldrin, 10 mg/kg/day, injected intraperitoneally for 5 days, did not appear to have any estrogenic action in mature male rats as the serum and urinary levels of $\alpha_2\mu$ -globulin were not significantly altered (Nagahori et al. 2001).

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3.3 GENOTOXICITY

Sister chromatid exchanges and chromosomal aberrations were studied in a population of floriculturists occupationally exposed to several pesticides, including aldrin (Dulout et al. 1985). A statistically significant increase in sister chromatid exchanges, but not exchange type chromosome aberrations, was seen in workers with clinical symptoms of pesticide exposure as compared to those without symptoms. There was an increase in exchange-type chromosome aberrations in this population when compared to nonfloriculturists. Interpretations based on this study are limited because the route and dose of exposure could not be determined, since the workers could have been exposed via inhalation or dermal contact following the spraying of the greenhouses with the pesticide aerosols. In addition, there was concomitant exposure to other organophosphorus, carbamate, and organochlorine insecticides.

Lymphocytes from workers in a dieldrin manufacturing facility were examined for chromosome aberrations (Dean et al. 1975). No statistically significant differences in either chromatid-type or chromosome-type aberrations were seen in current workers when compared to former workers or to unexposed controls. While there was no occupational exposure to other pesticides in this study, the exposure could have occurred via inhalation and/or dermal contact.

No studies were located regarding genotoxic effects in animals after inhalation exposure to aldrin or dieldrin.

No studies were located regarding genotoxic effects in humans after oral exposure to aldrin or dieldrin.

Studies in a variety of mammalian species have demonstrated a unique sensitivity of the mouse liver to dieldrin-induced hepatocarcinogenicity, and mechanistic studies suggest a nongenotoxic mode of action (Stevenson et al. 1999; WHO 1989). Aldrin and dieldrin were found to induce DNA synthesis in the mouse liver (Busser and Lutz 1987; Kamendulis et al. 2001). The effects of dieldrin on changes in hepatocyte DNA synthesis, mitosis, apoptosis, and ploidy were studied in rats and mice treated with a 0, 1, 3, or 10 mg dieldrin/kg diet (Kamendulis et al. 2001). Livers from mice fed only the highest dose (10 mg dieldrin/kg) exhibited significantly increased DNA synthesis and mitosis at 14, 28, or 90 days on the diet and a significant increase in octaploid (8N) hepatocytes. No changes were observed in rat livers. The apoptotic index in the liver of mice in any treatment group did not change over a 90-day treatment and study period. In another study in which single doses of aldrin were administered orally to male rats

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and male and female mice (0.016, 0.011, and 0.008 mmol/kg [5.84, 4.01, and 2.92 mg/kg], respectively), DNA synthesis in the liver was stimulated only in male mice (Busser and Lutz 1987).

Single doses of aldrin administered orally to three groups of male Swiss mice (13.0, 19.5, and 39.0 mg/kg) resulted in a statistically significant increase in the number of abnormal metaphases in dividing spermatocytes. There was also a significant increase at all doses of univalents, indicating a decreased pairing of meiotic chromosomes (Rani and Reddy 1986).

A dominant lethal assay was conducted using 40 male CF₁ mice orally dosed with 12.5 or 25 mg/kg of dieldrin (Dean et al. 1975). The results of this assay indicated that the overall mean percentage of implantations was significantly reduced in the females mated with males receiving 12.5 mg/kg dieldrin. However, a second series of experiments showed that the overall mean of successful implantations was significantly higher in the 25 mg/kg group than in the controls. Several doses of both aldrin and dieldrin were tested in a dominant lethal study conducted in mice (Epstein et al. 1972). Dieldrin did not meet any criteria for mutagenic effects. Females mated to males exposed to aldrin did show some reduction in implantations, but these were judged to be nonsignificant upon statistical analysis.

Present *in vivo* data have not established whether or not aldrin or dieldrin react directly with DNA to produce mutations in either the germ cells or in the somatic cells. The reduced meiotic pairing reported by Rani and Reddy (1986) does suggest that aldrin can cross the blood/testis barrier, but the results of Dean et al. (1975) offer no clear evidence that there are significant reactions with DNA.

No studies were located regarding genotoxic effects in animals after dermal exposure to aldrin or dieldrin.

In vitro studies assaying for genotoxicity of aldrin or dieldrin have been conducted in several species. Significant increases in chromosome aberrations have been reported in cultured human lung cells. Similar results have been observed in bone marrow cells of mice treated intraperitoneally with dieldrin (Majumdar et al. 1976). Sister chromatid exchanges were significantly increased in Chinese hamster ovary cells at doses of dieldrin that caused marked cell cycle delay when tested both with and without S9 (Galloway et al. 1987). However, no chromosome aberrations were seen in this study. In addition, only 3 of 4,800 cells from 48 Chinese hamsters exposed via intraperitoneal injection of 60 mg/kg of dieldrin showed aberrant chromosomes (Dean et al. 1975).

Mitotic gene conversion in *Saccharomyces cerevisiae* was negative in a host-mediated assay in which adult male CF₁ mice were orally dosed for 5 consecutive days with 5 or 10 mg/kg of dieldrin (Dean et al.

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1975). Micronuclei formation was increased in *Tradescantia* by 3.81 ppm dieldrin, but aldrin yielded negative results (Sandhu et al. 1989). The authors speculated that the immiscibility of aldrin in water contributed to the negative findings of that chemical.

Dieldrin-induced gene mutation has been reported to be positive in Chinese hamster V79 cells (Ahmed et al. 1977b) and in *Salmonella* (Ennever and Rosenkranz 1986; Majumdar et al. 1977) but negative in *Aspergillus nidulans* (Crebelli et al. 1986). Dieldrin-induced gene mutation in several strains of *Salmonella* has also been reported to be negative, with and without activation (De Flora et al. 1984; Glatt et al. 1983; Haworth et al. 1983; Marshall et al. 1976; Moriya et al. 1983; Shirasu 1975), but weakly positive results were reported in *Salmonella* following photoactivation with ultraviolet light (De Flora et al. 1989). Dieldrin produced positive results for focus formation in the BPV-1 DNA carrying C3H/10T(1/2) mouse embryo fibroblast cell line (T1) (Kowalski et al. 2000). Aldrin and dieldrin were not mutagenic in a *Bacillus subtilis* rec-assay (Shirasu 1975), or in *E. coli* (Ashwood-Smith et al. 1972; Fahrig 1974; Shirasu 1975) or *Saccharomyces cerevisiae* (Fahrig 1974). Aldrin was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (Moriya et al. 1983).

The preponderance of evidence appears to indicate that aldrin and dieldrin induce a carcinogenic response through nongenotoxic mechanisms (i.e., not acting directly on the DNA). There is some evidence that the activity of several specific transfer ribonucleic acids (tRNAs) is depressed by exposure to dieldrin, but it is uncertain whether this is due to decreased synthesis or to direct inactivation (Chung and Williams 1986). Other possible mechanisms for the cellular effects of aldrin and dieldrin include increasing unscheduled DNA synthesis (UDS), since increased DNA synthesis in hepatocytes was observed in B6C3F1 mice fed 4 mg dieldrin/kg for 7 days (Klaunig et al. 1995; Stevenson et al. 1995a), and a positive effect has been reported for dieldrin in SV-40 transformed human fibroblast cells in culture with and without metabolic activation (Ahmed et al. 1977a). However, UDS assays have been negative in both Fischer 344 rat (Probst et al. 1981) and Balb/c mouse (Klaunig et al. 1984) primary hepatocyte cultures.

Another possible mechanism for the nongenotoxic action of aldrin and dieldrin involves the inhibition of metabolic cooperation and gap junctional intercellular communication. These effects have been reported in Chinese hamster cells (Jones et al. 1985; Kurata et al. 1982; Trosko et al. 1987), rat and mouse hepatocytes (Klaunig and Ruch 1987; Klaunig et al. 1990), and human teratocarcinoma cells (Wade et al. 1986; Zhong-Xiang et al. 1986). While these effects are epigenetic, rather than genotoxic, these processes may offer insight into cellular changes in metabolism and proliferation that could explain cell

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cycle changes and the disparate results of genotoxicity assays. Key *in vivo* genotoxicity studies are presented in Table 3-5, and *in vitro* genotoxicity studies are presented in Table 3-6.

3.4 TOXICOKINETICS**3.4.1 Absorption****3.4.1.1 Inhalation Exposure**

Studies directly measuring absorption of aldrin or dieldrin in humans following inhalation exposure of known amounts of these pesticides were not located. However, results of a survey of women in pesticide-treated homes showed a correlation between the treatment and dieldrin levels in human breast milk (Stacey and Tatum 1985). Inhalation was suggested as the most probable route of exposure because absorption by skin contact with pesticide-treated surfaces was not believed to contribute significantly to the exposures. Measurable levels of aldrin and dieldrin in indoor air have been detected several years after pesticide treatment of homes (Dobbs and Williams 1983).

In vivo studies on absorption following inhalation exposure of animals to aldrin/dieldrin were not located. In an *in vitro* study using isolated perfused rabbit lungs, aldrin (0.25, 0.50, 1.0, 1.5, 2.0, 2.5, and 3.0 μmol) was taken up by simple diffusion and then metabolized at a slower rate to dieldrin in the lung. Dieldrin was detected 3 minutes after initiation of the experiment. The rate of uptake of aldrin by the lung was biphasic consisting of a rapid phase followed by a slower phase, which could be related to the metabolic turnover of aldrin to dieldrin (Mehendale and El-Bassiouni 1975).

3.4.1.2 Oral Exposure

Volunteers were fed dieldrin at concentrations of 0.0001, 0.0007, and 0.003 mg/kg/day for 18–24 months. A dose-related increase in blood and adipose tissue levels of dieldrin was found (Hunter and Robinson 1967; Hunter et al. 1969). However, no quantitative data specifically describing absorption of aldrin/dieldrin following oral exposure were found in the literature.

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Table 3-5. Genotoxicity of Aldrin/Dieldrin *In Vivo*

Species (test system)	End point	Results		Reference
		Without activation	With activation	
Human (occupational cohort)	Sister chromatid exchange	NA	+ (several pesticides including aldrin)	Dulout et al. 1985
Human (occupational cohort)	Chromosome aberrations	NA	– (dieldrin)	Dean et al. 1975
Swiss mice (oral exposure)	Increased abnormal metaphases	NA	+	Rani and Reddy 1986
	Increased number of univalents (decreased pairing of meiotic chromosomes)	NA	+	
Chinese hamsters (intraperitoneal)	Chromosome aberrations	NA	– (dieldrin)	Dean et al. 1975
Mice (intraperitoneal)	Chromosome aberrations	NA	+ (dieldrin)	Majumdar et al. 1976
Mice (oral exposure)	Increased hepatocyte DNA synthesis	NA	+ (dieldrin)	Kamendulis et al. 2001
	Mitosis	NA	+ (dieldrin)	
	Apoptosis	NA	– (dieldrin)	
	Ploidy	NA	+ (dieldrin)	
Rat (oral exposure)	Increased hepatocyte DNA synthesis	NA	– (dieldrin)	Kamendulis et al. 2001
	Mitosis	NA	– (dieldrin)	
	Apoptosis	NA	– (dieldrin)	
	Ploidy	NA	– (dieldrin)	

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable

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Table 3-6. Genotoxicity of Aldrin/Dieldrin *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Chinese hamster ovary cells	Sister chromatid exchange	+ (dieldrin)	+ (dieldrin)	Galloway et al. 1987
	Chromosome aberrations	– (dieldrin)	– (dieldrin)	
Chinese hamster V79 cells	Gene mutation	NA	+	Ahmed et al. 1977b
Cultured human lung cells	Chromosome aberrations	NA	+	Majumdar et al. 1976
<i>Saccharomyces cerevisiae</i>	Mitotic gene conversation	NA	–	Dean et al. 1975; Fahrig 1974
<i>Tradescantia</i>	Micronuclei formation	NA	+ (dieldrin)	Sandhu et al. 1989
		NA	– (aldrin)	
<i>Salmonella typhimurium</i>	Gene mutation	+	+	Ennevar and Rosenkranz 1986; Majumdar et al. 1977
		–	–	
			(+) (photoactivation)	
				De Flora et al. 1984; Glatt et al. 1983; Haworth et al. 1983; Marshall et al. 1976; Moriva et al. 1983; Shirasu 1975
				De Flora et al. 1989
<i>E. coli</i>	Gene mutation	NA	–	Ashwood-Smith et al. 1972; Fahrig 1974; Shirasu 1975
<i>Bacillus subtilis</i>	Gene mutation	NA	–	Shirasu 1975
<i>Aspergillus nidulans</i>	Gene mutation	NA	–	Crebelli et al. 1986
SV-40 transformed Human fibroblast	Unscheduled DNA synthesis	NA	+	Ahmed et al. 1977a

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Table 3-6. Genotoxicity of Aldrin/Dieldrin *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat hepatocyte	Unscheduled DNA synthesis	NA	–	Probst et al. 1981
Mouse hepatocyte	Unscheduled DNA synthesis	NA	–	Klaunig et al. 1984
Mouse embryo fibroblast	Focus formation	NA	+	Kowalski et al. 2000

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NA = not applicable

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Several metabolic studies indicate that dieldrin is absorbed from the gastrointestinal tract and is transported via the hepatic portal vein (Heath and Vandekar 1964). Following dosing with radiolabeled aldrin and dieldrin, high levels of radioactivity were detected in the liver, blood, and stomach and/or duodenum of dosed rats within 1–5 hours (Heath and Vandekar 1964; Iatropoulos et al. 1975). Twenty-four hours following a single oral administration to rats of 10 mg/kg, 50% of the dose was found in fat (Hayes 1974a).

3.4.1.3 Dermal Exposure

Although data are limited regarding absorption of aldrin and dieldrin following dermal exposure in humans, it appears to occur rapidly. Aldrin and dieldrin were first detected in urine 4 hours after dermal application of a single dose (0.004 mg/cm²) of aldrin and dieldrin, radiolabeled with carbon 14 (¹⁴C), to the forearm of six volunteers. Based on urinary ¹⁴C excretion, it was estimated that 7.8% of aldrin and 7.7% of dieldrin was absorbed over a 5-day period (Feldmann and Maibach 1974). The accuracy of these values is questionable since the dose used was small, the ¹⁴C recovery in the urine was low, the major route of excretion was in the feces (not the urine), and a large individual variation in data was reported.

Aldrin was rapidly absorbed into the skin of female rats following dermal application at doses of 0.006, 0.06, and 0.6 mg/cm² (Graham et al. 1987). Aldrin and dieldrin were detected in the skin 1 hour after aldrin application for all three dose levels. The amount absorbed was proportional to the dose applied. *In vitro* studies of rat skin strips incubated with aldrin showed absorption of aldrin was complete by 80 minutes (Graham et al. 1987). Absorption from fabric that had been impregnated with up to 0.04% dieldrin was also demonstrated in rabbits (Witherup et al. 1961).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution following inhalation exposure to aldrin or dieldrin in humans or animals.

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3.4.2.2 Oral Exposure

Aldrin is rapidly converted to dieldrin. Distribution of dieldrin is initially general, but within a few hours it is redistributed primarily to fat. A study was conducted on volunteers who ingested dieldrin in doses of 0, 0.0001, 0.0007, or 0.003 mg/kg/day for 24 months (Hunter and Robinson 1967; Hunter et al. 1969).

Dieldrin concentrations in blood and adipose tissue increased in a dose-related manner with a finite upper limit for the storage of dieldrin corresponding to a balance between the amount ingested and the amount eliminated daily. This was observed at about 15 months with the eventual body burden characteristic of a person and his particular daily intake (Hunter et al. 1969). The study also found that the concentrations of dieldrin in both adipose tissue and blood are proportional to the given daily dose (Hunter and Robinson 1967). The blood dieldrin concentrations increased by 4 and 10 times in the 0.0001- and 0.003-mg/kg/day dose groups, respectively, when compared to controls. Relationships were derived for the concentration of dieldrin in both adipose tissue and blood in terms of the given daily dosage. Using these relationships it was estimated that the exposure of the general population was equivalent to 0.025 mg/day (0.00033 mg/kg/day). For higher doses of dieldrin, a significant correlation existed between the concentration of dieldrin in blood and the concentration in adipose tissue. The average ratio of the concentration in the adipose tissue to that in the blood was 156:1 (Hunter and Robinson 1967). The existence of a functional relationship between the concentration of dieldrin in the adipose tissue and that in the blood gives strong support to the concept of a dynamic equilibrium in the distribution of dieldrin between these tissues. Animal experiments indicate that this type of equilibrium also exists between the concentrations in the blood and brain, and between those in the blood and liver. When dieldrin administration was terminated, its concentration in blood decreased exponentially following first order kinetics with an estimated half-life of approximately 369 days (range, 141–592 days) (Hunter et al. 1969).

A study of the body burden of dieldrin showed that the bioconcentration and rate of elimination of dieldrin were related to the lipid mass of the individual (Hunter and Robinson 1967, 1968). The highest concentrations of dieldrin in adipose tissue were found in the leanest subjects, and these subjects also exhibited the smallest total body burden. On the other hand, the proportion of the total exposure dose retained in the adipose tissue was highest in those subjects with the greatest total body fat (Hunter and Robinson 1968). The study also showed no increase in the concentration of dieldrin in whole blood during surgical stress or in periods of complete fasting, and it was concluded that the body burden of this compound in the general population constitutes no danger of intoxication as a result of tissue catabolism in times of illness or weight loss (Hunter and Robinson 1968).

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Samples of brain, liver, and adipose tissue were collected from 29 randomly selected autopsies of people in Holland (DeVlieger et al. 1968). These people, with three exceptions, lived in an area where a plant manufacturing aldrin, dieldrin, and endrin is situated, but were not employed at that plant. The mean concentration of dieldrin in the white matter of the brain was significantly greater (0.0061 mg/kg) than that in the gray matter (0.0047 mg/kg). In comparison, the mean concentrations of dieldrin in the liver and adipose tissue were 0.03 and 0.17 mg/kg, respectively. Levels of dieldrin were detected in samples of adipose tissue taken from autopsy patients (Adeshina and Todd 1990; Ahmad et al. 1988; Holt et al. 1986). Dieldrin was detected at concentrations ranging from 0.36 to 0.13 mg/kg. No aldrin was detected.

Placental transfer of dieldrin occurs (Polishuk et al. 1977b). A study of women and their offspring during labor showed higher concentrations of dieldrin in fetal blood than in the mother's blood (1.22 mg/kg and 0.53 mg/kg, respectively). Dieldrin levels were also higher in the placenta (0.8 mg/kg) than in the uterus (0.54 mg/kg) (Polishuk et al. 1977b).

Tissue distribution of ^{14}C following single-dose oral administration of ^{14}C -dieldrin (0.43 mg/kg) to rats indicated that the initial rapid uptake of ^{14}C by the liver during the first 3 hours after dosing is followed by a biphasic decrease and redistribution of the compound among body tissues including adipose tissue, kidney, and lymph nodes, with the majority being distributed to the adipose tissue. During the redistribution process, the lymphatic system seems to be the major transport pathway; the parallel increase of lymph node and adipose tissue values indicated an equilibrium between lymph and depot fat (Iatropoulos et al. 1975). Between 24 and 48 hours after a single oral dose of dieldrin was administered to rats, the amount of dieldrin in fat increased to about 50% of the dose. Dieldrin's affinity for fat is illustrated by the ratio of its concentration in fat to that in blood (>130:1) (Hayes 1974a). In female rats fed 2.5 mg/kg/day for 6 months, the ratio of the concentrations of dieldrin in the blood, liver, and fat was 1:30:500, respectively (Deichmann et al. 1968). Most of the dieldrin absorbed through the skin of guinea pigs, dogs, and monkeys is accumulated in the subcutaneous fat (Sundaram et al. 1978a, 1978b).

Species differences in tissue distribution of dieldrin in rodents have been reported (Hutson 1976). When male rats and mice were subjected to a single dose of ^{14}C -dieldrin (3 mg/kg), liver and fat residues were higher in the mice than in the rats 8 days after ingestion. The liver concentration in mice (0.94 mg/kg) was about nine times higher than in rats (0.11 mg/kg). Fat samples in mice contained dieldrin levels (11.6 mg/kg) that were twice as high as the levels in rats (5.6 mg/kg) (Hutson 1976). Sex differences in tissue distribution of dieldrin in rodents have also been reported (Davison 1973; Walker et al. 1969). Female rats fed dieldrin (0.002, 0.01, and 0.1 mg/kg/day) in their diet for 39 weeks had a higher

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proportion of the total dose in their carcasses than did male rats that were treated similarly (Davison 1973). Also, female rats fed dieldrin (0, 0.005, and 0.5 mg/kg/day) in their diet for 2 years had tissue concentrations of dieldrin between two and ten times that of male rats fed the same dietary concentration (Walker et al. 1969).

Following repeated dosing (2–104 weeks), an equilibrium or steady state is reached between the intake, storage, and excretion of dieldrin in various strains of rats and beagle dogs. Steady-state kinetics were determined by measuring both the level of radioactivity retained in fat, blood, liver, and brain and the percentage of the administered dose excreted at sublethal doses. The steady-state tissue concentration of dieldrin was dose- and time-dependent. In dogs receiving daily oral doses of 0.005 or 0.05 mg/kg/day dieldrin for 2 years, the steady-state blood residue levels were reached in 12–18 weeks or 18–30 weeks, respectively (Walker et al. 1969). In rats receiving 0.0002–2.5 mg/kg/day dieldrin in the diet, steady state was reached in 4–39 weeks; equilibrium was reached earlier in rats receiving higher doses of dieldrin (Baron and Walton 1971; Davison 1973; Ludwig et al. 1964; Walker et al. 1969). In rats receiving daily oral doses of 0.012 mg/kg/day ^{14}C -aldrin for 3 months, steady state was reached in 53 days (Ludwig et al. 1964).

In another study, the steady-state concentration in adipose tissues of rats receiving dietary concentrations of 1.25 mg/kg/day dieldrin for 8 weeks was reported to be 50 mg/kg dieldrin (Baron and Walton 1971). The elimination of dieldrin residues from the adipose tissue of rats subsequently placed on untreated diets was reasonably rapid with estimated half-lives reported to be 4.5 days (Baron and Walton 1971). The estimated half-lives for the adipose tissue and brain were 10.3 and 3 days, respectively, for rats on a basic diet for 12 weeks, following consumption of a diet containing 0.5 mg/kg/day dieldrin for 8 weeks (Robinson et al. 1969). The half-lives of dieldrin in the liver were estimated to be 1.3 and 10.2 days for the rapid and slower elimination, respectively, and similar values were estimated for the blood. The concentrations of dieldrin in adipose tissue were considerably greater than those in other tissues, with storage in the four tissues as follows: adipose tissue >> liver > brain > blood (Robinson et al. 1969).

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3.4.2.3 Dermal Exposure

No studies were located regarding distribution following dermal exposure to aldrin or dieldrin in humans.

Guinea pigs exposed dermally to dieldrin at concentrations varying from 0.0001 to 0.1% for 6 months showed the highest tissue distribution in adipose tissue, with lower concentrations in the liver and brain (Sundaram et al. 1978b). Rabbits exposed to fabric containing up to 0.04% dieldrin for 52 weeks also showed slight accumulation in the omental and renal fat (Witherup et al. 1961).

3.4.2.4 Other Routes of Exposure

The administration of dieldrin by the intraperitoneal route ensures more or less complete absorption. The ^{14}C -residues in tissues of rats dosed by intraperitoneal injection with a total dose of 0.01, 0.1, or 1.0 mg/kg were distributed among the brain, blood, liver, and subcutaneous fat with the highest levels in the fat. Radioactivity excreted by groups given dieldrin by intraperitoneal injection was not significantly different from that of orally treated groups (Lay et al. 1982).

In another study (Cooke et al. 2001) in male Sprague-Dawley rats injected intraperitoneally with 75 mg/kg ^{14}C -aldrin or 62 mg/kg ^{14}C -dieldrin once a week for 3 weeks, the highest levels of dieldrin ^{14}C -residues were also observed in the fat, whereas the distribution of aldrin ^{14}C -residues to the spleen was comparable to fat. In the reproductive organs, the testicular ^{14}C -residue content of both chemicals was always considerably lower than that of the epididymis, and the seminal vesicle fluid contained lower quantities of label than the seminal vesicles.

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3.4.3 Metabolism**3.4.3.1 Inhalation Exposure**

No studies were located regarding metabolism following inhalation exposure to aldrin or dieldrin in humans.

An *in vitro* study using rabbit lung perfusates showed that aldrin was metabolized to dieldrin within the endoplasmic reticulum. Aldrin metabolism was dose dependent. Up to 70% of aldrin was metabolized in 1 hour at low doses ($\bullet 3 \mu\text{mol}$) (Mehendale and El-Bassiouni 1975).

3.4.3.2 Oral Exposure

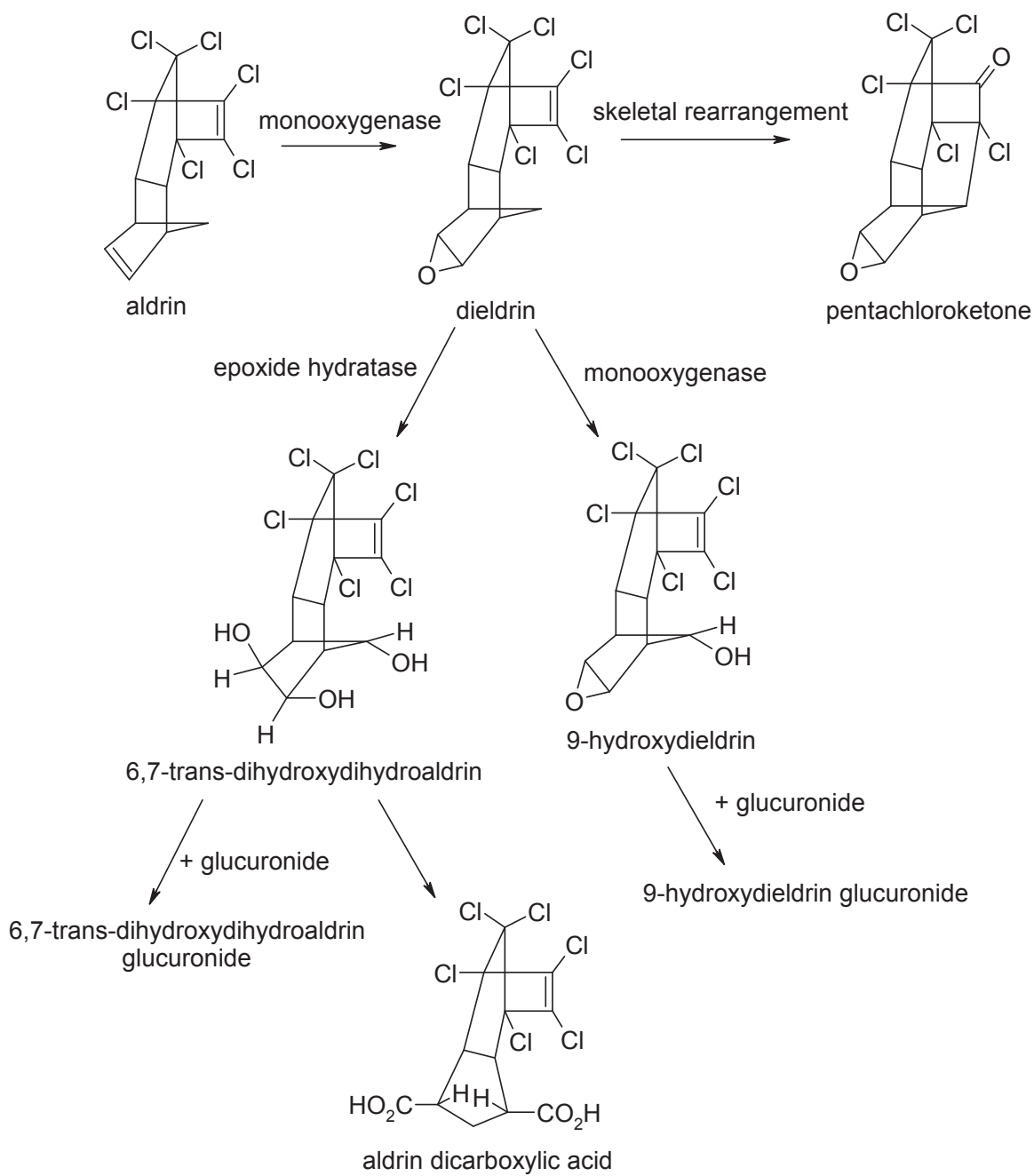
No studies were located specifically regarding metabolism following oral exposure to aldrin or dieldrin in humans.

The initial and major step in the biotransformation of aldrin in experimental animals is the formation of the corresponding epoxied dieldrin (Wong and Terriere 1965). Aldrin is readily converted to dieldrin primarily in the liver by mixed-function oxidases (Wong and Terriere 1965) and to a lesser extent in the lung (Lang et al. 1986) and skin (Graham et al. 1987; Lang et al. 1986). The known metabolic pathways of aldrin and dieldrin in laboratory animals are presented in Figure 3-3.

The formation of dieldrin by epoxidation of aldrin is a reaction catalyzed by monooxygenases in liver and lung microsomes. Aldrin epoxidation was studied in rat liver microsomes (Wolff et al. 1979).

Microsomes from phenobarbital-treated rats showed a three-fold increase in dieldrin formation, whereas 3-methylcholanthrene treatment markedly depressed enzyme activity. Thus, cytochrome P-450, not cytochrome P-448, seems to be involved in epoxidation. *In vitro* studies compared the oxidation of aldrin to dieldrin in extrahepatic and hepatic tissues of rats (Lang et al. 1986). The authors tried to identify the pathway by which aldrin is metabolized in liver, lung, seminal vesicle, and subcutaneous granulation tissue. Many organs and tissues possess low cytochrome P-450 content. In these cases, an alternative oxidative pathway mediated by prostaglandin endoperoxide synthase (PES) might be more important. PES consists of a cyclooxygenase which catalyzes the bisdioxygenation of arachidonic acid to prostaglandin G_2 (PGG₂). In a second step, a reduction by hydroperoxidase to prostaglandin H_2

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Figure 3-3. Proposed Metabolic Pathway for Aldrin and Dieldrin*

*Adapted from EPA 1987a

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(PGH₂) occurs. The aldrin epoxidation was completely nicotine adenine dinucleotide phosphate (NADPH)-dependent in liver microsomes and hepatocytes. In lung microsomes, two pathways were involved. The NADPH-dependent activity was 1.5% and the arachidonic acid-dependent aldrin epoxidation was 0.3% of the activity found in the liver. In seminal vesicle microsomes and granulation tissue microsomes, aldrin epoxidation was stimulated by arachidonic acid and inhibited by indomethacin (a specific inhibitor of cyclooxygenase). These results suggest that aldrin was epoxidized by a prostaglandin synthase-mediated pathway in extrahepatic tissues as an alternative enzyme in the cytochrome P-450-dependent monooxygenases (Lang et al. 1986).

In mammals, two major metabolism routes of dieldrin seem to be predominant: (1) direct oxidation by cytochrome oxidases, resulting in 9-hydroxydieldrin (the Chemical Abstract Service [CAS] numbering system equivalent of 12-hydroxydieldrin), and (2) the opening of the epoxied ring by epoxied hydases, resulting in 6,7-*trans*-dihydroxydihydroaldrin (the CAS numbering system equivalent of 4,5-*trans*-dihydroxy-dihydroaldrin) (Müller et al. 1975). Dieldrin is hydroxylated to 9-hydroxydieldrin by liver microsomal monooxygenases in rats, and the reaction is inhibited by the addition of the monooxygenase inhibitor, sesamex (Matthews and Matsumura 1969). Metabolism of dieldrin is 3–4 times more rapid in male than in female rats (Matthews et al. 1971). The difference is attributed to the greater ability of males to metabolize dieldrin to its more polar metabolites, primarily 9-hydroxydieldrin. Species differences in rates of metabolism have been observed in rats and mice. The hydroxylation reaction occurs more rapidly in rats than it does in mice as indicated by a higher ratio in rats of 9-hydroxy-¹⁴C-dieldrin to ¹⁴C-dieldrin (Hutson 1976).

The 9-hydroxydieldrin glucuronide is formed both *in vivo* and *in vitro*. It has been identified in the bile of rats (Chipman and Walker 1979); however, it is generally excreted in the feces in free form (Hutson 1976). The 9-hydroxydieldrin glucuronide is formed rapidly *in vitro* from dieldrin (which is hydroxylated first to 9-hydroxydieldrin) upon incubation with rat liver microsomes and uridine diphosphoglucuronic acid (Hutson 1976; Matthews et al. 1971).

Dieldrin is also metabolized by epoxide hydratase to form 6,7-*trans*-dihydroxydihydroaldrin, which was originally isolated and identified in rabbits and mice (Korte and Arent 1965) and later found also to form in other animals including Rhesus monkeys and chimpanzees (Müller et al. 1975). The 6,7-*trans*-dihydroxydihydroaldrin glucuronide is formed *in vitro* in hepatic microsomal preparations from rabbits or rats in the presence of uridine diphosphoglucuronic acid and NADPH (Matthews and Matsumura 1969).

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6,7-*trans*-Dihydroxydihydroaldrin can be further oxidized to aldrin dicarboxylic acid or conjugated to glucuronic acid (Baldwin et al. 1972; Hutson 1976).

Pentachloroketone, also known as Klein's metabolite, is a major urinary metabolite in male rats, but it is only found in trace amounts in the urine of female rats and male mice (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971). Pentachloroketone is formed by molecular rearrangement. It has been suggested that pentachloroketone is the product of rearrangement of the same intermediate that leads to 9-hydroxydieldrin (Bedford and Hutson 1976).

3.4.3.3 Dermal Exposure

No studies were located regarding metabolism following dermal exposure to aldrin or dieldrin in humans.

Data show that the skin is capable of metabolizing aldrin to the stable epoxied dieldrin (Graham et al. 1987). Dieldrin was detected in the skin of rats 1 hour after aldrin application at three dose levels (0.1, 1.0, and 10 mg/kg). The amount of conversion was greatest at the lowest dose levels suggesting enzyme saturation at higher doses. The authors concluded that, following topical application, up to 10% conversion of aldrin to dieldrin by skin enzymes can occur during percutaneous absorption (Graham et al. 1987). *In vitro* studies using mouse skin microsomal preparations and rat whole skin strips also showed that metabolism of aldrin to dieldrin took place in the skin (Graham et al. 1987).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion following inhalation exposure to aldrin or dieldrin in humans or animals.

