TOXICOLOGICAL PROFILE FOR
ENDOSULFAN

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

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UPDATE STATEMENT

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

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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.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
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*<u>Legislative Background</u>

     The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 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: 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 (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 2.7	**Children's Susceptibility**
Section 5.6	**Exposures of Children**

Other Sections of Interest:

Section 2.8	**Biomarkers of Exposure and Effect**
Section 2.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center
> **Phone:** 1-888-42-ATSDR or (404) 639-6357   ***Fax:***   (404) 639-6359
> **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: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1.   Dr. Joel Coats, Professor, Iowa State University, Department of Entomology, Ames, Iowa;

2.   Dr. Syed GhiasUddin, Consultant, Toxicologist, Indiana Department of Environmental Management, Indianapolis, Indiana; and

3.   Dr. Melvin Reuber, Consultant, Columbia, Maryland.

These experts collectively have knowledge of endosulfan's physical and chemical properties, toxico-kinetics, 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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about endosulfan and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Endosulfan has been found in at least 164 of the 1,577 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which endosulfan is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

1.1 WHAT IS ENDOSULFAN?

Endosulfan is a manufactured pesticide. It is used to control a number of insects on food crops such as grains, tea, fruits, and vegetables and on nonfood crops such as tobacco and cotton. It is also used as a wood preservative.

Endosulfan is sold as a mixture of two different forms of the same chemical (referred to as α- and β-endosulfan). It is a cream- to brown-colored solid that may appear crystalline or in flakes. It has a distinct odor similar to turpentine. Endosulfan does not burn.

1.2   WHAT HAPPENS TO ENDOSULFAN WHEN IT ENTERS THE ENVIRONMENT?

Endosulfan enters air, water, and soil when it is manufactured or used as a pesticide. Endosulfan is often applied to crops using sprayers. Some endosulfan in the air may travel long distances before it lands on crops, soil, or water. Endosulfan on crops usually breaks down within a few weeks. Endosulfan released to soil attaches to soil particles. Endosulfan found near hazardous waste sites is usually found in soil. Some endosulfan in soil evaporates into air, and some endosulfan in soil breaks down. However, it may stay in soil for several years before it all breaks down. Rainwater can wash endosulfan that is attached to soil particles into surface water. Endosulfan does not dissolve easily in water. Most endosulfan in surface water is attached to soil particles floating in the water or attached to soil at the bottom. The small amounts of endosulfan that dissolve in water break down over time. Depending on the conditions in the water, endosulfan may break down within 1 day or it may take several months. Some endosulfan in surface water evaporates into air and breaks down. Because it does not dissolve easily in water, only very small amounts of endosulfan are found in groundwater (water below the soil surface; for example, well water). Animals that live in endosulfan-contaminated waters can build up endosulfan in their bodies. The amount of endosulfan in their bodies may be several times greater than in the surrounding water. More information on the chemical and physical properties of endosulfan can be found in Chapter 3. More information on its occurrence and fate in the environment can be found in Chapter 5.

1.3   HOW MIGHT I BE EXPOSED TO ENDOSULFAN?

The most likely way for people to be exposed to endosulfan is by eating food contaminated with it. Endosulfan has been found in some food products such as oils, fats, and fruit and vegetable products. You can also be exposed to low levels of endosulfan by skin contact with contaminated soil or by smoking cigarettes made from tobacco that has endosulfan residues on it. Well water and public water supplies are not likely sources of exposure to endosulfan. Workers can breathe in the chemical when spraying the pesticide on crops. If you are a farmer who works with vegetable or tobacco crops, or if you work in a greenhouse to grow flowers like chrysanthemums, you may use endosulfan to control insects. Exposure can occur by breathing

the dust or getting the pesticide on your skin if you do not follow all the safety and handling procedures. Accidental spills and releases to the environment at hazardous waste disposal sites are also possible sources of exposure to endosulfan. The most likely exposure to endosulfan for people living near hazardous waste sites is through contact with soils containing it.

Endosulfan is usually not found in the air, and it is not found in soil and water very often. When endosulfan is found in soil and water, levels of less than 1 part of endosulfan in 1 billion parts of surface water (ppb) and less than 1 part of endosulfan in 1 million parts of soil (ppm) have been reported. For more information on human exposure to endosulfan, see Chapter 5.

1.4 HOW CAN ENDOSULFAN ENTER AND LEAVE MY BODY?

If you breathe air containing dust contaminated with endosulfan, it can enter your body through your lungs and pass into the bloodstream. We do not know how much of the endosulfan will pass into your bloodstream or how fast this will happen. If you swallow food, water, or soil contaminated with endosulfan, it will enter your body and some will pass from your stomach into the bloodstream, but we do not know how much or how fast this will occur. However, studies in animals show that endosulfan passes slowly through the stomach into the body tissues after it is taken in by mouth. If you touch soil containing endosulfan (for example, at a hazardous waste site), some endosulfan will pass through the skin into the bloodstream, but we do not know how much or how fast this will occur. Studies in animals also show that when endosulfan is applied to the skin, it passes slowly through the skin into the body tissues. If you have cuts on your skin or if you have covered your skin with oils or oily lotions, endosulfan will pass through the skin faster. Much of the endosulfan that you swallow leaves in the feces without actually entering the body tissues. For people living around waste sites or processing or storage facilities, the most likely way it will enter their bodies is from skin contact or breathing contaminated dusts. Once endosulfan is in the body, it may change in the liver and kidneys into other related chemicals called metabolites. Endosulfan and the metabolites leave your body in the urine and feces within a few days or a few weeks. Chapter 2 has more information on how endosulfan enters and leaves the body.

1.5 HOW CAN ENDOSULFAN AFFECT MY HEALTH?

Symptoms of endosulfan poisoning have been seen in some people who were exposed to very large amounts of this pesticide during its manufacture. Symptoms of endosulfan poisoning have also been seen in people who intentionally or accidentally ate or drank large amounts of endosulfan. Most of these people experienced convulsions or other nervous system effects. Some people who intentionally ate or drank large amounts of endosulfan died. The health effects in people exposed to smaller amounts of endosulfan for longer periods are not known. We do not know whether endosulfan has ever affected the ability of people to fight disease or has ever caused cancer in people. The Department of Health and Human Services (DHHS) (National Toxicology Program), the International Agency for Research on Cancer (IARC), and EPA have not classified endosulfan as to its ability to cause cancer.

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 exposure to very large amounts of endosulfan for short periods can cause adverse nervous system effects (such as hyperexcitability, tremors, and convulsions) and death. Because the brain controls the activity of the lungs and heart, lethal or near-lethal exposures in animals have also resulted in failure of these organs. Other effects seen in animals after short-term, high-level exposures include harmful effects on the stomach, blood, liver, and kidneys. One animal study suggested that after somewhat longer exposures, there is a possibility that the body's ability to fight infection may be impaired; however, this was not

directly demonstrated. The kidneys, testes, and possibly the liver are the only organs in laboratory animals affected by longer term exposure to low levels of endosulfan. The seriousness of these effects is increased when animals are exposed to higher concentrations of endosulfan. Because these effects occurred in animals, they might also occur in humans. Limited studies in animals show no evidence that endosulfan causes cancer in animals. Some studies in animals have shown that endosulfan causes damage to the genetic material within cells.

For more information on how endosulfan can affect your health, see Chapter 2.

1.6 HOW CAN ENDOSULFAN AFFECT CHILDREN?

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

Children can be exposed to endosulfan by eating food contaminated with the pesticide, by accidentally ingesting the pesticide if it is stored around the house, or by breathing air contaminated with the pesticide if it is sprayed on nearby fields. There are no known unique exposure pathways for children. We do not know if children's intake of endosulfan per kilogram of body weight is different than that of adults.

There have been no studies of health effects in young children exposed to endosulfan. Adults who accidentally or intentionally ingested amounts of endosulfan much greater than those found in the environment suffered convulsions and some died. The same adverse effects would probably occur in young children if they ingested large amounts of endosulfan. We do not know whether children differ from adults in their susceptibility to health effects from endosulfan exposure.

We do not know whether endosulfan affects the ability of people to have children or whether it causes birth defects in children. Studies in animals showed no evidence that endosulfan affects the ability of animals to have babies. Some studies show that large amounts of endosulfan

damage the testes, but it is unknown whether such large amounts affect the ability of animals to reproduce. Pregnant animals given endosulfan by mouth had some offspring with low birth weight and length, and some with skeletal variations. Often, these effects were seen at doses where the pregnant animals themselves showed signs of poisoning by the endosulfan. Because these effects occurred in animals, they might also occur in humans. We do not know for certain whether endosulfan or its breakdown products can cross the placenta, but it is likely that they can do so. Endosulfan has been found in human breast milk, but results of studies in animals that ate endosulfan while nursing their young suggest that only very small amounts of endosulfan can find their way into breast milk. More information on this topic can be found in Sections 2.7 and 5.6.

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

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

Endosulfan is a pesticide used in commercial agriculture and home gardening. Endosulfan has been found in some food items but in amounts much lower than those allowed by the EPA and the Food and Drug Administration (FDA). Still, it is a good idea to wash fruits and vegetables before consuming them.

Young children can sometimes be exposed to pesticides by playing in an area too soon after a pesticide has been applied. Carefully read and follow the directions on the pesticide label about how long to wait before re-entering the treated area. Pesticides and household chemicals should be stored out of the reach of young children to prevent accidental poisoning. Always store pesticides and household chemicals in their original labeled containers; never store pesticides or household chemicals in containers which young children would find attractive, such as old soda bottles.

Your children may be exposed to endosulfan if unqualified people apply pesticides around your home. In some cases, the use of pesticides that have been banned for use in homes has turned homes into hazardous waste sites. Your state licenses each person qualified to apply pesticides using EPA standards and further certifies each person qualified to apply "restricted use" pesticides. Ask to see the license and certification of anyone who applies pesticides for you. Also ask for the brand name of the pesticide, a material safety data sheet (MSDS), the name of the product's active ingredient, and the EPA registration number. Ask whether EPA has designated the pesticide "for restricted use" and what the approved uses are. This information is important if you or your family have a reaction to the product.

If you buy over-the-counter pesticide products to apply yourself, be sure the product is in an unopened pesticide container that is labeled and has an EPA registration number. You should be careful to follow the instructions on the label. If you plan to spray inside a building or your home, check to see if the pesticide is intended for indoor use. If you feel sick after a pesticide has been used in your home, see your doctor or call the local poison control center.

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

Endosulfan and its breakdown products can be measured in your blood, urine, and body tissues if you have been exposed to a large amount. Tests to measure endosulfan 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 endosulfan leaves the body fairly quickly, these methods are useful only for finding exposures that have occurred within the last few days. At this time, these methods can only be used to prove that a person has been exposed to endosulfan. The test results cannot be used to predict if you will have any adverse health effects. Exposure to other chemicals at the same time at hazardous waste sites could cause some confusion in understanding these results. More information about tests to find endosulfan in the body is presented in Chapters 2 and 6.

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 <u>can</u> 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 <u>cannot</u> be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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

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

The federal government has set standards and guidelines to protect people from the possible adverse health effects of endosulfan in drinking water and food. EPA recommends that the amount of endosulfan in lakes, rivers, and streams should not be more than 74 micrograms per liter (µg/L) or 74 parts per billion (74 ppb). This should prevent any harmful health effects from occurring in people who drink the water or eat fish or seafood that live in the water. FDA allows no more than 24 parts per million (24 ppm) of endosulfan on dried tea, and EPA allows no more than 0.1 to 2 ppm endosulfan on other raw agricultural products.

NIOSH recommends that workers should not breathe air that contains more than 0.1 milligram (mg) of endosulfan per cubic meter of air (0.1 mg/m^3) during a 10-hour workday, 40-hour workweek. For more information on limits and standards for endosulfan exposure, see Chapter 7.

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
> * Information line and technical assistance
>
> Phone: 1-888-42-ATSDR (1-888-422-8737)
> Fax: (404) 639-6359

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

> * To order toxicological profiles, contact
>
> National Technical Information Service
> 5285 Port Royal Road
> Springfield, VA 22161
> Phone: (800) 553-6847 or (703) 605-6000

2. HEALTH EFFECTS

2.1   INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of endosulfan. 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.

Technical-grade endosulfan contains at least 94% α-endosulfan and β-endosulfan. The α- and β-isomers are present in the ratio of 7:3, respectively. The majority of the studies discussed below used technical-grade endosulfan. However, a few examined the effects of the pure α- and β-isomers. Endosulfan sulfate is a reaction product found in technical-grade endosulfan as a result of oxidation, biotransformation, or photolysis. There is very little difference in toxicity between endosulfan and its metabolite, endosulfan sulfate. However, the α-isomer has been shown to be about three times as toxic as the β-isomer of endosulfan.

2.2   DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (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.

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

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

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.

2.2.1 Inhalation Exposure

Limited information is available regarding the effects of endosulfan in humans and animals after inhalation exposure. The reports of effects in humans are limited to case reports of adverse effects noted in workers exposed to large quantities of endosulfan during its manufacture. Exposures in these reports are likely to be a combination of inhalation and dermal exposures. Therefore, the findings from these case reports are also presented in the section on dermal exposures (Section 2.2.3).