3.4.4.2 Oral Exposure

Excretion in humans is primarily in the feces via the bile. 9-Hydroxydieldrin was found in the feces of seven workers occupationally exposed to aldrin and dieldrin (Richardson and Robinson 1971). An estimated half-life for dieldrin elimination is reported to be 369 days (Hunter et al. 1969). Dieldrin is also

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excreted via lactation in nursing mothers. Dieldrin concentrations of 19–26 ppb were found in breast milk (Schechter et al. 1989b).

In rats dosed with ^{14}C -aldrin at 0.012 mg/kg/day for 3 months, both aldrin and dieldrin were found in the feces, with lower concentrations of both compounds also found in the urine (Ludwig et al. 1964). Pentachloro ketone was also detected in the urine of rats fed diets containing 1.25 mg/kg/day of aldrin (Klein et al. 1968).

Following administration of single oral doses of ^{14}C -dieldrin to rats, mice, monkeys, and chimpanzees, radioactivity accounting for 95, 95, 79, and 79% of the dose, respectively, was excreted in the feces, which is the main route of excretion (Hutson 1976; Müller et al. 1975). The ratio of radioactivity excreted in the feces and in the urine is 19 in rats and mice and 3.8 in monkeys and chimpanzees (Müller et al. 1975). Unchanged dieldrin and 9-hydroxydieldrin and its glucuronide are the major components in the feces of rats, monkeys, and chimpanzees, with lesser amounts of 6,7-dihydroxydihydroaldrin and aldrin dicarboxylic acid (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971; Müller et al. 1975). 9-Hydroxydieldrin has also been found in the urine of monkeys given a single dose of 0.5 mg/kg of dieldrin (Müller et al. 1975) and in mouse urine (Hutson 1976). Elimination of aldrin dicarboxylic acid occurs mainly in the urine of mice and rats (Baldwin et al. 1972; Hutson 1976) and in the feces of rats (Hutson 1976). Unchanged dieldrin was found in the feces of mice, rats, rabbits, and monkeys at concentrations ranging from 0.3 to 9.0% of the single dose administered (0.5 mg/kg) (Müller et al. 1975).

Excretion of dieldrin is 3–4 times more rapid in male than in female rats (Matthews et al. 1971). The difference was attributed to the greater ability of males to metabolize dieldrin to its more polar metabolites. An *in vitro* study using rat liver perfusates showed a sexual difference in the hepatic excretion of dieldrin. The appearance of radioactivity in the bile of livers of males was approximately three times as rapid as the appearance of radioactivity in the bile of livers of females (Klevay 1970). Species differences have been reported for the excretion of dieldrin and/or its metabolites between male CFE rats and male CF_1 or LACG mice (Baldwin et al. 1972; Hutson 1976). Excretion was more rapid in the rat than in the mouse. The ratio of 9-hydroxy- ^{14}C -dieldrin to ^{14}C -dieldrin was higher in rats than in mice, indicating a slightly more rapid excretion by the rat (Hutson 1976).

In rabbits, 6,7-*trans*-dihydroxydihydroaldrin is the major metabolite excreted in the urine. Following administration of single oral doses of ^{14}C -dieldrin to rabbits, elimination was greater in urine, accounting for 81–83% of the dose (Müller et al. 1975). 6,7-*trans*-Dihydroxydihydroaldrin has also been identified

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in the urine of mice (Müller et al. 1975). 6,7-*trans*-Dihydroxydihydroaldrin glucuronide has been identified in urine of rabbits and monkeys (Müller et al. 1975).

Pentachloro-ketone is the major component in rat urine (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971). The mouse, unlike the rat, does not appear to excrete pentachloro-ketone as a urinary metabolite. Pretreatment of CFE rats with dieldrin caused an enhancement of the urinary excretion of pentachloro-ketone, but no effect on the pattern of excretion of urinary metabolites could be detected when CF₁ mice were given similar treatments (Baldwin et al. 1972). Aldrin dicarboxylic acid, unchanged dieldrin, and 9-hydroxydieldrin glucuronide have also been found in lower concentrations in the urine of rats (Hutson 1976; Müller et al. 1975).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion following dermal exposure to aldrin or dieldrin in humans or animals.

3.4.4.4 Other Routes of Exposure

Elimination of ¹⁴C following intraperitoneal or intravenous injection of ¹⁴C-dieldrin to male rats was either approximately equal to or slightly less than that observed following oral dosing (between 70 and 80% of the total dose was excreted by 2 weeks postdosing) (Cole et al. 1970; Lay et al. 1982). Excretion occurred primarily in the feces (about 90%). Biliary elimination was measured experimentally following intraperitoneal administration. The rate of ¹⁴C elimination in the bile increased following pretreatment of rats with phenobarbital (Chipman and Walker 1979).

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 (Clewett 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 et al. 1987; Andersen and Krishnan 1994). 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.

No PBPK models for aldrin or dieldrin were located.

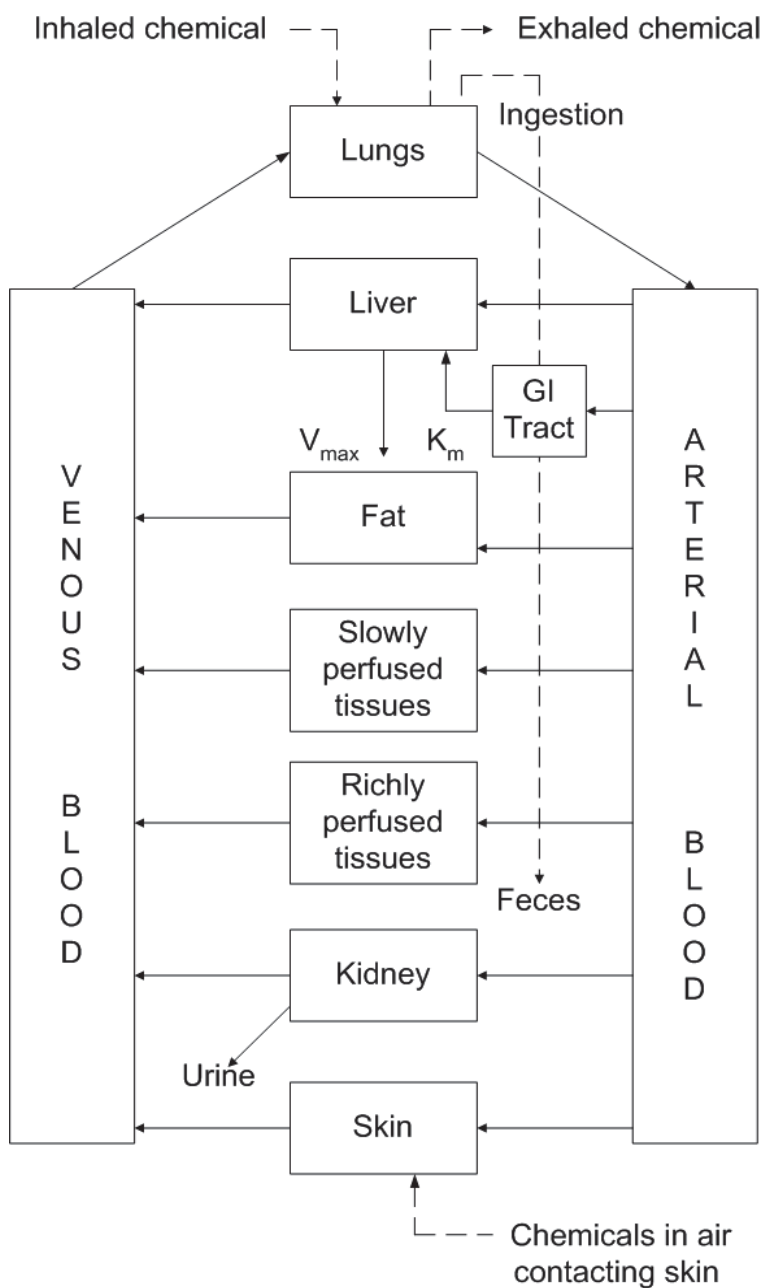
3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Mechanisms of aldrin or dieldrin absorption following inhalation, oral, or dermal exposure in humans or animals were not identified. However, since both aldrin and dieldrin are lipophilic substances, absorption via passive diffusion is likely. No information was located regarding transport mechanisms in the blood. Given the high degree of solubility of aldrin and dieldrin in lipids, one might expect these chemicals to be associated with the lipid fraction of blood. In biological systems, aldrin is rapidly converted to dieldrin. Following exposure to aldrin or dieldrin, animal data indicate that dieldrin is widely distributed initially (with rapid uptake by the liver), then redistributed primarily to fat (Deichmann et al. 1968; Hayes 1974a; Hutson 1976; Iatropoulos et al. 1975). The lymphatic system appears to be the major transport pathway during redistribution (Iatropoulos et al. 1975). Animal data also indicate that epoxidation of aldrin to dieldrin is catalyzed by monooxygenases, primarily in the liver (Wong and Terriere 1965), but also in lungs (Lang et al. 1986) and skin (Graham et al. 1987; Lang et al. 1986). The study of Lang et al. (1986) provides evidence that aldrin may also be epoxidized by a prostaglandin synthetase-mediated pathway in extrahepatic tissues. Results from a dermal study indicate that the metabolism of aldrin and dieldrin may be a saturable process (Graham et al. 1987). Further metabolism, such as the hydroxylation of dieldrin to 9-hydroxydieldrin, has also been shown to occur in the liver (Matthews and Matsumura 1969). In animals administered aldrin or dieldrin, fecal excretion (via the bile) of parent compound and metabolites is the main route of elimination, with lesser amounts found in the urine (Ludwig et al. 1964). Dieldrin is also excreted in the breast milk of nursing mothers (Schechter et al. 1989b).

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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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3.5.2 Mechanisms of Toxicity

A number of studies have investigated the mechanism of aldrin and dieldrin neurotoxicity. As discussed in Section 3.2.2.4, aldrin and dieldrin characteristically stimulate the central nervous system causing hyperexcitation and generalized seizures (convulsions). It is generally believed that the hyperexcitatory effects of these chemicals result from a generalized activation of synaptic activity throughout the central nervous system, although it is unclear whether aldrin and dieldrin act at the nerve terminal to facilitate neurotransmitter release, or if they cause excitation by depressing activity of inhibitory neurotransmitters within the central nervous system (Joy 1982; Shankland 1982).

Facilitation of neurotransmitter release by dieldrin has been proposed to occur as the result of the ability of aldrin or dieldrin to inhibit brain calcium ATPases (Mehrotra et al. 1988, 1989). These enzymes are involved in pumping calcium out of the nerve terminal. By inhibiting their activity, aldrin and dieldrin would cause a build-up of intracellular levels of calcium and an enhancement of neurotransmitter release.

Most recently, however, the role of aldrin and dieldrin in blocking inhibitory activity within the brain has received a great deal of attention as the probable mechanism underlying the central nervous system excitation. Based on the observed interaction of other cyclodiene insecticides with the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) (Matsumura and Ghiasuddin 1983), numerous studies were undertaken to assess the effects of aldrin and dieldrin on GABA receptor function. Both *in vitro* experiments using rat brain membranes and intravenous or intraperitoneal administration of aldrin and dieldrin to rats have shown that these agents are capable of blocking the activity of GABA by blocking the influx of chloride through the GABA_A receptor-ionophore complex (Abalis et al. 1986; Bloomquist 1992, 1993; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Ikeda et al. 1998; Lawrence and Casida 1984; Liu et al. 1997a, 1997b; Nagata and Narahashi 1994, 1995; Narahashi et al. 1992, 1995, 1998; Obata et al. 1988; Pomes et al. 1994). Overall, based on good correlations of effects from the molecular level to whole animal toxicity, the preponderance of evidence indicates that the convulsant and other neurotoxic effects of aldrin and dieldrin are consequent to a blocking action on the GABA_A receptor-chloride channel complex.

Pesticides have been implicated in the etiology of the Lewy body diseases, which involve intracellular deposits consisting of fibrils of α -synuclein. Dieldrin has been shown to stimulate α -synuclein fibril formation *in vitro* (Uversky et al. 2001). While α -synuclein is a natively unfolded protein, dieldrin induces a conformational change in α -synuclein, a time-dependent increase in secondary structure, which

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preceded the increase in fibril formation. The natively unfolded state of α -synuclein arises from the large net negative charge at neutral pH and the low intrinsic hydrophobicity. Uversky et al. (2001) proposed that nonpolar dieldrin binds to α -synuclein and shifts the equilibrium from the unfolded state to a folded intermediate conformation. The intermediate then associates, leading to fibril formation.

In a study of organochlorine compounds in human brain, there was a substantially higher concentration of dieldrin in Parkinson's disease tissue compared with Alzheimer's disease and nondemented nonparkinsonian controls tissue (Corrigan et al. 2000).

A preponderance of evidence from studies in a variety of mammalian species indicates a unique sensitivity of the mouse liver to aldrin- and dieldrin-induced hepatocarcinogenicity and mechanistic studies suggest a nongenotoxic mode of action (Stevenson et al. 1999; WHO 1989) via promotion of spontaneously initiated (background) liver cells (see Sections 3.2.2.7 and 3.3). The cellular and molecular mechanisms involved in the promotion of the liver tumors have not been fully elucidated, but appear to mainly involve species-specific susceptibility of the mouse to dieldrin-induced oxidative stress and inhibition of gap junctional communication (Jones et al. 1985; Klaunig and Ruch 1987; Klaunig et al. 1990, 1995, 1998; Kurata et al. 1982; Ruch and Klaunig 1986; Stevenson et al. 1999; Trosko et al. 1987; van Ravenzwaay and Kunz 1988; Wade et al. 1986; Zhong-Xiang et al. 1986). As discussed by Stevenson et al. (1999), the production of reactive oxygen species, depletion of hepatocyte antioxidant defenses such as vitamin E, and peroxidation of liver lipid have been shown to accompany oxidative metabolism of dieldrin in mice, apparently resulting in modulation of gene expression that favors the clonal expansion of spontaneously initiated cells.

The effects of dieldrin on changes in hepatocyte DNA synthesis, mitosis, apoptosis, and ploidy were studied in rats and mice treated with 0, 1, 3, or 10 mg dieldrin/kg diet (Kamendulis et al. 2001). No changes were observed in rat liver. Liver from mice fed only the highest dose (10 mg dieldrin/kg) exhibited significantly increased DNA synthesis and mitosis at 14, 28, or 90 days on the diet and a significant increase in octaploid (8N) hepatocytes. The apoptotic index in the liver of mice in any treatment group did not change over a 90-day treatment and study period.

The ability of chlorinated hydrocarbons to disrupt estrogen homeostasis, by up-regulating selected gene transcription, has also been hypothesized to be responsible for their oncogenic effects. Neither aldrin nor dieldrin showed evidence of estrogenicity as evidenced by lack of induction of transcriptional activation of an estrogen-responsive reported gene in transfected HeLa cells (Tully et al. 2000). There is evidence

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of a synergistic estrogenic effect of dieldrin and toxaphene on the bone mass density in rats. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 $\mu\text{mol/kg/day}$, 5 days/week, for 9 months, when administered with toxaphene (30 $\mu\text{mol toxaphene/kg/day}$ and 7.5 $\mu\text{mol/kg/day}$), bone mass density was significantly increased (Syversen et al. 2000). In contrast, the results of several estrogen-responsive assays in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based reporter gene assays, indicate that the activities of both dieldrin and toxaphene, as well as a binary mixture of the two were minimally estrogenic (Ramamoorthy et al. 1997a).

A single dose of dieldrin (37 mg/kg), administered to female rats by gavage significantly increased expression of cytochrome P450 CYP1A1, CYP1A2, and CYP1B1, which are involved in estrogen metabolism, in the liver, kidney, and mammary tissues (Badawi et al. 2000).

3.5.3 Animal-to-Humans

Most of the available human data come from cases of acute oral exposure to relatively high levels of aldrin or dieldrin (Black 1974; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951) or from chronically exposed workers (de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; Van Raalte 1977; Van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). In both humans and animals, high doses of aldrin or dieldrin result primarily in neurotoxicity. Epidemiologic studies involving chronic exposure to aldrin and/or dieldrin similarly indicate that the central nervous system is a major organ of toxicity. Chronic animal studies additionally demonstrate adverse effects in the kidney and liver; the liver being the most sensitive target. Liver effects are indicated in limited reports of humans exposed to levels of aldrin or dieldrin that result in neurotoxic symptoms (Black 1974; Garrettson and Curley 1969). Although the human data are extremely limited, at present, there is no evidence to suggest that noncancer effects seen in animal studies would be different from those in humans. Available information is suggestive of general similarity in the metabolic pathways and disposition of aldrin and dieldrin in humans and experimental animals (Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974a; Hunter and Robinson 1967; Hunter et al. 1969; Iatropoulos et al. 1975). However, elimination rates vary among animal species and between males and females, thus contributing to uncertainty in extrapolation of toxicokinetic data from animals to humans.

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Oral bioassays in animals have demonstrated that aldrin and/or dieldrin are liver carcinogens in mice, but not rats (Davis and Fitzhugh 1962; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; Meierhenry et al. 1983; NCI 1978a, 1978b; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1969, 1972). Based on the results of retrospective cancer mortality studies in aldrin and dieldrin production workers, there is inconclusive evidence of carcinogenicity in occupationally-exposed humans (Amoateng-Adjepong et al. 1995; Brown 1992; de Jong 1991; de Jong et al. 1997; Ditraglia et al. 1981; Jager 1970; Ribbens 1985; van Raalte 1977). As summarized in Section 3.5.2 (Mechanisms of Toxicity), accumulating evidence indicates that the species-specificity of dieldrin-induced hepatocarcinogenicity involves susceptibility of the mouse to dieldrin-induced oxidative stress, resulting in the promotion of spontaneously initiated (background) liver tumors. Because other species, including humans, appear to be resistant to dieldrin-induced oxidative stress (Jager 1970; Stevenson et al. 1999), it does not appear that the mouse carcinogenicity data can be extrapolated to humans with a high degree of certainty.

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 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

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affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans after exposure to aldrin or dieldrin.

In vivo studies in animals suggest that aldrin and dieldrin may disrupt normal reproductive hormone levels in male animals and be an endocrine disruptor in females. Decreased androgen production and degenerative changes in the germ cells were seen in male rats after intermediate-duration intraperitoneal exposures to aldrin. Aldrin also induced estrus changes and/or endometrial proliferation in treated dogs and ovariectomized rats. *In vitro* studies suggest that dieldrin may inhibit binding of 5 α -dihydro-testosterone and 17 β -estradiol to the androgen and estrogen receptors, respectively, as well as cause effects such as estrogenic induction of breast cell proliferation. Overall, *in vitro* evidence for dieldrin estrogenicity indicates weak potency compared to 17 β -estradiol. Apparently contradictory results were reported in different studies for several of the assays, indicating that caution should be used in interpreting the collective *in vitro* results.

Gonadotrophic effects were observed in male rats that were treated with 0.15 mg/kg/day aldrin by intraperitoneal injection for 26 days (Chatterjee et al. 1988a, 1988b, 1988c). These effects include decreased sperm count, degeneration of germ cells, decreased weights of seminal vesicles and prostate and coagulating glands, decreased seminiferous tubule diameter, decreased plasma and testicular testosterone, decreased prostatic fructose content and acid phosphatase activity, and decreased plasma luteinizing hormone and follicular stimulating hormone. Dieldrin caused changes in testosterone production and ultrastructure in rat interstitial (Leydig) testicular cells *in vitro*; significant increases in testosterone production were observed, and the Leydig cells had increased numbers of cytoplasmic vesicles which resembled lipid droplets (Ronco et al. 1998). Dieldrin also reduced the stimulatory effect of human chorionic gonadotropin (HCG) on Leydig cell testosterone production, although dieldrin-induced ultrastructural changes in HCG-stimulated Leydig cells were similar to those found in the unstimulated cells (Ronco et al. 1998). Other *in vitro* studies showed that dieldrin significantly inhibited binding of 5 α -dihydrotestosterone to the androgen receptor in rat prostate cytosol and to androgen-

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binding protein in rat epididymal cytosol, although binding to human sex hormone-binding globulin was not reduced (Danzo 1997; Wakeling et al. 1973).

Estrogenic effects have been observed in some studies of aldrin and dieldrin. Changes in dogs orally exposed to 0.15 or 0.30 mg/kg/day aldrin for 14 months prior to mating included delayed estrus, reduced libido, and lack of mammary function and development (Deichmann et al. 1971), although this study is limited by small numbers of animals. Uterine weight glycogen content were increased in immature female rats and ovariectomized mature rats that were subcutaneously treated with 1 mg/kg/day aldrin for 3 days (Chatterjee et al. 1992). The increased uterine weight was due to proliferation of the endometrium and endometrial glands in both the immature and ovariectomized mature rats. A persistent vaginal estrus was additionally induced in the treated ovariectomized rats (Chatterjee et al. 1992). Immature female rats that were intraperitoneally administered 3 mg/kg/day dieldrin for 3 days showed no changes in uterine and pituitary weights, uterine peroxidase activity, circulating thyroxine levels, or levels of follicular stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, and growth hormone in the pituitary gland (Wade et al. 1997). Dieldrin slightly decreased binding of 17β -estradiol to the estrogen receptor in extracts of uterine tissue from these rats (Wade et al. 1997). There were no significant dose-related changes in uterine weight, peroxidase activity, or estrogen or progesterone receptor binding in immature (21-day-old) mice that were intraperitoneally administered approximately 1–100 mg/kg/day dieldrin for 3 days (Ramamoorthy et al. 1997a).

In *in vitro* studies, dieldrin weakly induced proliferation of MCF-7 human breast cancer cells (an estrogenic effect) at a concentration that was an order of magnitude lower than cytotoxic levels; the potency of dieldrin relative to estradiol was 0.0001 (Soto et al. 1994, 1995). Results of other MCF-7 assays similarly showed that dieldrin was a weak inducer of cell growth or did not induce proliferation (Ramamoorthy et al. 1997a; Wade et al. 1997). Levels of estrogen and progesterone receptors in MCF-7 cells were slightly increased by dieldrin (Soto et al. 1995). Dieldrin did not significantly induce chloramphenicol acetyl transferase (CAT) activity in MCF-7 cells transiently transfected with plasmids containing estrogen-responsive 5'-promoter regions from the rat creatine kinase B and human cathepsin D genes (Ramamoorthy et al. 1997a). Binding of 17β -estradiol to the estrogen receptor in human MCF-7 cells, young rabbit uterine cells, or alligator oviduct cells was not competitively decreased by dieldrin (Danzo 1997; Ramamoorthy et al. 1997a; Vonier et al. 1996). Dieldrin had minimal estrogen receptor-mediated β -galactosidase (β -gal) activity in an estrogen-responsive reporter system in yeast (Ramamoorthy et al. 1997a).

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The overall *in vivo* and *in vitro* evidence indicates that aldrin and dieldrin may be disruptive of reproductive hormone levels in male animals and weakly estrogenic in females. Limited animal data further suggest that dieldrin is not disruptive of thyroid or pituitary hormone levels in females.

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

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Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Neurological symptoms (for example, convulsions, abnormal EEGs, hyperexcitability, restlessness) have been reported in adults and children following ingestion (accidental or intentional) of aldrin or dieldrin (Black 1974; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951). Two young children (2 and 4 years of age) experienced severe convulsions within 15 minutes after consuming an unknown quantity of a 5% solution of dieldrin; the younger child died whereas the older brother recovered completely after exhibiting evidence of liver dysfunction (Garrettson and Curley 1969). The observed effects could not be attributed solely to dieldrin because the ingested solution likely also contained solvents and emulsifiers. Among 11 people experiencing evidence of neurotoxicity associated with the consumption of wheat mixed with aldrin and lindane for a period of 6–12 months, a female infant was reported to suffer a severe convulsion, followed by death a few hours later (Gupta 1975). Since no symptoms had been observed among individuals previously consuming wheat mixed only with lindane, it was assumed that the neurotoxic effects were the result of aldrin poisoning. A 7-year-old child in this same group was thought to have developed mild mental retardation as a result of the poisoning. However, these limited oral human data do not conclusively indicate age-related differences in susceptibility to aldrin or dieldrin poisoning. Signs of neurotoxicity have also been reported in occupational studies of workers employed in the application or manufacture of aldrin or dieldrin where exposures may have been predominantly by inhalation (Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). No data were located regarding adverse effects in humans dermally exposed to aldrin or dieldrin, although both aldrin and dieldrin have been shown to pass through the skin and enter the blood of adults (Feldman and

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Maibach 1974). It is expected that children and adults would be similarly affected by dermal exposure to aldrin or dieldrin, although no data were available to substantiate this assumption.

Limited oral LD₅₀ studies indicate that newborn rats may be less sensitive than adult rats to high acute doses of dieldrin, while 2-week-old rats may be somewhat more sensitive than adults (Lu et al. 1965). In a study of adult cattle and calves given feed which was accidentally mixed with aldrin, mortality occurred exclusively among calves (Buck and Van Note 1968); however, information regarding the amount of aldrin in the feed, and relative consumption rates of calves and adult cattle were not available. No other information was available to suggest that children may be more susceptible than adults to aldrin or dieldrin.

It is generally believed that the neurotoxicity of both aldrin and dieldrin is based on alterations in synaptic activity within the central nervous system (Joy 1982; Shankland 1982). As discussed in Section 3.5.2, Mechanisms of Toxicity, recent *in vitro* and *in vivo* animal studies have shown that aldrin and dieldrin are capable of blocking the activity of the inhibitory neurotransmitter GABA, an indication that both chemicals may exert their neurotoxic effects via blockage of inhibitory activity within the brain. If neurological effects seen in response to aldrin and dieldrin exposure are dependent on maturation of the central nervous system, then immature nervous systems might be less sensitive to the effects elicited by aldrin and dieldrin.

There is conflicting information regarding the developmental toxicity of aldrin and dieldrin. In some cases, increased incidences of external malformations or skeletal anomalies were observed following oral exposure of pregnant laboratory animals to aldrin or dieldrin in mid-gestation (Chernoff et al. 1975; Ottolenghi et al. 1974); no significant malformations or anomalies were seen in other studies (Chernoff et al. 1975; Dix et al. 1977). These studies were limited in design and study details. A more consistently reported developmental effect was that of decreased postnatal survival in laboratory animals following *in utero* exposure to dieldrin (Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975, 1977). Dieldrin has been detected in human placenta, amniotic fluid, and fetal blood, and may be found in higher concentration in fetal blood than in the mother's blood (Polishuk et al. 1977b). Furthermore, dieldrin is excreted in the breast milk of nursing mothers (Schechter et al. 1989b). In an animal study designed to test whether decreased pup survival might be related to maternal postnatal care, mice born to dieldrin-exposed dams and then nursed by untreated dams exhibited similar survival rates to those nursed by their exposed dams, suggesting that decreased pup survival was correlated with *in utero*, rather than postnatal, exposure (Virgo and Bellward 1977). Intraperitoneal injection of aldrin in male rats

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resulted in plasma decreases in luteinizing hormone, follicular hormone, and testosterone, as well as decreases in testicular testosterone (Chatterjee et al. 1988a, 1988b, 1988c). In an *in vitro* study using rat interstitial testicular cells, dieldrin caused a significant increase in testosterone production (Ronco et al. 1998). There is some evidence that aldrin and dieldrin may be estrogenic. Oral administration of aldrin resulted in delayed estrous in dogs (Deichmann et al. 1971). Subcutaneous injection of aldrin resulted in a persistent vaginal estrous in ovariectomized rats (Chatterjee et al. 1992). Dieldrin slightly decreased binding of 17β -estradiol to the estrogen receptor in extracts of uterine tissue from immature female rats intraperitoneally administered dieldrin (Wade et al. 1997). Dieldrin weakly induced both cellular proliferation and slight increases in the levels of estrogen and progesterone receptors within MCF-7 human breast cancer cells (Soto et al. 1994, 1995). The overall evidence indicates that aldrin and dieldrin may be disruptive of reproductive hormone levels in male animals and weakly estrogenic in females; the developmental significance of these findings is not clear at present.

The pharmacokinetics of aldrin and dieldrin are expected to be similar in children and adults. No studies were located to indicate any age-dependent differences in absorption rates. As discussed in detail in Section 3.4, Toxicokinetics, aldrin is rapidly converted to dieldrin. Dieldrin (either absorbed or converted from aldrin) is found mainly in the liver during the first 3 hours following absorption, but is quickly distributed to fat and eliminated primarily in the feces (via the bile) with a calculated half time of elimination of 369 days. The slow elimination may play a role in the delayed onset of neurotoxicity symptoms seen in some cases of repeated exposure to relatively low doses of aldrin or dieldrin. Although there are no data to indicate age-related differences in the pharmacokinetics of aldrin or dieldrin, any age-related increases in average body fat could conceivably result in increased susceptibility. Aldrin is readily converted to dieldrin, primarily in the liver, through epoxidation catalyzed by monooxygenases (Wong and Terriere 1965). Available information indicates that cytochrome P-450 is involved (Wolff et al. 1979); however, specific enzymes have not been identified. In the rat, it has been shown that dieldrin is largely hydroxylated to 9-hydroxydieldrin by liver microsomal monooxygenases, which is then conjugated with glucuronide, to some extent, before excretion (Matthews and Matsumura 1969). Enzyme systems responsible for these metabolic pathways may operate in the very young at levels below those in adults (Calabrese 1978). This could result in increased toxic effects due to decreased rates of excretion in the young, although no supportive data are presently available.

There is some indication that aldrin and dieldrin may impair cellular immunity (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981). Aldrin- or dieldrin-induced impairment of the immature immune system

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of infants and children (Calabrese 1978) might result in a lower level of resistance to infections than adults.

There are no biomarkers of exposure or effect for aldrin or dieldrin that are unique to children or that have been validated in children or adults exposed as children. No studies were located regarding interactions of aldrin or dieldrin with other chemicals in children. Limited data concerning interactions with other chemicals in adults (see Section 3.9, Interactions With Other Chemicals) did not suggest that such interactions would be different in children. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to aldrin or dieldrin, reducing body burden, or interfering with the mechanism of action for toxic effects.

There is no information regarding possible transgenerational effects of aldrin or dieldrin exposure in humans, and limited animal data are inconclusive. Reduced meiotic pairing in dividing spermatocytes of mice orally administered single doses of aldrin indicates that aldrin can cross the blood/testis barrier (Rani and Reddy 1986). However, the mostly negative results of dominant lethal assays (Dean et al. 1975; Epstein et al. 1972) indicate little potential for significant reactions with DNA.

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

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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 aldrin/dieldrin are discussed in Section 3.8.1.

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

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3.8.1 Biomarkers Used to Identify or Quantify Exposure to Aldrin

Exposure to aldrin and dieldrin is measured almost exclusively by determining the level of dieldrin in the blood. Because aldrin is rapidly converted to dieldrin in the body, the detection of aldrin in body tissues is rare. Blood levels of dieldrin are specific for aldrin and dieldrin. Dieldrin levels measured in blood samples of members of the general population in the United States between 1976 and 1980 in the National Health and Nutrition Examination Survey (NHANES II) were found to be approximately 1.4 ppb (Murphy and Harvey 1985; Stehr-Green 1989). It is likely that current baseline blood levels in the general population would be lower.

Detection of dieldrin in the blood may indicate either recent or past exposure to aldrin or dieldrin. Dieldrin would be detected in the blood either immediately after inhalation, oral, or dermal absorption or as stores of dieldrin are slowly released from adipose tissue. In humans, dieldrin has a relatively long half-life in the body (Hunter and Robinson 1967; Hunter et al. 1969; Jager 1970). Hunter et al. (1969) calculated a mean half-life of 369 days, and Jager (1970) estimated a mean half life of 266 days. Thus, exposures of sufficient magnitude occurring several years earlier may still be detected in the blood. A GABA radioreceptor assay has been developed that could serve as a sensitive biomarker for exposure to dieldrin (Saleh et al. 1993). GABA (gamma aminobutyric acid) is the major inhibitory neurotransmitter in the central nervous system (see Section 3.5.2). Although potentially useful for reproducibly detecting nanogram levels of dieldrin in minute blood samples (0.1 mL), this method is not specific for aldrin and dieldrin because it would also detect other nervous system toxicants with high specific binding affinity to the chloride channel of GABA_A receptor-ionophore sites (e.g., endosulfan and other cyclodiene insecticides, hexachlorocyclohexanes, pyrethroids, bicycphosphates, and bicycloorthocarboxylate insecticides).

Because dieldrin rapidly redistributes to adipose tissue, the highest levels of dieldrin are found in fat (except immediately after exposure). Thus, fat levels of dieldrin are also a good source for identifying exposure to aldrin or dieldrin. However, obtaining fat samples requires at least minor surgery; therefore, this method is not commonly used. The 1982 Human Adipose Tissue Survey found dieldrin present in adipose tissue at a mean concentration of 458 ppb. It is likely that current levels would be lower.

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Because of its high fat content, breast-milk levels of dieldrin may give some information about prior exposures and accumulation of dieldrin in fatty tissues. Breast-milk levels of dieldrin may be lowered by frequent nursing (Ackerman 1980).

Following relatively long-term exposure to constant levels of aldrin or dieldrin, a steady state of body levels of dieldrin is achieved (Hunter and Robinson 1967; Hunter et al. 1969). Thus, when repeated and regular exposure is known to have occurred, the exposure level may be calculated from blood or fat levels using the equations described by Hunter et al. (1969) (exposure level equals the blood level divided by 0.086 or the fat level divided by 0.0185).

The metabolite of dieldrin, 9-hydroxydieldrin, has been detected in human feces (Richardson and Robinson 1971). However, this metabolite has not been routinely used to identify or quantify exposure to aldrin or dieldrin.

Prior to the use of blood levels to monitor exposure to aldrin and dieldrin, EEGs were used to monitor workers for possible overexposure to these substances (Hoogendam et al. 1962, 1965; Jager 1970). However, this technique is most reliable when a baseline EEG recording from each subject has been obtained prior to exposure. Also, any centrally acting neuroexcitatory substance could produce EEG changes similar to those produced by aldrin or dieldrin, limiting the specificity of this technique.

3.8.2 Biomarkers Used to Characterize Effects Caused by Aldrin

Although none of the following effects are specific for aldrin or dieldrin, measurement of a number of parameters may provide useful information when exposure to aldrin or dieldrin is suspected. In animals, microsomal enzyme induction is one of the earliest and most sensitive effects caused by organochlorine pesticides such as aldrin and dieldrin (Wright et al. 1972). Indicators that have been used to try to assess microsomal enzyme induction in humans following exposure to aldrin or dieldrin include urinary levels of D-glucaric acid and the ratio of urinary 6- β -hydroxycortisol to 17-hydroxy-corticosteroids (Jager 1970; Morgan and Roan 1974). Other substances such as barbiturates, phenytoin, chlorbutanol, aminopyrine, phenylbutazone, progesterone, and contraceptive steroids as well as other organochlorine pesticides also cause microsomal enzyme induction and cause changes in these parameters (Morgan and Roan 1974).

Central nervous system excitation culminating in convulsions is, in some cases, the only symptom of aldrin or dieldrin intoxication. EEG changes in occupationally exposed workers have been monitored in

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the past in an attempt to detect central nervous system changes prior to the onset of convulsions (Jager 1970). Characteristic changes include bilateral synchronous spikes, spike and wave complexes, and slow theta waves (Avar and Czegledi-Janko 1970; Garrettson and Curley 1969; Hoogendam et al. 1962, 1965; Jager 1970; Kazantzis et al. 1964; Spiotta 1951); however, these changes are not specific for aldrin or dieldrin overexposure and may be produced by several neuroexcitatory substances. A good correlation between blood levels of dieldrin and central nervous system toxicity has been established (Brown et al. 1964; Jager 1970). Thus, blood levels in excess of 0.2 mg/L are frequently associated with adverse central nervous system effects.

Studies of immune activity have not routinely been done in humans to assess immunosuppression caused by aldrin and dieldrin, but studies indicate that measurements of cytotoxic T-lymphocyte activity or of macrophage-antigen processing may be good indicators of the adverse effects of aldrin and dieldrin on the immune system (Loose 1982; Loose et al. 1981). However, such tests would not be specific for aldrin- or dieldrin-mediated immunosuppression.

Another potential adverse effect of aldrin and dieldrin on the immune system that has been reported only twice is the induction of immunohemolytic anemia. A Coomb's test can be used to measure the ability of the subject's serum to cause a positive immune reaction with dieldrin-coated red blood cells (Hamilton et al. 1978).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Limited information is available regarding the influence of other chemicals on the toxicity of aldrin and dieldrin. Administration of the pesticides Aramite, DDT, and methoxychlor with aldrin to rats did not cause an increase over the incidence of cancer observed in the presence of aldrin alone (Deichmann et al. 1967). However, no increase in cancer incidence was observed with any of these substances administered singly. Thus, it is unclear whether the conditions of this assay were adequate to detect an additive or synergistic effect if it existed.

Induction of microsomal enzymes by ochratoxin, a mycotoxin, was observed to enhance conversion of aldrin to dieldrin (Farb et al. 1973). Also, induction of microsomal enzymes by the pesticides hexachlorobenzene and DDT caused a decrease in storage in adipose tissue and/or an increased rate of excretion of the metabolites of aldrin and dieldrin in the feces and urine (Clark et al. 1981; Street and Chadwick 1967). However, these studies did not present information regarding the effects of these

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interactions on the toxicity of aldrin or dieldrin. Thus, it is unknown whether the changes in the pharmacokinetics of aldrin and dieldrin affected their toxicity.

The ability of chlorinated hydrocarbons to disrupt estrogen homeostasis, by up-regulating selected gene transcription, has been hypothesized to be responsible for their oncogenic effects. Neither aldrin nor dieldrin showed evidence of estrogenicity as evidenced by lack of induction of transcriptional activation of an estrogen-responsive reported gene in transfected HeLa cells (Tully et al. 2000). There is evidence of a synergistic estrogenic effect of dieldrin and toxaphene on the bone mass density in rats. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 $\mu\text{mol/kg/day}$, 5 days/week, for 9 months, when administered with toxaphene (30 $\mu\text{mol toxaphene/kg/day}$ and 7.5 $\mu\text{mol/kg/day}$), bone mass density was significantly increased (Syversen et al. 2000). In contrast, the results of several estrogen-responsive assays in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based reporter gene assays, indicate that the activities of both dieldrin and toxaphene, as well as a binary mixture of the two were minimally estrogenic (Ramamoorthy et al. 1997a).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

A susceptible population will exhibit a different or enhanced response to aldrin or dieldrin than will most persons exposed to the same level of aldrin or dieldrin in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 6.7, "Populations With Potentially High Exposure."

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Review of the literature regarding toxic effects of aldrin and dieldrin did not reveal any populations that are known to be unusually sensitive to aldrin or dieldrin. However, some populations that may potentially demonstrate unusual sensitivity include the very young with immature hepatic detoxification systems, persons with impaired liver function, and persons with impaired immune function.

Aldrin and dieldrin are metabolized in the liver primarily by microsomal mixed-function oxidases. To some extent, the oxidized metabolites 9-hydroxydieldrin and 6,7-*trans*-dihydroxydihydroaldrin are conjugated with glucuronide prior to excretion (Matthews and Matsumura 1969). In the very young, the microsomal enzyme system and the enzyme systems responsible for glucuronide conjugation operate at levels below those in adults (Calabrese 1978). Thus, the very young may experience increased toxic effects due to the decreased rates of excretion. Similarly, persons with impaired liver function may also experience increased toxicity because of their limited ability to fully metabolize aldrin or dieldrin. The suggestive evidence of bioconcentration of dieldrin in the fetus (Polishuk et al. 1977b) and the possibility of consumption of contaminated breast milk by infants indicate that these groups have an increased risk, because they may have higher body burdens of these pesticides than adults.

Persons suffering from compromised immune function may demonstrate an increased susceptibility to infections because of the ability of aldrin and dieldrin to impair cellular immunity (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981). Infants and children may also be susceptible because the human immune system does not reach maturity until 10–12 years of age (Calabrese 1978).

Although aldrin and dieldrin cause central nervous system excitation leading, in some cases, to convulsions, no evidence of an enhanced susceptibility to the excitatory effects of aldrin or dieldrin in persons with preexisting anomalous EEGs was observed (Jager 1970).

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3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to aldrin/dieldrin. 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 aldrin/dieldrin. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were located that provide specific information about treatment following exposures to aldrin/dieldrin.

3.11.1 Reducing Peak Absorption Following Exposure

General recommendations reported for reducing absorption following acute high-dose exposure to aldrin and dieldrin include removing the individual from the source of exposure and decontaminating exposed skin using alcohol or soap and water (HSDB 2001a, 2001b). Dermal absorption is fairly efficient, so decontamination attempts should be accomplished quickly. An initial soap and water wash, followed by an alcohol wash, followed by a second soap and water wash have been suggested for decontaminating skin and hair after aldrin or dieldrin exposure (Hall and Rumack 1992), but it is unclear whether this represents any true improvement over thorough washing with soap and water. A number of strategies have been suggested to minimize absorption from the gastrointestinal tract. Ipecac-induced emesis has been suggested for gastric emptying, although there is a risk of pulmonary aspiration of gastric contents and resultant pneumonitis from hydrocarbon solvents due to potential early onset of unconsciousness or convulsions (HSDB 2001a, 2001b). When emesis is contraindicated, gastric lavage has been suggested as an alternative method for emptying the stomach if ingestion was recent (within 60–90 minutes) (Klaassen 1990). A cuffed endotracheal tube is recommended if hydrocarbon solvents were also ingested. Since activated charcoal can adsorb aldrin and dieldrin, it has also been commonly used as a method for reducing intestinal uptake following ingestion (HSDB 2001a, 2001b). Another method for reducing absorption is the use of a cathartic; activated charcoal is frequently given mixed as a slurry with one of the saline cathartics or sorbitol (Hall and Rumack 1992; HSDB 2001a, 2001b). The mechanism by which aldrin and dieldrin are absorbed from the gastrointestinal tract is unknown; however, their highly lipophilic nature suggests dissolution in the cell membrane.

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3.11.2 Reducing Body Burden

There are no proven or accepted strategies for reducing the body burden of dieldrin. A majority of dieldrin's final metabolites are conjugated with glucuronic acid in the liver; most excretion is in the bile, with smaller amounts in the urine (Richardson and Robinson 1971). Fecal metabolites have been measured but not quantitatively compared with metabolites secreted through the bile duct; thus, it is unclear whether enterohepatic recirculation occurs. However, some biliary metabolites, such as 9-hydroxydieldrin glucuronide, seem to be deconjugated by gut microfloral glucuronidases since they are excreted in the feces in aglycone form (Chipman and Walker 1979; Hutson 1976). Deconjugation frequently favors enterohepatic recirculation (Sipes and Gandolfi 1991). If significant enterohepatic recirculation could be demonstrated, methods to interfere with the reabsorption from the gut into the systemic circulation might be effective in accelerating the excretion of aldrin and dieldrin metabolites. There are several possible strategies for reducing intestinal resorption of bile excretions; the simplest is repeated doses of activated charcoal (without cathartics) (Levy 1982). Another strategy, which has been effective in experiments with another lipophilic xenobiotic, chlordecone, is the oral administration of the anion exchange resin, cholestyramine (Boylan et al. 1978). However, its effectiveness with aldrin or dieldrin poisoning is unknown.

The pharmacokinetics of aldrin and dieldrin are not completely understood. Once absorbed by the gastrointestinal tract, these pesticides are transported to the liver via the portal vein (Heath and Vandekar 1964). They are found mainly in the liver for the first 3 hours but have also been found in the blood, lymph, kidneys, fetus, and adipose tissue (Heath and Vandekar 1964; Iatropoulos et al. 1975). The interval immediately after absorption may be a window of opportunity for removing the xenobiotic from the circulation before it partitions into adipose tissue. Potential strategies include hemodialysis and hemoperfusion (Klaassen 1990). However, the large molecular weights and lipophilic nature of these compounds argues against effective removal by hemodialysis. Another potential strategy for removal would be to attempt to increase dieldrin excretion by enhancing its metabolism. Dieldrin's metabolism to 9-hydroxydieldrin and excretion are substantially greater in male than in female rats (Matthews et al. 1971), indicating that a specific form of cytochrome P-450 may be more prevalent in male rats. If the specific form(s) of cytochrome P-450 responsible for the more rapid metabolism and excretion could be identified, specific inducers could be used to speed dieldrin's excretion in humans (Sipes and Gandolfi 1991). Long-term storage is in adipose tissue, primarily in the form of dieldrin (Hutson 1976), but initially some residues are also found in the liver and brain. It is unclear whether detrimental effects would be expected from this storage, although there is equilibrium between dieldrin in fat and blood.

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Release of dieldrin from fat has not resulted in a significant health hazard in people with low body burdens of dieldrin (Hunter and Robinson 1968).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism for aldrin and dieldrin toxicity is not equally well understood for all target organs. The central nervous system is the most sensitive target for acute toxicity; aldrin and dieldrin are stimulants that can cause excitation, convulsions, and seizures (Wagner and Greene 1978; Woolley et al. 1985). There are multiple theories about the mechanism of action; it is unclear whether dieldrin facilitates excitatory neurotransmitter release or interferes with inhibitory neurotransmitter action.

One hypothesis is that the majority of dieldrin's neurotoxicity is due to its interactions with a receptor for the inhibitory neurotransmitter GABA (see Section 3.5.2). Dieldrin is thought to be a competitive inhibitor of binding to the GABA_A receptor t-butylbicyclophosphorothionate (TBPS) binding site (Lawrence and Casida 1984), and *in vitro* experiments have shown that it blocks the chloride channel in GABA_A- receptor complex (Abalis et al. 1986; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Lawrence and Casida 1984; Obata et al. 1988). Administration of benzodiazepines, which act at the GABA receptor to potentiate GABA binding (Bloom 1990), has been suggested as a method for treating aldrin- or dieldrin-induced seizures (HSDB 2001a, 2001b). This standard method of reducing central nervous system excitation might be acting at the same molecular site as dieldrin and, thus, specifically interfering with its mechanism of action. If GABA_A- receptor interactions are the major mechanism of central nervous system toxicity, potential research approaches for interfering with the mechanism of action would include the use of agonists such as muscimol or GABA to compete for binding at the receptor, inhibitors of GABA re-uptake such as guvacine or nipecotic acid, and blocking GABA catabolism with aminooxyacetic acid (Bloom 1990). Although benzodiazepines are safer, barbiturates also act at the GABA receptor to potentiate GABA binding and might reduce the central nervous system toxicity of dieldrin (Bloom 1990). Phenytoin has been used for seizures refractory to treatment with diazepam or barbiturate (Hall and Rumack 1992).

Adrenergic β -blockers were used effectively to control blood pressure in a dieldrin-poisoned individual (Black 1974), suggesting that such treatment may be effective in other dieldrin-poisonings where elevated blood pressure occurs.

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A potential investigative strategy to reduce aldrin toxicity might be to channel aldrin metabolism to the liver where it is more likely to immediately continue to be metabolized to less toxic metabolites. While most conversion of aldrin to dieldrin occurs in the liver, some aldrin is converted to dieldrin outside of the liver. Since further metabolism and conjugation of dieldrin for excretion take place mainly in the liver, any dieldrin created outside the liver has a greater chance of causing toxic effects. Aldrin is converted to dieldrin outside the liver by the more ubiquitous prostaglandin endoperoxidase synthetase. A possible method for reducing the extrahepatic transformation of aldrin to dieldrin would be to inhibit the activity of prostaglandin endoperoxidase synthetase with the cyclooxygenase inhibitors aspirin and indomethacin. Also, ascorbic acid supplementation during dieldrin treatment has been observed to partially reduce the hepatic and renal toxicity of dieldrin treatment in experimental animals (Bandyopadhyay et al. 1982b). However, the reproducibility, effectiveness in humans, and potential mechanism for the reduction in toxicity are unknown.

Mitigation strategies that may be developed in the future for other lipophilic pesticides should be considered for their applicability to aldrin and dieldrin.

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 aldrin/dieldrin 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 aldrin/dieldrin.

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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3.12.1 Existing Information on Health Effects of Aldrin

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to aldrin/dieldrin are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of aldrin. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Populations in areas that contain hazardous waste sites may be exposed to aldrin or dieldrin for brief periods. Exposure would most likely occur by the inhalation or oral routes, but dermal exposure is also possible. There are acute-duration oral exposure data in humans from cases of accidental or intentional poisonings that indicate that the central nervous system is a major target organ of aldrin and dieldrin toxicity by the oral route. Convulsions have been observed following ingestion of very high concentrations of aldrin and dieldrin (Black 1974; Garrettson and Curley 1969; Spiotta 1951). Also, acute oral exposure in humans has been reported to cause renal toxicity (Spiotta 1951). Renal toxicity has not been reported in studies in animals after acute-duration ingestion of high concentrations of aldrin or dieldrin; however, the number of studies examining systemic effects associated with acute-duration exposures is quite limited. Studies in laboratory animals examining the effects of ingestion of aldrin or dieldrin have supported the conclusion that the nervous system is a major target organ of aldrin and dieldrin toxicity (Burt 1975; Carlson and Rosellini 1987; Mehrotra et al. 1989; Treon et al. 1953a; Wagner and Greene 1978; Woolley et al. 1985). In such studies, convulsions as well as impaired responding in operant behavioral paradigms were reported. In addition, immune suppression (Krzyszyniak et al. 1985; Loose et al. 1981), developmental toxicity (Al-Hachim 1971; Ottolenghi et al. 1974), and adaptive changes in the liver (Wright et al. 1972) have been observed in acutely exposed animals. Results of these studies indicate that the immune system may be the most sensitive target organ for the effects of brief oral exposures to aldrin or dieldrin. An acute-duration oral MRL was not derived

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Figure 3-5. Existing Information on Health Effects of Aldrin/Dieldrin

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

Human

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

Animal

- Existing Studies

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for dieldrin because the database indicates that the most sensitive target of toxicity is the immune system in rats administered acute doses of dieldrin (Loose et al. 1981) and there are no data to suggest that the immune system may be a target of toxicity in humans following ingestion of dieldrin. An acute-duration oral MRL was derived for aldrin based on a neurological effect (altered electroconvulsive shock threshold) and decreased body weight in offspring of treated mice (Al-Hachim 1971).

No information is available regarding acute-duration inhalation exposure to aldrin or dieldrin in humans, and extremely limited information is available from studies in animals (Treon et al. 1957b). Although the volatility of aldrin and dieldrin is quite low and levels in the atmosphere are expected to be quite low, absorption of these compounds by the lungs occurs to a significant extent (Mehendale and El-Bassiouni 1975). Toxicokinetic data do not indicate that dissimilar target organs would be affected as a result of inhalation exposure to aldrin or dieldrin. Thus, additional studies examining the effects of acute inhalation exposure to saturating concentrations of aldrin or dieldrin would be helpful in determining whether toxic effects would occur as a result of brief inhalation exposure.

Information regarding the acute effects of dermal exposure of aldrin or dieldrin is limited to lethality studies in animals (Gaines 1960; Treon et al. 1953a). Dermal exposure to aldrin and dieldrin is possible in contaminated soil, and toxicokinetic studies indicate that dermally applied aldrin and dieldrin are absorbed (Feldmann and Maibach 1974; Graham et al. 1987; Witherup et al. 1961). Toxicokinetic data do not suggest that dissimilar target organs would be affected as a result of dermal exposure. Thus, studies examining the effects of acute dermal exposure to aldrin or dieldrin would be useful.

Intermediate-Duration Exposure. Few reports were located regarding effects in humans after intermediate-duration exposure to aldrin or dieldrin by any route. In one study, exposure was by the oral route (Gupta 1975). In two other studies, exposure most likely occurred as the result of combined inhalation and dermal (and possibly oral) exposures (Fletcher et al. 1959; Patel and Rao 1958). These studies showed that the nervous system is a major target organ in humans after intermediate-duration exposures. Studies in laboratory animals confirm this observation (Burt 1975; Mehrotra et al. 1988; Smith et al. 1976; Treon et al. 1951b; Wagner and Greene 1978). Other targets identified in intermediate-duration oral studies in animals include the immune system (Loose 1982), the developing neonate (Al-Hachim 1971; Deichmann et al. 1971; Harr et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975), the reproductive system (Treon et al. 1954a; Virgo and Bellward 1975, 1977), the kidney (Ahmed et al. 1986a; Bandyopadhyay et al. 1982b), and the liver (Ahmed et al. 1986a; Shakoori et al. 1982; Treon et al. 1951a, 1951b). An intermediate-duration oral MRL for aldrin was not derived due to lack of

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suitable effect levels. Intermediate-duration studies of aldrin are essentially limited to studies that found frank neurotoxic effects (e.g., tremors, convulsions) at the lowest tested doses; LOAELs for serious end points are inappropriate for deriving MRLs. An intermediate-duration oral MRL was developed for dieldrin based on a NOAEL for impaired learning in monkeys (Smith et al. 1976).

No data were located regarding intermediate-duration inhalation exposures in animals, and human exposure levels were not quantified. Therefore, no intermediate-duration inhalation MRL was derived for either aldrin or dieldrin. Also, only limited information was located regarding lethality, neurological effects, and dermal effects after intermediate-duration dermal exposures (Bundren et al. 1952; Treon et al. 1953a). As noted above, absorption occurs by both the inhalation and dermal routes, and toxicokinetic data indicate that similar target organs would be affected following exposure to either route; thus, additional studies examining the effects of aldrin and dieldrin by the inhalation and dermal routes would be helpful.

Chronic-Duration Exposure and Cancer. A number of epidemiological studies have been conducted on workers exposed chronically to aldrin and dieldrin (de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). In these studies, doses are usually not well quantified, and concomitant inhalation, dermal, and possibly oral exposures have occurred. Follow-up and expansion of previously identified worker cohorts could provide additional useful information on chronic effects. It is difficult to recommend new populations for future epidemiological studies of effects caused by chronic-duration inhalation, oral, or dermal exposure because (1) these agents have not been manufactured in the United States since 1974, and (2) workers who have been involved in the use of the remaining stocks of these agents are likely to have been also exposed to a variety of other pesticides. Data from the existing epidemiological studies indicate that the nervous system is a major target organ for chronic inhalation, dermal, and possibly oral exposures in humans (Hoogendam et al. 1962, 1965; Jager 1970; Sandifer et al. 1981). Chronic oral studies in animals also indicate that the nervous system is a major target organ (Fitzhugh et al. 1964; Harr et al. 1970; Kitselman 1953; NCI 1978a, 1978b; Walker et al. 1969), but additionally demonstrate adverse effects of aldrin and dieldrin on the kidney (Deichmann et al. 1967; Fitzhugh et al. 1964; Harr et al. 1970; Treon et al. 1955b) and liver (Fitzhugh et al. 1964; Kitselman 1953; NCI 1978a; Thorpe and Walker 1973; Treon et al. 1955b; Walker et al. 1969). The liver was the most sensitive target of toxicity in chronic-duration studies and hepatic effect levels in rats (Fitzhugh et al. 1964; Walker et al. 1969) were used as the basis of chronic oral MRLs for both aldrin and dieldrin. No chronic animal studies were located for the inhalation

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route; only one animal study was located examining the effects of chronic dermal exposure (Witherup et al. 1961). Studies examining the effects caused by low-level chronic exposures by both the inhalation and oral routes would be valuable for determining whether such exposures could cause toxicity in populations exposed to aldrin and dieldrin near hazardous waste sites for extended periods.

Epidemiological studies examining cancer mortality in two series of workers exposed to aldrin and dieldrin provide no conclusive evidence of carcinogenicity in humans (Amoateng-Adjepong et al. 1995; Brown 1992; de Jong 1991; de Jong et al. 1997; Ditraglia et al. 1981; Jager 1970; Ribbens 1985; van Raalte 1977). Possible increases in liver, biliary, and rectal cancer were suggested in some of the later studies, but additional follow-up of these populations is needed to establish the effects. Several studies in mice have shown that oral exposure to aldrin or dieldrin caused an increase in the incidence of malignant liver tumors (Davis and Fitzhugh 1962; Meierhenry et al. 1983; NCI 1978a; Tennekkes et al. 1981; Thorpe and Walker 1973; Walker et al. 1972). However, studies in rats (Cabral et al. 1979; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; NCI 1978b; Walker et al. 1969) have been either equivocal or flawed. Although aldrin and dieldrin are generally regarded as mouse-specific carcinogens, additional studies by the oral route in a species other than the mouse would help to clarify the carcinogenic potential. If species differences in the carcinogenic potential of these chemicals are verified, additional studies related to the mechanism of species specificity would be informative for predicting human susceptibility. Also, studies by routes other than oral would clarify whether inhalation or dermal exposures could also cause cancer. Toxicokinetic data do not indicate that any different response would be expected following exposures by these routes. Accumulating evidence indicates that aldrin and dieldrin are nongenotoxic tumor promoters acting through species-specific susceptibility of the mouse to induction of oxidative stress and inhibition of gap junctional communication (Jones et al. 1985; Klaunig and Ruch 1987; Klaunig et al. 1990, 1995, 1998; Kurata et al. 1982; Ruch and Klaunig 1986; Trosko et al. 1987; van Ravenzwaay and Kunz 1988; Wade et al. 1986; Zhong-Xiang et al. 1986). Additional mechanistic studies would be useful for better understanding the apparent species-specific carcinogenicity of aldrin and dieldrin in animals and relating these findings to humans.

Genotoxicity. There were only two studies on *in vivo* exposure of humans to aldrin or dieldrin. Both were limited due to concomitant exposure to other pesticides and inconclusive route and dose of exposure (Dean et al. 1975; Dulout et al. 1985). Additional genotoxicity assays using tissues from humans exposed *in vivo* would be useful if these were accompanied by adequate quantitative exposure measurements.

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Numerous studies investigating the *in vitro* genotoxic effects of aldrin or dieldrin were available in the current literature (Ahmed et al. 1977a, 1977b; Crebelli et al. 1986; Dean et al. 1975; De Flora et al. 1984, 1989; Ennever and Rosenkranz 1986; Galloway et al. 1987; Glatt et al. 1983; Haworth et al. 1983; Klaunig et al. 1984; Majumdar et al. 1976, 1977; Marshall et al. 1976; Probst et al. 1981; Sandhu et al. 1989). They provide no conclusive evidence for genotoxic effects, particularly for direct action on the DNA molecule. The positive studies are primarily from the same research group, and while differences in results could be due to different concentrations used, different strains of test species, or other laboratory protocol differences, it would be useful to have independent confirmation or refutation of these studies using adequate techniques (especially in mammalian systems). Results of such studies would provide useful information on potential genotoxic effects in humans.

Reproductive Toxicity. One study in humans attempted to correlate blood levels of dieldrin with premature labor or spontaneous abortions in pregnant women (Saxena et al. 1980); however, this study failed to establish causality. No other human data regarding reproductive effects of aldrin or dieldrin were located. Studies in laboratory animals exposed orally to aldrin or dieldrin present conflicting data on the ability of these agents to cause decreased fertility (Dean et al. 1975; Epstein et al. 1972; Good and Ware 1969; Harr et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975). Some of these studies are limited. Additional studies examining the effects of oral exposure to aldrin or dieldrin would be helpful for clarifying this issue. No studies in animals were found regarding reproductive effects of exposure by the inhalation or dermal routes. Thus, studies examining effects on reproduction by inhalation or dermal exposure would also be useful. Animal studies performed using intraperitoneal injection of aldrin demonstrate adverse effects on male reproductive capacity (Chatterjee et al. 1988a, 1988b, 1988c). Additional studies examining fertility in animals exposed by the oral, dermal, or inhalation routes would be helpful in determining whether the effects are specific to intraperitoneal injection.

Developmental Toxicity. No human studies are available on developmental effects for any exposure route. Similarly, no studies are available for animals exposed via the inhalation route, and negligible information is available for animals exposed via the dermal route (Glastonbury et al. 1987). Several studies report a decrease in postnatal survival for offspring of dogs, rats, and mice exposed to aldrin or dieldrin by the oral route (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975), although many of these studies are flawed. Additional studies assessing postnatal survival after maternal exposure by all three routes would be helpful. Also, additional studies attempting to clarify the mechanism of the postnatal mortality would be informative. Adverse developmental effects have been observed following maternal oral exposure to aldrin (Al-Hachim 1971),

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and an acute-duration oral MRL for aldrin was derived based on the decrease in pup body weight and increased electroconvulsive shock threshold of pups observed in this study. Teratogenic effects have been observed in only a limited number of the studies performed to assess developmental toxicity (Ottolenghi et al. 1974); additional well-conducted studies examining this parameter may help clarify this issue.

Immunotoxicity. Isolated cases of dieldrin-induced immunohemolytic anemia have been reported in humans exposed by the inhalation, oral, and dermal routes (Hamilton et al. 1978; Muirhead et al. 1959). However, in epidemiological studies of workers exposed to these substances, similar effects have not been reported (de Jong 1991; Jager 1970). Thus, this effect may be idiosyncratic in nature. As large populations exposed to aldrin or dieldrin may be difficult to find, this response may be better studied in one of the strains of mice known to have a propensity for developing autoimmune diseases. Studies in animals via the oral (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981) and intraperitoneal routes (Bernier et al. 1987, 1988; Fournier et al. 1986, 1988; Hugo et al. 1988a, 1988b; Jolicoeur et al. 1988; Krzystyniak et al. 1986, 1987, 1989) indicate that aldrin and dieldrin may be immunosuppressive agents, at least during acute- and short intermediate-duration exposures. These studies have also examined the mechanism for the immune suppression. However, additional studies examining potential longer-term effects on the immune system by all three routes as well as short-term effects by the inhalation and dermal routes would be important for estimating human susceptibility for populations exposed for varying amounts of time at hazardous waste sites.

Neurotoxicity. Numerous human studies across all three routes indicate that the central nervous system is a major target of aldrin and dieldrin toxicity (Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958; Spiotta 1951). Studies in animals tend to support these findings, although studies in animals have been primarily by the oral route (Burt 1975; Mehrotra et al. 1989; NCI 1978a, 1978b; Smith et al. 1976; Treon et al. 1951b, 1953a; Wagner and Greene 1978; Walker et al. 1969; Woolley et al. 1985). An intermediate-duration oral MRL was developed for dieldrin based on impaired learning in monkeys (Smith et al. 1976). Both *in vitro* and *in vivo* studies in animals have provided a well-defined mechanism of action for neuroexcitation (Abalis et al. 1986; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Lawrence and Casida 1984; Matsumura and Ghiasuddin 1983; Obata et al. 1988; Shankland 1982). Reports of human intoxication have provided information regarding blood levels that may be associated with the production of severe neurotoxic symptoms (convulsions, muscle jerks) (Brown et al. 1964; Jager 1970). However, information regarding the mechanism of action suggests that more subtle adverse

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effects of neurologic origin may be produced by aldrin and dieldrin. Thus, studies focusing on less severe forms of neurotoxicity (i.e., affective changes) may be informative. Studies in animals using behavioral paradigms designed to detect such changes or studies in persons exposed to aldrin or dieldrin would be useful for further defining these effects and the exposure levels associated with them.

Epidemiological and Human Dosimetry Studies. Human studies on aldrin and dieldrin consist of either case reports of accidental or intentional poisonings (Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958; Spiotta 1951) or epidemiological studies of workers employed in the manufacture or application of these agents (de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). Exposures in the case reports are virtually all oral, whereas exposures in the epidemiological studies are mainly inhalation and dermal, with very slight potential for accidental oral intake. Additional follow-up of cohorts from previously conducted epidemiological studies would be the best approach for obtaining additional human data. Locating new populations for future epidemiological studies is likely to be difficult because aldrin and dieldrin have not been manufactured in the United States since 1974 and the use of these agents has been restricted to termite extermination. Also, because aldrin and dieldrin have not been imported into the United States since 1985, use has been limited to the use of remaining pre-1985 stocks. Thus, at the present time, very few persons are likely to be exposed to aldrin or dieldrin. The only subgroups of the population with possible exposure are termite exterminators and persons who have recently had their homes exterminated. If such groups are located, information regarding immunologic, reproductive, and developmental effects and correlation of these effects with blood levels of dieldrin associated with exposure would be useful.

Biomarkers of Exposure and Effect.

Exposure. Exposure to aldrin and dieldrin is currently measured almost exclusively by determining the level of dieldrin in the blood (Jager 1970). This measure is specific for both aldrin and dieldrin. However, because aldrin is rapidly converted to dieldrin in the body (Wong and Terriere 1965), it is impossible to determine which of the two substances caused the blood levels of dieldrin to rise. Because dieldrin has a long half-life of elimination in humans (Hunter and Robinson 1967; Hunter et al. 1969; Jager 1970), measurement of dieldrin levels in the blood does not give any information about whether an acute-, intermediate-, or chronic-term exposure has occurred, whether such exposures have occurred recently, or whether a substantial period of time has elapsed since exposure occurred. The sensitivity of

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this biomarker of exposure appears to be sufficient to measure even background levels in the population; thus, no new biomarkers of exposure appear to be needed at this time.

Effect. The central nervous system excitation resulting from aldrin or dieldrin exposure can be monitored, to a great extent, by monitoring EEG changes (Hoogendam et al. 1962, 1965; Jager 1970). Characteristic changes include bilateral synchronous spikes, spike and wave complexes, and slow theta and delta waves (Avar and Czegledi-Janko 1970; Garrettson and Curley 1969; Hoogendam et al. 1962, 1965; Jager 1970; Kazantzis et al. 1964; Spiotta 1951). However, similar changes may be recorded in cases of central nervous system excitation caused by other agents. Thus, this measure is not specific for aldrin- or dieldrin-induced neurotoxicity. Blood levels of dieldrin have been correlated with adverse neurological effects caused by aldrin and dieldrin (Brown et al. 1964; Jager 1970). Such a measurement may also be used to monitor for adverse neurotoxic effects caused by these agents. Also, as understanding of the fundamental mechanism by which aldrin and dieldrin cause central nervous system excitation develops, tests may be developed to specifically monitor for the underlying neurological changes caused by aldrin and dieldrin.

No tests specific for aldrin- or dieldrin-induced toxic effects on the liver or kidney exist; however, standard liver and kidney function tests should be able to identify the hepatic or renal toxicity that is produced. Microsomal enzyme induction may be measured by determining parameters such as urinary levels of D-glucaric acid and the ratio of urinary 6- β -hydroxycortisol to 17-hydroxycorticosteroids. However, these tests are not specific for aldrin or dieldrin. Immune suppression of the type produced by aldrin or dieldrin may be detected by challenge with a T-lymphocyte-dependent antigen; however, this test also is not specific for aldrin or dieldrin.

Absorption, Distribution, Metabolism, and Excretion. Human and animal data are available that show that aldrin and dieldrin are absorbed after exposure via all three routes (Feldmann and Maibach 1974; Graham et al. 1987; Hayes 1974a; Heath and Vandekar 1964; Hunter and Robinson 1967; Hunter et al. 1969; Mehendale and El-Bassiouni 1975; Stacey and Tatum 1985). Quantitative data on the absorption of aldrin and dieldrin in humans and animals following exposure via all routes are limited. Animal studies indicate that aldrin and dieldrin are absorbed rather quickly and that the amount absorbed is proportional to the dose applied for the oral and dermal routes (Graham et al. 1987; Heath and Vandekar 1964; Iatropoulos et al. 1975). However, data concerning absorption rates are needed for all three routes. Because of the limited number of absorption studies for all three routes in general, it would

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be helpful to have additional quantitative data in animals that might serve as a basis for estimates of absorption in humans.

No studies were located regarding distribution following inhalation exposure to aldrin or dieldrin in humans or animals. Data on distribution via the dermal route for humans were not located. However, numerous data exist that describe distribution after oral administration of aldrin or dieldrin (Adeshina and Todd 1990; Ahmad et al. 1988; Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974a; Holt et al. 1986; Hunter and Robinson 1967, 1968; Hunter et al. 1969; Iatropoulos et al. 1975). These studies indicate that dieldrin is distributed in the blood to adipose tissue, brain, and liver tissues, and is then redistributed primarily to fat. Concentrations of dieldrin have been shown to increase in a dose-related manner in blood and adipose tissues of humans and eventually reach a steady state (Hunter and Robinson 1967; Hunter et al. 1969). Kinetic studies in rats and dogs support these findings and provide further information on steady state kinetics following repeated dosing (Baron and Walton 1971; Davison 1973; Ludwig et al. 1964; Walker et al. 1969). Because data are sufficient regarding distribution following oral exposure to aldrin or dieldrin, no more studies via this route are needed. However, inhalation and dermal studies investigating distribution would be valuable because the potential exists for exposure to occur in humans via these routes.

No studies were located regarding metabolism of aldrin or dieldrin in humans and animals via the inhalation route. Also, human data on metabolism via the oral and dermal routes were not located. Metabolism has been characterized in animals following oral exposure (Baldwin et al. 1972; Bedford and Hutson 1976; Chipman and Walker 1979; Hutson 1976; Korte and Arent 1965; Matthews and Matsumura 1969; Matthews et al. 1971; Müller et al. 1975; Wolff et al. 1979; Wong and Terriere 1965). Sex-related and species differences have been observed in metabolism in animals (Baldwin et al. 1972; Hutson 1976; Korte and Arent 1965; Matthews and Matsumura 1969; Matthews et al. 1971). 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 human or animal data were located regarding excretion following inhalation or dermal exposure to aldrin or dieldrin. There are, however, a number of studies in animals (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968; Klevay 1970; Ludwig et al. 1964; Matthews et al. 1971; Müller et al. 1975) and a limited number of studies in humans (Hunter et al. 1969; Richardson and Robinson 1971; Schechter et al. 1989b) that describe excretion following oral exposure to aldrin or dieldrin. These studies are sufficient to characterize excretion following oral exposure to aldrin or dieldrin. These studies show quantitatively

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that the metabolites are excreted primarily in the feces in both humans and animals. Species and sex-related differences in excretion of metabolites have been observed following oral exposure in animals (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968; Klevay 1970; Ludwig et al. 1964; Matthews et al. 1971; Müller et al. 1975). Also, sex-related and species differences have been observed in the rates of excretion. Studies on excretion following inhalation and dermal exposure to aldrin or dieldrin would be useful to determine if excretion patterns vary with different routes.