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to endosulfan. LC_{50} (lethal concentration, 50% kill) values of 12.6 mg/m^3 and 34.5 mg/m^3 for female and male rats, respectively, were obtained after a 4-hour nose-only exposure to aerosolized endosulfan (Hoechst 1983a). No deaths were observed among male and female rats exposed to aerosolized endosulfan (nose-only) at concentrations as high as 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c). Acute LC_{50} values for male and female rats are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

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

Respiratory Effects.   No studies were located regarding respiratory effects in humans after inhalation exposure to endosulfan.

Irregular respiration was observed in both male and female rats after a 4-hour nose-only inhalation exposure to aerosolized endosulfan (Hoechst 1983a). In both male and female rats, dyspnea was observed at the lowest concentrations tested (12.3 and 3.6 mg/m^3 for males and females, respectively). Autopsies of the rats that died revealed dark-red, pinhead-sized foci on the lungs. It is unclear whether these effects represent direct effects of inhaled endosulfan on respiratory tissues or whether they are secondary to central nervous system effects on respiratory function. No treatment-related effects were

Table 2-1. Levels of Significant Exposure to Endosulfan - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	4 hr				12.6 F (LC$_{50}$)	Hoechst 1983a Technical
2	Rat (Wistar)	4 hr				34.5 M (LC$_{50}$)	Hoechst 1983a Technical
Systemic							
3	Rat (Wistar)	4 hr	Resp			3.6 F (dyspnea)	Hoechst 1983a Technical
Neurological							
4	Rat (Wistar)	4 hr				3.6 F (trembling; ataxia)	Hoechst 1983a Technical

Table 2-1. Levels of Significant Exposure to Endosulfan - Inhalation (continued)

Key to figure [a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
INTERMEDIATE EXPOSURE							
Systemic							
5	Rat (Wistar)	21 d 5 d/wk 6 hr/d	Resp	2.0			Hoechst 1984c Technical
			Cardio	2.0			
			Gastro	2.0			
			Hemato	2.0			
			Musc/skel	2.0			
			Hepatic	2.0			
			Renal	2.0			
			Endocr	2.0			
			Dermal	2.0			
			Ocular	2.0			
			Bd Wt		2.0 M (decreased body weight gain)		
				2.0 F			
Immunological/Lymphoreticular							
6	Rat (Wistar)	29 d 5 d/wk 6 hr/d		2.0			Hoechst 1984c Technical
Neurological							
7	Rat (Wistar)	21 d 5 d/wk 6 hr/d		2.0			Hoechst 1984c Technical

[a]The number corresponds to entries in Figure 2-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest- observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s).

Figure 2-1. Levels of Significant Exposure to Endosulfan - Inhalation

Acute (≤14 days)

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	other than
q-Cow	a-Sheep	g-Guinea Pig				Cancer
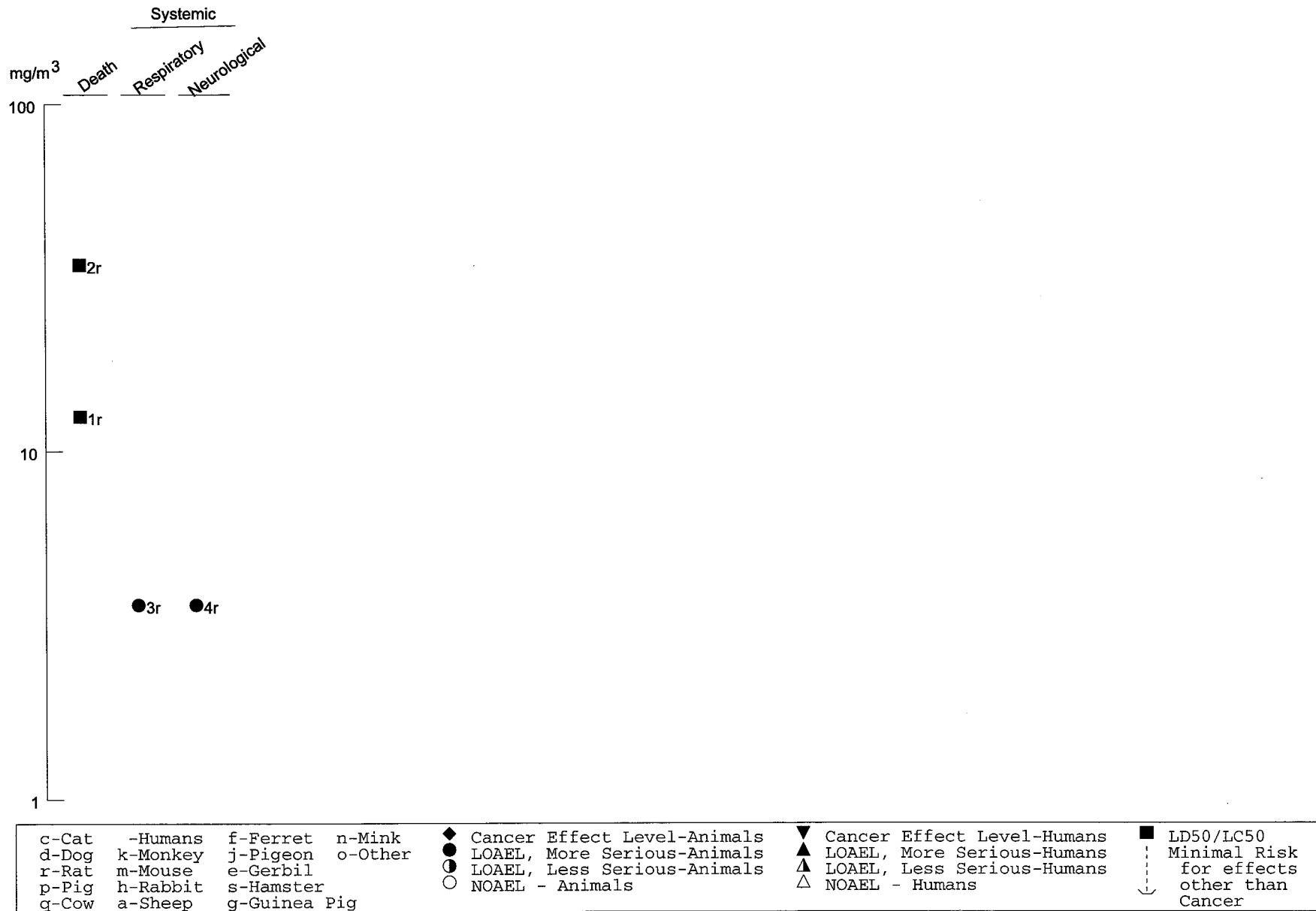
Figure 2-1. Levels of Significant Exposure to Endosulfan - Inhalation (Continued)

Intermediate (15-364 days)

Systemic

mg/m³

Respiratory Cardiovascular Gastrointestinal Hematological Musculoskeletal Hepatic Renal Endocrine Dermal Ocular Body Weight Immuno/Lymphor Neurological

10

○5r ○5r ○5r ○5r ○5r ○5r ○5r ○5r ○5r ○5r ◑5r ○5r ○5r ○6r

1

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

revealed by routine gross and histopathologic examination of the nasal cavity, trachea, and lungs of male and female rats exposed (nose-only) to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Cardiovascular Effects.   No studies were located regarding cardiovascular effects in humans after inhalation exposure to endosulfan. Routine gross and histopathologic examination of the heart and aorta of rats exposed (nose-only) to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days revealed no treatment-related effects (Hoechst 1984c).

Gastrointestinal Effects.   No studies were located regarding gastrointestinal effects in humans after inhalation exposure to endosulfan. Routine gross and histopathologic examination of tissues of the gastrointestinal system (parotid and submandibular glands, esophagus, stomach, small and large intestines, and pancreas) revealed no treatment-related effects following exposure to aerosolized endosulfan for 6 hours/day, 5 days/week for a total of 21 out of 29 days at concentrations of up to 2 mg/m^3 (Hoechst 1984c).

Hematological Effects.   No studies were located regarding hematological effects in humans after inhalation exposure to endosulfan.

Routine gross and histopathologic examination of hematopoietic organs (spleen and bone marrow) and routine hematological analyses did not reveal any effects of nose-only exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Musculoskeletal Effects.   No studies were located regarding musculoskeletal effects in humans after inhalation exposure to endosulfan.

Routine gross and histopathologic examination of skeletal muscle and the diaphragm revealed no treatment-related effects following nose-only inhalation exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Hepatic Effects.   No studies were located regarding hepatic effects in humans after inhalation exposure to endosulfan.

2. HEALTH EFFECTS

Routine gross and histopathologic examination of the liver did not reveal any effects of nose-only exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Renal Effects.   No studies were located regarding renal effects in humans after inhalation exposure to endosulfan.

Routine gross and histopathologic examination of the kidneys and urinary bladder did not reveal any effects of nose-only exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Endocrine Effects.   No studies were located regarding endocrine effects in humans after inhalation exposure to endosulfan.

Routine gross and histopathologic examination of the pituitary gland did not reveal any effects in rats exposed nose-only to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Dermal Effects.   No studies were located regarding dermal effects in humans after inhalation exposure to endosulfan. Routine gross and histopathologic examination of the skin did not reveal any effects of nose-only exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Ocular Effects.   No studies were located regarding ocular effects in humans after inhalation exposure to endosulfan. Routine gross and histopathologic examination of the eyes did not reveal any effects of nose-only exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c).

Body Weight Effects.   No studies were located regarding body weight effects in humans after inhalation exposure to endosulfan. Body weight gain was significantly reduced in male, but not female, rats exposed nose-only to concentrations of endosulfan of 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c). No significant effect was seen at an exposure level of 1 mg/m^3.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to endosulfan.

Routine gross and histopathologic examination of the lymph nodes, thymus, and spleen did not reveal any effects of nose-only exposure of rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c). No studies directly assessing immunologic function were located.

2.2.1.4 Neurological Effects

Neurotoxicity is the primary effect observed in humans following occupational exposure to endosulfan. Convulsions were reported in nine individuals exposed to the endosulfan-containing insecticide Thiodan$^®$ during bagging (Ely et al. 1967). Other effects noted in at least one of the subjects prior to the onset of convulsions included malaise, nausea, vomiting, dizziness, confusion, and/or weakness. In addition, a case of long-term, possibly permanent brain damage in an industrial worker was attributed by Aleksandrowicz (1979) to endosulfan exposure. This worker was exposed by cleaning vats that contained residues of endosulfan solution. The acute phase of the poisoning was manifested by repeated convulsions and impaired consciousness. After recovery from the repeated seizure episode, the patient became disoriented and agitated. Two years later, he exhibited cognitive and emotional deterioration, memory impairment, and impairment of visual-motor coordination manifested by an inability to perform small tasks. However, modest alcohol consumption (1L of wine consumed per week) may have been a contributing factor. Limitations associated with these reports include lack of quantitative exposure data, lack of data on the duration of exposure, the possibility of multiple routes of exposure (i.e., oral and dermal, as well as inhalation) and possible concurrent exposure to other chemicals. Therefore, this information can only provide qualitative evidence of neurotoxicity associated with inhalation exposure to endosulfan in humans.

Evidence of neurotoxicity was also observed in animal studies. Nose-only exposure of rats to endosulfan at concentrations of 3.6 mg/m^3 in females and 12.3 mg/m^3 in males resulted in trembling and ataxia (Hoechst 1983a). At higher concentrations in both sexes, tremors, tonic-clonic convulsions, and reduced corneal, pupillary, placing, shock, paw-pinch, and cutaneous reflexes were observed. Nose-only exposure of male and female rats to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for

a total of 21 out of 29 days resulted in no observed behavioral disturbances (Hoechst 1984c). In addition, routine gross and histopathologic examination of the cerebrum, cerebellum, brain stem, optic nerve, and pituitary demonstrated no treatment-related abnormalities.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to endosulfan.

No studies were located that examined reproductive function in animals after inhalation exposure to endosulfan. However, routine gross and histopathological examination of the reproductive organs (testes, epididymides, seminal vesicles, prostate, ovaries, and uterus) of rats exposed (nose-only) to concentrations of endosulfan of up to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days revealed no adverse effects (Hoechst 1984c).

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

DNA damage in mononuclear leukocytes, as measured with the alkaline comet assay, was significantly increased in two of four French agricultural workers on the day following the application of pesticide mixtures, including endosulfan, compared to levels of DNA damage prior to application (Lebailly et al. 1998). However, the contribution of endosulfan to the observed effect is uncertain because of co-exposure to fungicides, herbicides, and other insecticides. Evaluations for micronuclei in human peripheral blood lymphocytes provided mixed results, depending on the analytical method used. No increase over control levels was observed in the frequency of micronuclei in peripheral blood lymphocytes of Chilean pesticide sprayers, using the cytochalasin-B method of arresting cytokinesis (Venegas et al. 1998), although endosulfan was reportedly applied by the workers only 3.7% of the time. In Italian greenhouse workers who applied a variety of pesticides including endosulfan, the frequency of micronuclei was increased compared to controls in an assay that used the 5-bromodeoxyuridine DNA-labeling technique (Falck et al. 1999), but not in an assay utilizing cytochalasin-B to arrest cytokinesis

(Scarpato et al. 1996a, 1996b). Previous studies in the same greenhouse worker group also showed no increase in chromosome aberrations or sister chromatid exchanges (Scarpato et al. 1996a, 1996b, 1997). The results of all of these genotoxicity studies in humans should be treated with caution because the multiple-chemical exposures confound the interpretation, and exposure levels of endosulfan were not reported.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in animals after inhalation exposure to endosulfan.

In a case-control study of the relation between occupational exposures to various suspected estrogenic chemicals and the occurrence of breast cancer, the breast cancer odds ratio (OR) was not elevated above unity (OR=0.8; 95% CI=0.2–3.2) for occupational exposure to endosulfan compared to unexposed controls (Aschengrau et al. 1998); however, the sample sizes were very small (three exposed; seven not exposed), and co-exposure to other unreported chemicals also reportedly occurred. Both of these factors may have contributed to the high degree of uncertainty in the OR indicated by the wide confidence interval.

2.2.2 Oral Exposure

2.2.2.1 Death

Acute accidental or intentional ingestion of large amounts of endosulfan has resulted in death in humans. Five cases of acute lethal poisoning in humans resulting from ingestion of Thiodan® were reported by Terziev et al. (1974). In two cases of suicide, the ingested dose was reported to be up to 100 mL of Thiodan® (concentration of endosulfan in this particular formulation was not specified); in the other three poisonings, the victims drank liquids containing the pesticide, but the ingested doses were not specified. Initial clinical symptoms of endosulfan poisoning included gagging, vomiting, diarrhea, agitation, writhing, loss of consciousness, cyanosis, dyspnea, foaming at the mouth, and noisy breathing. Autopsies performed in three out of five cases revealed edema of the brain and lungs, hemorrhage of the medullary layer of the kidneys, acute lung emphysema, and chromatolysis of the neurons. Two cases of lethal ingestion of endosulfan-containing formulations were reported by Demeter and Heyndrickx (1978). In

one, a 40-year-old man who consumed Posidor (20% endosulfan and 30% dimethoate in xylene) and alcohol died within 3 hours. His body was dark-red/purple, and his face was cyanotic. Autopsy revealed edematous lungs. The authors suggested that death was due to the combined effects of dimethoate (an organophosphate insecticide compound and potent cholinesterase inhibitor) and endosulfan. In the other case, a 28-year-old man ingested a fatal dose of Thiodan® powder (20% endosulfan) in conjunction with alcohol. Postmortem findings included congested and edematous lungs. Death was due to asphyxiation, which the authors suggested was caused by a synergistic effect of alcohol and endosulfan. In neither case was the ingested dose of endosulfan quantified. In the case of a 55-year-old female who died following intentional ingestion of an unspecified amount of endosulfan dispersed in a colorless liquid containing 55% xylene, autopsy revealed no gross anatomical or histological abnormalities attributed to endosulfan (Bernardelli and Gennari 1987). The presence of malignant melanoma and the concurrent ingestion of xylene may have been contributing factors in the death of this woman.

A more recent lethal case of a woman who ingested an unknown amount of endosulfan mistakenly added to food was reported (Blanco-Coronado et al. 1992). One to four hours after ingestion she had tonic-clonic convulsions, nausea, vomiting, headache, and dizziness. On admission to the hospital, the concentration of endosulfan (both isomers) in the gastric contents, blood, and urine was 55.4, 2.9, and 3 mg/L, respectively. She died 8 days after admission to the hospital following acute renal failure, disseminated intravascular coagulation, thrombi in the pulmonary arteries and aorta, and cardiogenic shock. Postmortem finding included bilateral pleural effusions, congested and edematous lungs with exudative areas and pulmonary edema, hyaline membranes, microatelectasia, polymorphonuclear lymphocytes and red cells in the alveoli, and interstitial fibrosis. A similar lethal case of a man who died 10 days after ingesting an unknown amount of endosulfan was described by Lo et al. (1995). The cause of death was described as cardio-respiratory arrest and heart failure and pulmonary edema. None of these case reports provide sufficient data to estimate a lethal dose of endosulfan in humans.

An estimated oral dose of 260 mg endosulfan/kg caused severe seizures in a 43-year-old man, and brain death from cerebral herniation and massive cerebral edema occurred within 4 days of exposure (Boereboom et al. 1998); there were no signs of myocardial infarction and only slight congestion of the heart, but pulmonary congestion and atelectasis were evident at autopsy.

Signs of acute lethal endosulfan poisoning in animals are similar to those observed in humans and include hyperexcitability, dyspnea, decreased respiration, and fine tremors followed by tonic-clonic convulsions. Oral LD_{50} (lethal dose, 50% kill) values for technical-grade endosulfan vary depending on species, sex,

formulation tested, and nutritional status of the animal (Gupta and Gupta 1979; WHO 1984). With regard to species sensitivity, mice appear to be quite sensitive to endosulfan's lethal effects, with a reported LD_{50} value of 7.36 mg/kg in males (Gupta et al. 1981) and 2 out of 10 male mice dying after administration of 7.5 mg technical endosulfan/kg in the diet for 7 days (Wilson and LeBlanc 1998). In contrast, LD_{50} values in male rats range between 40 and 121 mg/kg (Boyd and Dobos 1969; Boyd et al. 1970; Hoechst 1990; Lindquist and Dahm 1957). A single oral dose of 20 mg/kg of technical endosulfan killed 3 out of 14 male rats within hours of dosing, following seizure activity (Gilbert and Mack 1995). Six of 19 male rats died during the first 2 weeks of gavage treatment with 7.5 mg technical endosulfan/kg/day (Ansari et al. 1984). An LD_{50} value of 76.7 mg/kg has been calculated from the results of one dog study (sex and breed not indicated) (Hoechst 1970). However, endosulfan causes vomiting in dogs, and one study found that all dogs died that did not vomit after ingesting doses of at least 30 mg/kg (FMC 1958). Thus, the value of the dog LD_{50} may reflect both the dose and whether or not the dogs vomited. The acute toxicity of endosulfan also has been tested in rabbits, a species in which a single gavage dose of 15.1 mg of technical endosulfan/kg killed five out of seven animals (Ceron et al. 1995). Three of these died 15–20 minutes following dosing after experiencing clonic-tonic convulsions and fine generalized tremors. The other two showed similar signs and died 2–3 hours after dosing.

In rats, exposed males and females appear to have different sensitivities to the lethal effects of endosulfan exposure. Summary data submitted by Hoechst (1990) showed that female LD_{50} values ranged between 10 and 23 mg/kg, whereas male LD_{50} values ranged between 40 and 125 mg/kg. Thus, female rats appear to be 4–5 times more sensitive to the lethal effects of technical-grade endosulfan than male rats. This difference may be related to differences in the toxicokinetics of endosulfan in male and female rats (see also Section 2.3). Insufficient data were available to determine whether differences in sensitivity to lethal effects exist between males and females of species other than the rat.

The effects of protein deficiency on endosulfan toxicity were studied in Wistar rats (Boyd and Dobos 1969; Boyd et al. 1970). Rats fed a diet totally deficient in protein for 28 days prior to administration of a single oral dose of endosulfan had an LD_{50} of 5.1 mg/kg of endosulfan. Rats fed a low-protein diet (3.5% protein) for 28 days had an LD_{50} of 24 mg/kg of endosulfan. Rats fed standard laboratory chow (26% protein) had an LD_{50} of 102–121 mg/kg. The immediate cause of death in all animals was respiratory failure following tonic-clonic convulsions. This study demonstrated that, while a protein-deficient diet does not affect the nature of the toxic reaction, it may affect the sensitivity of rats to the lethal effects of endosulfan.

2. HEALTH EFFECTS

The two isomers of endosulfan (α-and β-) also have different LD_{50} values in rats. The α-isomer is more toxic than the β-isomer in female rats, with an oral LD_{50} value of 76 mg/kg versus an LD_{50} value of 240 mg/kg for β-endosulfan (Hoechst 1975, 1990; Maier-Bode 1968). The same difference was reported in female albino mice, the lethal dose for α-endosulfan being 11 mg/kg versus 36 mg/kg for β-endosulfan (Dorough et al. 1978). The lethal dose for endosulfan sulfate in mice was comparable to that of the α-isomer, 8 mg/kg (Dorough et al. 1978). Also, Hoechst (1966a, 1966b) had reported an LD_{50} of 14 mg/kg for α-endosulfan and 17 mg/kg for β-endosulfan in female mice.

In rats, daily administration of 5 or 10 mg/kg doses of endosulfan by gavage in corn oil during gestational days (Gd) 6–14 or 6–19 produced a dose-related increase in maternal deaths in these test groups (FMC 1980a; Gupta et al. 1978).

In intermediate-duration studies, rats tolerated 6-day/week gavage doses of 20 mg/kg endosulfan for 7 weeks (Garg et al.1980), whereas increased mortality was observed in male and female mice at doses of 7.3 mg/kg/day and 7.52 mg/kg/day, respectively, for 13 weeks (Hoechst 1984b). Two out of 19 rats administered 7.5 mg technical endosulfan/kg/day died in a 60-day study (Ansari et al. 1984). A more recent study also found female rats to be more sensitive than males, since 3 out 10 females died during a 30-day feeding study, but no deaths occurred in male groups (Paul et al. 1995). An additional intermediate-duration study reported that 4 out of 15 male rats (females not tested) died after administration of 10 mg technical endosulfan/kg, 3 times a week for 4–5 weeks (Gilbert 1992). Male and female dogs orally administered time-weighted average (TWA) doses of 2.9 and 2.6 mg/kg/day, respectively, were sacrificed at the end of 146 days because of severe neurological symptoms (Hoechst 1989c).

Increased mortality was observed in both male rats (at doses of 20.4 mg/kg/day and above) and male mice (at doses of 0.46 mg/kg/day and above) in a 2-year bioassay conducted by the National Cancer Institute (NCI 1978). The authors attributed the excessive mortality in the male rats to treatment-related toxic nephropathy. The high mortality in male mice was possibly due to fighting since no other treatment-related cause for the deaths could be determined. Survival in females of both species was unaffected by endosulfan (NCI 1978). However, survival was significantly decreased in female rats that consumed 5 mg/kg/day for 2 years (FMC 1959b), and in female mice that consumed approximately 2.9 mg technical endosulfan/kg/day for 2 years (Hack et al. 1995; Hoechst 1988b). In these studies, survival in male rats was not affected at 5 mg/kg/day for 2 years (FMC 1959b) and survival in male mice was not affected at 2.51 mg/kg/day for 2 years (Hoechst 1988b).

All reliable LD_{50} and LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

2.2.2.2 Systemic Effects

Case reports of human poisonings and studies in animals indicate that during acute oral exposure to lethal or near-lethal amounts of endosulfan, involvement of a large number of organ systems (respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal) is observed. However, during longer-term exposure, the liver and kidney appear to be the primary systemic target organs.

The highest NOAEL values and all reliable LOAEL values for systemic effects for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

Respiratory Effects.   Respiratory effects have been observed in cases of lethal poisonings from intentional or accidental ingestion of large quantities of endosulfan. Cyanosis, dyspnea, foaming at the mouth, and noisy breathing have been observed in several subjects prior to death (Blanco-Coronado et al. 1992; Terziev et al. 1974). At autopsy, acute emphysema and/or congested and edematous lungs were frequently observed in persons following ingestion of lethal quantities of endosulfan (Blanco-Coronado et al. 1992; Boereboom et al. 1998; Demeter and Heyndrickx 1978; Lo et al. 1995; Terziev et al. 1974). Respiratory effects were also part of the clinical syndrome displayed by a 20-year-old man who attempted suicide by ingesting 200 mL of a 30% endosulfan formulation (Thionax®) (Shemesh et al. 1988). Although the man's stomach was pumped and he was given activated charcoal to limit gastrointestinal absorption during the first 16 hours following ingestion, hypoxia (due to alveolar hypoventilation and pulmonary edema) was evident. In the following 2 weeks, the patient had recurrent aspiration pneumonia and a persistent need for mechanical ventilation. Although it is possible that these respiratory effects were due, in part, to a direct action of endosulfan on the lungs, it is more likely that many of the observed effects were secondary to endosulfan's direct effects on the central nervous system and its control of respiratory activity. It is unclear whether other ingredients in the Thionax® contributed to the effects observed. Respiratory effects were also reported in other nonlethal cases of acute intoxication with endosulfan. Pulmonary infiltrate was reported in 3 out of 4 cases 4 hours after ingesting an unknown amount of endosulfan, and 4 of these 5 cases required mechanical ventilation (Blanco-Coronado et al.