Comparative Toxicokinetics. Numerous studies using a variety of animal species indicate that the kinetics of aldrin and dieldrin differ across species (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968; Klevay 1970; Ludwig et al. 1964; Matthews et al. 1971; Müller et al. 1975). The differences are primarily quantitative. Although the kinetic data alone do not allow for the identification of target organs common to humans and animals, the distribution data coupled with toxicity data appear to suggest that target organs are similar. Interspecies differences and sex-related differences in rats and mice have been observed for the metabolism and excretion of aldrin and dieldrin. These interspecies differences coupled with a lack of data across different routes indicate that it may be difficult to compare the kinetics of aldrin or dieldrin in animals with that in humans. Further studies across several species and via all three exposure routes would be useful in determining similarities and differences between humans and animals.

Methods for Reducing Toxic Effects. The mechanism by which aldrin and dieldrin are absorbed from the gastrointestinal tract is unknown but is presumed to involve dissolution in the cell membrane. Current methods for reducing absorption from the gastrointestinal tract involve removing these chemicals from the site of absorption (HSDB 2001a, 2001b; Klaassen 1990). Additional studies examining the method of absorption would provide valuable information for developing methods that interfere with gastrointestinal absorption. Numerous studies have examined the distribution of aldrin and dieldrin after gastrointestinal absorption (Adeshina and Todd 1990; Ahmad et al. 1988; Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974a; Holt et al. 1986; Hunter and Robinson 1967, 1968; Hunter et al. 1969; Iatropoulos et al. 1975). Additional studies on distribution are not necessary at this time. No established method exists for reducing the body burden of aldrin and dieldrin. However, available information indicates that reducing enterohepatic recirculation or removal from the blood before these chemicals partition to tissue may be effective (Chipman and Walker 1979; Heath and Vandekar 1964; Iatropoulos et al. 1975; Richardson and Robinson 1971; Sipes and Gandolfi 1991). Studies examining the effectiveness of repeated doses of activated charcoal, cholestyramine, hemodialysis, and hemoperfusion in reducing body burden would be useful. The neurotoxicity of aldrin and dieldrin is believed to result, at least in part, from interference with GABA function (Abalis et al. 1986; Bloomquist

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and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Lawrence and Casida 1984; Obata et al. 1988), and benzodiazepines and barbiturates have been effective in mitigating some of the neurological symptoms of aldrin and dieldrin overexposures (Black 1974; Garrettson and Curley 1969; Spiotta 1951). However, additional studies examining the effectiveness of potentiating the GABAergic function in mitigating aldrin and dieldrin's neurologic effects would be helpful. A decrease in the hepatic and renal effects of dieldrin has been observed when animals received ascorbic acid supplements during dieldrin treatment (Bandyopadhyay et al. 1982b). Further study clarifying this effect and identifying a potential mechanism for the mitigating effects of ascorbic acid would be valuable.

Children's Susceptibility. The information on health effects of aldrin and dieldrin in humans is derived mainly from cases of accidental or intentional exposure of adults to high amounts of the pesticide, and the main adverse effect is neurotoxicity. Limited reports of adverse effects in aldrin- or dieldrin-exposed children (Garrettson and Curley 1969; Gupta 1975) indicate similar signs and symptoms to those in adults. Limited animal data indicate that young animals may respond to aldrin or dieldrin differently than adult animals (Buck and Van Note 1968; Lu et al. 1965), but there is no conclusive evidence to suggest that young animals are more susceptible than older ones. Further studies that evaluate a number of different end points in young as well as older organisms would provide valuable information.

No information was located concerning whether the developmental process is altered in humans exposed to aldrin or dieldrin either prenatally or postnatally. Studies in animals have provided conflicting evidence regarding developmental malformations and anomalies (Chernoff et al. 1975; Dix et al. 1977; Ottolenghi et al. 1974), and further well-conducted research would be helpful to clarify this issue. Although animal studies suggest that aldrin and dieldrin may be disruptive of reproductive hormone levels in males and weakly estrogenic in females, additional well-designed studies are needed to clarify the developmental significance of these findings.

No data were located concerning whether pharmacokinetics of aldrin or dieldrin in children are different from adults. Although dieldrin has been detected in human placenta, amniotic fluid, fetal blood, and breast milk (Polishuk et al. 1977b; Schecter et al. 1989b), additional quantitative studies in animals would provide valuable information. There are no PBPK models for aldrin or dieldrin in either adults or children. There is no information to evaluate whether absorption, distribution, metabolism, or excretion of aldrin or dieldrin in children might be different than in adults.

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There are no biomarkers of exposure or effect that have been validated in children. There are no data on interactions of aldrin or dieldrin with other chemicals in children, and extremely limited data in adults which are inadequate to determine whether the same effects will be observed in children. There are no pediatric-specific methods to reduce peak absorption of aldrin or dieldrin following exposure, or to reduce body burden, or to interfere with mechanisms of action for aldrin or dieldrin.

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

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3.12.3 Ongoing Studies

On-going studies regarding the health effects of aldrin and/or dieldrin were reported in the Federal Research in Progress File (FEDRIP 2001) database. Table 3-7 presents a summary of ongoing studies that address the health effects of aldrin or dieldrin.

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Table 3-7. Ongoing Studies on Aldrin and Dieldrin^a

Investigator	Affiliation	Research description	Sponsor
Ahmed SA	Virginia Polytechnic Institute, College of Veterinarian Medicine, Blacksburg, VA	The effect of environmental estrogens on the lymphocytes: immunologic cell culture	USDA
Bloomquist JR	Virginia Polytechnic Institute, Blacksburg, VA	Insecticide neurotoxicity and Parkinson's diseases	USDA
Dillon G	University of North Texas, Fort Worth, TX	Neurotoxin interactions with ligand-gated ion channels	NIEHS
Freedman J	Duke University, Durham, NC	Mechanism of stress induced developmental abnormalities	NIEHS
Gross T	University of Florida, Gainesville, FL	Organochlorine pesticides and developmental mortality	NIEHS
Lauder J	University of NC at Chapel Hill, Chapel Hill, NC	Organochlorine pesticides and serotonergic development	NIEHS
Narahashi T	Northwestern University, Chicago, IL	Mode of action of insecticides—electrophysiologic	NINDS
Schwartz S	Fred Hutchinson Cancer Research Center, Seattle, WA	Phytoestrogens, organochlorines and fibroid risk	NIEHS

^a Derived from FEDRIP 2001

NIEHS = National Institute of Environmental Science; NINDS = National Institute of Neurological Disorders and Stroke; USDA = U.S. Department of Agriculture

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

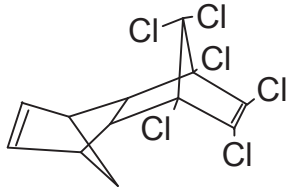
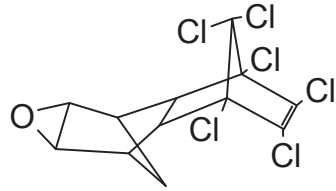
Information regarding the chemical identity of aldrin/dieldrin is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of aldrin/dieldrin is located in Table 4-2.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Aldrin and Dieldrin^a

Characteristic	Aldrin	Dieldrin
Synonym(s)	1,2,3,4,10,10-Hexachloro-1,4,4 α 5,8,8 α -hexahydro-exo-1,4-endo-5,8-dimethano- naphthalene; HHDN ^b	1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4 α ,5,6,7,8,8 α -octa-hydro-1,4-endo,exo-5,8-dimethanonaphthalene; HEOD ^b
Registered trade name(s)	Aldrec; Aldrex; Drinox; Octalene; Seedrin; Compound 118	Alvit; Dieldrix; Octalox; Quintox; Red Shield ^c
Chemical formula	C ₁₂ H ₈ Cl ₆	C ₁₂ H ₈ Cl ₆ O
Chemical structure ^d		
Identification numbers:		
CAS registry	309-00-2	60-57-1
NIOSH RTECS	IO2000000	IO1750000
EPA hazardous waste	P004	PO37
OHM/TADS	7215090 ^c	7216516 ^c
DOT/UN/NA/IMCO shipping	IM06.1 NA2762	UN2761
HSDB	199	322
NCI	C00044	C00124

^aAll information obtained from HSDB 2001a or 2001b unless otherwise noted.^bTomlin 1997^cOHM/TADS 1990b^dVerschueren 2001

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

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Aldrin and Dieldrin^a

Property	Aldrin	Dieldrin
Molecular weight	364.91	380.91
Color	White (pure); tan to brown (technical grade)	White (pure); light brown (technical grade)
Physical state	Crystalline solid ^b	Crystalline solid ^b
Melting point	104–105.5 •°C; 49–60 •°C (technical grade) ^c	176–177 •°C; 95 •°C (technical grade) ^d
Boiling point	Decomposes ^e	Decomposes ^e
Density	1.6 g/L at 20 •°C ^f	1.75 g/L at 25 •°C ^f
Odor	Mild chemical odor ^e	Mild chemical odor ^e
Odor threshold:		
Water	No data	No data
Air	0.017 mg/kg ^c	0.041 mg/kg ^c
Solubility:		
Water at 20 •°C	0.011 mg/L ^g	0.110 mg/L ^g
Organic solvents	Very soluble in most organic solvents ^b	Moderately soluble in common organic solvents except aliphatic petroleum solvents and methyl alcohol ^b
Partition coefficients:		
Log K _{ow}	6.50 ^h	6.2 ^c
Log K _{oc}	7.67 ⁱ	6.67 ⁱ
Vapor pressure:		
at 20 •°C	7.5x10 ⁻⁵ mmHg ^b	3.1x10 ⁻⁶ mmHg ^b
at 25 •°C	1.2x10 ⁻⁴ mmHg	5.89x10 ⁻⁶ mmHg ^j
Henry's law constant:		
at 25 •°C	4.9x10 ⁻⁵ atm-m ³ /mol ^k	5.2x10 ⁻⁶ atm-m ³ /mol ^k
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Nonflammable ^f	Nonflammable ^f
Conversion factors	1 ppm=14.96 mg/m ³ at 25 •°C, 1 atm	1 ppm=15.61 mg/m ³ at 25 •°C, 1 atm ^l
Explosive limits	Stable ^f	Stable ^f

^aAll information obtained from HSDB 2001a or 2001b unless otherwise noted.^bBudavari et al. 2001^cVerschueren 2001^dHayes 1982^eNIOSH 1997^fWeiss 1986^gBus and Leber 2001^hHansch et al. 1995ⁱBriggs 1981^jGrayson and Fosbraey 1982^kGuerin and Kennedy 1992^lEPA 1987a

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

5.1 PRODUCTION

Aldrin was first synthesized in the United States as a pesticide in 1948 (EPA 1986d). Aldrin and dieldrin have not been produced in the United States since 1974 (Sittig 1985). It is not known how much aldrin and dieldrin are presently stored in the United States.

Aldrin and dieldrin are included on the most recent Toxics Release Inventory (TRI99) as reportable chemicals when released or transferred from TRI99 facilities (TRI99 2001). EPA received one TRI99 form from Safety Keen (Deer Park) Inc. located in Deer Park, Texas. This facility performed the waste treatment of aldrin and reported no other uses. There was no other information available from the TRI99 database concerning aldrin or dieldrin.

Aldrin was manufactured by the Diels-Alder condensation of hexachlorocyclopentadiene with bicyclo[2.2.1]-2,5-heptadiene. The final condensation reaction was usually performed at approximately 120 °C and at atmospheric pressure. Excess bicycloheptadiene was removed by distillation. The final product was usually further purified by recrystallization (Sittig 1980). In 1967, the composition of technical-grade aldrin was reported to be as follows: 90.5% hexachlorohexahydrodimethanonaphthalene (HHDN); 3.5% other polychlorohexahydrodimethanonaphthalene compounds (isodrin); 0.6% hexachlorobutadiene; 0.5% octachlorotetrahydromethanoindene (chlordan); 0.5% octachlorocyclopentene; 0.3% toluene; 0.2% hexachlorocyclopentadiene; 0.1% HHDN di-adduct; <0.1% hexachloroethane; <0.1% bicycloheptadiene; and 3.6% other compounds (IARC 1974a).

Dieldrin was manufactured by the epoxidation of aldrin. The epoxidation of aldrin was obtained by reacting it either with a peracid (producing dieldrin and an acid byproduct) or with hydrogen peroxide and a tungstic oxide catalyst (producing dieldrin and water) (Sittig 1980). Peracetic acid and perbenzoic acid were generally used as the peracid acid (HSDB 2001b). When using a peracid, the epoxidation reaction was performed noncatalytically or with an acid catalyst such as sulfuric acid or phosphoric acid. When using hydrogen peroxide, tungsten trioxide was generally used as the catalyst (Sittig 1980). Dieldrin contained not <85% by weight HEOD and not >15% by weight of insecticidally related compounds (Clayton and Clayton 1994).

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

5.2 IMPORT/EXPORT

Before the 1974 near-total ban by EPA on aldrin and dieldrin use, aldrin and dieldrin were not imported into the United States. Aldrin was imported from Shell International (Holland) for formulation and limited use in the United States from 1974 to 1985, except when imports were temporarily ceased in 1979 and 1980. Between 1981 and 1985, an estimated 1–1.5 million pounds of aldrin were imported annually. EPA reports that aldrin has not been imported since 1985 (EPA 1986d). No information could be found that explicitly provided information about dieldrin importation.

No information could be found regarding the exportation of aldrin or dieldrin.

5.3 USE

Aldrin and dieldrin are active against insects by contact or ingestion (Hayes 1982). Thus, their primary use was for the control of termites around buildings, corn pests by application to soil and in the citrus industry (EPA 1980a). Other past uses included general crop protection from insects; timber preservation; and termite-proofing of plastic and rubber coverings of electrical and telecommunication cables, and of plywood and building boards (Worthing and Walker 1983). In 1966, aldrin use in the United States peaked at 19 million pounds, but by 1970, use had decreased to 10.5 million pounds. During this same period (1966–1970), annual dieldrin use dropped from 1 million to 670,000 pounds. These decreases were attributed primarily to increased insect resistance to the two chemicals, and to the development and availability of more effective and environmentally safer pesticides (EPA 1980a).

In 1970, the U.S. Department of Agriculture canceled all uses of aldrin and dieldrin based on the concern that these chemicals could cause severe aquatic environmental change and are potentially carcinogenic (EPA 1980a). Early in 1971, EPA initiated cancellation proceedings for aldrin and dieldrin, but did not order the suspension of aldrin and dieldrin use. In 1972, under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act as amended by the Federal Pesticide Control Act of 1972, an EPA order lifted the cancellation of aldrin and dieldrin use in three cases: subsurface ground insertion for termite control; dipping of nonfood plant roots and tops; and moth-proofing in manufacturing processes using completely closed systems (EPA 1980a, 1986d). In 1974, these last two registered uses were voluntarily abandoned by the registrant, Shell Chemical Company (EPA 1986d). The final registered use of aldrin and dieldrin as termiticides was voluntarily canceled by the Scallop Corporation (part of the Shell Chemical Company) on May 15, 1987 (EPA 1989a). Chapman Chemical Company, however, still used

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

aldrin as the active ingredient in their termiticide formulation ALDREC. Chapman's failure to disclose the exact formulation of ALDREC to the EPA forced the EPA to cancel all use of the compound on February 21, 1989. Since this time, all uses of aldrin and dieldrin have been canceled (EPA 1990b).

5.4 DISPOSAL

Aldrin and dieldrin are classified as hazardous wastes (EPA 1988a, 1990c). Subtitle C of the Resource Conservation and Recovery Act of 1976 (RCRA) creates a comprehensive program for the safe management of hazardous waste. Section 3004 of RCRA requires owners and operators of facilities that treat, store, or dispose of hazardous waste to comply with standards established by EPA that are "necessary to protect human health and the environment" (EPA 1987h).

The Chemical Manufacturers Association recommends disposing of aldrin and dieldrin by incineration (HSDB 2001b). Incineration by rotary kiln (at 820–1,600 •°C), liquid injection (at 877–1,038 •°C), and fluidized bed (at 450–980 •°C), with residence times of seconds for gases and liquids and hours for solids, is recommended (HSDB 2001a). Aldrin and dieldrin are often mixed with vermiculite, sodium bicarbonate, or a sand-soda ash mixture prior to incineration (OHM/TADS 1990a). The incineration of these chemicals emits highly toxic fumes of hydrogen chloride and chlorinated breakdown products (HSDB 2001a). Thus, incinerators used for disposal of aldrin and dieldrin must have an acid scrubber and an after-burner (OHM/TADS 1990a). Also, prior to incineration, local air and fire authorities must be contacted (OHM/TADS 1990a, 1990b).

Another recommended disposal method for aldrin and dieldrin is burying the chemicals in landfills. Contaminated material should be buried 8–12 feet underground in an isolated area away from water supplies, with a layer of clay, a layer of lye, and a second layer of clay beneath the wastes (OHM/TADS 1990a). Gravity filtration of solids, followed by dual-media filtration of the liquids, followed by activated carbon adsorption (100–300 pounds of carbon per pound of soluble material) is also an approved disposal method (OHM/TADS 1990b). Finally, disposal of small amounts of aldrin and dieldrin can be accomplished through degradation by active metals (sodium or lithium) in liquid ammonia (HSDB 2001b; Sittig 1985).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Aldrin was first synthesized in the United States as a pesticide in 1948 (EPA 1986d) while dieldrin was first used by cotton growers in the 1950s (Clayton and Clayton 1994). By 1970, the U.S. Department of Agriculture canceled all uses of aldrin and dieldrin (EPA 1980a). Restrictions on their use as termiticides, for dipping of non-food plant roots and tops, and for moth-proofing were lifted by EPA in 1972. In 1974, however, the latter two uses were voluntarily canceled by the manufacturer, Shell Chemical Company (EPA 1986d). The final registered use of aldrin and dieldrin as termiticides was voluntarily canceled by the Scallop Corporation (part of the Shell Chemical Company) on May 15, 1987 (EPA 1989a). The Chapman Chemical Company, however, continued to use aldrin in their termiticide formulation until it was ultimately canceled by the EPA on February 21, 1989.

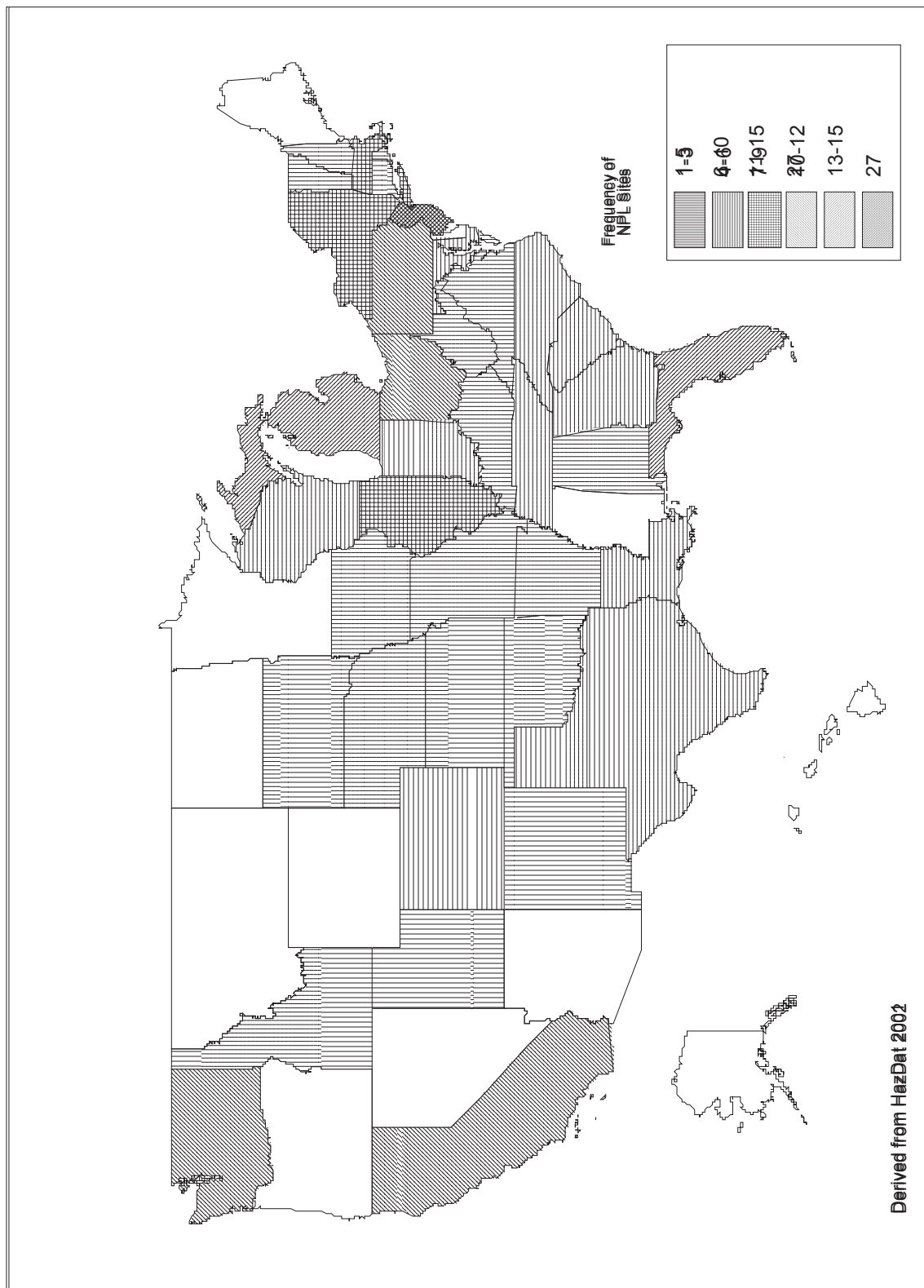
Aldrin is readily converted to dieldrin, which is ubiquitous in the environment. Dieldrin persists because it is more resistant to biotransformation and abiotic degradation than aldrin. As a result, it is found in all environmental media, even at a distance from the site of concentration. Dieldrin bioconcentrates and biomagnifies through the terrestrial and aquatic food chains. Transport of aldrin and dieldrin in soils is minimal because these compounds tend to bind tightly to soil. Based on their physical properties, volatilization from moist soil surfaces is expected. Most dieldrin and aldrin found in surface water are the result of runoff from contaminated soil. Aldrin undergoes photolysis to dieldrin, which in turn may be degraded by ultraviolet radiation or microbial action into the more persistent compound, photo dieldrin.

Past agricultural uses of aldrin and dieldrin have resulted in persisting soil residues and uptake in a wide range of crops. Exposure of the general population to aldrin and dieldrin may occur through ingestion of contaminated water or food products and through inhalation of contaminated air, especially in homes that have been treated with either pesticide.

Aldrin has been identified in at least 207 of the 1,613 hazardous waste sites while dieldrin has been identified in at least 287 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 aldrin and dieldrin is not known. The frequency of these sites can be seen in Figures 6-1 and 6-2. Of these

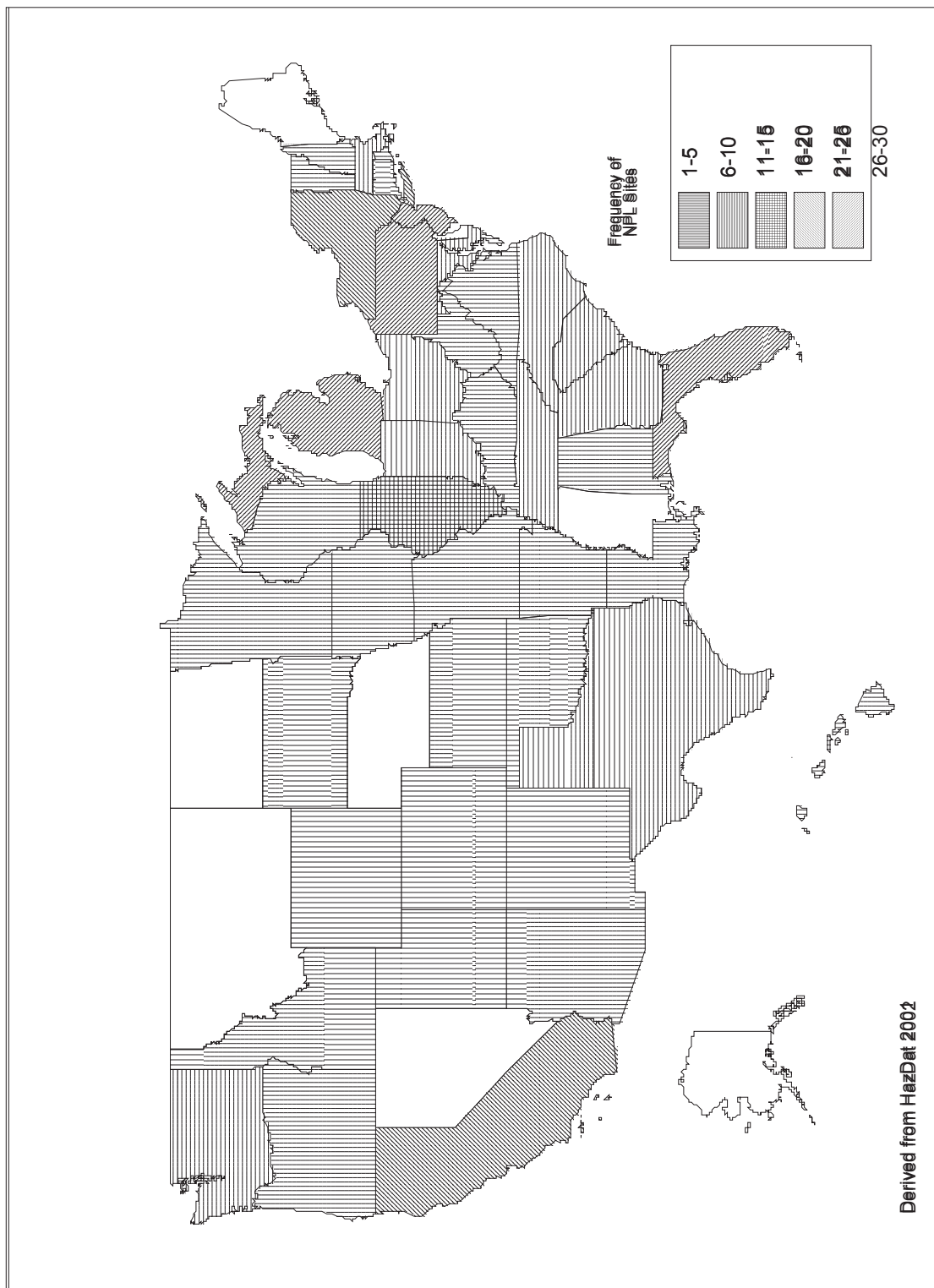
6. P_O TENTIAL FOR HUMAN EXPOSURE

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



6. pO TENTIAL FOR HUMAN EXPOSURE

Figure 6-2. Frequency of NPL Sites with Dieldrin Contamination



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sites, 205 of the 207 aldrin sites are located within the United States, 1 is located in the Virgin Islands (not shown), and 1 is located in Puerto Rico (not shown). For dieldrin, 285 of the 287 sites are located within the United States and 2 are located in the country of Guam.

6.2 RELEASES TO THE ENVIRONMENT

Aldrin and dieldrin production and use in the United States has been canceled by the EPA (EPA 1990b). Because of the persistent nature of these compounds, however, these compounds are still present in the environment. Aldrin and dieldrin have been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 207 and 287 of the 1,613 NPL hazardous waste sites, respectively (HazDat 2002).

Aldrin and dieldrin are included on the most recent Toxic Chemical Release Inventory (TRI99) as reportable chemicals when released or transferred from TRI99 facilities (TRI99 2001). EPA received one TRI99 form from Safety Keen (Deer Park) Inc. located in Deer Park, Texas. This facility performed the waste treatment of aldrin and reported no releases to the environment. EPA received no other release data for aldrin or dieldrin, indicating that no reportable releases to the environment occurred in 1999.

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

Aldrin has been identified in air samples collected at 6 of the 207 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002). Dieldrin has been identified in air samples collected at 14 of the 287 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002).

Past application of aldrin and dieldrin for termite control is a continuing source of contamination of indoor air. In addition, these compounds may be released to the atmosphere from previously treated soil and contaminated surface waters. Release of aldrin and dieldrin into the air may also occur as a result of atmospheric dispersal of contaminated soils at NPL sites and farmlands where these compounds had been used.

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6.2.2 Water

Aldrin has been identified in 20 surface water and 93 groundwater samples collected at 207 of the 1,613 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002). Dieldrin has been identified in 40 surface water and 107 groundwater samples collected at 287 of the 1,613 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002).

Aldrin and dieldrin may be released to surface waters as a result of runoff from contaminated croplands and NPL sites. Although aldrin and dieldrin are no longer permitted for general use, dieldrin, in particular, has been detected in many waterways and cropping soils. Due to the persistence of these compounds, especially dieldrin, they have been detected in a wide variety of aquatic systems. Aldrin and dieldrin have been detected in seawater samples (Sauer et al. 1989), industrial effluents and fresh water samples (Staples et al. 1985). The high organic carbon partition coefficient (K_{oc}) values for aldrin and dieldrin suggest movement through soil and contamination of groundwater will be minimal. The only reports of aldrin or dieldrin contamination of groundwater occurred at sites with high concentrations of these compounds.

6.2.3 Soil

Aldrin has been identified in 145 soil and 45 sediment samples collected at 207 of the 1,613 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002). Dieldrin has been identified in 243 soil and 89 sediment samples collected at 287 of the 1,613 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002).

Possible releases of aldrin and dieldrin to soil may come from the improper disposal of old stocks. Wet and dry deposition of particulate phase aldrin and dieldrin from the atmosphere is another potential source of soil contamination.

6.3 ENVIRONMENTAL FATE**6.3.1 Transport and Partitioning**

Experimental log K_{oc} values for aldrin range from 5.38 to 7.67 (Briggs 1981; Ding and Wu 1995). Based on a classification scheme, these log K_{oc} values indicate that aldrin is expected to be immobile in soil (Swann et al. 1983). The mobility of aldrin and dieldrin in the soil environment, however, can be

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enhanced at hazardous waste sites where organic solvents may be present. These organic solvents have the ability to increase the water solubility of nonpolar compounds which in turn increases their mobility in soil (Sawhney 1989). The organic solvents in a sense act as a transport medium for chemicals that would normally bind strongly to soil. 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 organochlorine compounds such as aldrin and dieldrin. The lipid materials in bacterial cell membranes may lead to a repartitioning of aldrin and dieldrin sorbed to soil colloids. This can lead to a phenomenon called facilitated transport where the mobility of hydrophobic pollutants 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. This appears to be true in light of the small number of reports of aldrin and dieldrin groundwater contamination at locations other than NPL sites. Volatilization of aldrin from soil is more rapid when it is applied to the soil surface rather than incorporated into the soil. A loss of 50% from a surface application was estimated to occur within 1–2 weeks after application compared to 10–15 weeks for soil-incorporated aldrin (Caro and Taylor 1971; Elgar 1975). The relatively rapid loss of both aldrin and dieldrin from soil during the first few months after application has been attributed to loss by volatilization. The volatilization potential of field-applied dieldrin (10 ppm) was studied for 5 months using three different soil moisture regimes (Willis et al. 1972). The three soil moisture regimes included: (1) flooded to a depth of 10 cm; (2) moist; and (3) nonflooded with no water added except for natural rainfall. The results showed that the soil moisture had an effect on the volatilization rate. About 18% of the applied dieldrin volatilized from a moist plot in 5 months, but only 2 and 7% volatilized from the flooded and nonflooded plots, respectively. Flooding retarded the volatilization potential of surface-applied dieldrin. Volatilization of dieldrin from the non-flooded plot tended to increase with increasing precipitation (Willis et al. 1972).

Volatilization of aldrin from water surfaces is expected (Thomas 1990) based upon a Henry's law constant of 4.9×10^{-5} atm/m³/mole (Guerin and Kennedy 1992). Volatilization from water surfaces, however, may be attenuated by adsorption to suspended solids and sediment in the water column. The volatile loss of aldrin from sterile, deionized water kept at 30 •C was studied over a 30 day period (Guerin and Kennedy 1992); the volatilization half-life of aldrin from the open flask was 5.8 days. In one study, the desorption of aldrin from sediment into water was investigated (Ding and Wu 1993). Researchers simulated a river bed by spiking a sediment sample with 287.6 ng aldrin/g sediment and passing 7,780 mL water/day over the sediment. The concentration of aldrin detected in the effluent water after one day was 0.135 ng/mL

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while by day 40, the concentration decreased to 0.06 ng/mL. The concentration of dieldrin was not measured in this study.

According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman 1988), aldrin, which has a vapor pressure of 1.2×10^{-4} mmHg at 25 •C (HSDB 2001a), will exist in both the vapor and particulate phases in the ambient atmosphere. Particulate-phase aldrin may be transported through the atmosphere by wind and later removed from air by wet and dry deposition (Millet et al. 1997).

The logarithm of the *n*-octanol/water partition coefficient ($\log K_{ow}$) is a useful preliminary indicator of potential bioaccumulation of a compound. The $\log K_{ow}$ for aldrin ranges from 5.68 (McLean et al. 1988) to 7.4 (Briggs 1981), indicating a high potential for bioaccumulation. In modeling ecosystem tests, bioconcentration factors (BCFs) for aldrin were 3,140 in fish and 44,600 in snails (Metcalf et al. 1973). The BCF of aldrin in orange-red killifish was studied over an 8 week period in a semi-static system at 25 •C (CITI 1992.). At a concentration of 1 mg/L, aldrin had BCFs ranging from 3,490 to 20,000, while at 0.1 mg/L, aldrin had BCFs ranging from 1,550 to 9,450.

Experimental evidence indicates that aldrin is rapidly metabolized to dieldrin by some organisms, which then bioconcentrates and biomagnifies (EPA 1980a; Metcalf et al. 1973). Radiolabeled aldrin added to a model ecosystem was rapidly converted to dieldrin. Of the radiolabel stored in organisms, 95.9% of the total stored in the fish *Gambusia affinis*, 91.6% stored in the snails of the genus *Physa*, and 85.7% stored in the algae *Oedogonium cardiacum* were in the form of dieldrin.

Aldrin also bioconcentrates in terrestrial ecosystems. In a model ecosystem study, 2.09 ppm radiolabeled aldrin was applied to a vermicullite soil (Cole et al. 1976). After 20 days, researchers detected only 0.463 ppm aldrin and 0.159 ppm dieldrin. Corn, that had been grown on the vermicullite soil for 14 days, contained 2.83 ppm radiolabeled carbon with 0.762 ppm being aldrin and 1.538 ppm dieldrin. Approximately 78% of the plant residue was in the roots and 22% in the shoots. On day 15, a prairie vole (*Microtus ochrogaster*) was introduced to the model ecosystem. After 5 days of exposure, the concentrations of aldrin and dieldrin in the vole were 0.08 and 3.56 ppm, respectively. To study the uptake of pesticides in plants, radiolabeled aldrin and dieldrin were monitored over one week in a controlled laboratory setting (Kloskowski et al. 1981). After 1 week of exposure of barley plants to 2 ppm of both pesticides, the concentrations of aldrin and dieldrin in plant tissue were 9.7 and 4.0 ppm, respectively. One research study, however, observed no plant uptake of either aldrin or dieldrin in maize

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and pearl millet over a 3-year period grown in a clay loam soil (Gupta et al. 1979). Aldrin was applied at a rate of 3, 9, and 15 kg active ingredient (ai) per hectare (ha) once per year before the sowing of crops and mixed up to a depth of 10 cm. No residues of either aldrin or dieldrin could be detected in plant tissues from any of the years of experimentation, even at the highest dosage of 15 kg ai/ha.

Biotransfer factors (BTFs) for beef and cow's milk have been determined for aldrin. The concept of biotransfer is useful since it takes into account exposure through both food and water pathways. Biotransfer factors for beef and milk are defined as the concentration of a compound in beef or milk (mg/kg) divided by the daily intake of the compound by the animal (mg/day). The biotransfer values for beef and milk were estimated to be 0.085 and 0.023, respectively (Travis and Arms 1988). Biotransfer factors for aldrin in beef and milk are directly proportional to the K_{ow} . In addition, a BCF for aldrin in vegetables was also determined. The bioconcentration factor was defined as the ratio of the concentration in aboveground parts (mg of compound/kg of dry plant) to the concentration in soil (mg of compound/kg of dry soil); the BCF was estimated to be 0.021 (Travis and Arms 1988). The vegetation bioconcentration factor is inversely proportional to the square root of K_{ow} . The regression equations for beef, milk, and vegetation provide a technique for predicting a chemical's BTF in beef and milk and BCF in vegetation. Consequently, regression analyses will be of value in more precisely quantifying human exposure to organics through the terrestrial food chains (Travis and Arms 1988).

Dieldrin is nonpolar and, therefore, has a strong affinity for organic matter and sorbs tightly to soil particulates based on its log K_{oc} of 6.7 (Briggs 1981). Volatilization is the principal loss process of dieldrin from soil; however, the process is relatively slow due to its low vapor pressure and strong sorption to soil. It may also be impeded by low soil moisture or incorporation of the compound into the soil (Cliath and Spencer 1971). Volatilization of dieldrin from dry soil is slower than aldrin (<10 g/hectare/day) based on its vapor pressure of 5.89×10^{-6} mmHg at 25 •C (Grayson and Fosbraey 1982). The volatilization rate decreases with time (Nash 1983) and increases with increasing temperature to a maximum at 25 •C (Nash and Gish 1989). In one experiment, 150 grams of dieldrin was applied to a sandy loam soil and monitored for volatile loss (Nash 1983). After 11 days, 53.1 ± 14.2 mg had volatilized, while 110 ± 18.6 mg had remained on the soil surface. Based on the Henry's law constant and the K_{oc} , the volatilization half-life of dieldrin from soil has been estimated to be 868 days (Jury et al. 1987b). Movement of dieldrin through the soil solution is extremely slow, indicating little potential for groundwater contamination. Using a low pollution potential scenario (soil with a high organic content and a high average water content), it is estimated that it will take 2,594 years for dieldrin to travel to a depth of 3 meters. Even with a high pollution potential scenario (soil with a low organic content and a

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low water content), it would still take an estimated 270 years for dieldrin to reach a depth of 3 meters (Jury et al. 1987b). Analysis of environmental groundwater samples, however, have shown that on some occasions, dieldrin has contaminated groundwater systems (EPA 1986i; Hallberg 1989; HazDat 2001). Dieldrin has been estimated to have a sorption coefficient on mixed-liquor solids (typical of municipal waste water treatment plants) of 38.9 mg/g at an equilibrium concentration of 1.0 mg/L (Dobbs et al. 1989). Movement of dieldrin in waterborne sediment is a major loss pathway from treated soil (Caro and Taylor 1971; Eye 1968; Hardee et al. 1964).

Volatilization of dieldrin from water surfaces is expected (Thomas 1990) based upon a Henry's law constant of 5.2×10^{-6} atm/m³/mole (Guerin and Kennedy 1992). Volatilization from water surfaces, however, may be attenuated by adsorption to suspended solids and sediment in the water column. The volatile loss of dieldrin from sterile, deionized water kept at 30 •C was studied over a 30-day period (Guerin and Kennedy 1992). The study found that the half-life for the volatilization of dieldrin from the open flask was 17 days.

According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman 1988), dieldrin, which has a vapor pressure of 5.89×10^{-6} mmHg at 25 •C (Grayson and Fosbraey 1982), will exist in both the vapor and particulate phases in the ambient atmosphere. Dieldrin may be transported great distances in the atmosphere and be removed by wet or dry deposition (Baldwin et al. 1977; Millet et al. 1997). Snowpack samples were collected at 12 sites in the Northwest Territories, Canada, in the winter of 1985–1986; dieldrin was found in all 21 samples at a mean concentration of 0.75 ng/L (Gregor and Gummer 1989). There were no known local sources of dieldrin in the Canadian Arctic snow. Dieldrin was detected with a mean concentration close to 1 pg/m³ in arctic air measured at Alert, Canada; Tagish, Canada; and Dunai Island, Canada-Russia in the 1990s (Bidleman 1999).

Like aldrin, dieldrin has a high potential for bioaccumulation as indicated by a log K_{ow} value that ranges from 4.32 (Geyer et al. 1987) to 6.2 (Briggs 1981). Measured bioconcentration factors for dieldrin are 2,700 in fish and 61,657 in snails (Metcalf et al. 1973). A second study using the same model ecosystem found bioconcentration factors for dieldrin to be 6,145 in fish, 7,480 in algae, 247 in crabs (*Uca minax*), 1,015 in clams (*Corbicula manilensis*), 1,280 in the water plant *Elodea*, and 114,935 in snails (Sanborn and Yu 1973). A BCF of 2,095 has been determined for the ciliate *Tetrahymena pyriformis* exposed to 1 µg/mL dieldrin for 12 hours (Bhatnagar et al. 1988). A biomagnification factor of 1.0 has been determined for dieldrin for rainbow trout on a lipid weight basis; the average wet weight bioconcentration factor is 2.3 (Connell 1989). Channel catfish, exposed to varying concentrations of dieldrin, were used to

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determine when equilibrium was reached between uptake of dieldrin and elimination from muscle tissue. At 13 ppt, equilibrium was reached after 56 days, whereas, at 49 ppt, equilibrium was not reached even after 70 days of exposure (Shannon 1977). The bioaccumulation factor of dieldrin in orange-red killifish was studied over an 8-week period in a semi static system at 25 °C (CITI 1992). At a concentration of 1 mg/L, dieldrin had BCFs ranging from 4,860 to 14,500 while at 0.1 mg/L, dieldrin had a BCF ranging from 5,390 to 12,500.

Biotransfer factors for beef and cow milk and a bioconcentration factor for vegetables have been determined for dieldrin. The biotransfer values for dieldrin in beef and milk were estimated to be 0.008 and 0.011, respectively, while the BCF for vegetables was estimated to be 0.098 (Travis and Arms 1988).

In a biomagnification study, the concentrations of organochlorine compounds in sediments, amphipods, isopods, and sculpins from the Bothnian Bay and the Bothnian Sea were measured (Strandberg et al. 2000). Dieldrin was detected in sediments (three samples), amphipods (three samples), isopods (five samples), and sculpins (three samples) in the Bothnian Bay with mean concentrations of 0.39, 87, 92, and 42 ng/g lipid, respectively. Dieldrin was detected in sediments (three samples), amphipods (four samples), isopods (five samples), and sculpins (three samples) with mean concentrations of 0.51, 110, 55, and 80 ng/g lipid, respectively. Possible explanations given for the low biomagnification factor potential of the sculpin were that it could have less capacity to accumulate hydrophobic organic environmental contaminants or a greater ability to metabolize or excrete the compounds.

Uptake of dieldrin by redworms (*Eisenia foetida*) was determined for Chester and silt loam samples that had been aged with dieldrin for periods of 49 and 30 years, respectively (Morrison et al. 2000). The worms assimilated 10.8% of the dieldrin in unaged Chester loam resulting in a tissue concentration of 53.5 mg/kg. The worms assimilated 4.48% of the dieldrin in the Chester loam aged 49 years resulting in a tissue concentration of 15.1 mg/kg. In unaged silt loam, the worms assimilated 12.8% of the dieldrin resulting in a tissue concentration of 40.0 mg/kg, while the worms in the silt loam aged 30 years assimilated 19.9% of the dieldrin resulting in a tissue concentration of 6.13 mg/kg. It was suggested that the aging dieldrin in field soils reduced acute toxicity and therefore bioavailability to earthworms.

Data indicate that dieldrin is taken up by various crops (Beall and Nash 1969, 1971). To determine whether foliar contamination of soybean plants occurred via root sorption or vapor sorption, 20 ppm ¹⁴C-dieldrin was applied to surface or subsurface soil, and residue levels in soybean plants were

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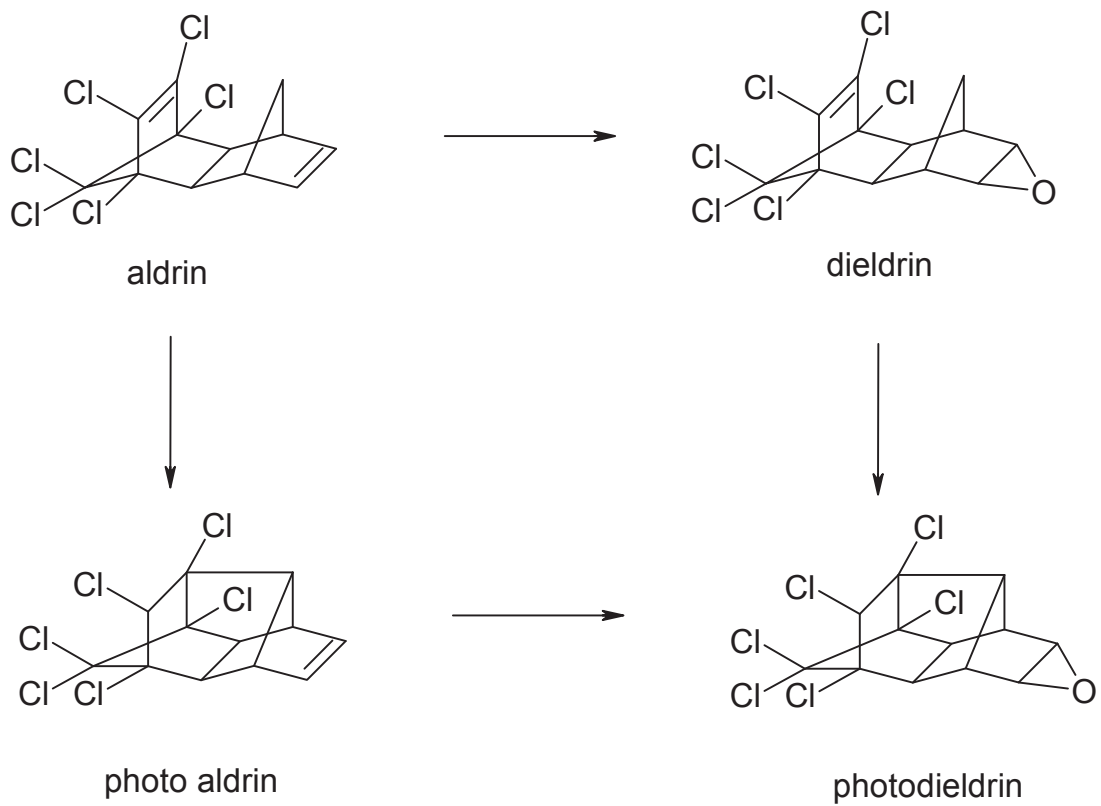
determined (Beall and Nash 1971). The results indicated that foliar contamination by dieldrin occurred by both root sorption (10.8 ppm) and vapor sorption (8.5 ppm) (Beall and Nash 1971). In a greenhouse experiment, various crop seedlings took up dieldrin from soils treated with 0.5 or 5.0 ppm dieldrin (Beall and Nash 1969). Mean concentrations of dieldrin found in soybeans, wheat, corn, alfalfa, brome grass, and cucumber treated with 0.5 ppm dieldrin were 0.017, 0.147, 0.017, 0.031, 0.075, and 0.070 ppm (dry weight). Mean concentrations of dieldrin found in soybeans, wheat, corn, alfalfa, brome grass, and cucumber treated with 5.0 ppm dieldrin were 0.194, 1.385, 0.171, 0.350, 0.808, and 0.185 ppm (dry weight) (Beall and Nash 1969).

6.3.2 Transformation and Degradation

6.3.2.1 Air

While the evidence supports the view that a considerable proportion of the aldrin and dieldrin used in agriculture reaches the atmosphere, it seems probable that atmospheric degradation and wet and dry deposition prevents accumulation of aldrin. In laboratory studies, vapor-phase aldrin is photochemically isomerized and epoxidated by sunlight to photoaldrin, dieldrin, or photodieldrin (see Figure 6-3) (Glotfelty 1978). In order to determine the potential for photodegradation to occur in the ambient atmosphere, the degradation of aldrin and dieldrin was studied on thin film plates and exposed to environmental ultraviolet (UV) radiation (>290 nm) (Chen et al. 1984). Aldrin and dieldrin had photodegradative half-lives of 113 and 153 hours, respectively. Researchers also reported that aldrin and dieldrin have UV absorbance maximums of 227 and 229 nm, respectively. Irradiation of aldrin (5 mg) vapor with ultraviolet light for 45 hours resulted in the formation of photoaldrin (20–30 ug) and dieldrin (50–60 ug). Irradiation of either photoaldrin (2 mg) or dieldrin (0.5 mg) vapor for 65 hours and 91 minutes, respectively, resulted in a single photoproduct, photodieldrin (20–30 ug), which was resistant to further photolyses (Crosby and Moilanen 1974). Since photodieldrin no longer contains a chromophore, it is believed to be a stable photoproduct of aldrin (dieldrin) (Glotfelty 1978). Results of a

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Figure 6-3. Aldrin Degradation

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laboratory study, however, revealed that photolysis of photoaldrin and photodieldrin in the presence of triethylamine gave photometabolites arising from the loss of chlorine atoms (Dureja et al. 1986).

Information regarding the persistence of photodieldrin in the atmosphere was not located; however, air samples taken in 1973 in Ireland contained dieldrin, but neither aldrin nor the photoproducts of aldrin or dieldrin were detected (Baldwin et al. 1977).

Vapor-phase aldrin and dieldrin are expected to degrade in the atmosphere by reaction with photochemically-produced hydroxyl radicals. The half-lives for this reaction in air are estimated to range from 1 to 10 hours for aldrin and 3 to 30 days for dieldrin based on an estimated rate constant (Kwok and Atkinson 1995). Vapor-phase aldrin may also be degraded in the atmosphere by reaction with ozone. Although there are no experimental data, reaction with ozone is expected to be an important atmospheric degradation reaction for aldrin in the vapor phase. An estimated half-life for this reaction ranges from 19 minutes to 2 hours (Atkinson and Carter 1984). Studies indicate that aldrin will also react with nitrogen dioxide in the ambient atmosphere to produce dieldrin (Nojima et al. 1982). After 3 hours of exposure to nitrogen dioxide and UV radiation >290 nm, 32% of vapor-phase aldrin was converted to dieldrin. Aldrin and dieldrin may be more stable than implied by these lifetimes if they are associated with particulate matter in the atmosphere. Particulate-phase aldrin and dieldrin, however, will not participate in hydroxyl radical reactions in the atmosphere.

6.3.2.2 Water

The resistance of aldrin and dieldrin to soil leaching generally precludes their appearance in groundwater. The general absence of aldrin and dieldrin from groundwater samples supports this conclusion (Richard et al. 1975; Spalding et al. 1980). The potential for surface runoff of aldrin and dieldrin in soils is supported by reports of detectable quantities of these compounds in surface waters (Hindin et al. 1964; Richard et al. 1975).

Aldrin, irradiated with ultraviolet light in an oxygenated aqueous solution, underwent little change except in the presence of amino acids and humic acids present in natural waters (Ross and Crosby 1975, 1985). In filtered natural field water, aldrin was photooxidized by 75% to dieldrin after 48 hours of irradiation at 238 nm (Ross and Crosby 1985). More than 80% of the initial dieldrin added to natural water (from a drainage canal in an agricultural area) was present after 15 weeks of incubation in the dark (Sharom et al. 1980). Dieldrin exposed to sunlight is converted to photodieldrin, a stereoisomer of dieldrin. It is unlikely, however, that photodieldrin occurs widely in the environment. Microorganisms isolated from

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lake water and lake-bottom sediments may convert dieldrin to photodieldrin under anaerobic conditions (Fries 1972). The stability of dieldrin and aldrin was determined in distilled (pH 6.8) and roof water (pH 7.4) (McDougall et al. 1994). The samples were kept in the dark, at 23 °C over a 36-week period. The study found that after 36 weeks, dieldrin remained stable while aldrin degraded in both roof water and distilled water. The half-lives of aldrin in distilled water and roof water were 4.9 and 5.1 weeks, respectively. The study did not find dieldrin as a breakdown product of aldrin degradation. An extrapolated hydrolysis rate constant of $3.8 \times 10^{-5} \text{ hour}^{-1}$ at pH 7 and 25 °C has been determined for aldrin based on a measured value at 75 °C (EPA 1989d). The half-life for this reaction is 760 days.

Aldrin was degraded under anaerobic conditions in biologically active waste water sludge (pH 7–8, 35 °C) with a half-life of <1 week (Hill and McCarty 1967). Under aerobic conditions, however, only 1.5% of aldrin degraded when exposed to an activated sewage sludge (Freitag et al. 1985). Aldrin has a reported biodegradation half-life of 24 days in surface waters based on a non-acclimated river die-away test (Eichelberger and Lichtenberg 1971). Dieldrin does not undergo any significant degradation in biologically active waste water sludge or by sewage sludge microorganisms under anaerobic conditions (Battersby and Wilson 1988; Hill and McCarty 1967). After 48 hours of continuous anaerobic digestion with primary sludge, dieldrin was degraded by only 11% (Buisson et al. 1990). Likewise, when incubated for 32 days with anaerobic sludge, only 24% of the dieldrin was removed (Kirk and Lester 1988). In contrast, aerobic incubation with activated sludge removed 55% of the dieldrin in 9 days (Kirk and Lester 1988). A mixed, anaerobic microbial enrichment culture was able to degrade 10 µg/mL dieldrin by 50% in 30 days. Syn-monodechlorodieldrin and anti-monodechlorodieldrin, both of which are resistant to microbial degradation, were identified as the initial degradation products (Maule et al. 1987). In another study, dieldrin was degraded by 30–60% using activated sludge treatment, with the most effective removal by activated sludge aged 4 days as opposed to sludge aged 6 and 9 days (Buisson et al. 1988). Both aldrin and dieldrin, present at 100 mg/L, reached 0% of their theoretical biological oxygen demand (BOD) in 2.5 weeks using an activated sludge inoculum at 30 mg/L and the Japanese Ministry of International Trade and Industry (MITI) test (CITI 1992).

Dieldrin undergoes minor degradation to photodieldrin in marine environments. The marine algae of the genus *Dunaliella* had the maximum degradation activity, degrading 23% of aldrin to dieldrin and 8.5% of dieldrin to photodieldrin (Patil et al. 1972).

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6.3.2.3 Sediment and Soil

In the soil, aldrin is converted to dieldrin by epoxidation (Gannon and Bigger 1958). Aldrin epoxidation occurs in all aerobic and biologically active soils, with 50–75% of end-season residues detected as dieldrin. The transformation of aldrin to aldrin acid also occurs in soils. The half-life of aldrin in soil is estimated to be 53 days. Mathematical modeling estimates that aldrin, applied to soil up to 15 cm in depth, will degrade to dieldrin by 69% after 81 days. At a typical soil application rate of 1.1–3.4 kg/hectare, the half-life of aldrin was estimated to be 0.3 years with 95% disappearance in 3 years (Freedman 1989). Loam soils treated with aldrin at 25 pounds per 5-inch acre over a 5-year period from 1958 to 1962 contained in the fall of 1968, 4–5% of the applied dosages mainly in the form of dieldrin. Aldrin treated soils also contained photodieldrin, which amounted to 1.5% of the recovered dieldrin (Lichtenstein et al. 1970). The degradation of aldrin and dieldrin was studied under upland and flooded soil conditions (Castro and Yoshida 1971). For the upland soil condition, water was added to give 80% of the maximum water-holding capacity of the soil. For the flooded soil condition, the water level was maintained 5 cm above the soil surface resulting in an anaerobic environment. Results showed that aldrin was more persistent in flooded than in upland soil. After 2 months of incubation under upland conditions, 33–58% of added aldrin remained in the soil. Under flooded conditions, 64–81% remained in the soil (Castro and Yoshida 1971).

The change in aldrin concentration and its conversion to dieldrin was also studied over a 3-year period in a clay loam soil in India (Gupta et al. 1979). Aldrin was applied at a rate of 3, 9, and 15 kg active ai/ha once per year before the sowing of crops and mixed up to a depth of 10 cm. After the first year of application at 3, 9, and 15 kg ai/ha, the concentrations of aldrin in soil were 1.801, 3.665, and 8.797 ppm, respectively. By the end of the third year, the concentrations of aldrin was 1.824, 3.453, and 9.736 ppm for the three application rates of 3, 9, and 15 kg ai/ha, respectively. Dieldrin was detected as a breakdown product of aldrin by the third year at a concentration of 0.055, 0.245, and 0.695 ppm for the three application rates, respectively. Maize and pearl millet grown on the treated soil were also analyzed for aldrin and dieldrin concentrations. No residues of either aldrin or dieldrin could be detected in plant samples from any of the years of experimentation, even at the highest application rate of 15 kg ai/ha.

Dieldrin is much more resistant to biodegradation than aldrin (Castro and Yoshida 1971; Gannon and Bigger 1958; Jagnow and Haider 1972; Willis et al. 1972). Of 20 soil microbes that were able to degrade dieldrin, only 13 of them could also degrade aldrin to dieldrin (Patil et al. 1970). The bacteria *Aerobacter aerogenes* aerobically degraded approximately 12% of dieldrin to aldrin diol within 5 days, but no further

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degradation was detected with increased incubation periods (Wedemeyer 1968). At a soil application rate of 1.1–3.4 kg/hectare, dieldrin was estimated to have a half-life of 2.5 years and a 95% disappearance from soil in 8 years (Freedman 1989), although other studies indicate that dieldrin loses between 75 and 100% of its biological activity in 3 years (Jury et al. 1987b). After 6 months, dieldrin persisted in moist, flooded, and nonflooded soils, indicating that these three soil moisture conditions had no effect on the degradation of soil-incorporated dieldrin (Willis et al. 1972). The roots of grass grown on the plots contained 11.6 ppm dieldrin while the aerial grass parts contained only 0.05 ppm (Voerman and Besemer 1975). Twenty-one years after the application of dieldrin to the foundation of a house at an application rate commonly used for termite control, 10% of the original dieldrin remained, primarily in the upper 6 inches of soil (Bennett et al. 1974). Aldrin and dieldrin applied to soil may also undergo degradation by ultraviolet light to form photodieldrin; this reaction may occur as a result of microbial action as well (Matsumura et al. 1970; Suzuki et al. 1974). After ultraviolet irradiation for 168 hours, dieldrin applied to various environmental media was found to be photodecomposed by 9.6% on loam soil, 1.2% on clay soil, and 44% on activated charcoal; the degradation products were photodieldrin and an unknown compound (Elbeit et al. 1983). Residues in soil samples found after application of dieldrin to soil (0.83 kg/hectare in soil that already contained 0.521 ppm dieldrin) consisted largely of unchanged dieldrin (2.581 ppm) and photodieldrin (0.029 ppm).

6.3.2.4 Other Media

No studies were located regarding the degradation or transformation of aldrin or dieldrin in other media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Aldrin is readily converted to dieldrin in the environment. Dieldrin is subject to atmospheric transport, and, as a result, is ubiquitous in the environment. Dieldrin persists because it is relatively resistant to biotransformation and abiotic degradation. Thus, it is found in low levels in all media (air, water, and soil).

6. POTENTIAL FOR HUMAN EXPOSURE

6.4.1 Air

Aldrin and dieldrin enter the atmosphere through various mechanisms such as spray drift during application of the compounds as insecticides, water evaporation, and suspension of particulates to which the compounds are absorbed. The analysis of 2,479 air samples from 16 states from 1970 to 1972 revealed the following ambient concentrations: aldrin, mean 0.4 ng/m^3 (3×10^{-5} ppb), 13.5% of samples positive; dieldrin, mean 1.6 ng/m^3 (1×10^{-4} ppb), 94% of samples positive (Kutz et al. 1976).

The annual atmospheric deposition of dieldrin to the five Great Lakes was estimated based on measurements taken in the late 1970s (Eisenreich et al. 1981). The results indicated that 0.54, 0.38, 0.55, 0.17, and 0.13 metric tons/year were deposited into Lake Superior, Lake Michigan, Lake Huron, Lake Erie, and Lake Ontario, respectively. The annual mean gas-phase, particulate-phase, and precipitation concentrations of dieldrin were studied over the U.S. Great Lakes from 1990 to 1992 (Hoff et al. 1996). The annual mean gas-phase concentrations of dieldrin over Lakes Superior, Michigan, Erie, and Ontario were 14, 34, 30, and 23 pg/m^3 , respectively. The particulate-phase concentrations of dieldrin over Lakes Superior, Michigan, Erie, and Ontario were 1.5, 1.9, 3.2, and 1.6 pg/m^3 , respectively. Finally, the concentrations of dieldrin in precipitation falling over Lakes Superior, Michigan, Erie, and Ontario were 0.4, 0.99, 0.8, and 0.6 ng/L , respectively. The total wet deposition of dieldrin in 1992 for Lakes Superior, Michigan, Erie, and Ontario was 21, 58, 28, and 11 kg, respectively. More recent data on the atmospheric concentrations of aldrin and dieldrin were gathered in 1986, approximately 10 years after the use of aldrin and dieldrin was restricted in the Great Lakes Basin (Chan and Perkins 1989). It was found that aldrin was present in 5 of 75 wet precipitation samples at three of four sampling sites located around the basin. Two of the three sites had a mean concentration of 0.01 ng/L (1.0×10^{-5} ppb), while the third site had a mean concentration of 0.24 ng/L (2.4×10^{-4} ppb). Dieldrin was detected at all four sites and in >60% of the samples at mean concentrations ranging from 0.41 to 1.81 ng/L (4.1×10^{-4} – 1.8×10^{-3} ppb). The highest concentrations of both aldrin and dieldrin were found in samples collected at Pelee Island at the western end of Lake Erie (maximum concentrations of 3.4 ng/L [3.4×10^{-3} ppb] and 5.9 ng/L [5.9×10^{-3} ppb], respectively). In 1979–1980, dieldrin was detected in the ambient air and rainfall over College Station, Texas, at average concentrations of 0.08 ng/m^3 (5.1×10^{-6} ppb) and 0.80 ng/L (8×10^{-4} ppb), respectively (Atlas and Giam 1988). The washout ratio (concentration in rain/concentration in air) for dieldrin was calculated to be 8.9. Dieldrin was present in rainfall measured at three points in Canada during 1984, at mean concentrations of 0.78 ng/L (7.8×10^{-4} ppb) over Lake Superior, 0.27 ng/L in New Brunswick, and 0.38 ng/L (3.8×10^{-4} ppb) over northern Saskatchewan (Strachan 1988).

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Between 1991 and 1993, 18 fogwater samples, 31 rainwater samples, and 17 atmosphere (gas and particles) samples were analyzed for aldrin and dieldrin from a rural area in Colmar, east of France (Millet et al. 1997). The mean concentrations of aldrin and dieldrin in fogwater collected from 1991 to 1993 were 3.5 and 5 ng/mL, respectively. The mean concentrations of particle bound aldrin and dieldrin in fogwater collected from 1991 to 1993 were 15 and 17 ng/mL, respectively. The mean concentrations of aldrin and dieldrin in rainwater collected in 1992 were 0.05 and 0.5 ng/ml, respectively. The mean concentration for both aldrin and dieldrin in the vapor-phase collected in 1992 was the same at 0.7 ng/cm³. Finally, the mean concentrations of aldrin and dieldrin in the particulate phase collected in 1992 were 0.6 and 0.7 ng/mL, respectively.

The atmospheric concentration of both aldrin and dieldrin were studied in the National Park of Ordesa, Spain from April to August 1995 (Nerin et al. 1996). The study found that on April 10 and August 23, the concentration of aldrin was below detection limit (1 pg/m³) while on June 23, the concentration of aldrin was 12 pg/m³. The concentration of dieldrin on April 10 was also below the detection limit (1 pg/m³), but was detected at a concentrations of 6 and 3 pg/m³ on June 23 and August 23, respectively.

6.4.2 Water

A comprehensive study of U.S. drinking water samples (1975) revealed that <17% of the samples contained dieldrin, with 78% of the positive samples containing concentrations between 4 and 10 ng of dieldrin per L of water (0.004–0.01 ppb) (EPA 1980a). In a recent study, the concentration of various pesticides were measured six times from September 1995 to September 1996 in drinking water samples from 80 randomly selected residences of Maryland (MacIntosh et al. 1999). Dieldrin was not detected in any of the samples taken during this test (limit of detection=25 µg/L). Between November 1, 1983 and July 1, 1992, the California EPA tested various wells for pesticide residues throughout the state of California (California EPA 1995). Aldrin and dieldrin were not detected in any of the 1,304 wells (covering 33 counties) sampled during this study. In another study, dieldrin residues were analyzed for in 208 well water samples collected from nine urban areas from across the United States (Kolpin et al. 1997). Dieldrin was detected in 2.4% of wells samples (detection limit=0.005 µg/L) at a maximum concentration of 0.045 µg/L. Along the north coast of Australia, 659 water samples were surveyed for pesticide residues (McDougall et al. 1994); 20% of storage tanks of domestic water supplies were contaminated with dieldrin at or above 0.05 µg/L.

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In earlier studies, dieldrin was found more often than any other pesticide in water samples collected from all major river basins (mean concentration, 7.5 ng/L [0.0075 ppb]) in the United States (Weaver et al. 1965). In 1976, dieldrin was reported in many fresh surface waters of the United States with mean concentrations ranging from 5 to 395 ng/L (0.005–0.395 ppb) (EPA 1980a). Data maintained in the STORET database for 1980–1982 included aldrin and dieldrin concentrations in industrial effluent, ambient water, sediments, and biota. Median values from all STORET stations were as follows (Staples et al. 1985):

Media	Aldrin		Dieldrin			Percentage detectable
	Median (ppb)	Number of samples	Percentage detectable	Median (ppb)	Number of samples	
Effluent	<0.01	677	3.1	<0.01	676	3.7
Water	0.001	7,891	40.0	0.001	7,609	40.0
Sediment	0.1	2,048	33.0	0.8	1,812	33.0
Biota	<0.1	211	0	0.03	530	41

Influent and effluent samples from New York City's 14 water pollution control plants were collected and analyzed six times during the course of 5 years (1989–1993) to determine the concentration of chemical contaminants (Stubin et al. 1996). Of the 168 samples collected, aldrin was detected in 12 influent water samples in 1990, once in 1992 and 9 times in 1993. The concentration of aldrin in influent samples ranged from 0.024 to 1.1 µg/L. Aldrin was also detected in effluent samples 11 times in 1990, twice in 1992, and six times in 1993. The concentration of aldrin in effluent samples ranged from 0.008 to 0.44 µg/L. Dieldrin, however, was not detected in any influent samples, and was only detected in two effluent samples taken in 1993. The concentration of dieldrin in the effluent samples ranged from 0.012 to 0.028 µg/L.

In 1980, aldrin and dieldrin were detected in water samples taken from the Inner Harbor Navigation Canal of Lake Pontchartrain (New Orleans, Louisiana) on the ebb and flood tides at a depth of 1.5 meters; respective concentrations were 0.3 ng/L (0.0003 ppb) and 5.6 ng/L (0.0056 ppb) for aldrin and 0.6 ng/L (0.0006 ppb) and 5.9 ng/L (0.0059 ppb) for dieldrin (McFall et al. 1985). In 1987, dieldrin was detected in seawater samples taken from the Gulf of Mexico at concentrations ranging from 0.009 to 0.02 ng/L (9×10^{-6} – 2×10^{-5} ppm) and from seawater off the southeastern United States at 0.007–0.01 ng/L (7×10^{-6} – 1×10^{-5} ppm); aldrin was also detected in the southeastern U.S. coastal waters at concentrations of 0.31–1.5 ng/L (0.0003–0.001 ppb) (Sauer et al. 1989). Aldrin and dieldrin were detected in water and

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sediment samples taken between 1975 and 1980 at 160–180 stations on major rivers of the United States as part of the National Pesticide Monitoring Program. Aldrin and dieldrin were both detected in 0.2% of the 2,946 water samples and in 0.6 and 12% of the approximately 1,016 sediment samples, respectively (USGS 1985). In 1988, dieldrin was detected in 9% of 422 groundwater samples taken from a sandy, alluvial aquifer in Illinois at a median concentration of 0.01 $\mu\text{g/L}$ (1.0×10^{-5} ppb), and in 4% of groundwater well samples taken in the vicinity of an agrichemical dealer facility, at a mean concentration of 0.03 $\mu\text{g/L}$ (3.0×10^{-5} ppb) (Hallberg 1989). Out of 2,459 sites from the largest river basins and aquifers in the United States tested between 1992 and 1996, dieldrin had a frequency of detection of 1.63% and a maximum concentration of 0.068 $\mu\text{g/L}$ (Koplin et al. 2000).