Table 2-2. Levels of Significant Exposure to Endosulfan - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	

ACUTE EXPOSURE

Death

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	Reference Chemical Form
1	Human	once				260 M (lethal dose)	Boereboom et al. 1998 Technical
2	Rat (albino)	60 d 1x/d (GO)				7.5 M (6/19 died; 2 on day 3 and 4 on day 14)	Ansari et al. 1984 Technical
3	Rat (Wistar)	once (GO)				24 M (LD_{50}; low protein diet)	Boyd and Dobos 1969 Technical
4	Rat (Sprague-Dawley)	Gd 6-19 2 wk 1x/d (G)				6 F (2/25 died)	FMC 1980b Technical
5	Rat (Long- Evans)	once (GO)				20 M (3 of 14 died following seizure activity)	Gilbert and Mack 1995 Technical
6	Rat (albino)	Gd 6-14 9 d 1x/d (GO)				10 F (5/32 died)	Gupta et al. 1978 Technical
7	Rat (Wistar)	once (GW)				240 F (LD_{50})	Hoechst 1975 Beta
8	Rat (Wistar)	once (GW)				65.7 F (LD_{50})	Hoechst 1988a Beta

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
9	Rat (Wistar)	once (GW)				1740 M (LD$_{50}$)	Hoechst 1988a Beta
10	Mouse (albino)	once (GW)				11 F (lethal dose)	Dorough et al. 1978 Alpha
11	Mouse (albino)	once (GW)				36 F (lethal dose)	Dorough et al. 1978 Beta
12	Mouse (albino)	once (GW)				8 F (lethal dose)	Dorough et al. 1978 endosulfan sulfate
13	Mouse (albino)	NS (GO)				7.4 M (LD$_{50}$)	Gupta et al. 1981 Technical
14	Mouse	once (GW)				14 F (LD$_{50}$)	Hoechst 1966a Alpha
15	Mouse	once (GW)				17 F (LD$_{50}$)	Hoechst 1966b Beta
16	Mouse (CD-1)	7 d (F)				7.5 M (2 of 10 died)	Wilson and LeBlanc 1998 Technical
17	Dog	once (C)				77 (LD$_{50}$)	Hoechst 1970 Technical
18	Rabbit (New Zealand)	once (GW)				15.1 M (5 of 7 died following seizure activity)	Ceron et al. 1995 Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Systemic							
19	Human	once	Resp			260 M (pulmonary congestion, atelectasis)	Boereboom et al. 1998 Technical
			Cardio			260 M (blood pressure drop)	
			Gastro	260 M			
			Hemato		260 M (elevated hemoglobin and white cell count)		
			Hepatic		260 M (liver congestion, fatty degeneration)		
			Renal	260 M			
20	Rat (Charles Foster)	1 or 5 d 1x/d (G)	Endocr		5 (degranulation of beta-cells of islets of Langerhans)		Barooah et al. 1980 Technical
			Metab		5 (decreased serum glucose)		
21	Rat (albino)	once (GO)	Metab		40 M (increased blood glucose)		Garg et al. 1980 Technical
22	Rat (Wistar)	once (GW)	Resp	63 F		70 F (lungs congestion)	Hoechst 1988a Beta
			Gastro			63 F (blood in small intestines; mucus in stomach)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
23	Rat (Kasauli)	4 d 1x/d (GO)	Hemato		12.5 F (decreased erythrocyte [Na+, K+]--ATPase activity)		Kiran and Varma 1988 Technical
			Hepatic		12.5 F (decreased liver aldolase)		
			Metab		12.5 F (increased blood glucose; decreased liver glycogen)		
24	Rat (NS)	1 d 1x/d (G)	Resp			200 M (dyspnea, emphysema, lung hemorrhages; cyanosis)	Terziev et al. 1974 Technical
			Cardio			200 M (myocardial hemorrhages)	
			Renal			200 M (hemorrhages in the kidney)	
25	Dog (Mongrel)	3 d 1x/d (C)	Gastro		2.5 (vomiting)		FMC 1959a Technical
26	Dog	once (C)	Resp			50 (respiratory paralysis; congestion of the lungs)	Hoechst 1970 Technical
			Gastro		50 (congestion in the stomach and small intestine)		
			Hepatic		50 (congestion of the liver)		
			Renal		50 (congestion of the kidneys)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
27	Rabbit (New Zealand)	once (GW)	Gastro		15.1 M (watery diarrhea)		Ceron et al. 1995 Technical
			Hemato		15.1 M (reduced red blood cell counts, packed cell volume and hemoglobin)		
			Hepatic		15.1 M (increased serum AP, AST, and ALT activities)		
			Bd Wt		15.1 M (12% body weight loss)		
			Other		15.1 M (82% reduction in food intake)		
Immunological/Lymphoreticular							
28	Rat (Wistar)	10 d (GO)		4.5 F			Hoechst 1988c Technical
Neurological							
29	Human	once				260 M (convulsions, cerebral edema, cerebral herniation, sustained epileptic state)	Boereboom et al. 1998 Technical
30	Rat (Sprague-Dawley)	Gd 6-19 14 d (GO)				2.5 F (poor muscle tone;head swaying)	FMC 1980a Technical
31	Rat (Long- Evans)	once (GO)				5 M (seizures)	Gilbert and Mack 1995 Technical
32	Rat (Wistar)	once (GW)				80 F (hyperactivity; convulsions; tremors)	Hoechst 1984e Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Rat (Wistar)	once (GW)				63 F (clonic spasms)	Hoechst 1988a Beta
34	Rat (Kasauli)	4 d 1x/d (GO)				12.5 F (tremors)	Kiran and Varma 1988 Technical
35	Rat (Wistar)	8 d 1 x/d (GO)			6 (changes in transmitter levels in several brain areas)		Lakshmana and Raju 1994 Technical
36	Rat (NS)	once (G)				200 M (brain edema, convulsions)	Terziev et al. 1974 Technical
37	Mouse	once (GW)				10 F (convulsions)	Hoechst 1966a Alpha
38	Mouse	once (GW)				12.5 F (convulsions)	Hoechst 1966b Beta
39	Dog	3 d 1x/d (C)				2.5 (convulsions; salivation; tremors; rapid respiration; pupillary dilation)	FMC 1959a Technical
40	Dog	once (C)		39.5		50 (convulsions, respiratory paralysis)	Hoechst 1970 Technical
41	Rabbit (New Zealand)	10 d 1x/d (GO)		0.7		1.8 F (tachypnea; hyperactivity; convulsions in dams)	FMC 1981 Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive							
42	Rat (Sprague-Dawley)	Gd 6-19 2 wk 1x/d (G)		6 F			FMC 1980b Technical
Developmental							
43	Rat (Sprague-Dawley)	Gd 6-19 2 wk 1x/d (G)			6 (increased skeletal variations; decreased birth weight and length)		FMC 1980b Technical
44	Rat (albino)	Gd 6-14 9 d 1x/d (GO)				5 (increased resorptions and skeletal variations)	Gupta et al. 1978 Technical
INTERMEDIATE EXPOSURE							
Death							
45	Rat (albino)	60 d 1x/d (GO)				7.5 M (2/19 died on days 32 and 58)	Ansari et al. 1984 Technical
46	Rat (Long- Evans)	7 wk 3 x/wk (GO)				10 M (4/16 died following 4-5 weeks of dosing)	Gilbert 1992 Technical
47	Rat (Wistar)	30 d (F)				6 F (3 out 10 died)	Paul et al. 1995 Technical
48	Mouse (CD-1)	13 wk ad lib (F)				7.3 M (10/20 died) 7.5 F (11/20 died)	Hoechst 1984b Technical

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

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Systemic						
49	Rat (albino)	9-18 wk ad lib (F)	Hemato	5			Das and Garg 1981 Technical
			Hepatic	5			
			Renal	5			
			Bd Wt	5			
50	Rat (albino)	30 d 1x/d (GO)	Hemato	1.5 F	5 M (increased RBC and neutrophil count)		Dikshith et al. 1984 Technical
			Hepatic		1.5 F (increased liver alkaline phosphatase)		
				1.5	5 M (increased relative liver weight)		
			Renal	1.5			
			Bd Wt	1.5			
51	Rat (Wistar)	26 wk ad lib (F)	Hemato	5			FMC 1959b Technical
52	Rat (albino)	7 wk 6 d/wk 1x/day (GO)	Metab	0.625 M	5 M (decreased blood calcium)		Garg et al. 1980 Technical

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

| Key to figure [a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
53	Rat (albino)	15 d 1x/d (GO)	Resp	5 M	10 M (inflammation of lungs; dilation of alveoli)	10 M (more severe necrosis; inflammation, dilation, and congestion of central veins and sinusoids)	Gupta and Chandra 1977 Technical
			Gastro	10 M			
			Hepatic		5 M (increased absolute and relative liver weight; dilation of sinusoids; necrosis)		
			Renal	5 M		10 M (congestion and degeneration of kidney tubules)	
			Endocr	10 M			
			Bd Wt			10 M (30% less weight gain than controls)	
54	Rat (albino)	15 d 1x/d (GO)	Hepatic	5.0 F			Gupta and Gupta 1977a Technical
			Endocr	5.0 F			
			Bd Wt	5.0 F			
55	Rat (CrL:COBS CD)	84 d ad lib (F)	Bd Wt	0.8	3.8 (decreased body weight gain in dams)		Hoechst 1984a Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
56	Rat (Sprague-Dawley)	13 wk ad lib (F)	Hemato		0.8 (decreased hemoglobin)		Hoechst 1985a Technical
			Hepatic	3.8 M	23.4 M (granular brown pigment; increased liver weight)		
				3.8 F	23.4 F (increased liver weight; centrilobular enlargement, increased serum lipids and cholesterol)		
			Renal	1.9	3.9 (yellow protein in tubule lumen; eosinophilic droplets in cells of proximal convoluted tubules; increased kidney weights)	23.4 M (proteinuria)	
			Dermal	2.3	4.6 F (hair loss)		
57	Rat (Sprague-Dawley)	13-26 wk ad lib (F)	Hemato	2.9			Hoechst 1989a Technical
58	Rat (Wistar)	30 d (F)	Hepatic		3 F (increased serum and liver AST, ALT and AP activities)		Paul et al. 1995 Technical
					6 M (increased liver AST, ALT and liver and serum AP activities)		
			Bd Wt	6			
59	Rat (albino)	30 d 1x/d (GO)	Resp		1.5 F (transient dyspnea)		Raizada et al. 1991
			Endocr	1.5 F			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
60	Rat (Wistar)	15-30 d 1x/d (GO)	Endocr		7.5 M (reduced testicular and plasma hormones, decreased enzyme activity levels)		Singh and Pandey 1990 Technical
61	Rat (Druckrey)	70 d 5 d/wk (GO)	Bd Wt	10 M			Sinha et al. 1995 Technical
62	Mouse (CD-1)	13 wk ad lib (F)	Resp	2.1		7.3 (vascular congestion in lungs)	Hoechst 1984b Technical
			Cardio	7.3			
			Gastro	7.3			
			Hemato	7.3			
			Musc/skel	7.3			
			Hepatic	7.3			
			Renal	7.3			
			Endocr	7.3			
			Ocular	7.3			
63	Mouse (NMRI)	42 d ad lib (F)	Ocular	3.7			Hoechst 1985b Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
64	Dog (Beagle)	146-147 d ad lib (F)	Resp	2.6			Hoechst 1989c Technical
			Cardio	2.6			
			Gastro	2.6			
			Hemato	2.6			
			Musc/skel	2.6			
			Hepatic		2.6 (elevated serum alkaline phosphatase)		
			Renal	2.6			
			Endocr	2.6			
			Dermal	2.6			
			Ocular	2.6			
65	Rabbit (New Zealand)	Gd 6-28 23 d 1x/d (G)	Resp		1.8 F (noisy and rapid breathing)		FMC 1981 Technical
Immunological/Lymphoreticular							
66	Rat (Wistar)	8-22 wk ad lib (F)		0.45[b] M	0.9 M (decreased humoral and cell-mediated response)		Banerjee and Hussain 1986 Technical
67	Rat (Wistar)	6 wk ad lib (F)		0.9 M	2.7 M (decrease in humoral antibody and cell-mediated immune response)		Banerjee and Hussain 1987 Technical
68	Rat (Wistar)	3 wk ad lib (F)		5 M			Vos et al. 1982 Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
69	Mouse (CD-1)	13 wk ad lib (F)		2.1 M	7.3 M (decreased neutrophils and relative spleen weight)		Hoechst 1984b Technical
Neurological							
70	Rat (NS)	60 d 1x/d (GO)		2.5 M		7.5 M (hyperactivity; tremors; convulsions)	Ansari et al. 1984 Technical
71	Rat (albino)	30 d 1x/d (GO)				1.5 (hyperexcitation and tremors)	Dikshith et al. 1984 Technical
72	Rat (Long- Evans)	20 d 1 x/d (GO)				5 M (increased seizure activity)	Gilbert 1992 Technical
73	Rat (CrL:COBS CD)	84 d (F)		0.8	3.8 F (increased brain weight in dams)		Hoechst 1984a Technical
74	Rat (Sprague-Dawley)	13 wk ad lib (F)		2.3	4.6 F (increased brain weight)		Hoechst 1985a Technical
75	Rat (Wistar)	23 d 1 x/d (GO)			6 (changes in transmitter levels in several brain areas; impaired learning of a task)		Lakshmana and Raju 1994 Technical
76	Rat (Wistar)	90 d 1 x/d (GW)				2 M (inhibition of learning and memory processes)	Paul et al. 1994 Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
77	Rat (Wistar)	30 d (F)				3 (impaired learning and memory processes)	Paul et al. 1995 Technical
78	Rat (albino)	30 d 1x/d (GO)			1.5 F (transient hyperactivity, tremor, salivation)		Raizada et al. 1991
79	Mouse (CD-1)	13 wk ad lib (F)				7.3 (convulsions)	Hoechst 1984b Technical
80	Dog (Beagle)	146-147 d 1x/d (F)				2.6 (extreme sensitivity to noise and optical stimuli; muscle spasms in extremeties, face, and jaw; placing and righting reflexes absent)	Hoechst 1989c Technical