Analysis of urban storm water runoff collected between 1979 and 1983 in the Canadian Great Lakes Basin found dieldrin to be present in approximately 32 of 124 water samples at a mean concentration of 5.1×10^{-4} $\mu\text{g/L}$ (5.1×10^{-4} ppb) and in approximately 17 of 110 runoff sediment samples at a mean concentration of 4.4×10^{-3} mg/kg (4.4 ppb). Aldrin was found in approximately 13 of 129 runoff sediment samples at a mean concentration of 1.2×10^{-3} mg/kg (1.2 ppb) but was not detected in any water samples (Marsalek and Schroeter 1988). These concentrations resulted in mean annual loadings to the Canadian Great Lakes Basin of 0.2 kg/year for aldrin and 0.6 kg/year for dieldrin. In 1982, water samples taken from 19 U.S. cities for the National Urban Runoff Program, found aldrin to be present only in samples taken from Washington, D.C., at a concentration of 0.1 $\mu\text{g/L}$ (0.1 ppb) (6% of samples), and dieldrin was detected only in water from Bellevue, Washington, at 0.008–0.1 $\mu\text{g/L}$ (0.008–0.1 ppb) (2% of samples) (Cole et al. 1984). Water sampling conducted during the 1986 spring isothermal period in the Great Lakes did not detect aldrin in any samples. Dieldrin, however, was present in all samples at mean concentrations ranging from 0.300 ng/L (0.0003 ppb) for Lake Superior to 0.402 ng/L (4.2×10^{-4} ppb) in Lake Erie (Stevens and Neilson 1989).

Aldrin was identified in leachate from the Love Canal industrial landfill in Niagara Falls, New York, at a concentration of 0.023 mg/L (23 ppb) (data were gathered prior to 1982) (Brown and Donnelly 1988). In 1986, a waste site was identified in Clark County, Washington, that contained buried drums believed to have originally held chemicals used at a plywood manufacturing plant. Analysis of the soil and water contamination found aldrin to be present in groundwater samples taken from shallow wells on site at a maximum concentration of 2.12 $\mu\text{g/L}$ (2.12 ppb) and in groundwater samples from nearby private wells at 0.79 $\mu\text{g/L}$ (0.79 ppb) (EPA 1986i). At a hazardous waste site in Gallaway, Tennessee, drums and bottles containing chemicals from a pesticide blending operation had been emptied or discarded into a number of

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small ponds on the site. Dieldrin was present in on-site surface waters at 0.40–1.4 ppb, but was not detected in any off-site water samples (EPA 1987i).

6.4.3 Sediment and Soil

As a result of the rapid conversion of aldrin to dieldrin, soil residues of dieldrin are found in higher concentration and with greater frequency than residues of aldrin, even though aldrin was applied more frequently to the soil. The amount of dieldrin and aldrin residues in soils was monitored from 12 separate farm lands located in the Fraser Valley of British Columbia, Canada in 1989 (Szeto and Price 1991). Each farm had a known history of at least 25 years of vegetable growing and use of various pesticides. Aldrin was detected on one farmland with muck soil at a mean concentration of 78 ppb dry weight, while dieldrin was detected on two farmlands containing muck soils at a mean concentration of 692 ppb dry weight (range from 104 to 1,280). In a separate study, the concentration ranges of dieldrin in agricultural soil samples taken in 1995 and 1996 from Alabama, Ohio, Indiana, and Illinois were not detected (nd)–23, nd–4250, nd–69, and nd–13 ng/g dry weight, respectively (Bidleman 1999).

An analysis of sediment samples taken from Lake Ontario in 1981 showed that dieldrin levels had increased from approximately 26 ng/g (26 ppb) in 1970 to 48 ng/g (48 ppb) in 1980, although the use of dieldrin was banned in much of the Great Lakes Basin in the early 1970s (Eisenreich et al. 1989). The National Soils Monitoring Program (Kutz et al. 1976) detected dieldrin in soils at varying concentrations and areas throughout 24 states; the mean concentration ranged from 1 to 49 ppb. At a hazardous waste site in Gallaway, Tennessee, drums and bottles containing chemicals from a pesticide blending operation had been emptied or discarded into a number of small ponds on the site. Dieldrin was present in sediment samples from on-site ponds at 1,400 ppb and in one off-site sediment sample (concentration not specified) (EPA 1987i). Sediment samples taken from two lakes near the U.S. Army Rocky Mountain Arsenal, Colorado in 1983, indicated that aldrin and dieldrin persisted in the sediments long after deposition ceased. Concentrations up to 2,050 ppb for aldrin and 100 ppb for dieldrin at a core depth of approximately 21 cm were found in one lake. A second lake also had elevated levels of aldrin and dieldrin contamination, but at lower concentrations (approximately 250 ppb for aldrin and 40 ppb for dieldrin) and at a lower core depth, indicating that most of the deposition had occurred at an earlier date (Bergersen 1987). The concentration of dieldrin and aldrin was also studied in sediment samples from three coastal lagoons in the southeast of the Gulf of Mexico (Botello et al. 1994). The average concentrations of aldrin in sediment samples taken from the Carmen, Machona, and Alvarado lagoons were 0.70, 1.15, and 2.11 ng/g dry weight, respectively. The average concentrations of dieldrin in

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sediment samples taken from the Carmen, Machona, and Alvarado lagoons were 6.84, 0.59, and 2.05 ng/g dry weight, respectively. A monitoring survey of 17 wetland areas in the north central United States, found dieldrin to be present in only one Iowa sediment sample at 170 ng/g (170 ppb) dry weight (Martin and Hartman 1985).

6.4.4 Other Environmental Media

The persistence of dieldrin in the environment is demonstrated by a monitoring survey conducted in and around cotton fields in four counties in Alabama between 1972 and 1974. Although cotton farmers had not used aldrin or dieldrin "for several years," dieldrin was found to be present at 7–40 ppb in 50% of the soil samples; at <100 ppb in 50% of forage samples with levels declining over time; at an average concentration of 1,490 ppb in 11 of 19 rat tissue samples with number of positive samples increasing between 1973 and 1974; at low levels in some quail tissue samples (maximum level=790 ppb); at levels declining from 302 to 70 ppb between 1972 and 1974 for mockingbird tissue samples; and at <30 ppb in most of the 25% positive fish tissue samples taken from farm ponds (Elliott 1975). Aldrin was estimated to have a half-life of 1.7 days on crops with the half-life of dieldrin ranging from 2.7 to 6.8 days depending on the crop and formulation (Willis and McDowell 1987). These half-life values were based on the disappearance of aldrin and dieldrin due to volatilization, adsorption to plant surfaces, relative humidity, rain, wind, temperature, and sunlight.

Dieldrin was detected in the liver and fat of arctic ground squirrels trapped near three lakes located at the foothills of the Brooks Range, Alaska between 1991 and 1993 (Allen-Gil et al. 1997). The mean concentrations of dieldrin in squirrel liver from Elusive Lake (seven samples), Feniak Lake (seven samples), and Schrader Lake (seven samples) were 10.91, 1.53, and 14.42 µg/g wet weight, respectively. The mean concentrations of dieldrin in squirrel fat from Elusive Lake (no samples), Feniak Lake (seven samples), and Schrader Lake (five samples) were below the minimum detectable limit, 0.0, and 0.5 µg/g wet weight, respectively.

Blood samples were collected and analyzed for dieldrin concentrations from nestling bald eagles at active nests in the Canadian portion of the Great Lakes Basin from 1990 to 1994 (Donaldson et al. 1999). Mean dieldrin concentrations in eagle blood samples taken from Lake Erie, Huron, Nipigon, Superior, and Woods were 0.003 (30 samples), 0.007 (1 sample), 0.0031 (7 samples), 0.0051 (11 samples), and 0.0031 mg/kg wet weight (2 samples), respectively. Residue levels of dieldrin in unhatched bald eagle eggs collected along Lake Erie from 1974 to 1980 (six samples) and from 1989 to 1994 (six samples)

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were 1.28 and 0.49 mg/kg wet weight, respectively. Seven bald eagle eggs from the Tanana River, Alaska collected in 1990 and 1991 contained dieldrin with a mean concentration of 0.028 ppm (Ritchie and Ambrose 1996). Peregrin falcon eggs from Rankin Inlet collected from 1991 to 1994 (20 samples) and from 1982 and 1986 (36 samples) contained dieldrin at mean concentrations of 0.361 (range of 0.13–1.66) and 0.41 (range of 0.045–1.80) $\mu\text{g/g}$ wet weight, respectively (Braune et al. 1999). Osprey eggs collected at five locations on the Fraser River from 1991 to 1997 contained dieldrin; the highest concentrations were reported at the Fraser River site below Quesnel with a mean value of 5.2 $\mu\text{g/kg}$ wet weight (Elliott et al. 2000). Lower concentrations were reported for eggs collected at the other locations with mean values generally <2 $\mu\text{g/kg}$ wet weight. dieldrin was detected with a mean concentration of 0.25 $\mu\text{g/g}$ in 75 out of 312 double-crested cormorant eggs and embryos collected from Cat Island, Green Bay, Wisconsin in 1994 and 1995 (Custer et al. 1999). The mean concentration of dieldrin in tree swallow eggs and tree swallow nestlings collected in 1998 at Pigeon Creek, Iowa (three samples); Duck Creek, Iowa (three samples); and Lindsey Harbor, Iowa (seven samples) along the Upper Mississippi River was 0.03 $\mu\text{g/g}$ wet weight (Custer et al. 2000).

Waterfowl from Northern Canada were collected from 1988 to 1995 and divided into browsers, grazers, omnivores, molluscivores, and piscivores (Braune et al. 1999). The highest concentrations of dieldrin were found in tissues of waterfowl feeding at the upper trophic levels. Concentrations of dieldrin ranged from nd to 5.0 ng/g wet weight, nd to 3.2 ng/g wet weight, nd to 15.9 ng/g wet weight, nd to 120 ng/g wet weight, and nd to 54.7 ng/g wet weight, respectively.

Mean concentrations of dieldrin in snapping turtle eggs collected at four sites along the St. Lawrence River in the Mohawk territory of Akwesasne during June, 1998 ranged from 4 to 280 ng/g wet weight with an overall mean concentration of 38.13 ng/g wet weight (de Solla et al. 2001). Aldrin and dieldrin were detected in the plasma of juvenile alligators from three lakes in central Florida (Guillette et al. 1999). The mean concentrations of dieldrin in males from Lake Woodruff, Lake Apopka, and Orange Lake were 0.24, 1.68, and 0.75 ng/mL plasma, respectively. The mean concentrations of dieldrin in females from these lakes were 0.31, 2.87, and 0.39 ng/mL plasma, respectively. The mean concentration of aldrin for juvenile alligators in all three lakes was 0.34 ng/mL plasma.

In 1985, fish samples taken from the lower Savannah River in Georgia and South Carolina were found to occasionally contain dieldrin but at concentrations of <0.01 $\mu\text{g/g}$ (10 ppb) (Winger et al. 1990); common carp and white bass samples from a lake in Kansas located in an agricultural area had mean concentrations of 0.069 and 0.058 ppb, respectively (Arruda et al. 1988). Fish samples taken from

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tributary rivers around the Great Lakes in 1980–1981 had dieldrin levels up to 0.15 mg/kg (150 ppb) (average concentration=0.03 mg/kg [30 ppb]) (DeVault 1985). Fish taken from Lake Huron between 1970 and 1980 had mean dieldrin concentrations ranging from 0.01 to 0.50 mg/kg (10–500 ppb) (EPA 1985e); however, by 1984, mean concentrations of dieldrin in Lake Michigan coho salmon had dropped to 0.01 µg/g (10 ppb) from 0.06 µg/g (60 ppb) in 1980 (DeVault et al. 1988). An analysis of 315 composite samples of whole fish collected from 107 sites nationwide in 1980–1981 as part of the National Pesticide Monitoring Program found that the mean concentrations of dieldrin were essentially unchanged since 1978–1979. In 1978, dieldrin was detected in 81% of the samples, and in 1980, in 75% of the samples at mean concentrations of 0.05 µg/g (50 ppb) wet weight and 0.04 µg/g (40 ppb), respectively (Schmitt et al. 1985). Three of eight samples of bluegill (*Lepomis macrochirus*) collected from the San Joaquin Valley in July 1981 contained dieldrin at concentrations ranging from 0.005 to 0.008 mg/kg (5–8 ppb) wet weight; four of the eight common carp (*Cyprinus carpio*) obtained from the same sites contained dieldrin at concentrations ranging from 0.015 to 0.067 mg/kg (15–67 ppb) wet weight (Saiki and Schmitt 1986). Dieldrin was also detected in a variety of fish taken from a section of Lake Oconee in Georgia that received storm runoff from insecticide-treated areas between 1981 and 1982. Dieldrin concentrations ranged from <10 to 200 µg/kg (10–200 ppb). Dieldrin was not detected in fish taken from the lake after 1982 (Bush et al. 1986). A survey of 17 wetland areas in the north central United States found dieldrin in two fish samples taken from Kansas and Iowa at concentrations of 6 ng/g (6 ppb) and 9 ng/g (9 ppb), respectively (Martin and Hartman 1985). Dieldrin was found in 5 of 20 raw bluefish fillets collected in Massachusetts waters in 1986, at concentrations of 0.02–0.04 ppm (20–40 ppb); after cooking, dieldrin was still detected in the fillets, indicating that heating does not degrade the pesticide in foods (Trotter et al. 1989). Aldrin and dieldrin were detected in shrimp (*Penaeus setiferus* and *Penaeus aztecus*) collected from the Calcasieu River Basin in an industrial area of Louisiana in 1985–1986. Aldrin was present in shrimp taken from 7 of 30 stations at concentrations ranging from 0.01 to 0.12 µg/g (10–120 ppb), and dieldrin was present in 21 of 30 samples at concentrations of 0.05–9.47 µg/g (50–9,470 ppb) (average concentration 1.57 µg/g [1,570 ppb]) (Murray and Beck 1990). Between October 1981 and September 1986, over 12,044 imported and 6,391 domestic commodities were sampled for pesticide residues. Dieldrin was detected in 420 imported and 44 domestic products; however, the tolerance (the maximum amount of a residue expected in a food when a pesticide is used according to label directions, provided that the level does not present an unacceptable health risk) for dieldrin was exceeded in only eight imported products and one domestic product, indicating that most agricultural products do not contain harmful levels of dieldrin (Hundley et al. 1988).

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The concentrations of dieldrin and aldrin were studied in bivalve mollusks obtained from three coastal lagoons in the southeast of the Gulf of Mexico (Botello et al. 1994). The average concentration of aldrin in bivalve mollusks collected from the Carmen, Machona, and Alvarado lagoons were 2.56, 1.61, and 6.61 ng/g dry weight, respectively. Dieldrin was not detected in any bivalve mollusks collected from the Carmen, Machona, and Alvarado lagoons. Dieldrin concentrations were analyzed for in nine marine mammal species samples collected in 1987 (Becker et al. 1997). The means and standard deviations of dieldrin in northern fur seal, ringed seal, pilot whale, harbor porpoise, beluga whale from the Arctic, and beluga whale from Cook Inlet were 13.6, 43.2 ± 53.8 , 262 ± 240 , 963 ± 294 , 290 ± 106 , and 105 ± 66.2 ng/g wet weight, respectively.

One study examined persistent organochlorines concentrations in blubber samples from 16 dead beluga whales collected during 1993–1994 in the St. Lawrence River estuary (Muir et al. 1996). The mean concentrations of dieldrin in seven female and nine male beluga whales were 1,360 ng/g lipid weight (lw) (range=326–2,360 ng/g lw) and 2,020 ng/g lw (range=1,440–2,620 ng/g lw), respectively. The study found a temporal upward trend in dieldrin concentration in female beluga whales and slightly augmented levels of dieldrin in males. The average dieldrin concentration in female beluga whales in 1987 was 450 ng/g lw while in males, the average concentration of dieldrin measured from 1986 to 1988 was 1,650 ng/g lw. In a separate study, biopsies were collected from Right whales in the Bay of Fundy in 1994 (30 samples), 1995 (17 samples), and 1996 (15 samples) and at sites in Georgia and Cape Cod Bay in 1997 (Weisbrod et al. 2000). For each collection period mean concentrations were 513 and 93 ng/g sample lipid content and nd, respectively, for aldrin and 1,141, 1,349, and 4,244 ng/g sample lipid content, respectively, for dieldrin. Zooplankton samples collected in 1995 and 1996 from Georges Bank, Bay of Fundy, and Cape Cod Bay contained aldrin at concentrations that were undetectable to 8.9 ng/g sample lipid content and dieldrin at concentrations that were undetectable to 23 ng/g sample lipid content.

Dieldrin concentrations were determined in archived samples of whole lake trout collected yearly from eastern Lake Ontario between 1977 and 1993 (Huestis et al. 1996). The mean concentrations of dieldrin in trout collected in 1977, 1980, 1983, 1986, 1989, 1990, 1992, and 1993 were 313, 218, 135, 103, 97.3, 99.0, 73.1, and 78.4 ng/g, respectively. An investigation of the temporal trends of pesticide residues in fish from Lake Michigan indicated a decrease in dieldrin concentrations from 1982 to 1990 (Miller et al. 1992). Total dieldrin concentrations in lake trout decreased 68% from 410 ± 50 µg/kg in 1982 to 130 ± 30 µg/kg in 1990. In Lake Superior, dieldrin concentrations in fish did not appear to as much over a 3-year period. The total dieldrin concentration in lake trout in 1982 was 50 ± 10 µg/kg while in 1985, the concentration was 40 ± 10 µg/kg. In a separate study (Zabik et al. 1996), concentrations of dieldrin in

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skin-off lake trout collected from both Lake Huron and Lake Michigan, and siscowets from Lake Superior were reported as 0.029, 0.076, and 0.027 ppm, respectively.

During the fiscal years 1989 to 1994, the U.S. Food and Drug Administration (FDA) collected and analyzed 545 domestic surveillance samples of mixed feed rations for pesticide residues (Lovell et al. 1996). The mixed feed rations represented feed fed to cattle, poultry, swine, pets, fish, and other miscellaneous animals. The results indicated that dieldrin was detected in five samples (three trace, two quantifiable) at 10 µg/kg.

Lichens collected in the Arctic between 1993 and 1994 contained detectable residues of dieldrin; concentrations of below detection to 0.72 ng/g dry weight were reported with the highest concentrations found in samples collected from Makinson Inlet and King Edward Point in the Northwest Territories (Braune et al. 1999). Saxifrage samples from Ellesmere Island and Axel Heiberg Island, collected in 1990, contained dieldrin at mean concentrations of 0.46 and 0.44 ng/g dry weight, respectively.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Use of aldrin and dieldrin for pest control on crops such as cotton, corn, and citrus products was canceled by the EPA in 1974 (EPA 1974a), while use for extermination of termites was voluntarily canceled by the manufacturer in 1987 (EPA 1990b). However, during the period of widespread use and production of aldrin and dieldrin, intake by workers who manufactured these compounds was estimated to range from 0.72 to 1.10 mg/person/day with a good correlation between levels in tissue (fat, serum, and urine) and total length of exposure or intensity of exposure (Hayes and Curley 1968). The National Occupational Exposure Survey, conducted by NIOSH between 1980 and 1983, estimated that 647 employees were exposed to aldrin and 760 employees were exposed to dieldrin in the workplace (NOES 1990). One pest control operator was found to have 0.5 and 0.3 µg dieldrin on his left and right hands, respectively, >2 years after his last exposure to aldrin; serum blood levels taken at the same time showed 10 ppb dieldrin. A further analysis of individuals exposed to dieldrin found no correlation between the pesticide levels on their hands and in their sera (Kazen et al. 1974). A 1981 survey of Florida citrus field workers found dieldrin to be present in >3% of the 567 serum samples, at a mean concentration of 1.8 ppm (1,800 ppb) (Griffith and Duncan 1985). Workers cleaning up hazardous waste sites may also be exposed, but no information on monitored levels of exposure was found.

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In one pilot study, food, beverage, and biological specimens (blood and urine) were collected and analyzed for pesticides from six farm families living in Iowa and North Carolina (Brock et al. 1998). Although dieldrin concentrations were below detection limits (0.23 ng/mL) in five of the families studied, one family in particular had elevated levels. One farmer from Iowa had a mean dieldrin concentration of 20.55 ± 2.61 ng/mL while that person's spouse had a mean concentration of 7.52 ± 0.68 ng/mL. Solid food samples from this farm also contained elevated levels of dieldrin ranging from 15.0 to 28.0 ng/g. On the other five farms, dieldrin concentrations in solid food samples were below the detection limit (0.75 ng/g). Finally, dieldrin levels in beverages were below the detection limit in five of the farm families studied except for the one family from Iowa with elevated dieldrin levels, which had an average concentration of 11.0 ng/g.

The National Health and Nutrition Examination Survey (NHANES II) conducted between 1976 and 1980, found that an estimated 10.6% of the population aged 12–74-years-old, were exposed to dieldrin based on an analysis of blood serum and urine specimens (Stehr-Green 1989). When specimens from populations in the northeast, midwest and south regions of the United States were examined almost 20% of the adults aged 45–74 years had quantifiable levels of dieldrin (mean concentration 1.4 ppb), while only 1.5% of the adults aged 12–24-years-old had quantifiable levels (mean concentration 1.4 ppb) (Murphy and Harvey 1985; Stehr-Green 1989). Dieldrin was found in 14 of 46 adipose tissue samples taken from cadavers and surgical patients during the 1982 Human Adipose Tissue Survey conducted by EPA on a nationwide basis. Concentrations of dieldrin in wet tissue were in trace amounts ranging from 0.053 to 3.84 $\mu\text{g/g}$ (53–3,840 ppb) (mean concentration, 0.458 $\mu\text{g/g}$ or 458 ppb). Aldrin was not present in any of the samples; the detection level was 0.010 $\mu\text{g/g}$ (10 ppb) for a 20-g tissue sample (EPA 1986a). In 1976 and 1984, human adipose tissue samples were taken from cadavers of Canadians from the Great Lakes region and examined for the presence of a variety of compounds. Dieldrin was found in 100% of the tissue samples taken each year at a mean concentration of 0.049 $\mu\text{g/g}$ (49 ppb) wet weight in 1976 (Mes et al. 1982) and 0.047 $\mu\text{g/g}$ (47 ppb) wet weight in 1984 (Williams et al. 1988). Adipose tissue collected from 46 infertile women in Belgium between 1996 and 1998 contained dieldrin at a mean concentration of 13.1 ± 6.6 ng/g. Dieldrin was not detected in the serum of the women (Pauwels et al. 2000). Based on a study with 12 male volunteers who ingested up to 225 μg dieldrin per day for up to 2 years, a wet weight BCF of 30 was calculated, although the BCF for the lipid fraction of body weight was 45. Other studies have found wet weight BCFs ranging from 38 to 77 (mean, 48.7) and lipid basis BCFs ranging from 55 to 115 (mean, 70.9) (Geyer et al. 1986, 1987). Blood samples taken from residents of El Paso, Texas, during 1982–1983, showed aldrin to be present in 39 of 112 samples (34%) at a mean concentration of 4.6 ppb (Mossing et al. 1985).

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Individuals living in homes contaminated by past termiticide treatment constitute a significant group exposed to aldrin and dieldrin in indoor air. Measurements of air concentrations in homes 1–10 years after termiticide treatment showed dieldrin levels ranging from 0.0006 to 0.03 ppb in living rooms and bedrooms and all interior areas (Dobbs and Williams 1983). Air samples were taken and analyzed for aldrin over the course of 6 months from 29 dwellings treated with aldrin for prevention of termite infestation (Gun et al. 1992). Blood samples were also analyzed for dieldrin levels of one occupant from each dwelling. The concentration of atmospheric aldrin was recorded for the first six months of the study. Prior to treatment, the median concentration of aldrin was $0.044 \mu\text{g}/\text{m}^3$; 1 week post-treatment $2.6 \mu\text{g}/\text{m}^3$; 6 weeks post-treatment, $0.72 \mu\text{g}/\text{m}^3$; and 6 months post-treatment, $0.57 \mu\text{g}/\text{m}^3$. Prior to treatment, the median concentration of dieldrin in blood was $0.75 \text{ ng}/\text{mL}$ while 3 months post-treatment the median concentration was $1.2 \text{ ng}/\text{mL}$.

The levels of aldrin and dieldrin were monitored in human blood samples taken from the general population from the rural town of Ahmedabad, India (Bhatnagar et al. 1992). Blood samples from 31 male subjects, ages 18–57 (mean 28.4 years), were collected from 1989 to 1990. The concentration of aldrin and dieldrin ranged from 0 to $0.813 \mu\text{g}/\text{L}$ (mean $0.200 \mu\text{g}/\text{L}$) and from 0 to $3.730 \mu\text{g}/\text{L}$ (mean $2.152 \mu\text{g}/\text{L}$), respectively.

A pilot study of non-occupational general population exposure to pesticides in ambient air inside and outside the home was conducted in nine homes in Florida in August 1985. Air was monitored for 24 hours outside the house and inside the house, and personal air monitors were worn by one occupant of each house. Aldrin and dieldrin were detected in indoor air at 6 and 5 of the 9 households, respectively; outdoors at 4 of the 9 households each; and by personal monitors for 3 and 5 of the 9 individuals, respectively. In one designated high-pesticide-use household, aldrin and dieldrin were detected in the indoor air at average concentrations of $0.058 \mu\text{g}/\text{m}^3$ (0.004 ppb) and $0.038 \mu\text{g}/\text{m}^3$ (0.002 ppb), respectively. Neither compound was detected in the outdoor air immediately adjacent to the home, and concentrations detected with personal air monitors were half (aldrin) to one-third (dieldrin) the concentrations for ambient indoor air (Lewis et al. 1988). A composite sample of the dust from four Seattle homes collected in 1988–1989 showed dieldrin to be present at 1.1 ppm, although none of the homeowners could remember using the pesticide. It was suggested that the source of the dieldrin was soil surrounding the homes; however, since the use of dieldrin is restricted to termite control, and Seattle has few termites, the source of the contaminated soil is unknown (Roberts and Camann 1989).

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Atmospheric sampling of aldrin and dieldrin conducted from 1970 to 1972 indicated that aldrin and dieldrin were present at mean concentrations of 0.4 ng/m^3 (2.7×10^{-5} ppb) and 1.6 ng/m^3 (1.02×10^{-4} ppb), respectively (Kutz et al. 1976). Combining these figures and assuming that 20 m^3 of air are inspired each day, average daily intake of aldrin plus dieldrin from the atmosphere would be 0.57 ng/kg body weight in 1972. However, the cancellation of the use of these compounds suggests that current inhalation intake will be much less. Guicherit and Schulting (1985) used data on air samples collected in the western part of the Netherlands in 1979–1981 and calculated the average daily intake by inhalation to be $0.02 \text{ ng dieldrin/kg}$ body weight and $0.01 \text{ ng aldrin/kg}$ body weight.

A significant source of general population exposure to dieldrin is through diet. In the absence of occupational or domestic use as a pesticide, food is probably the primary source of dieldrin residues in human adipose tissues (Ackerman 1980). Because of the rapid epoxidation of aldrin in the environment, it is not considered to be an important human dietary contaminant, with an average intake of $<0.001 \text{ } \mu\text{g/kg/day}$. Dieldrin, however, may be ingested as a result of eating contaminated fish, milk, and other foods with a high fat content including meat. EPA established tolerances for aldrin and dieldrin in or on raw agricultural commodities at maximums of $0.0\text{--}0.1 \text{ ppm}$, depending on the crop (Sittig 1980). Table 6-1 shows a summary of dieldrin residues in adult dietary components analyzed in 1981–1982 (Gartrell et al. 1986a). A 1985 Canadian survey of foods found that although aldrin was not detected in any of the food samples analyzed, dieldrin was detected in all food composites at $0.00011 \text{ } \mu\text{g/g}$ in fruit; $0.0019 \text{ } \mu\text{g/g}$ in milk; $0.0031 \text{ } \mu\text{g/g}$ in leafy vegetables, eggs, and meat; and $0.023 \text{ } \mu\text{g/g}$ in root vegetables (Davies 1988). Dieldrin residues may persist in foods such as milk butterfat and subcutaneous fat in cattle with an estimated half-life in butterfat of 9 weeks (Dingle et al. 1989). Samples of ultra-pasteurized heavy cream and cow's milk purchased in Binghamton, New York, in 1986 had dieldrin levels of 0.006 and 0.003 ppm , respectively (Schechter et al. 1989a).

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Table 6-1. Dieldrin Residues in Adult Dietary Components (1980–1982)^a

Food group	Residue range (ppm)	Average concentration (µg/day)
Dairy	Trace to 0.003	0.0006
Fish, poultry, meat	Trace to 0.004	0.0012
Potatoes	Trace to 0.002	0.0004
Root vegetables	Trace to 0.005	0.0004
Leaf vegetables	Trace to 0.002	0.0002
Legumes	ND	ND
Garden fruits	Trace to 0.011	0.0021
Fruits	0.001	0.0001
Cereals and grain	0.004	0.0001
Oils and fats	Trace to 0.002	0.0003
Sugar	ND	ND
Beverages	ND	ND

^aDerived from Gartrell et al. 1986a

ND = not detected

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During the period of 1965–1970, total U.S. dietary intake was reported to be 0.05–0.08 ug dieldrin/kg/day and 0.0001–0.04 ug aldrin/kg/day (IARC 1974b). Since 1970, the use of aldrin and dieldrin on food has been cancelled, and dietary intake has decreased. An FDA Total Diet Study, conducted between 1982 and 1984, found that aldrin intake was <0.001 µg/kg/day for all age and sex groups (Gunderson 1988; Lombardo 1986). Adults had a dieldrin intake of 0.007 µg/kg/day (25–30-year-old males). Dieldrin was found in 15% of the food samples analyzed. These values represent a decrease from the 1980 Total Diet Study. Between 1980 and 1982–1984, daily intakes of dieldrin decreased from 22 ng/kg/day to 8 ng/kg/day for adults (Gunderson 1988). Recently, a Total Diet Study conducted by FDA, found dieldrin in only 6% of the food items analyzed from 1990 (FDA 1991). A daily intake of 0.0016 µg/kg body weight was estimated for 60–65-year-old females, respectively (FDA 1991). The average daily dietary intake of chemical contaminants in food were estimated for 116,957 U.S. adults in 1990 based on annual diet as part of the annual U.S. FDA Total Diet Study (MacIntosh et al. 1996). The estimated mean dietary exposure of dieldrin for 78,882 adult females and 38,075 adult males studied ranged from 0.08 to 0.43 µg/day (mean=0.5 µg/day) and from 0.02 to 4.0 µg/day (mean=0.5 µg/day), respectively. High levels of dietary exposures to dieldrin were estimated to be primarily due to frequent consumption of summer and winter squash, while those with low exposure were dominated by foods that contained residue levels below the limits of detection. During the Total Diet Study conducted by the FDA from November 1993 to June 1994, dieldrin was detected 58 times (concentrations and estimated daily intakes not specified) out of a total of 783 foods sampled (FDA 1995). Assuming that 2 L of water are ingested each day, the average drinking water contribution of dieldrin may range from 0.1 to 0.29 ng/kg/day for a 70 kg adult. These levels are well below the Acceptable Daily Intake (ADI) of 0.1 µg/kg/day recommended by the World Health Organization (WHO) for dieldrin (Geyer et al. 1986). Organohalogen residue levels were monitored from May 1990 to July 1991 in 806 composite milk samples collected from 63 cities within the United States (Trotter and Dickerson 1993). Dieldrin was detected in 172 milk samples ranging from trace amounts to 2 µg/L (detection limit=0.5 µg/L).

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

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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).

The widespread use of agricultural pesticides in California has raised concerns about exposures in nearby residential communities, particularly to children (Bradman et al. 1997). To determine the potential exposure to dieldrin, house dust and handwipe samples from children were collected and analyzed from 11 homes, 5 of which had at least 1 farmworker resident. Dieldrin was detected in house dust from one home of a farmworker at a concentration of 0.10 $\mu\text{g/g}$. Dust loading (the fraction dislodgeable by vacuum) of dieldrin was 0.45 $\mu\text{g/m}^2$. These data indicates that the highest chronic daily intake for children would be 1.0×10^{-3} $\mu\text{g/kg/day}$. Nine middle-income households located in the Raleigh-Durham-Chapel Hill area of North Carolina were evaluated for children's pesticide exposure (Lewis et al. 1994). Each house had at least one child in the 6-month to 5-year range. Aldrin was detected in five of the houses, while dieldrin was detected in all nine houses in various matrices (soil samples, dust samples, air samples, etc.). Since dieldrin was detected so often and at higher concentrations, it was studied more intently. The researchers found that the mean concentration of dieldrin was 0.12 $\mu\text{g/g}$ in house dust samples, <0.01 $\mu\text{g/g}$ in child hand rinse samples, 0.01 $\mu\text{g/m}^3$ in air samples taken from the living room, and 0.03 $\mu\text{g/g}$ in play area soil. The estimated exposures of children by respiration and ingestion of house dust ranged from not detectable to 0.13 $\mu\text{g/day}$ and from not detectable to 0.04 $\mu\text{g/day}$, respectively. Judging by these results, it appears that inhalation of indoor air from houses contaminated with aldrin and dieldrin is a major route of child exposure. Due to the greater persistence of dieldrin in the environment, children are expected to have greater exposure to dieldrin than aldrin.

Inhalation of aldrin and dieldrin in outdoor ambient air, however, is not expected to be a significant source of exposure for children. During a study of atmospheric concentrations of chemical contaminants from 1970 to 1972, researchers found that the mean concentrations for aldrin and dieldrin were 0.4 and 1.6 ng/m^3 , respectively (Kutz et al. 1976). Since all but one of their uses were canceled by the EPA in 1974, ambient air concentrations of aldrin and dieldrin are expected to be much lower today. Children living near NPL sites containing high concentrations of aldrin and dieldrin, however, may be exposed to higher than normal atmospheric concentrations. Studies of this nature, however, have not been located. Inhalation exposure may be important during a spill of aldrin or dieldrin before environmental equilibrium is attained. Under these conditions, high concentrations of both compounds would be found in the atmosphere, especially closer to the ground since both compounds are heavier than air. This

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situation, however, is not expected to occur since aldrin and dieldrin are no longer produced or used commercially.