Reproductive

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
81	Rat (Sprague-Dawley)	170+ d ad lib (F)		2.5			FMC 1965 Technical
82	Rat (albino)	15 d 1x/d (GO)		5 M		10 M (degeneration of seminiferous tubule epithelium)	Gupta and Chandra 1977 Technical
83	Rat (Sprague-Dawley)	11 wk ad lib (F)		8			Hoechst 1982 Technical
84	Rat (CrL:COBS CD)	84 d (F)		3.8			Hoechst 1984a Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
85	Rat (Druckrey)	70 d 5 d/wk (GO)					2.5 M	(reduced sperm count; changes in enzyme activity indicating altered spermatogenesis)	Sinha et al. 1995 Technical
86	Rat (Druckrey)	90 d 5 d/wk (GO)					2.5 M	(reduced sperm and spermatids count and daily sperm production; increased abnormal sperm; changes in enzyme activity indicating altered spermatogenesis)	Sinha et al. 1997 Technical
87	Mouse (Swiss albino)	35 d 1x/d (GW)					3 M	(4/5 reduction in sperm count; increased frequency of sperm with head abnormalities)	Khan and Sinha 1996 Technical
88	Rabbit (New Zealand)	Gd 6-28 23 d 1x/d (G)		1.8 F					FMC 1981 Technical
Developmental									
89	Rat (Sprague-Dawley)	11 wk ad lib (F)		4	6	(decreased mean litter weights during lactation)	8	(increased pup mortality post-weaning)	Hoechst 1982 Technical
90	Rat	84 d (F)		0.2	0.8	(decreased litter weights prior to weaning)			Hoechst 1984a Technical

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

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
91	Rabbit (New Zealand)	Gd 6-28 23 d 1x/d (GO)		1.8			FMC 1981 Technical

CHRONIC EXPOSURE

Death

92	Rat (Wistar)	2 yr ad lib (F)				5.0 F (decreased survival)	FMC 1959b Technical
93	Mouse (NMRI)	104 wk (F)				2.88 F (28% survival compared to 45% in controls)	Hack et al. 1995 Technical
94	Mouse (NMRI)	24 mo ad lib (F)				2.9 F (decreased survival)	Hoechst 1988b Technical

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
95	Rat (Wistar)	2 yr ad lib (F)	Resp	5.0			FMC 1959b Technical
			Cardio	5.0			
			Gastro	5.0			
			Hemato	5.0			
			Hepatic	1.0	5.0 M (hydropic hepatic cells)		
			Renal	1.0		5.0 M (increased kidney weight; renal tubule dilation, degeneration of renal tubule epithelium; albuminous casts; focal interstitial nephritis)	
			Endocr	5.0			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
96	Rat (Sprague-Dawley)	104 wk (F)	Resp	3.5 F			Hack et al. 1995 Technical
			Cardio	3.5 F			
			Gastro	3.5 F			
			Hemato	3.5 F			
			Hepatic	3.5 F			
			Renal	0.7 F	3.0 M (greater number of aneurysms in kidneys, increased incidence of progressive glomeulonephrosis) 3.5 F (enlarged kidneys)		
			Ocular	3.5 F			
			Bd Wt		0.6 M (15% less weight gain) 0.7 F (11% less weight gain)	3.0 M (29% less weight gain 3.5 F (21% less weight gain)	
			Metab	3.5 F			
			Other	3.5 F			

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

Key to figure [a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
97	Rat (Sprague-Dawley)	2 yr ad lib (F)	Resp	2.9			Hoechst 1989a Technical
			Cardio	0.6	2.9 M (aneurysms of blood vessels)		
			Gastro	2.9			
			Hemato	2.9			
			Musc/skel	2.9			
			Hepatic	2.9			
			Renal	0.6		2.9 M (severe glomerulonephrosis)	
			Endocr	2.0			
			Bd Wt	0.6	2.9 M (signif. reduced body wt gain)		
			Dermal	2.0			
			Ocular	2.0			
98	Rat (Osborne-Mendel)	74-82 wk ad lib (F)	Cardio			20 M (calcium deposits in the heart, coronary and mesenteric arteries)	NCI 1978 Technical
			Renal			11 (degeneration of proximal convoluted tubule; degeneration of tubular epithelium; fibrosis and focal mineralization)	
			Endocr		11 (parathyroid hyperplasia; calcification of organs)		
			Bd Wt			20 M (body weight reduced by 23% relative to controls at week 80)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
99	Mouse (NMRI)	104 wk (F)	Resp	2.88 F			Hack et al. 1995 Technical
			Cardio	2.88 F			
			Gastro	2.88 F			
			Hemato	2.88 F			
			Hepatic	2.88 F			
			Renal	2.88 F			
			Bd Wt	0.97 F	2.52 M (17% less weight gain)		
			Other	2.88 F			
100	Mouse (NMRI)	24 mo ad lib (F)	Resp	2.5			Hoechst 1988b Technical
			Cardio	2.5			
			Gastro	2.5			
			Hemato	2.5			
			Musc/skel	2.5			
			Hepatic	2.5			
			Renal	2.5			
			Endocr	2.5			
			Dermal	2.5			
			Ocular	2.5			
			Bd Wt	0.8	2.5 M (decreased body weight)		
101	Dog (Mongrel)	1 yr 6 d/wk 1x/d (C)	Resp	0.8			FMC 1959a Technical
			Cardio	0.8			
			Gastro	0.8			
			Hemato	0.8			
			Hepatic	0.8			
			Renal	0.8			
			Endocr	0.8			

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

| Key to figure [a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
102	Dog (Beagle)	2 yr ad lib (F)	Resp	1.0			FMC 1967 Technical
			Cardio	1.0			
			Gastro	1.0			
			Hemato	1.0			
			Musc/skel	1.0			
			Hepatic	1.0			
			Renal	1.0			
			Endocr	1.0			
103	Dog (Beagle)	1 yr ad lib (F)	Resp	1.8			Hoechst 1989c Technical
			Cardio	1.8			
			Gastro	0.6			
			Hemato	1.8			
			Musc/skel	0.6		1.8 (abdominal and jaw muscle spasms)	
			Hepatic	0.18[c]	0.6 (increased serum alkaline phosphatase)		
			Renal	1.8			
			Endocr	1.8			
			Dermal	1.8			
			Ocular	1.8			

Immunological/Lymphoreticular

| 104 | Rat (Sprague-Dawley) | 2 yr ad lib (F) | | 2.9 | | | Hoechst 1989a Technical |

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
105	Rat (Sprague-Dawley)	2 yr ad lib (F)		2.9			Hoechst 1989a Technical
106	Mouse (NMRI)	24 mo ad lib (F)		2.5			Hoechst 1988b Technical
107	Dog (Beagle)	2 yr ad lib (F)		1.0			FMC 1967 Technical
108	Dog (Beagle)	1 yr ad lib (F)		0.6		1.8 (abdominal and jaw muscle spasms)	Hoechst 1989c Technical
Reproductive							
109	Rat (Osborne-Mendel)	74-82 wk ad lib (F)		20 M		48 M (testicular necrosis aspermatogenesis)	NCI 1978 Technical

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral minimal risk level (MRL) of 0.005 mg/kg/day; 0.45 mg/kg body weight dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic oral minimal risk level (MRL) of 0.002 mg/kg/day; 0.18 mg/kg body weight dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; ALT = alanine amino transferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; ATPase = adenosine triphosphatase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observable- adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; wk = week(s); x = time(s); y = year(s).

Figure 2-2. Levels of Significant Exposure to Endosulfan - Oral
Acute (≤14 days)

c-Cat	-Humans	f-Ferret	n-Mink
d-Dog	k-Monkey	j-Pigeon	o-Other
r-Rat	m-Mouse	e-Gerbil	
p-Pig	h-Rabbit	s-Hamster	
q-Cow	a-Sheep	g-Guinea Pig	

◆ Cancer Effect Level-Animals
◑ LOAEL, More Serious-Animals
◐ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
△ LOAEL, Less Serious-Humans
△ NOAEL - Humans

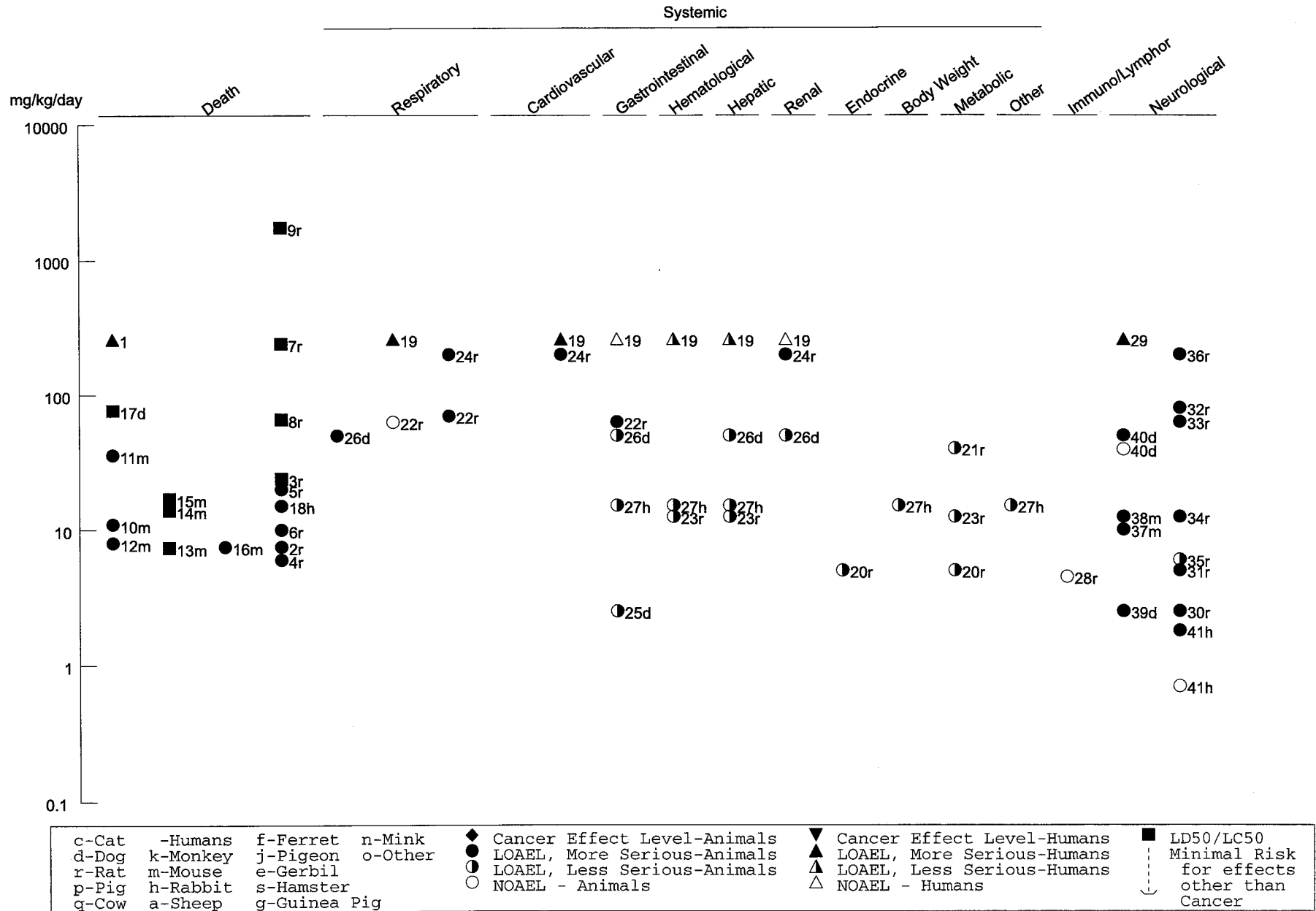■ LD50/LC50
┊ Minimal Risk
  for effects
  other than
  Cancer

Figure 2-2. Levels of Significant Exposure to Endosulfan - Oral (Continued)
Acute (≤14 days)