In Streaky Bay, a rural community located on the west coast of South Australia, the contamination of a school by aldrin was studied (Calder et al. 1993). Between August and November 1986, a 0.5% aqueous aldrin emulsion was used within the school as a termiticide. The geometric mean air concentrations of aldrin sampled within the school were $0.09 \mu\text{g}/\text{m}^3$ in March 1987, $0.11 \mu\text{g}/\text{m}^3$ in May 1988, $0.05 \mu\text{g}/\text{m}^3$ in August 1988, and $0.06 \mu\text{g}/\text{m}^3$ in September 1988. Aldrin contamination was highest in carpet samples with concentrations ranging from 31,600 to 77,000 $\mu\text{g}/100 \text{ cm}^2$. Aldrin is rapidly metabolized to dieldrin and was therefore monitored for in school attendants (Calder et al. 1993). The arithmetic mean concentration of dieldrin in serum samples collected from 138 people was 1.41 ng/mL with a maximum concentration of 9.3 ng/mL in 1987. One year later in 1988, the arithmetic mean concentration of dieldrin decreased to 0.74 ng/mL with a maximum of 2.2 ng/mL.

The FDA Total Diet studies are based on levels found in representative commercially available food products. However, many infants receive human breast milk as a major dietary component rather than milk purchased in grocery stores. Therefore, the daily intake of aldrin and dieldrin by infants may be more closely related to concentrations of dieldrin found in mother's milk. Infants are particularly sensitive to aldrin and dieldrin due to their higher intestinal permeability and immature detoxification system. Dieldrin was found in the breast milk of 80.8% of 1,436 nursing women sampled in 1980, with the greatest percentage (88.9%) in samples collected in the southeastern United States and the lowest percentage from samples collected in the northeast (63.9%) (Savage et al. 1981). The mean fat-adjusted residue level of these samples was 164 ppb. Assuming that milk fat accounts for approximately 3% of whole milk, this would correspond to approximately 5 ppb in whole milk. Of 54 nursing mothers studied in Hawaii (1979–1980), 94% had dieldrin in their milk (Takei et al. 1983). The mean concentration in milk fat was 42 ppb, which would correspond to a concentration of 1.3 ppb in whole milk. Of 57 nursing women sampled in 1973–1974 in Arkansas and Mississippi, 28% had a dieldrin residue level of 4 ppb in their milk (Strassman and Kutz 1977). A level of 0.5 ppb was found in a national survey of the general Canadian population (Davies and Mes 1987).

Several factors may influence the levels of dieldrin found in breast milk. For example, a highly significant ($p < 0.001$) association was reported in women with low levels of dieldrin in breast milk and a history of breast-feeding several children (Ackerman 1980). In addition, women who consume foods lower on the food chain, i.e., vegetarians, had dieldrin levels in their breast milk that were only 1–2% as

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high as the average levels in the United States (Hergenrather et al. 1981). Also, a mother's total body weight may influence the concentration of dieldrin found in breast milk. In a study of Israeli women conducted in 1975, those weighing over 72 kg had significantly lower levels of dieldrin in their breast milk (6 ppb) than those weighing under 63 kg (8.7 ppb) (Polishuk et al. 1977a). This difference was observed despite similar plasma levels of dieldrin in the two groups. A Swedish study found that dieldrin levels in mother's milk decreased from 0.076 µg/g (44 ppb) to 0.010 µg/g (10 ppb) between 1967 and 1984–1985; the use of dieldrin in Sweden was prohibited in 1970 (Norén and Meironyte 2000). A survey of 14 human milk donors whose homes in western Australia had been treated yearly with various pesticides for termite control found dieldrin residues in the milk ranging from 2 to 35 ng/g (2–35 ppb) (mean of 13 ng/g [13 ppb]) (Stacey and Tatum 1985). Milk levels of dieldrin peaked at 7–8 months after house treatment. Three of the 14 houses had recently been treated with aldrin, and the houses of the 11 other donors had been treated with aldrin previously. Dietary intake may have contributed partially to the milk levels since there was not a good correlation between dieldrin and the most recent use of aldrin.

A total of 412 breast milk samples from women in all provinces of Canada were analyzed for organochlorine residues in 1986 (Mes et al. 1993). Dieldrin was detected in 94% of all samples (detection limit=0.009 ng/g) at a mean concentration of 0.46 ng/g (maximum=4.42 ng/g). The study also examined dieldrin concentrations from earlier years. In both 1967 and 1970, the mean concentration of dieldrin in Canadian breast milk samples was 5 ng/g, in 1975, it was 2 ng/g, while in 1982, the concentration dropped to 1 ng/g. Breast milk samples were collected from 23 primiparous mothers and analyzed for their total amount of organochlorine residues from January to November 1992 (Quinsey et al. 1996). The results indicated that the mean daily intake of dieldrin from breast milk would be 0.32 µg/kg body weight/day with a range of 0.06 to 2.24 µg/kg body weight/day. The difference in organochlorine pesticide concentrations in human milk and infant formulas was examined in 1993 (Pico et al. 1995). Human milk samples were obtained from 15 women aged 29–40 living along the Spanish Mediterranean coastal area. The infant formulas analyzed included 11 starting formulas, 11 follow-up formulas, 4 adapted infant formulas, and 17 specialized formulas. Aldrin and dieldrin were not detected in either human milk nor formula samples (detection limit for aldrin=5.1 µg/L, detection limit for dieldrin=6.0 µg/L).

Studies show that transplacental transfer of aldrin and dieldrin occurs. A study of organochlorine compounds in mothers and fetuses during labor found that dieldrin concentrations in extracted lipids of fetal blood (1.22 ppm) and placenta (0.80 ppm) greatly exceeded those in maternal blood (0.53 ppm) and uterine muscle (0.54 ppm) (Polishuk et al. 1977b). In a study measuring contaminant levels in the cord

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blood of newborn aboriganals and non-aboriginals of the Northwest Territories and Southern Quebec, Canada, mean concentrations of aldrin were found to be 0.01 µg/L in all populations (Van Oostdam et al. 1999). A study of four Iraqi women with no known exposure to organochlorine pesticides found dieldrin levels in the placenta to range from 0.006 to 0.020 mg/kg total tissue weight and average dieldrin levels in their milk to range from 0.007 to 0.023 mg/kg whole milk. However, there was no correlation between the level of dieldrin in the placenta and the level in milk for each individual (Al-Omar et al. 1986).

An FDA Total Diet Study, conducted between 1982 and 1984, found that aldrin intake was <0.001 µg/kg/day for all age and sex groups and that toddlers (2-years-old) had the highest intake levels for dieldrin at 0.016 µg/kg/day, followed by infants at 0.010 µg/kg/day (Gunderson 1988; Lombardo 1986). In 1980 and from 1982 to 1984, daily intakes of dieldrin decreased from 33 to 10 µg/kg/day for infants and from 46 to 16 ng/kg/day for toddlers (Gunderson 1988). The average daily dietary intake for adolescent males (14–16-year-olds) was 0.08 µg/kg/day in 1984. Recently, a Total Diet Study conducted by the FDA found dieldrin residues in only 6% of the food items analyzed from 1990 (FDA 1991). Daily intakes of 0.0014 and 0.0016 µg/kg body weight were estimated for infants 6–11 months old and for 14–16-year-old adolescents in 1990 (FDA 1991). During the Total Diet Study conducted by the FDA from November 1993 to June 1994, dieldrin was detected 58 times (concentrations and estimated daily intakes not specified) out of a total of 783 foods sampled (FDA 1995). The Total Diet Study food list includes many foods eaten by infants and children.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Infants and toddlers are possibly exposed to higher levels of aldrin or dieldrin in the diet than are adults. Table 6-2 is a listing of calculated daily dietary intakes of dieldrin for adults, toddlers, and infants. Infant and toddler dietary intakes decreased significantly from 1978 to 1982. They remained elevated, however, when compared with adult dietary intake.

Higher exposure rates can be expected for large segments of the population residing in homes treated with aldrin or dieldrin for termite control. Measurements of air concentrations in homes 1–10 years after

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Table 6-2. Calculated Dietary Intakes ($\mu\text{g}/\text{kg}$ of Body Weight/Day) of Dieldrin for Three Population Groups^a

Group	1981–1982	1980	1979	1978
Adults	0.016	0.022	0.016	0.017
Infants	0.020	0.033	0.048	0.045
Toddlers	0.023	0.046	0.036	0.039

^aDerived from Gartrell et al. 1986a, 1986b

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pesticide treatment showed dieldrin concentrations ranging from 0.002 to 0.17 ppb in roof voids and from 0.0006 to 0.03 ppb in living rooms and bedrooms and all interior areas (Dobbs and Williams 1983). The indoor air concentrations of aldrin and dieldrin were monitored in the basement, main level, and upstairs area of a treated home from September 1987 to April 1995 (Wallace et al. 1996). In this particular home, aldrin had been poured directly into the foundation blocks during construction. Initially, the aldrin concentrations in air samples taken from the living area and the basement in September 1987 were 300 and 5,000 ng/m³, respectively, while dieldrin concentrations were 7 and 28 ng/m³, respectively. By June 1989, levels of aldrin in the living area and basement were 20 and 300 ng/m³, respectively, while dieldrin concentrations were 5 and 20 ng/m³, respectively. At the end of the study in April 1995, levels of aldrin in the living area and basement were 2 and 12 ng/m³, respectively, while dieldrin concentrations were 3 and 20 ng/m³, respectively. The concentrations of aldrin and dieldrin in air collected outside the home in April 1995 were <0.05 and 0.3 ng/m³, respectively. Eight years after the initial treatment, aldrin and dieldrin were still detected in the living space of the home.

An assessment of the environmental contamination of a residential community built on a thick layer of harbor sludge in the Netherlands, found that the maximal combined daily intake of aldrin, dieldrin, isodrin, and telodrin by soil ingestion, inhalation of contaminated indoor air, and diet exceeded the ADI by a factor of three (Van Wijnen and Stijkel 1988). The concentrations of these compounds were highest in soil samples taken from the top 40 cm. The total indoor air concentrations of the compounds in the living rooms of homes built on contaminated soil were 10 times higher than outdoor air levels (9.9 ng/m³ versus 0.8 ng/m³); levels in the crawl spaces of these homes were 100 times higher (88.7 ng/m³) than outdoor levels although no explanation was given for these elevated levels. Dieldrin concentrations were also elevated in vegetables grown in the soil (up to 40 mg/kg fresh weight) and resulted in a recommendation against the consumption of home-grown vegetables. Dieldrin concentrations were not elevated in drinking water samples in any of the homes tested.

Persons with chronic skin disease may be at increased risk from occupational exposure to pesticides. A formulator with scleroderma had higher blood and tissue levels of dieldrin than did his associates with similar exposures (Hayes 1982). Residents who live near hazardous waste sites that contain aldrin or dieldrin may also have greater exposure to these compounds as a result of contact with contaminated environmental media. Although aldrin is unlikely to persist, dieldrin may enter surface water as a result of surface runoff of contaminated soil. Only limited information is available regarding the extent of contamination at hazardous waste sites and the levels to which individuals may be exposed.

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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 aldrin and dieldrin 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 aldrin and dieldrin.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of aldrin and dieldrin are sufficiently well defined to allow assessments of the environmental fate of the compounds to be made (Budavari 1996; Clayton and Clayton 1994; Guerin and Kennedy 1992; Hayes 1982; HSDB 2001a, 2001b; NIOSH 1997; Verschueren 1996). No additional information is needed.

Production, Import/Export, Use, Release, and Disposal. The risk for exposure of the general population to substantial levels of aldrin or dieldrin is quite low. Aldrin and dieldrin have not been produced in the United States since 1974, nor is there any indication that U.S. production of either of these two chemicals will resume (EPA 1990b). Aldrin has not been imported into the United States since 1985 (EPA 1986d). No information was available regarding exports of aldrin or dieldrin, nor was information available regarding the amount of these insecticides currently stockpiled in the United States. Information regarding stockpile levels of aldrin and dieldrin would prove useful.

Currently, all uses of aldrin and dieldrin have been canceled (EPA 1990b). However, due to the persistence of dieldrin in the environment, the likelihood of its bioconcentration, and the former widespread use of both aldrin and dieldrin, these agents are still found at low levels in foods such as root crops and meat and dairy products. Concentrations of dieldrin are significantly higher than aldrin

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residues due to the high rate of conversion of aldrin to dieldrin in the environment and dieldrin's relative stability in environmental matrices.

The soil around dwellings that have been treated with termiticides containing aldrin and dieldrin is the environmental media most likely to be contaminated with significant quantities of aldrin and dieldrin. The air within treated homes may also contain elevated levels of these agents.

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 Toxic Chemical Release Inventory (TRI), which contains this information for 1997, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions. However, for aldrin and dieldrin, there are no TRI data, indicating that no industrial releases of either of these chemicals were reported for 1997.

Incineration and activated-carbon adsorption have >99% efficiencies as methods for disposing of aldrin or dieldrin (HSDB 2001a, 2001b). However, no information is available regarding the amounts of aldrin or dieldrin disposed of by each method. Additional information on current disposal patterns would prove useful.

Environmental Fate. Aldrin released to surface and shallow subsurface soils partitions to the atmosphere where it is transported (Caro and Taylor 1971; Elgar 1975; McLean et al. 1988). In deeper subsurface soils, aldrin generally is sorbed to soil particulates (McLean et al. 1988); under most environmental conditions, aldrin should not leach to groundwater (McLean et al. 1988). Aldrin is biotransformed to dieldrin in aerobic soils (Gannon and Bigger 1958; Gupta et al. 1979). Additional information is needed on the transformations of aldrin in anaerobic soils and sediments.

Dieldrin sorbs to soils and sediments (Briggs 1981; Cliath and Spencer 1971). The compound also partitions to biota and slowly volatilizes from soils to the atmosphere (Nash 1983). Dieldrin is transported in the particulate phase in surface water runoff (Caro and Taylor 1971; Eye 1968; Hardee et al. 1964) and in the atmosphere (Baldwin et al. 1977). In deep subsurface soils, dieldrin is sorbed to particulates and does not leach to groundwater (Dobbs et al. 1989). The compound is persistent in environmental media, being resistant to biodegradation and abiotic transformation (Gannon and Bigger 1958; Jagnow and Haider 1972). Based on dieldrin's vapor pressure, it will exist in both the vapor and particulate phase in the atmosphere (Grayson and Fosbraey 1982). Vapor-phase dieldrin is expected to

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react with hydroxyl radical; while particulate phase dieldrin will be removed from the atmosphere by wet and dry deposition. Information concerning the relative percentage of dieldrin that will exist in the particulate and vapor-phase in the environment would prove useful in predicting its atmospheric fate.

Bioavailability from Environmental Media. Limited available pharmacokinetic data indicate that the compounds are absorbed by humans following inhalation of contaminated air (Stacey and Tatum 1985). Absorption also occurs following oral and dermal exposures (Feldmann and Maibach 1974; Heath and Vandekar 1964; Hunter and Robinson 1967; Hunter et al. 1969; Iatropoulos et al. 1975). Additional information is needed on the absorption of the compounds following ingestion of contaminated drinking water and soils. This information would be useful in evaluating the importance of various routes of exposure to populations living in the vicinity of hazardous waste sites.

Food Chain Bioaccumulation. Aldrin and dieldrin are bioconcentrated by plants, animals, and aquatic organisms and biomagnified in aquatic and terrestrial food chains (Bhatnagar et al. 1988; Cole et al. 1976; Connell 1989; Donaldson et al. 1999; Metcalf et al. 1973; Sanborn and Yu 1973; Shannon 1977; Travis and Arms 1988). Food chain bioaccumulation appears to be a more important fate process for dieldrin, which is very persistent in nature, than for aldrin, which is rapidly converted to dieldrin (EPA 1980a; Metcalf et al. 1973). No additional information is necessary.

Exposure Levels in Environmental Media. Aldrin and dieldrin have historically been detected in ambient air (Hoff et al. 1996), surface water (EPA 1980a; Stubin et al. 1996), drinking water (EPA 1980a), soils (Eisenreich et al. 1989; Kutz et al. 1976), sediments (Bergersen 1987; Staples et al. 1985), and foods (EPA 1985e; Hundley et al. 1988). Many current monitoring studies indicate that the concentrations of both aldrin and dieldrin in environmental matrices are decreasing (California EPA 1995; MacIntosh et al. 1999; Miller et al. 1992). Aldrin has been identified in at least 207 of the 1,613 hazardous waste sites and dieldrin has been identified in at least 287 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 2002). Recent estimates of dietary intake, which is believed to be the most important source of exposure for most members of the general population, are also available (FDA 1991, 1995). More recent monitoring data would be useful in more accurately predicting human exposure.

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Exposure Levels in Humans. The presence of dieldrin in human blood and adipose tissue has been used as an indicator of exposure to aldrin and dieldrin (Brock et al. 1998). The compounds have also been widely detected in human breast milk (Davies and Mes 1987; Quinsey et al. 1996; Savage et al. 1981; Takei et al. 1983). Additional information on the concentration of these compounds in the biological tissue and fluids of populations living in the vicinity of NPL sites would be helpful in assessing the extent to which these populations have been exposed to these compounds.

Exposures of Children. With the detection of dieldrin in drinking water (Kolpin et al. 1997), studies that detail the exposure of infants fed formula prepared from tap water would prove helpful. More data are needed to properly assess aldrin and dieldrin exposure to children who live, play, or attend school near NPL sites and farmlands that have been treated with these pesticides. Information regarding the number of houses in the United States that have been treated with aldrin and dieldrin formulations in the past would be useful in determining the number of children that would be potentially exposed today. The stability of these compounds, especially dieldrin, suggests the possibility that they may be brought home by farm workers who work on farmlands previously treated with these compounds. More exposure studies that monitor aldrin and dieldrin exposure to children of farm workers would be extremely valuable.

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

Exposure Registries. No exposure registries for aldrin and dieldrin were located. These substances are not currently any of the compounds for which subregistries have been established in the National Exposure Registry. These substances 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 these substances.

Information is particularly needed on the size of the populations potentially exposed to aldrin and dieldrin through contact with contaminated media in the vicinity of hazardous waste sites. The development of an exposure registry would provide a useful reference tool in assessing exposure levels and frequencies. It would also facilitate the conduct of epidemiological or health studies to assess any adverse health effects resulting from exposure to aldrin and/or dieldrin. In addition, a registry developed on the basis of exposure sources would allow an assessment of the variations in exposure levels from one source to

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another and the effect of geographical, seasonal, and regulatory action on the level of exposure within a certain source. These assessments, in turn, would provide a better understanding of the needs for research or data acquisition on the current exposure levels.

6.8.2 Ongoing Studies

A pilot project is under way in South Dakota to identify types and levels of pesticide residues in breast milk of South Dakota residents and to evaluate the effect of diet and maternal weight change on proximate composition and pesticide excretion levels in milk. The project will also estimate pesticide loading in breast-fed and non-breast-fed infants. To date, trace amounts of dieldrin (>0.001 ppm) have been detected in human milk samples. Levels of dieldrin appear to decrease from week 1 to week 7 postpartum.

Remedial investigations and feasibility studies conducted at the NPL sites contaminated with aldrin and dieldrin will add to the available database on exposure levels in environmental media and in humans and will contribute information for exposure registries. Investigations at the sites will also increase the current knowledge regarding the transport and transformation of aldrin and dieldrin at hazardous sites. No other long-term research studies regarding the environment fate and transport of aldrin and dieldrin or the occupational and general population exposure to these compounds were identified.

The Federal Research in Progress (FEDRIP 2001) database and the Current Research and Information System database funded by the U.S. Department of Agriculture (CRIS/USDA 2001) provide additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-3.

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Table 6-3. Ongoing Studies on the Potential for Human Exposure to Aldrin and Dieldrin

Investigator	Affiliation	Research description	Sponsor	Source
Childress C	Department of Interior, U.S. Geological Survey, Water Resources Division, North-Central North Carolina	There is no long-term regional water-quality monitoring data for many of the streams and tributaries to the drinking water supplies of the Research Triangle area of North Carolina. Many of these streams continue to receive a complex combination of treated industrial and municipal waste, in addition to nonpoint urban and agricultural runoff. This study is aimed at documenting the spatial differences in regional surface-water quality. The study will test for dieldrin concentrations.	U.S. Geological Survey	FEDRIP 2001
Morlock S	Department of Interior, U.S. Geological Survey, Water Resources Division, Northwest Indiana	To build an extensive database of major contaminants in the most contaminated tributaries of Lake Michigan and to assess the mobility of these contaminants. This information can be used to estimate the loads of these contaminants to Lake Michigan. The contaminants to be studied are 100 polychlorinated biphenyl (PCB) congeners, dieldrin, and chlordane.	U.S. Geological Survey	FEDRIP 2001

7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Analytical methods exist for measuring aldrin, dieldrin, and their metabolites in blood, body tissues, breast milk, urine, food, fish, and feces. The primary method used is gas chromatography (GC) coupled with electron capture detection (ECD). Since aldrin is metabolized rapidly to dieldrin, exposure to aldrin or dieldrin is measured exclusively by determining levels of dieldrin in blood. Exposure is also measured by determining the levels of dieldrin in fat since it is rapidly distributed to adipose tissue. Metabolites of aldrin and dieldrin have been measured in feces and urine; however, they are not routinely used to quantify exposure to aldrin or dieldrin (Klein et al. 1968; Walker et al. 1969). A summary of the methods for various biological media is presented in Table 7-1.

Dieldrin is determined in blood and fat using GC/ECD. Two commonly used preparation methods for determining levels of dieldrin in blood are the acetone extraction procedure and the hexane extraction procedure (EMMI 1997; Robinson et al. 1967). The difference between the two is in the initial step where dieldrin is extracted from blood with either acetone or hexane. Both preparation methods are followed by concentration and extraction with hexane. A comparison of the two methods showed that the concentration of dieldrin in the blood with the hexane extraction method is only 65–70% of the concentration of dieldrin in blood using the acetone extraction method. The authors suggest that the relationship may indicate a partitioning of dieldrin between hexane and whole blood (Robinson et al. 1967). The reproducibility of the acetone technique is better than that of hexane. One preparation

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Table 7-1. Analytical Methods for Determining Aldrin/Dieldrin in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (dieldrin)	Hexane extraction.	GC/ECD	1 ng/mL	100%	MacCuaig 1976
Blood or serum	Samples are extracted using hexane. Concentrate down to 0.5 mL in hexane. Dilution may be necessary.	GC/ECD HERL Method 004	NR	NR	EMMI 1997
Serum (dieldrin)	Denature with methanol, mixed solvent extraction with hexane/ethylether, elute from activated silica gel.	GC/ECD	NR	70–75%	Burse et al. 1983
Adipose tissue	Samples are extracted using petroleum ether and acetonitrile. Filter through sodium chloride. Concentrate to 5 mL in petroleum ether.	GC/ECD HERL Method 001	NR	NR	EMMI 1997
Tissue and human milk	Samples are extracted using acetonitrile and concentrated down using hexane.	GC/ECD HERL Method 003	NR	NR	EMMI 1997
Milk (aldrin and dieldrin)	Milk sample homogenized, fat extraction. Florisil clean-up, elution with hexane and acetonitrile.	GC/ECD	NR	NR	Stacey and Tatum 1985
Milk	Homogenize milk. Multiresidue extraction through microcartridge. Elution with hexane and methanol.	GC/ECD	NR	aldrin 99% dieldrin 70%	Barcarolo et al. 1988

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Table 7-1. Analytical Methods for Determining Aldrin/Dieldrin in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Samples are extracted using methyl cyanide. Residues are concentrated in petroleum ether and purified using Florisil.	GC/ECD AOAC Method 970.52	NR	• 80%	Helrich 1990
Fatty foods	Samples are extracted using petroleum ether and acetonitrile. Clean-up using Florisil.	GC/ECD FDA Method 211.1	NR	NR	EMMI 1997
Non-fatty foods	Samples are extracted with acetonitrile or water-acetonitrile. Residues are transferred into petroleum ether.	GC/ECD FDA Method 212.1	NR	NR	EMMI 1997
Fish	Blended fish samples are extracted using petroleum ether and acetonitrile. Concentration and cleanup of extrant is done using an alumina or silica column.	GC/ECD USGS Method O9104	NR	NR	EMMI 1997
Feces (9-hydroxy-dieldrin)	Feces homogenized and extracted with acetone, then hexane. Florisil clean-up. Elute with acetone and hexane.	GC/ECD GC/MS	NR	NR	Richardson and Robinson 1971

7. ANALYTICAL METHODS

Table 7-1. Analytical Methods for Determining Aldrin/Dieldrin in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (urinary metabolites of aldrin and dieldrin)	Urine mixed with ethyl ether and petroleum ether. Dried over anhydrous sulfate, concentrated. Florisil clean-up. Elution with ethyl ether/petroleum ether to remove aldrin and ethyl ether/acetone to remove dieldrin.	GC/ECD	NR	NR	Klein et al. 1968
Fat, liver, brain (dieldrin)	Tissues extracted with hexane/acetone solution. Fats partitioned between hexane and dimethyl formamide. Florisil clean-up. Elution with 10% ether in hexane.	GC/ECD	0.5 ng	95%	Walker et al. 1969

AOAC = Association of Official Analytical Chemists; FDA = Food and Drug Administration; GC/ECD = gas chromatography/electron capture detector; GC/MS = gas chromatography/mass spectrometry; ng = nanogram; NR = not reported; USGS = U.S. Geological Survey

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method used for measuring levels of dieldrin in fat includes extraction with hexane/acetone solution, partitioning between hexane and dimethylformamide (DMF), clean-up, and elution in hexane. Recovery and sensitivity of this technique are good. Precision was not reported (Walker et al. 1969).

Aldrin and dieldrin have also been measured in samples of milk using GC/ECD (Barcarolo et al. 1988; EMMI 1997; Stacey and Tatum 1985; Takei et al. 1983). Sample preparation steps for milk involve homogenization, lipid extraction with hexane and acetone, residue extraction with acetonitrile, and partitioning into hexane. Recovery was adequate for dieldrin and good for aldrin. Precision was good. Sensitivity was not reported (Barcarolo et al. 1988).

A method describing the extraction of aldrin and dieldrin from fish samples employs similar procedures (EMMI 1997). This method is only applicable for fish tissue containing at least 0.1 µg/kg of analyte. A specific detection limit, however, was not mentioned for aldrin or dieldrin. Homogenized fish samples are extracted using petroleum ether and concentrated in acetonitrile. Cleanup is performed using an alumina or silica column. A GC/ECD is used to determine the total concentration of aldrin or dieldrin in the sample. Percent recovery was not reported.

7.2 ENVIRONMENTAL SAMPLES

Methods exist for determining aldrin and dieldrin in air, water, municipal effluents, sludge, and soil (Clesceri et al. 1998a; EPA 1986j; NIOSH 1984; OSW 1986a). The most common methods involve separation by GC coupled with ECD, electrolytic conductivity detector, or mass spectrometry (MS). GC has also been used with Fourier transform infrared spectroscopy (FTIR). Table 7-2 summarizes the methods that have been used to analyze for aldrin and dieldrin in environmental samples. The primary methods used for analyzing aldrin and dieldrin in air are GC/ECD and GC/electrolytic conductivity detector. The preparation method recommended by NIOSH for analysis of aldrin in air samples involves trapping the air on a glass fiber filter and extraction in an isooctane gas bubbler (NIOSH 1984). An alternative procedure to this method is the replacement of the gas bubbler with a stainless steel trapping tube packed with Tenax[®]GC (Wallace and Sherren 1986). Tenax[®]GC is an efficient absorbent for aldrin. The solvent trapping efficiency for the isooctane procedure ranges from 83 to 94% while the trapping

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Table 7-2. Analytical Methods for Determining Aldrin/Dieldrin in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (aldrin)	Adsorption on Tenax®-GC, elution with acetone/petroleum spirit.	GC/ECD	0.003 ppb	76–110%	Wallace and Sherren 1986
Air (aldrin)	Collection on glass fiber filter; extract in isooctane glass bubbler.	GC/ECD NIOSH Method 5502	2.2 ppm	103%	NIOSH 1984
Water	Samples extracted with methylene chloride. Solvent exchange to hexane prior to GC analysis.	GC/ECD Method OSW 8080A	aldrin 0.004 ppb dieldrin 0.002 ppb	aldrin 81% dieldrin 90%	EPA 1986j
Water	Samples extracted with methylene chloride, dried and concentrated. Solvent exchange to hexane.	GC/MS	1 ppb for aldrin and dieldrin)	aldrin 83–96% in reagent water; 94% river water dieldrin 97–106% in reagent water, 90% in river water	Alford-Stephens et al. 1986
Municipal and industrial effluent	Samples extracted with methylene chloride. Heat solution to 80 •C and add hexane. Concentrate.	GC/ECD APHA Method 6630C	aldrin 0.004 ppb dieldrin 0.002 ppb	aldrin 100% dieldrin 100%	Clesceri et al. 1998a
Municipal and industrial effluent	Sample is extracted with methylene chloride at pH>11 and then at pH<2. Extract is dried, concentrated, and analyzed.	GC/MS APHA Method 6410B	aldrin 1.9 ppb dieldrin 2.5 ppb	aldrin 1–166% dieldrin 29–136%	Clesceri et al. 1998b

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Table 7-2. Analytical Methods for Determining Aldrin/Dieldrin in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Samples extracted with acetone. Solvent exchange to hexane, dried over sodium sulfate; acetone added.	GC/MS	5 ng (aldrin and dieldrin)	aldrin 76–102% dieldrin 84–101%	Kobayashi et al. 1983
Soil	Soil mixed with acetone, filtered dried, extracted with hexane.	GC/MS	5 ng	aldrin 90% dieldrin 94%	Kobayashi et al. 1983
Solid waste, soils, and groundwater	Sample extraction varies depending on the matrix being tested.	GC/MS OSW Method 8250A	aldrin 1.9 ppb (water) dieldrin 2.5 ppb (water)	aldrin 0.1–166% dieldrin 29–136%	OSW 1986b
Soil/sludge	Samples are extracted with hexane-acetone (1:1) or methylene chloride-acetone (1:1). If necessary, an appropriate clean-up procedure is performed prior to analysis.	Narrow Bore Capillary Column with ECD OSW Method 8081B	aldrin 0.8 ppb (sludge) dieldrin 0.49 ppb (sludge)	aldrin 92% in sludge, 92% in clay dieldrin 89% in sludge, 113% in clay	OSW 1986a

APHA = American Public Health Association; EPA = Environmental Protection Agency; GC/ECD = gas chromatography/electron capture detector; GC/MS = gas chromatography/mass spectrometry; ng = nanogram; NIOSH = National Institute for Occupational Safety and Health; OSW = Office of Solid Waste

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efficiency for Tenax[®]GC is >99%. Also, use of Tenax[®]GC does not require frequent replenishment of the volatile solvent needed for the isooctane bubbler, and the Tenax[®]GC trapping tube can be transported easily from sampling sites to the laboratory (Wallace and Sherren 1986). The sensitivity of these methods is in the low- to sub-ppb range. Precision is good. Recoveries for these methods are generally good but can range from 76 to 110%, depending on the series of solvents used in the preparation method. The methods most frequently used to analyze water samples containing aldrin and dieldrin are GC/ECD and GC/MS. Interferences by phthalate esters can pose a problem in pesticide determinations when using the ECD. Interferences from phthalates can best be minimized by avoiding contact with any plastic materials. The contamination from phthalate esters can be completely eliminated with an electrolytic conductivity detector (EPA 1986j).

Aldrin and dieldrin are isolated from aqueous media by extraction in methylene chloride followed by drying with sodium sulfate, concentration, and solvent exchange to hexane (Alford-Stevens et al. 1986; EPA 1986j; Marsden et al. 1986). The limit of detection for both aldrin and dieldrin is in the low- to sub-ppb range for GC/ECD and GC/MS, respectively. Accuracy is generally good with the percent recoveries for dieldrin (90–106%) being higher than those for aldrin (81–96%). The precision obtained using GC/MS was better than that obtained using GC/ECD. The majority of analytical laboratories continue to rely on ECD for determination of aldrin and dieldrin. The main reason is that ECD provides a greater degree of sensitivity than MS. The difference in sensitivity has been reported to be as much as 2–3 orders of magnitude. The sensitivity of this method, however, depends on the level of interferences. Samples may require cleanup with a Florisil[®] column. The ECDs, however, do not provide the molecular structure information that is obtained with an MS detector. The structural information increases the level of confidence that the compound being measured has been correctly identified (Alford-Stevens et al. 1986). GC/FTIR has also been used to measure aldrin and dieldrin in water. However, this is not the recommended method because chlorinated pesticides are weak infrared absorbers (Gomez-Taylor et al. 1978).

Aldrin and dieldrin in solid samples such as soil and sediment are quantified mainly by GC/ECD and GC/MS (EPA 1986j; Kobayashi et al. 1983; Marsden et al. 1986). The soil or sediment samples are prepared for analysis by extraction with a mixture of methylene chloride and acetone, followed by drying with sodium sulfate, and solvent exchange to hexane. Recoveries are generally good, and detection limits are in the low- to sub-ppb range for GC/MS and GC/ECD, respectively. While GC/ECD is highly sensitive, this method requires a complicated clean-up procedure to remove interferences in the sample that produce peaks having the same retention times. The MS detector is a simple, rapid, and selective

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method for the determination of aldrin and dieldrin in soil and is free from sample-related interferences (Kobayashi et al. 1983). Aldrin and dieldrin have been measured in fruits and vegetables using GC/ECD. Sample preparation involves boiling in water with a cyclic steam distillation unit with 2,2,4-trimethylpentane in the solvent trap. Variations in recoveries were reported. Sensitivity and precision were not reported (Santa Maria et al. 1986).

7.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of aldrin and dieldrin are 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 aldrin and dieldrin.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods exist for determining aldrin and dieldrin in blood (Burse et al. 1983; MacCuaig 1976; Robinson et al. 1967), milk (Barcarolo et al. 1988; Stacey and Tatum 1985; Takei et al. 1983), body tissues (Walker et al. 1969), feces (Richardson and Robinson 1971), and urine (Klein et al. 1968). These methods are sensitive for measuring levels at which health effects might occur, as well as background levels in the population. Methods for determining dieldrin in blood are relatively precise; however, improvements in recovery of dieldrin are needed. These improvements would allow for better evaluation of exposure to aldrin or dieldrin. Sensitive techniques exist for measuring dieldrin in tissues;

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however, precision data are lacking. Data on the determination of dieldrin or its metabolites in milk, urine, and feces are limited. More information on the sensitivity and recovery obtained for these methods is needed to evaluate the value of using levels of dieldrin or its metabolites as an indicator of exposure.

Effect. The methods for determining biomarkers of effect are the same as those for exposure, and are subject to the same limitations. Improved methods could allow a better assessment of the relationship between levels of dieldrin in blood, body tissues, and fluids and the known health effects associated with these chemicals.

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Methods for determining levels of aldrin and dieldrin in air (NIOSH 1984; Wallace and Sherren 1986), water (Alford-Stevens et al. 1986; EPA 1986j), and soil (EPA 1986j; Kobayashi et al. 1983; Marsden et al. 1986) are sensitive enough to measure background levels in the environment, as well as levels at which health effects might occur. Analytical procedures for the analysis of aldrin and dieldrin in foods were also located (EMMI 1997). Research investigating the relationship between levels measured in air, water, soil, and foods and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed.

7.3.2 Ongoing Studies

No ongoing studies regarding new analytical methods for determining aldrin and dieldrin in environmental media or food products were reported in either the CRIS/USDA database or the Federal Research in Progress database (CRIS/USDA 2001; FEDRIP 2001).

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

ATSDR has developed two MRL values for aldrin. An acute-duration oral MRL of 2×10^{-3} mg/kg/day was derived for aldrin based on its ability to cause decreased body weight and neurological changes (increased electroconvulsive shock threshold) in offspring of mice exposed during gestation (Al-Hachim 1971). A chronic-duration oral MRL of 3×10^{-5} mg/kg/day was derived for aldrin based on liver effects in rats (hepatocellular enlargement, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation) (Fitzhugh et al. 1964). ATSDR has also derived two MRL values for dieldrin. An intermediate-duration oral MRL of 1×10^{-4} mg/kg/day was derived for dieldrin based on impaired learning of a successive discrimination reversal task in monkeys (Smith et al. 1976). A chronic-duration oral MRL of 5×10^{-5} mg/kg/day was derived for dieldrin based on liver parenchymal cell changes in rats (Walker et al. 1969).

EPA (IRIS 2002a, 2002b) has derived oral reference doses (RfDs) for aldrin and dieldrin of 3×10^{-5} and 5×10^{-5} mg/kg/day, respectively, based on liver toxicity in rats (Fitzhugh et al. 1964; Walker et al. 1969). No inhalation MRLs or reference concentrations (RfCs) have been derived for aldrin or dieldrin.

Aldrin and dieldrin are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1999c).

All uses of aldrin and dieldrin were canceled in 1974, except for subsurface ground insertion for termite control, dipping of nonfood roots and tops, and moth-proofing by manufacturing processes in a closed system (EPA 1974a). In 1987, these final three uses were voluntarily canceled by the sole manufacturer (EPA 1989a).

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Table 8-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin

Agency	Description	Information		Reference
<u>INTERNATIONAL</u>				
Guidelines:				
IARC	Carcinogenicity classification Aldrin and dieldrin	Group 3 ^a		IARC 2001
<u>NATIONAL</u>				
Regulations and Guidelines:				
a. Air				
ACGIH	TWA Aldrin and dieldrin ^b	0.25 mg/m ³		ACGIH 2001
NIOSH	TWA-REL			NIOSH 2001
	Aldrin and dieldrin	0.25 mg/m ³		
	IDLH			
	Aldrin	0.25 mg/m ³		
	Dieldrin	0.50 mg/m ³		
OSHA	8-hour TWA Aldrin and dieldrin ^b	0.25 mg/m ³		OSHA 2001b 29CFR1910.1000
	8-hour TWA for construction industry Aldrin and dieldrin ^b	0.25 mg/m ³		OSHA 2001c 29CFR1926.55
	8-hour TWA for shipyard industry Aldrin and dieldrin ^b	0.25 mg/m ³		OSHA 2001a 29CFR1915.1000
b. Water				
EPA	Drinking water standards and health advisories			EPA 2000
	Aldrin			
	10-kg child			
	1-day and 10-day	3x10 ⁻⁴ mg/L		
	DWEL ^c	1x10 ⁻³ mg/L		
	Dieldrin			
	10-kg child			
	1-day and 10-day	5x10 ⁻⁴ mg/L		
	DWEL ^c	2x10 ⁻³ mg/L		
	Groundwater monitoring	<u>Method</u>	<u>PQL (µg/L)</u>	EPA 2001d 40CFR264 Appendix IX
	Aldrin and dieldrin	8080	0.05	
		8270	10	

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin (*continued*)

Agency	Description	Information	Reference
<u>NATIONAL</u> (<i>cont.</i>)			
EPA	Land disposal restrictions— universal treatment standards		EPA 2001g 40CFR268.48
	Aldrin		
	Wastewater standard	0.021 mg/L ²	
	Non-wastewater standard	0.066 mg/kg ²	
	Dieldrin		
	Wastewater standard	0.017 mg/L ²	
	Non-wastewater standard	0.130 mg/kg ²	
	National recommended water quality criteria		EPA 1999h
	Aldrin		
	Freshwater	3.0 µg/L	
	Saltwater	1.3 µg/L	
	Human health consumption		
	Water and organism	1.3x10 ⁻⁴ µg/L	
	Organism only	1.4x10 ⁻⁴ µg/L	
	Dieldrin		
	Freshwater	0.24 µg/L	
	Saltwater	0.71 µg/L	
	Human health consumption		
	Water and organism	1.4x10 ⁻⁴ µg/L	
	Organism only	1.4x10 ⁻⁴ µg/L	
	Reportable quantity of hazardous substance designated pursuant to Section 311 of the Clean Water Act—aldrin and dieldrin	1 pound	EPA 2001b 40CFR117.3
	Requirement to monitor unregulated contaminant—aldrin and dieldrin		EPA 1999i 64 FR 1495
	Toxic pollutant effluent standards—ambient water criterion for aldrin/dieldrin in navigable waters	0.003 µg/L	EPA 2001l 40CFR129.100
	Water programs—designation of hazardous substance in accordance with Section 311(b)(2)(A) of the Act		EPA 2001m 40CFR116.4

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Table 8-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin (*continued*)

Agency	Description	Information	Reference
<u>NATIONAL</u> (<i>cont.</i>)			
c. Food			
USDA	Labeling of seed treated with aldrin (technical) and dieldrin	"This seed has been treated with poison"	USDA 2001 7CFR201.31a
d. Other			
ACGIH	Carcinogenicity classification Aldrin Dieldrin	A3 ^d A4 ^e	ACGIH 2001
EPA	Aldrin		IRIS 2001a
	Carcinogenicity classification	B2 ^f	
	Oral slope factor	$1.7 \times 10^1 \text{ (mg/kg/day)}^{-1}$	
	Drinking water unit risk	$4.9 \times 10^{-4} \text{ (}\mu\text{g/L)}^{-1}$	
	Inhalation unit risk	$4.9 \times 10^{-3} \text{ (}\mu\text{g/m}^3\text{)}^{-1}$	
	RfC	Not available	
	RfD	$3 \times 10^{-5} \text{ mg/kg/day}$	
	Dieldrin		IRIS 2001b
	Carcinogenicity classification	B2 ^f	
	Oral slope factor	$1.6 \times 10^1 \text{ (mg/kg/day)}^{-1}$	
	Drinking water unit risk	$4.6 \times 10^{-4} \text{ (}\mu\text{g/L)}^{-1}$	
	Inhalation unit risk	$4.6 \times 10^{-3} \text{ (}\mu\text{g/m}^3\text{)}^{-1}$	
	RfC	Not available	
	RfD	$5 \times 10^{-5} \text{ mg/kg/day}$	
	Effluent guidelines and standards; toxic pollutant designated pursuant to Section 307(a)(1) of the Act—aldrin and dieldrin		EPA 2001c 40CFR401.15
	Health-based limits for exclusion of waste-derived residues—residue concentration limits Aldrin and dieldrin	$2 \times 10^{-5} \text{ mg/kg}$	EPA 2001e 40CFR266 Appendix VII
	Identification and listing as a hazardous waste and identified as an acute hazardous waste Aldrin Dieldrin	P004 P037	EPA 2001f 40CFR261.33(e)
	Pesticide classification for aldrin and dieldrin	Chlorinated organic pesticide	EPA 2001j 40CFR180.3(e)(4)

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Table 8-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin (*continued*)

Agency	Description	Information	Reference
<u>NATIONAL</u> (<i>cont.</i>)			
EPA	Reportable quantity designated as a CERCLA hazardous substance under Section 311(b)(4) and 307(a) of the Clean Water Act and RCRA Section 3001—aldrin and dieldrin	1 pound	EPA 2001a 40CFR302.4
	Risk specific doses		EPA 2001h
	Aldrin	2.0×10^{-3} ug/m ³	40CFR266
	Dieldrin	2.2×10^{-3} ug/m ³	Appendix V
	Superfund, extremely hazardous substance and threshold planning quantity—aldrin	500/10,000 pounds	EPA 2001i 40CFR355 Appendix A
	Toxic chemical release reporting; Community right-to-know—effective date		EPA 2001k 40CFR372.65
	Aldrin	01/01/87	
<u>STATE</u> Regulations and Guidelines:			
a. Air			
Washington	Toxic air pollutant and acceptable source impact levels (annual average at 10^{-6} risk)		BNA 2001
	Aldrin	2.0×10^{-4} µg/m ³	
	Dieldrin	2.2×10^{-4} µg/m ³	
Wisconsin	Hazardous air contaminants acceptable ambient concentrations		WI Department of Natural Resources 1997
	Aldrin and dieldrin		
	<25 feet emission point	0.020880 pounds/hour	
	• 25 feet emission point	0.086400 pounds/hour	
b. Water			
Arizona	Drinking water guideline		HSDB 2001a,b
	Aldrin	0.002 µg/L	
	Dieldrin	0.001 µg/L	
California	Drinking water guideline		HSDB 2001a,b
	Aldrin and dieldrin	0.05 µg/L	

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Table 8-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin (*continued*)

Agency	Description	Information	Reference
<u>STATE</u> (<i>cont.</i>)			
Florida	Drinking water guideline Aldrin Dieldrin	0.05 µg/L 0.1 µg/L	HSDB 2001a,b
Hawaii	Unregulated contaminant	Monitoring is required	HI Department of Health 1999a
Hawaii	Water quality standards Aldrin Freshwater Acute Chronic Saltwater Acute Chronic Fish Consumption Dieldrin Freshwater Acute Chronic Saltwater Acute Chronic Fish Consumption	 3.0 µg/L No standard 1.3 µg/L No standard 2.6x10 ⁻⁵ µg/L 2.5 µg/L 1.9x10 ⁻³ µg/L 0.71 µg/L 1.9x10 ⁻³ µg/L 2.5x10 ⁻⁵ µg/L	BNA 2001
Illinois	Primary drinking water standard Aldrin and dieldrin	1 µg/L	BNA 2001
Kansas	Water quality standards Aldrin Aquatic life Acute Chronic Agriculture Livestock Public health Food procurement Dieldrin Aquatic life Acute Chronic Agriculture Livestock Public health Food procurement	 3 µg/L 1x10 ⁻³ µg/L 1 µg/L 7.9x10 ⁻⁵ µg/L 1.0 µg/L 1.9x10 ⁻³ µg/L 1.0 µg/L 7.6x10 ⁻⁵ µg/L	BNA 2001

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Table 8-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin (*continued*)

Agency	Description	Information	Reference
<u>STATE</u> (<i>cont.</i>)			
Maine	Drinking water guideline Dieldrin	0.02 µg/L	HSDB 2001b
New Hampshire	Drinking water guideline Aldrin and dieldrin	0.002 µg/L	HSDB 2001a,b
New Jersey	Ground water quality criteria Aldrin and dieldrin	0.002 µg/L	BNA 2001
South Dakota	Unregulated chemicals—aldrin and dieldrin	Required monitoring by all community and non- transient non- community water systems	BNA 2001

^aGroup 3: not classifiable as to its carcinogenicity to humans

^bSkin notation: danger of cutaneous absorption

^cDWEL: A lifetime exposure concentration protective of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from a drinking water source.

^dA3: confirmed animal carcinogen with unknown relevance to humans

^eA4: not classifiable as a human carcinogen

^fB2: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FR = Federal Register; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PQL = practical quantitation limits; RCRA = Resource Conservation Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; USDA = U.S. Department of Agriculture

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (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_(LO) (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—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 points. These models advance the importance of physiologically based models in that they clearly

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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, 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 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₍₅₀₎ (TD₅₀)—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. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used;

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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.

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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.

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MRL WORKSHEET

Chemical Name: Aldrin
CAS Number: 309-00-2
Date: April, 2002
Profile Status: Third Draft, Post Public
Route: ☐ Inhalation ☒ Oral
Duration: ☒ Acute ☐ Intermediate ☐ Chronic
Key to Figure: 7m
Species: mouse

Minimal Risk Level: 0.002 ☒ mg/kg/day ☐ ppm

Reference: Al-Hachim GM. 1971. Effect of aldrin on the condition avoidance response and electroshock seizure threshold of offspring from aldrin-treated mother. Psychopharmacologia 21:370-373.

Experimental design: Pregnant albino mice (7/group) were given aldrin at 0, 2, or 4 mg/kg by gavage during the third trimester of pregnancy for 5–7 days. The 0 mg/kg/day dose group received only corn oil. Litters were weaned at 30 days of age. Three groups of 10 offspring were randomly selected from each group of maternal animals and were subsequently tested for effects of prenatal exposure to aldrin. From the time of weaning until they were 37 days old, the offspring were tested for the acquisition of conditioned avoidance response. On post partum day 38, the offspring were tested for electroshock seizure threshold.

Effects noted in study and corresponding doses: At both 2 and 4 mg/kg/day, offspring showed decreased body weight and increased electroconvulsive shock thresholds. Values at both levels were statistically significant, but the effects seen at 4 mg/kg/day were not of greater magnitude than those seen at 2 mg/kg/day. Conditioned avoidance responding was not affected.

Dose and end point used for MRL derivation: 2 mg/kg/day; decreased body weight and electroconvulsive shock threshold in offspring of treated mice.

☐ NOAEL ☒ LOAEL

Uncertainty Factors used in MRL derivation:

- ☒ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

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

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Other additional studies or pertinent information that lend support to this MRL: Another study showed developmental toxicity at higher doses of aldrin in mice and hamsters (Ottolenghi 1974). Hamsters showed increased fetal mortality at 50 mg/kg when aldrin was administered on gestation days 7, 8, or 9, and mice showed an increase in the incidence of webbed feet at 25 mg/kg when aldrin was administered on gestation day 9. These results support the developmental toxicity of aldrin. The end points measured in the MRL study may be more sensitive indicators of fetal toxicity than fetal death or malformations.

Agency Contact (Chemical Manager): G. Douglas Hanley

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MRL WORKSHEET

Chemical Name: Aldrin
CAS Number: 309-00-2
Date: June, 2002
Profile Status: Third Draft, Post Public
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Key to Figure: 21r
Species: rat

Minimal Risk Level: 0.00003 ☒ mg/kg/day ☐ ppm

Reference: Fitzhugh OG, Nelson AA, Quaife ML. 1964. Chronic oral toxicity of aldrin and dieldrin in rats and dogs. Food Cosmet Toxicol 2:551-562.

Experimental design: Weanling Osborne-Mendel strain rats (24/dose, evenly divided by sex) were administered aldrin (recrystallized, •99% purity) in the diet at concentrations of 0, 0.5, 2, 10, 50, 100, or 150 ppm for 2 years. Aldrin was dissolved in corn oil prior to mixing in the diet. Feed and water were available *ad libitum*. During the exposure period, the rats were evaluated for body weight (weekly), clinical observations, and mortality; it is unclear how often observations for clinical signs and mortality were made. At the end of the exposure period, surviving rats were sacrificed and autopsied. Animals that died before the end of the first year of exposure were autopsied, but organ weights were not recorded. Only 68% (115/168) of the rats in the study were examined microscopically; most of these only had the liver, kidneys, testes, and gross lesions or tumors examined. The other animals had a more extensive histopathological examination that included lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal gland, thyroid, tumors, and gross lesions; additionally, the urinary bladder and prostate were frequently examined.

Effects noted in study and corresponding doses: Significant increases in liver to body-weight ratio and hepatic histopathological changes consistent with exposure to chlorinated hydrocarbons were observed at doses as low as 0.5 ppm. The hepatic lesions at 0.5 and 2 ppm were slight (e.g., enlarged centrilobular hepatocytes with cytoplasmic eosinophilia somewhat increased, and peripheral migration of the basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation), but progressed in severity with increasing dose. At 10 ppm, an increase in vacuolation of hepatic cells was observed. Survival was reduced at 50 ppm and above, and distended and hemorrhagic bladders were seen in males dying before termination of the study. In animals exposed to 100 and 150 ppm, an increase in the severity of nephritis was observed. This occurred predominantly in males. Reassessment of the renal histopathology data by Reuber (1980) found that male rats ingesting 10 ppm and above had an increased incidence and greater severity of nephritis than did control animals. Some of the animals that consumed high doses and died early had diffuse necrosis of the renal tubules.

A number of the changes at 0.5 ppm are consistent with a marked hepatic adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. The observation of hepatocellular hypertrophy is consistent with adaption. Increased cytoplasmic eosinophilia in this case is likely associated with the adaptive response of marked proliferation of the smooth endoplasmic reticulum (SER). The peripheralization of cytoplasmic basophilic granules is most likely the result of outward compression of detached ribosomes by massively expanding SER. Ribosomal detachment has been observed in chlorinated hydrocarbon toxicity. Cytoplasmic vacuolation is a common manifestation of cellular degeneration. Bile duct proliferation is

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known to occur in response to chronic toxic injury. Modifications occurring in the mixed function oxidase system consequent to the adaptive response may result in its functional enhancement or neutralization. This in turn has the consequence of potentiating or inhibiting toxic responses to other exogenous substances. While the mechanism of aldrin-mediated hepatotoxicity has not been elucidated, the adaptive response is considered to be an adverse effect of aldrin. The cellular adaption that results from aldrin toxicity creates a liver that potentially has a tremendously heightened state of metabolic activity, which correspondingly may have a similarly heightened capacity to toxify or detoxify upon continued exposure to aldrin.

Dose and end point used for MRL derivation: 0.5 ppm (0.025 mg/kg/day); enlarged hepatocyte, increase in cytoplasmic eosinophilia with peripheral migration of basophilic granules, and possible increases in vacuolation and bile duct proliferation.

[] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? ppm doses (mg/kg diet) were multiplied by a food factor of 0.05 kg diet/kg body weight/day (EPA 1986m). The resulting doses were 0, 0.025, 0.1, 0.5, 2.5, 5, and 7.5 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: Other adverse hepatic effects observed in chronic-duration studies with aldrin include hyaline droplet degeneration in dogs that ingested 0.12–0.25 mg/kg/day of aldrin for 15.7 months (Treon et al. 1955b) and slight-to-moderate fatty degeneration in dogs exposed to 1 mg/kg/day of aldrin for 25 months (Fitzhugh et al. 1964). These studies are, however, limited in that the number of dogs tested was quite small. Several chronic duration studies with dieldrin also showed adverse hepatic effects. Rats exposed to 0.16–0.063 mg/kg/day dieldrin throughout their lifetime were reported to have hepatic lesions consisting of centrilobular degeneration and peripheral hyperplasia (Harr et al. 1970), but incidence data and statistical analyses were not provided to support this conclusion and the use of a semisynthetic diet may have compromised the rats. Also mice exposed to 1.3 mg/kg/day dieldrin for 2 years had livers with occasional necrotic areas (Thorpe and Walker 1973), but incidence was not reported and it is unclear whether the necrotic areas were secondary to tumor development. In the 2-year study used to derive the MRL for dieldrin, absolute and relative liver weights were increased in female rats at • 0.05 mg/kg/day, and liver parenchymal cell changes, “considered to be characteristic of exposure to organochlorine insecticide” but not otherwise specified, were increased at 0.5 mg/kg/day.

The chronic oral MRL is the same as the EPA RfD for aldrin (IRIS 2002a), as the value (3×10^{-5} mg/kg/day) is based on the same study (Fitzhugh et al. 1964), species (rat), end point (liver

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effects), and effect level (0.025 mg/kg/day LOAEL). The chronic oral MRL remains the same as that reported previously by ATSDR (1993).

Agency Contact (Chemical Manager): G. Douglas Hanley

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MRL WORKSHEET

Chemical Name: Dieldrin
CAS Number: 60-57-1
Date: June, 2002
Profile Status: Third Draft, Post Public
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Key to Figure: 44K
Species: monkey

Minimal Risk Level: 0.0001 ☒ mg/kg/day ☐ ppm

Reference: Smith RM, Cunningham WL, Van Gelder GA. 1976. Dieldrin toxicity and successive discrimination reversal in squirrel monkeys (*Saimiri sciureus*). J Toxicol Environ Health 1:737-747.

Experimental design: Technical dieldrin was dissolved in absolute ethanol and injected into marshmallows in 10 μ L amounts, which resulted in doses of 0.01 or 0.1 mg dieldrin/kg/day when fed to squirrel monkeys. The low- and high-dose groups consisted of three and four monkeys, respectively; another group of two monkeys served as controls. All monkeys were tested for their ability to learn a visual nonspatial successive discrimination reversal task during a 55-day period of daily dosing with dieldrin.

Effects noted in study and corresponding doses: Signs of impaired learning were apparent within 15 days of treatment initiation in the 0.1 mg/kg/day dose group, and persisted throughout the 55 days of treatment. The monkeys consuming 0.01 mg dieldrin/kg/day did not appear to be adversely affected with respect to learning ability when compared to controls.

Dose and end point used for MRL derivation: 0.01 mg/kg/day; impaired learning of a successive discrimination reversal task.

☒ NOAEL ☐ LOAEL

Uncertainty Factors used in MRL derivation:

- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

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

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Other additional studies or pertinent information that lend support to this MRL: The choice of this end point is supported by the study of Burt (1975) in which impaired maze training was noted in rats treated for 60–120 days with a diet containing 5 ppm of dieldrin (converted to a dose of 0.25 mg/kg/day using reference values from EPA 1986m).

Agency Contact (Chemical Manager): G. Douglas Hanley

APPENDIX A

MRL WORKSHEET

Chemical Name: Dieldrin
CAS Number: 60-57-1
Date: June, 2002
Profile Status: Third Draft, Post Public
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Key to Figure: 59r
Species: rat

Minimal Risk Level: 0.00005 ☒ mg/kg/day ☐ ppm

Reference: Walker AIT, Stevenson DE, Robinson J, et al. 1969. The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. Toxicol Appl Pharmacol 15:345-373.

Experimental design: Rats (25/sex/dose; 45/sex/controls) were fed diet containing 0, 0.1, 1.0, or 10.0 ppm dieldrin for 2 years. Based on intake assumptions reported by investigators (1 ppm=0.0475 mg/kg/day in males and 0.0582 mg/kg/day in females), doses were • 0.005, 0.05, and 0.5 mg/kg/day. Study end points included clinical observations, food intake, body weight, clinical chemistry, hematology, urine indices, organ weights, gross pathology, and histology (including liver, heart, lungs, spleen, lymph nodes, stomach, intestines, kidneys, bladder, thyroid, parathyroid, adrenals, pancreas, reproductive tissues, brain, muscle, skin, and eyes). Liver-related clinical chemistry indices included plasma alkaline phosphatase, SGOT, and bile pigments in the urine.

Effects noted in study and corresponding doses: Effects in the rats included increased absolute and relative liver weights in females at • 0.05 mg/kg/day. Liver parenchymal cell changes, “considered to be characteristic of exposure to organochlorine insecticide” but not otherwise specified, were increased in high-dose females; total incidences during 2 years of exposure were 0/23, 0/23, 0/23, and 6/23 females at 0, 0.005, 0.05, and 0.5 mg/kg/day, respectively. In males, these liver parenchymal changes were only observed in one high-dose animal (i.e., 1/23 at 0.5 mg/kg/day). Two of the 0.5 mg/kg/day females and one control female also showed focal hyperplasia of the hepatic parenchymal cells, forming microscopic nodules. Other kinds of hepatic lesions (focal parenchymal necrosis, proliferated ductules, focal fibrosis, and/or cystic hyperplasia of intrahepatic bile ducts) were seen in a few rats of both sexes, but were not treatment-related as they were dispersed among the test and control groups (5/23, 0/23, 2/23, and 5/23 in females and 4/43, 0/23, 1/23, and 2/23 in males at 0, 0.005, 0.05, and 0.5 mg/kg/day, respectively). There were no indications of dieldrin-related changes in serum alkaline phosphatase or SGPT, histology of non-liver tissues, or body weight in any of the exposed groups, although irritability, tremors, and occasional convulsions (characteristic signs of dieldrin neurotoxicity) occurred at 0.5 mg/kg/day. These behavioral changes usually occurred during handling, did not progress after 3 months of exposure, and did not affect well-being.

Dose and end point used for MRL derivation: 0.005 mg/kg/day. Liver weight was increased at the LOAEL (0.05 mg/kg/day), with progression to parenchymal cell changes including focal hyperplasia at 0.5 mg/kg/day.

☒ NOAEL ☐ LOAEL

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Uncertainty Factors used in MRL derivation:

- ☐ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No. Dietary ppm concentration was converted to mg/kg/day dose using reported intake assumptions as indicated in the experimental design summarized above.

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: Other studies in rats and dogs support the choice of liver toxicity as the end point for the chronic oral MRL (Fitzhugh et al. 1964; Harr et al. 1970). Exposure for 2 years caused slight hepatic histopathological changes in rats at 0.025 and 0.1 mg/kg/day that were considered to be adverse effects of dieldrin (Fitzhugh et al. 1964). At 2.5 mg/kg/day and above, the changes were considered to be marked and included an increase in the severity of hepatic cell vacuolation. In the Harr et al. (1970) study, centrilobular degeneration and pyknosis of hepatic cell nuclei were reported in rats fed “critical levels of dieldrin” (0.016–0.063 mg/kg/day) throughout their lifetimes. However, the specific doses at which these effects were observed were not noted. Chronic studies in dogs also indicated that dieldrin produced degenerative effects in the liver (Fitzhugh et al. 1964; Kitselman 1953). In the Fitzhugh et al. (1964) study, a slight fatty change in the liver and a slight hepatic cell atrophy was reported at 0.5 mg/kg/day. This study was limited, however, in that no controls were used and only 1–2 males and females per dose were tested. In Kitselman (1953), slight degeneration of the liver was reported in one of three dogs fed 0.2 mg/kg/day and in all three dogs fed 0.6 mg/kg/day for a year. This study is also limited in that too few animals were tested (a total of three dogs per dose), replacement dogs were used, and details of the study protocol were incomplete.

The chronic oral MRL is the same as the EPA RfD for dieldrin (IRIS 2002b), as the value (5×10^{-5} mg/kg/day) is based on the same study (Walker et al. 1969), species (rat), end point (liver effects), and effect level (0.005 mg/kg/day NOAEL). The basis of the MRL (species and end point) differs from that used in the previous version of the ATSDR profile (ATSDR 1993), although the actual value (5×10^{-5} mg/kg/day) is unchanged. The basis of the MRL has been changed to address misinterpretations of the critical study in the previous ATSDR profile (ATSDR 1993).

The MRL was previously based on a NOAEL of 0.005 mg/kg/day for liver effects in dogs from the Walker et al. (1969) study. In the dog study, groups of five males and five females were given capsules containing 0, 0.005, or 0.05 mg/kg/day dieldrin for 2 years. The study end points were essentially the same as in the Walker et al. (1969) rat study, but additionally included assessments of SGPT, BSP clearance (control and high-dose groups), and neurology (EEG recordings in control and high-dose groups). Effects in the dogs occurred at 0.05 mg/kg/day and included increased absolute and relative liver weights in females, increased serum alkaline phosphatase in males and females beginning after 30 weeks of exposure, and decreased total serum proteins in males. There were no changes in histology of the liver or other tissues, histochemical distribution of fat or alkaline phosphatase activity in the liver, or liver function as assessed by BSP clearance. The origin of the increased serum alkaline phosphatase

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activity was unknown, but was not believed to be due to bone disorders or biliary obstruction (i.e., the usual clinical interpretation of elevated serum alkaline phosphatase in dogs [Cornelius 1970; Walker et al. 1969]). The decrease in total serum proteins was slight and considered to have no clinical or toxicological significance since the electrophoretic pattern of the proteins was unchanged. There were no exposure-related behavioral changes as found in the rats. ATSDR (1993) previously interpreted the high dose in dogs (0.05 mg/kg/day) as a LOAEL for liver effects based on the increases in liver weight and serum alkaline phosphatase, and used the NOAEL (0.005 mg/kg/day) to derive the MRL. Considering the lack of histological changes in the liver, evidence that the increased serum alkaline phosphatase is not liver-related, and lack of effect on liver function as assessed by BSP clearance, as well as the investigators' conclusions that there were no histopathologic liver lesions attributable to dieldrin in the dogs, the evidence indicates that 0.05 mg/kg/day should be classified as a NOAEL rather than a LOAEL. The 0.05 mg/kg/day NOAEL in dogs is not used to derive the MRL, however, because re-evaluation of the rat data shows that this dose is a LOAEL in rats, as discussed below.

ATSDR (1993) previously classified all of the doses in the Walker et al. (1969) rat study as NOAELs. This classification was based on an interpretation that hepatotoxic effects (focal hyperplasia of hepatic parenchymal cells, focal parenchymal necrosis, proliferated ductules, focal fibrosis, and cystic hyperplasia of intrahepatic bile ducts) were observed in both treated and control animals with no indication of an increase in incidence or severity in treated animals. Re-evaluation of the report shows that there are actually two categories of tabulated liver data (i.e., one labeled "Liver^a" and one labeled "Organochlorine insecticide changes"). The lesions tabulated as "Organochlorine insecticide changes" are in fact liver parenchymal effects that are characteristic of dieldrin and other organochlorine insecticides (and are treatment-related in the dog study), whereas other kinds of liver lesions (i.e., those simply tabulated as "Liver^a") are the effects that were dispersed throughout the control and treated groups and not attributable to exposure. In other words, ATSDR previously correctly interpreted the "Liver" data as negative, but did not recognize that the other category of liver effects (i.e., the organochlorine insecticide changes) provides positive evidence. This interpretation is supported by the footnote to the "Liver^a" heading, which states that these liver lesions "...are considered not to be associated with exposure to organochlorine insecticide", the investigators' conclusion that "Histopathologic liver lesions attributable to dieldrin were observed in the rats (10 ppm) but not in dogs", and the fact that the dieldrin-attributable liver effects are discussed in the report text using the incidences from the "Organochlorine insecticide changes" column in the table. Therefore, there is a progression of liver effects as shown by increased liver weight at 0.05 mg/kg/day and histological changes at 0.5 mg/kg/day. Consequently, 0.005 and 0.05 mg/kg/day are reclassified as a NOAEL and LOAEL, respectively, and the NOAEL is used as the basis of the MRL.

Agency Contact (Chemical Manager): G. Douglas Hanley

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.

APPENDIX B

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/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 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

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

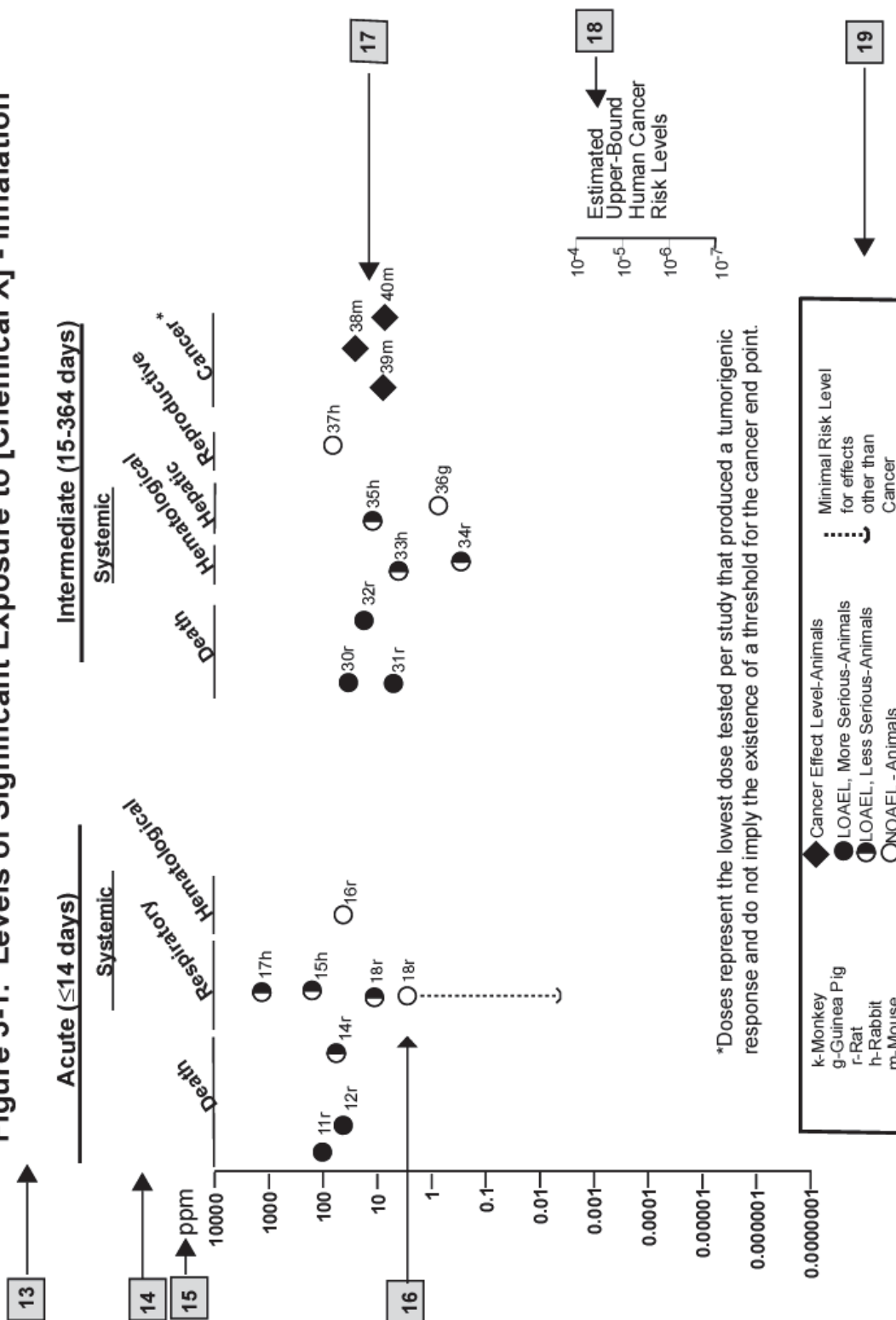
Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation						
Key to figure ^a	Species	Exposure frequency/ duration	System	LOAEL (effect)		Reference
				NOAEL (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE						
1	5	6	7	8	9	10
2	•	••	••	•	•••	••
3	18	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981
4						
CHRONIC EXPOSURE						
Cancer				11	••	
38	Rat	18 mo 5 d/wk 7 hr/d		20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d		10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d		10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

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

^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5x10⁻³ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	<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 _d	adsorption ratio
kg	kilogram
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT ₅₀	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 ₅₀	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
••	greater than or equal to
=	equal to
<	less than
••	less than or equal to
%	percent

APPENDIX C

α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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