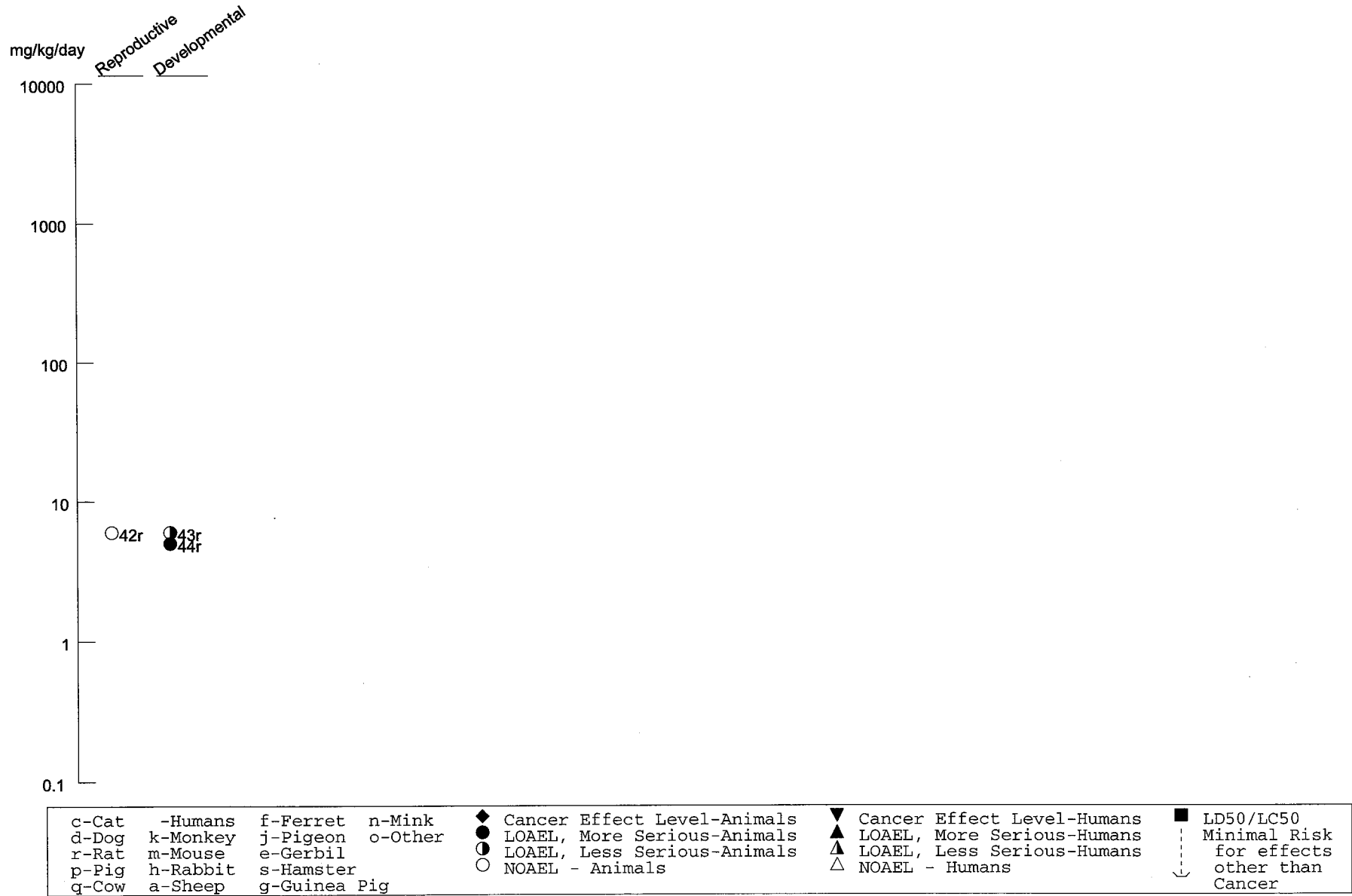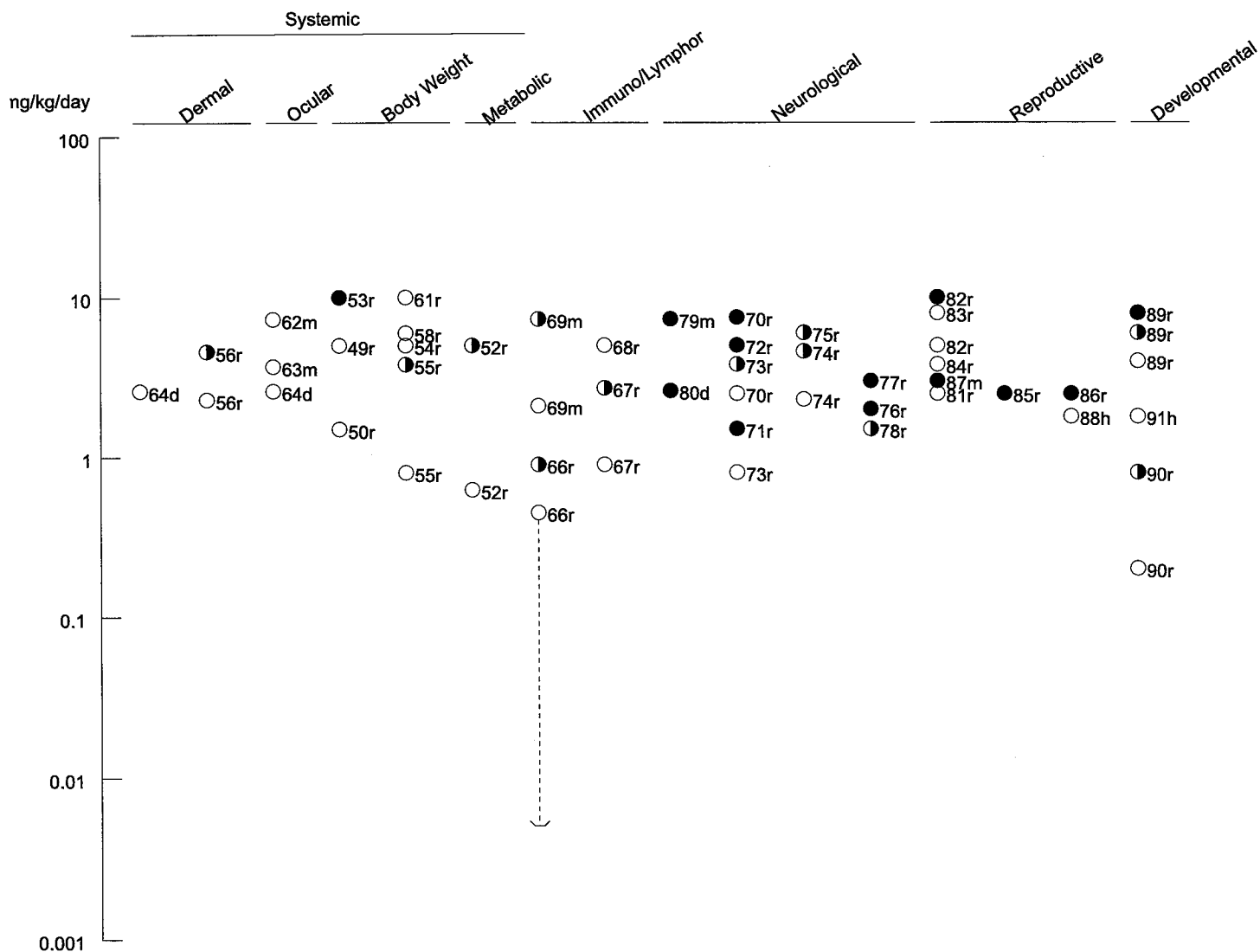# Figure 2-2. Levels of Significant Exposure to Endosulfan - Oral (Continued)
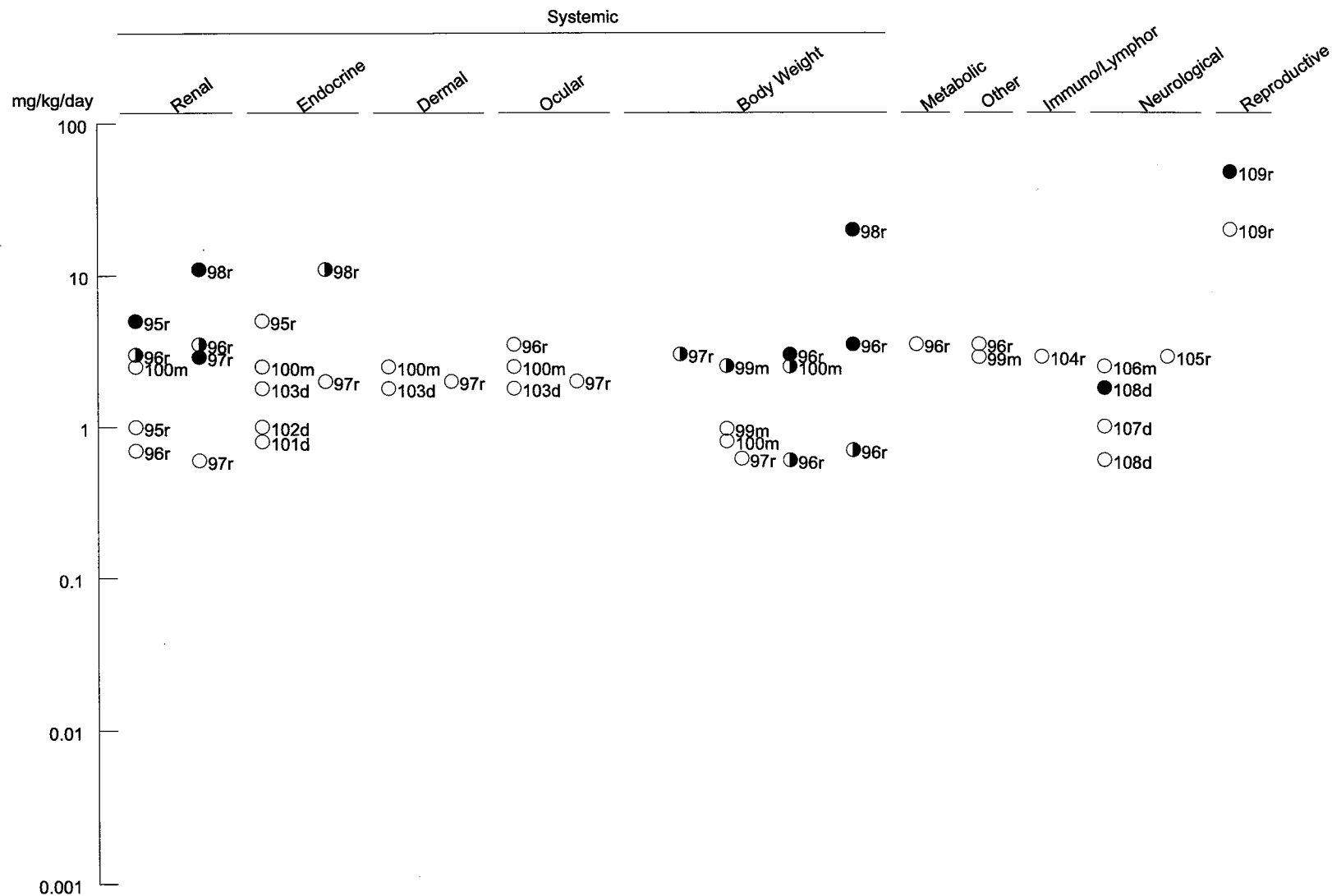
Intermediate (15-364 days)

Systemic

mg/kg/day

Death · Respiratory · Cardiovascular · Gastrointestinal · Hematological · Musculoskeletal · Hepatic · Renal · Endocrine

```
100 ┌

                                                                    ◑56r  ◑56r        ●56r

 10 ┤        ●46r  ◑53r  ●53r        ○53r                                              ●53r   ○53r
     ●48m ●48m ●45r ●62m                ○62m ○62m ○62m           ○62m ○62m             ○62m   ○62m  ◑60r
          ●47r  ○53r              ○49r ◑50r ○51r              ○49r ○50r ◑53r ○54r ◑58r ○49r   ○53r  ○54r
                                                                       ○56r  ○56r           ◑56r
                                                                             ◑58r
          ○64d        ○64d  ○64d  ○64d              ○57r  ○64d  ◑64d                    ○64d   ○64d
          ○62m              ◑65h              ○50r                                            ○56r
                           ◑59r                                 ◑50r  ○50r             ○50r   ○59r

  1 ┤                                                  ◑56r

0.1 ┤

0.01 ┤

0.001 └
```

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

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

Intermediate (15-364 days)

ng/kg/day

Systemic

Dermal   Ocular   Body Weight   Metabolic   Immuno/Lymphor   Neurological   Reproductive   Developmental

100

10
- ●53r ○61r
- ○62m
- ◐69m ●79m ●70r ◐75r ●82r ●89r
- ○83r ◐89r
- ◐56r ○49r ○58r ◐52r ○68r ●72r ◐74r ○82r ○89r
-                ○54r   ◐73r ○84r
-                ◐55r   ●87m
- ○64d ○56r ○63m   ◐81r
- ○64d ○64d ◐67r ●80d ○70r ○74r ●77r ●85r ●86r ○89r
-                                    ●76r ○88h
- ○50r ○69m   ●71r   ◐78r   ○91h

1
- ○55r ◐66r ○67r ○73r ◐90r
- ○52r
- ○66r

- ○90r

0.1

0.01

0.001

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

Chronic (≥365 days)

	c-Cat	-Humans	f-Ferret	n-Mink
	d-Dog	k-Monkey	j-Pigeon	o-Other
	r-Rat	m-Mouse	e-Gerbil	
	p-Pig	h-Rabbit	s-Hamster	
	q-Cow	a-Sheep	g-Guinea Pig	

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

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
▲ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
┊ Minimal Risk
  for effects
↓ other than
  Cancer

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

1992). Boereboom et al. (1998) observed minor lung hemorrhaging and atelectasis at autopsy of a man
who ingested approximately 260 mg/kg endosulfan 4 days prior to death.

Similar to the data from humans, respiratory effects have been observed in animals almost exclusively in
acute, lethal-dose exposure situations. Male rats given single gavage doses of 200 mg/kg of endosulfan
exhibited dyspnea and cyanosis prior to death (Terziev et al. 1974). Necropsy revealed hemorrhages in
the interalveolar partitions of the lung and acute emphysema of the lungs. Studies in which a limited
number of dogs were given single oral doses of endosulfan as low as 10 mg/kg (FMC 1958) or 50 mg/kg
(Hoechst 1970) demonstrated respiratory paralysis and death. Autopsy of the dogs revealed congestion of
the lungs. It is not clear whether these effects were a result of direct action on the lungs or were
associated with the generalized convulsions. In another study in which female rats were given a single
gavage dose of β-endosulfan, lung congestion was observed at 70 mg/kg, but not at 63 mg/kg (Hoechst
1988a). These dose levels caused lethality in the rats.

Local inflammation of the lungs and dilated alveoli were observed in rats administered 10 mg/kg/day of
endosulfan in peanut oil by gavage for 15 days (Gupta and Chandra 1977). However, there was high
mortality in this dose group (3 of 8 animals died prior to study termination), and it is not clear if these
effects were observed primarily in the intercurrent deaths or in animals surviving for the full 15 days of
exposure.

With the exception of the effects reported by Hoechst (1988a) in female rats, no effects on respiratory
tissues were observed during gross and histopathological examinations in intermediate- and chronic-
duration studies in rats, mice, and dogs at sublethal doses (FMC 1959a, 1959b, 1967; Hack et al. 1995;
Hoechst 1984b, 1988b, 1989a, 1989c).

Cardiovascular Effects.   Cardiovascular effects were part of the clinical syndrome displayed by a
20-year-old man who attempted suicide by ingesting 200 mL of a 30% endosulfan formulation
(Thionax®) (Shemesh et al. 1988). Although the man's stomach contents were aspirated and he was given
activated charcoal to limit absorption during the first 16 hours following ingestion, episodes of
tachycardia and hypertension occurred, followed by cardiogenic shock. It is not clear whether these
cardiovascular effects were due to a direct action of endosulfan on the cardiovascular system or a result of
a more general toxic insult (e.g., convulsions). It is also unclear whether other ingredients in the
Thionax® may have contributed to the effects observed. A similar picture was described in another lethal
case of acute intoxication with endosulfan (Lo et al. 1995). Severe cardiovascular effects developed in a

woman who ingested an unknown amount of endosulfan mistakenly mixed into food (Blanco-Coronado et al. 1992). On admission to the hospital, she had transient hypotension (60/30 mm Hg). Over the next few days her hemodynamic parameters remained abnormal, and she died 8 days after admission following acute renal failure, disseminated intravascular congestion, thrombi in the pulmonary arteries and aorta, and cardiogenic shock. A man who ingested approximately 260 mg/kg endosulfan experienced a drop in arterial blood pressure on the day of exposure, and focal cardiac inflammation and "slight" heart congestion on autopsy 4 days after exposure (Boereboom et al. 1998). No other information was located regarding the cardiovascular effects of ingested endosulfan in humans.

Male rats given a single oral dose of 200 mg/kg of endosulfan had myocardial hemorrhages (Terziev et al. 1974). It is not clear whether this effect was due to a direct effect of endosulfan on the heart or secondary to other toxicity such as damage occurring in response to effects of endosulfan on neural control of the heart.

In general, longer-term exposure of animals to sublethal concentrations of endosulfan has not resulted in gross or microscopic evidence of cardiovascular toxicity (FMC 1959a, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989c). However, three rat studies indicated possible toxic effects. Male rats that consumed 0.75 mg/kg/day for at least 84 days had an increase in relative heart weight (Hoechst 1984a). Also, male rats that consumed 2.9 mg/kg/day for 2 years had an increased incidence of aneurysms in blood vessels (Hoechst 1989a). Female rats were not similarly affected at doses up to 3.8 mg/kg/day for 2 years (Hoechst 1989a). In light of the large number of negative studies that used similar doses of endosulfan, the biological significance of the isolated observations of blood vessel aneurysms is unknown. An additional chronic study in rats, that used larger doses (20 and 48 mg/kg/day), reported calcification of the heart and the aorta and mesenteric arteries in male rats (NCI 1978). The calcification was thought to be caused by parathyroid hyperplasia, which in turn was secondary to kidney disease.

Gastrointestinal Effects.   Nausea, gagging, vomiting, and diarrhea were part of the clinical syndrome exhibited by persons who consumed high doses (lethal in some cases) of endosulfan either intentionally or accidentally (Blanco-Coronado et al. 1992; Pradhan et al. 1997; Terziev et al. 1974). However, it is unclear whether these effects were the result of gastrointestinal irritation or were mediated by effects of endosulfan on central nervous system control of gastrointestinal function. Mucosal inflammation of the stomach and the proximal small intestinal were postmortem observations in a man who purposely ingested an unknown amount of endosulfan (Lo et al. 1995). In contrast, a man who

ingested endosulfan once at approximately 260 mg/kg did not show any apparent stomach or intestinal lesions at autopsy 4 days later (Boereboom et al. 1998).

Female rats that received a single gavage dose of 63 mg of β-endosulfan/kg, a dose which was lethal, had blood in the small intestines and mucus in the stomach (Hoechst 1988a). Studies in dogs indicate that acute exposure to relatively high doses of endosulfan may cause stomach irritation and vomiting. Dogs that consumed 2.5 mg/kg/day for 3 days vomited (FMC 1959a), and dogs given a single oral dose of 30 mg/kg exhibited vomiting and stomach irritation (FMC 1958). Following a single oral dose of 50 mg/kg, dogs had congestion in the stomach and small intestine (Hoechst 1970). Similarly, rats given single unspecified doses of endosulfan in an LD_{50} determination showed irritant gastroenteritis (Boyd et al. 1970). Rabbits treated with a single dose of 15.1 mg technical endosulfan/kg had watery diarrhea for 3–4 days after dosing, but eventually recovered (Ceron et al. 1995); this dose level was lethal to some of the treated rabbits.

Longer-term exposure of animals to sublethal doses of endosulfan has generally not resulted in observable signs of gastrointestinal toxicity. Routine gross and histopathological examination of the gastrointestinal tract revealed no adverse effects in rats, mice, or dogs in such studies (FMC 1959a, 1959b, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989a, 1989c). However, convulsive spasms of the abdominal and jaw muscles without vomiting were observed in male and female dogs that consumed 2.0 mg/kg/day and 1.8 mg/kg/day, respectively, for 1 year (Hoechst 1989c). No adverse gross or histopathological findings were noted following examination of the gastrointestinal tracts of these animals, indicating that the spasms may have been a neurological effect rather than the result of gastrointestinal irritation.

Hematological Effects.   Leukocytosis and decreased platelet counts were reported in a group of subjects shortly after they ingested an unknown amount of endosulfan (Blanco-Coronado et al. 1992). One subject from that study, who eventually died, had prolonged partial thromboplastin time and prothrombin time with thrombocytopenia, and decreased fibrinogen two days after being admitted to the hospital. Elevated white cell count was also observed in an additional case of fatal acute poisoning with endosulfan (Lo et al. 1995). Significantly elevated hemoglobin (61.2 g/100 mL compared to a reference range of 13–18 g/100 mL) and slightly elevated white cell count (12,600/mm^3 compared to a reference range of 5000–10,000/mm^3), but normal hematocrit, were seen in a male patient at approximately 40 minutes after ingesting 260 mg endosulfan/kg; the man subsequently died (Boereboom et al. 1998).

No further information was located regarding hematological effects in humans after oral exposure to endosulfan.

Treatment-related effects on red blood cells have been noted following high-dose acute-duration oral exposure of animals to endosulfan. For example, decreased erythrocyte Na^+-K^+ ATPase activity was observed in female rats treated daily with 12.5 mg technical endosulfan/kg for 4 days (Kiran and Varma 1988). Female rats treated with a single gavage dose of 22 mg endosulfan/kg had decreased hemoglobin at sacrifice 24 hours after dosing; a group treated with a 33 mg/kg dose showed decreases in red blood cells, hemoglobin, and packed cell volume (Siddiqui et al. 1987b); however, these dose levels may have been close to lethal doses. Rabbits administered a single gavage dose of 15.1 mg endosulfan/kg also showed a decrease in red blood cells, hemoglobin, and packed cell volume; this dose was lethal to 5 out of 7 rabbits (Ceron et al. 1995).

Mixed results have been obtained in studies examining longer-term exposures to endosulfan. Adverse hematological effects were observed in a well conducted study in which rats were administered endosulfan in the diet for 13 weeks (Hoechst 1985a). At 6 weeks, effects observed in male rats that consumed 1.9 mg/kg/day included decreased hemoglobin, red blood cell count, and mean corpuscular hemoglobin concentration, and increased mean corpuscular volume. Decreased mean corpuscular hemoglobin concentration was observed in female rats at a similar dose. At higher doses in this study, the magnitude of the effects increased, and effects comparable to those observed in males were observed in females. At 13 weeks, males exhibited decreased hemoglobin concentration at 3.8 mg/kg/day and above, whereas decreased hemoglobin was seen in females at 0.8 mg/kg/day. Following a 4-week withdrawal period, spleen weights were significantly increased in males at $1.9 mg/kg/day. However, hematological determinations performed in other intermediate- and chronic-duration studies in rats using doses comparable to those noted above do not support the ability of endosulfan to cause anemia (Das and Garg 1981; Dikshith et al. 1984; FMC 1959b; Hack et al. 1995; Hoechst 1989a). In fact, increased red blood cell count was observed in male rats treated with 5 mg of technical endosulfan/kg/day for 30 days (Dikshith et al. 1984). Also, no effects on hematological parameters or on routine gross and histopathological examination of bone marrow and the spleen were observed in mice or dogs during intermediate- and chronic-duration studies (FMC 1959a, 1967; Hoechst 1984b, 1988b, 1989c).

The adverse effects on the blood observed in the study by Hoechst (1985a) cannot be totally discounted as spurious. A possible explanation for the discrepancy between the findings in the Hoechst study (1985a) and the other studies noted above may be provided by the results of the study by Das and Garg

(1981). These authors found decreased red blood cells in rats reared on a low-protein diet (3.5% protein) that contained endosulfan at levels calculated to be equivalent to doses of 0.025 and 5 mg/kg/day of endosulfan for 9–18 weeks. However, no effect was observed at these doses in rats given normal protein diets prior to exposure, indicating that protein deficiency enhances the anemia-inducing capacity of endosulfan. Thus, some subtle stressor may have affected the response of rats in the study by Hoechst (1985a) such that they responded similarly to rats that consumed a protein-deficient diet.

Musculoskeletal Effects.   No studies were located regarding musculoskeletal effects in humans following oral exposure to endosulfan. Only limited information was obtained regarding effects of endosulfan on muscle and/or bone in animals. Routine gross and microscopic examination of samples of bone and/or muscle obtained from animals in intermediate-duration (Hoechst 1984b, 1989c) and chronic-duration (FMC 1967; Hoechst 1988b, 1989a, 1989c) studies revealed no adverse effects of endosulfan on these tissues.

Hepatic Effects.   Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were reported in a woman 2 days after being admitted to the hospital because of ingestion of endosulfan-contaminated food (Blanco-Coronado et al. 1992). The patient died 8 days after admission, following acute renal failure, disseminated intravascular coagulation, thrombi in the pulmonary arteries and aorta, and cardiogenic shock. Postmortem examination revealed dilation and congestion of hepatic sinusoids. Centrilobular congestion and slight prominence of the bile canaliculi were among postmortem observations in an additional fatal case of acute poisoning with endosulfan (Lo et al. 1995). A man who ingested approximately 260 mg/endosulfan/kg showed liver congestion on autopsy 4 days after exposure (Boereboom et al. 1998). No further information was located regarding hepatic effects in humans after oral exposure to endosulfan.

Studies in experimental animals indicate that both toxic effects and adaptive effects may be seen in the liver following oral exposure to endosulfan.

Autopsy of dogs that ingested single lethal doses of endosulfan (10 mg/kg, FMC 1958; 50 mg/kg, Hoechst 1970) revealed liver congestion. Similarly, autopsied rats that received unspecified doses of endosulfan in an LD_{50} study were reported to have liver congestion (Boyd et al. 1970). Rats receiving a single oral dose of 33 mg/kg of endosulfan had increased serum glutamate-pyruvate transferase activity, indicating hepatic damage (Siddiqui et al. 1987b). Female rats treated daily by gavage with 12.5 mg technical endosulfan/kg for 4 days showed decreased activity of liver aldolase (Kiran and Varma 1988).

Rabbits that were administered a single gavage dose of 15.1 mg of technical endosulfan/kg, a dose that caused severe general toxicity, had significantly increased serum alkaline phosphatase (AP), ALT, and AST activities (suggesting liver damage) in the days following treatment (Ceron et al. 1995); no histopathology was conducted in this study. These observations are consistent with findings in humans acutely exposed to high doses of endosulfan.

Adaptive effects (including increased microsomal enzyme activity, increased liver weight, increased smooth endoplasmic reticulum, and decreased pentobarbital-induced sleeping time) in the absence of any signs of toxicity have also been observed in female rats in acute-duration studies at doses as low as 2.5 mg/kg/day for 7 days (Gupta and Gupta 1977a) or 14 days (FMC 1980a) and in male rats at doses as low as 5 mg/kg/day for 2 days (Misra et al. 1980) or 10 mg/kg/day for 14 days (Den Tonkelaar and Van Esch 1974).

Increased liver weight has also been observed in several intermediate-duration studies. For example, increased liver weight has been observed in female rats exposed to 2.5 mg/kg/day for 15 days (Gupta and Gupta 1977a) and in maternal animals exposed to 0.75 mg/kg/day endosulfan for approximately 84 days (Hoechst 1984a). In male rats, increased liver weight was observed at doses as low as 5 mg/kg/day after 15 days (Gupta and Chandra 1977) or 30 days (Dikshith et al. 1984) and at doses as low as 3.75 mg/kg/day for approximately 84 days (Hoechst 1984a). In a more recent study, doses of 3 mg technical endosulfan/kg/day in the food for 30 days significantly increased serum and liver AP, AST, and ALT activities in female rats, but not in males (Paul et al. 1995); these effects were seen in the males at a dose level of 6 mg/kg/day. The seemingly greater toxicity in the females was attributed to differences in metabolism between males and females. Evidence of microsomal enzyme induction (decreased pentobarbital-induced sleeping time) was also observed in female rats at 2.5 mg/kg/day for 30 days (Gupta and Gupta 1977a). In general, increases in liver weight have not been accompanied by adverse histopathological changes (Dikshith et al. 1984; Hoechst 1984a); however, exposure of male rats to 5 mg/kg/day for 15 days was reported to result in moderate dilation of the sinusoids, areas of focal necrosis, Kupffer cell hyperplasia, and bile duct proliferation with more severe necrosis, inflammation, and dilation at 10 mg/kg/day (Gupta and Chandra 1977). Also, increased serum AP was observed in male and female rats in the study by Dikshith et al. (1984), suggesting that both adaptive and toxic effects may be observed in some intermediate-duration studies.

In studies of somewhat longer duration, effects on liver weight were not observed or were observed only at high doses. Exposure of female rats to doses as high as 5 mg/kg/day for up to 18 weeks and male rats

to doses as high as 3.85 for 13 weeks (Hoechst 1985a) had no effect on liver weight (Das and Garg 1981; Hoechst 1985a). Increases in liver weight were observed after 13 weeks only at doses of 23.41 mg/kg/day in males and 27.17 mg/kg/day in females (Hoechst 1985a). In this study, granular brown pigment was observed in livers of males at 23.41 mg/kg/day, and centrilobular enlargement was observed in livers of females at 27.17 mg/kg/day; however, these changes were no longer apparent following a 4-week "withdrawal" period during which the animals were no longer exposed to endosulfan. In mice, an increase in liver weight was observed in females at 4.6 mg/kg/day but not in males at doses as high as 3.7 mg/kg/day for 42 days (Hoechst 1985b). No effect on mouse liver weight was observed at doses as high as 7.3 mg/kg/day (males) and 7.52 mg/kg/day (females) for 13 weeks (Hoechst 1984b). In both mouse studies, no adverse histopathological findings were observed during routine microscopic examination of the livers. Similarly, no adverse histopathological findings were observed during routine microscopic examination of the livers of dogs exposed to TWA doses of 2.9 mg/kg/day (males) and 2.6 mg/kg/day (females) for 146 days (Hoechst 1989c), but serum alkaline phosphatase was elevated in females treated with the 2.6 mg/kg/day dose.

Chronic-duration studies have generally not shown adaptive or adverse effects on the liver. Routine gross and microscopic pathology has not revealed adverse hepatic effects in mice exposed to 2.51 mg/kg/day (males) or 2.86 mg/kg/day (females) for 2 years (Hack et al. 1995; Hoechst 1988b), in rats exposed to #5 mg/kg/day (females) or 2.9 mg/kg/day (males) for 2 years (Hack et al. 1995; FMC 1959a; Hoechst 1989a), or in dogs exposed to 1 mg/kg/day for 2 years (FMC 1967). Serum alkaline phosphatase was, however, elevated in dogs exposed to 0.67 mg/kg/day (males) or 0.6 mg/kg/day (females) for 1 year, suggesting adverse effects on the liver; however, no effects on liver weight, liver function, or microscopic pathology were observed (Hoechst 1989c). A chronic-duration oral MRL of 0.002 mg/kg/day was derived based on the NOAEL level of 0.18 mg/kg/day determined in this study. An increase in the incidence of hydropic hepatic cells in the liver of male rats exposed to 5 mg/kg/day for 2 years (FMC 1959b) was also observed, indicating that hepatic toxicity may be observed in chronic studies when sufficiently high doses are administered.

Renal Effects.   Hemorrhage of the medullary layer of the kidneys was reported in three persons who died following ingestion of endosulfan (Terziev et al. 1974). Acute renal failure was a major contributor to the deaths of two individuals who ingested unknown amounts of endosulfan (Blanco-Coronado et al. 1992; Lo et al. 1995). In both cases, postmortem examination revealed extensive tubular necrosis. In contrast, no kidney lesions were found in a man who died 4 days after ingesting approximately 260 mg endosulfan/kg (Boereboom et al. 1998).

Ingestion of acutely lethal doses of endosulfan has also been associated with renal hemorrhage and congestion in studies in rats and dogs (FMC 1958, 1980a; Hoechst 1970; Terziev et al. 1974). Hemorrhagic areas on the kidney were observed at doses as low as 20 mg/kg/day for 14 days in a range-finding study using small numbers of pregnant rats (FMC 1980a). Congestion and hypertrophy were observed following a single dose as low as 10 mg/kg in a study using a limited number of dogs (FMC 1958).

In intermediate-duration studies in rats, congestion and focal degeneration in the epithelial lining of kidney tubules were observed in males treated with doses of 10 mg/kg/day for 15 days (Gupta and Chandra 1977). Also, yellow protein aggregates in the lumen and eosinophilic droplets in the cells of some proximal convoluted tubules were observed in rats following consumption of a diet that provided 3.9 mg/kg/day of technical endosulfan for 13 weeks (Hoechst 1985a). At 23.4 mg/kg/day males exhibited proteinuria (Hoechst 1985a). At lower doses, however, effects in rats have been limited to increases in kidney weight and changes in cellular pigmentation (Dikshith et al. 1984; FMC 1965; Hoechst 1984a, 1985a). Increases in relative kidney weight have been observed in rats at doses as low as 3.75 mg/kg/day for 84 days (Hoechst 1984a). Increases in yellow discoloration of the cytoplasm of cells of the proximal convoluted tubules have been observed following consumption of doses as low as 0.64 mg/kg/day for 13 weeks by male rats (Hoechst 1985a). Granular clumped pigment was also observed in cells of the straight portions and occasionally in the proximal convoluted tubules in male rats in this study at doses as low as 3.85 mg/kg/day at the end of 13 weeks of exposure and at doses as low as 1.92 mg/kg/day at the end of the 4-week withdrawal period. In mice, consumption of 7.3 mg/kg/day (males) or 7.52 mg/kg/day (females) for 13 weeks resulted in no gross or microscopically evident adverse effects (Hoechst 1984b). Similarly, in dogs given TWA doses of 2.9 mg/kg/day (males) or 2.6 mg/kg/day (females) for 146 days, routine gross and histopathological examination of the kidneys and urinary bladder revealed no adverse effects (Hoechst 1989c).

The toxicological relevance of the yellow discoloration of the cytoplasm of the cells of the proximal convoluted tubules and the increase in relative kidney weight that was observed in the study by Hoechst (1985a) was investigated in a subsequent study (Hoechst 1987) because toxicokinetic studies indicated that endosulfan accumulated in the kidneys of animals following intermediate-duration exposure (Ansari et al. 1984; Dorough et al. 1978; Nath and Dikshith 1979). Thus, the yellow discoloration and increase in kidney weight may have been merely a reflection of endosulfan storage within the cells of the proximal convoluted tubules rather than a toxic effect. In the latter study, light and electron microscopy of the kidneys of rats that consumed either 34 or 68 mg/kg/day for 4 weeks showed pigment deposits and an

increase in the number and size of lysosomes in the cells of the proximal convoluted tubules (Hoechst 1987). Other cell compartments were not affected, and the lysosomes were not reported to contain membrane fragments, indicating the absence of significant renal cell damage. A simultaneous determination of endosulfan residues in the kidney showed that α-endosulfan levels in the kidney were quite high relative to levels in the liver and blood. Relative kidney weights were also increased when compared to the controls. When given a 30-day recovery period, the kidney weight, yellow pigmentation, size and number of lysosomes, and the levels of α-endosulfan in the kidneys decreased considerably. The authors interpreted these results as showing that, at the doses and the exposure duration tested, endosulfan accumulates in the kidney without causing detectable toxicity. When given an endosulfan-free recovery period, the storage dissipated (i.e., the yellow discoloration and detectable levels of endosulfan were no longer observed in many of the rats). The increased kidney weights were proposed to reflect the increased storage and/or metabolism of the endosulfan. Therefore, based on the absence of evidence of autophagy of damaged organelles, the yellow discoloration and increases in the relative kidney weight were considered to be adaptive effects similar to the increases in liver weight and microsomal enzyme activity produced by many xenobiotic substances. However, no assessment of renal function was performed in this study. Therefore, it remains unclear whether the yellow discoloration occurs in the absence of renal toxicity.

Minor changes of questionable biological significance observed in rats administered 5 mg/kg/day of endosulfan in a low-protein diet for 9 weeks include a decrease in capsular space and an increase in perirenal adipose tissue (Das and Garg 1981).

Chronic ingestion of endosulfan by rats has been reported to result in nephrotoxicity. Consumption of technical-grade endosulfan by rats for 78 weeks (followed by a 33-week observation period) at TWA doses of 20 mg/kg/day (males) and 11.1 mg/kg/day (females) resulted in toxic nephropathy characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla (NCI 1978). Cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium were also evident. Reuber (1981) re-analyzed the histological sections from the NCI study, and found that chronic renal fibrosis was evident in 100% of exposed male rats, and that there was a significantly increased incidence of female rats with acute necrosis of the tubules. Similar results were obtained at lower doses in male rats in studies by FMC (1959b) and Hoechst (1989a). At doses of 5 mg/kg/day for 2 years an increase in kidney weight, renal tubule dilation, albuminous casts, focal interstitial nephritis, and degeneration of renal tubule epithelium were observed in male rats (FMC 1959b). Similarly, at doses of approximately 3 mg/kg/day for 2 years, progressive glomerulonephrosis was observed in male rats (Hack

et al. 1995; Hoechst 1989a). No evidence of renal toxicity was observed in female rats in these studies following consumption of doses of 5 mg/kg/day (FMC 1959b) or 3.8 mg/kg/day (Hack et al. 1995; Hoechst 1989a) for 2 years other than enlarged kidneys. These results indicate that male rats are more susceptible to the renal toxicity of endosulfan than female rats.

In contrast to the effects seen in rats following chronic-duration exposure, mice and dogs have not shown any evidence of nephrotoxicity at the doses that have been tested. Ingestion by mice of doses of endosulfan of 2.51 mg/kg/day (males) and 2.86 mg/kg/day (females) for up to 2 years resulted in no grossly or microscopically evident adverse effects on the kidneys or urinary bladder (Hack et al. 1995; Hoechst 1988b; NCI 1978). Similarly, ingestion by dogs of doses as high as 2 mg/kg/day (males) and 1.8 mg/kg/day (females) for 1 year (FMC 1959a; Hoechst 1989c) or 1 mg/kg/day (males and females) for 2 years (FMC 1967) resulted in no evidence of nephrotoxicity. Thus, rats appear to be more sensitive to the nephrotoxic effect of endosulfan.

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

Administration of a single oral dose of 5 mg of endosulfan/kg to rats resulted in degranulation of the β-cells of the islets of Langerhans of the pancreas (Barooah et al. 1980). This effect, however, was not observed after the same dose was administered daily for five days. Both administration protocols caused dilation of the blood vessels of the islets of Langerhans. Administration of 5 mg technical endosulfan/kg/day for 7 days to rats did not significantly alter the weight of the adrenals (Gupta and Gupta 1977a).

Routine gross and/or microscopic examination of the adrenals, pituitary, thyroid, or parathyroid did not reveal any adverse effects following intermediate exposure of rats, mice, or dogs to doses ranging from 2.5 to 10 mg/kg/day (FMC 1965; Gupta and Chandra, 1977; Hoechst 1984b, 1988b, 1989c). Similar lack of effects were reported in rats administered up to 5 mg endosulfan/kg/day for up to 2 years (FMC 1959b; Hoechst 1989a), dogs treated with up to 1 mg/kg/day for 2 years (FMC 1967) or mice administered 2.5 mg/kg/day for 2 years (Hoechst 1988b). Parathyroid hyperplasia and mineralization (calcium deposits) in several tissues were observed in male rats treated for 74–82 weeks, with estimated doses of 20 mg technical endosulfan/kg/day (NCI 1978). Both of these lesions were secondary to chronic renal failure (NCI 1978). Reuber (1981) re-evaluated the histological sections from the NCI study, and

indicated that the incidence of rats with parathyroid hyperplasia was significantly increased at both treatment levels among males, but not among females.

Endosulfan administered by gavage at 1.5 mg/kg/day for 30 days to ovariectomized rats did not influence the relative weights or histology of the uterus, cervix, or vagina compared to ovariectomized control rats that did not receive endosulfan (Raizada et al. 1991). Rats in a positive control group received intraperitoneal injections of estradiol and showed increased relative organ weights and normal development of female reproductive tissues compared to the untreated ovariectomized control rats. Organ weights and tissue development in rats administered both endosulfan and estradiol were not significantly different from those seen in rats that received estradiol alone. The study results indicate that endosulfan was neither estrogenic nor anti-estrogenic under the conditions of this assay.

Significantly increased serum testosterone and decreased testicular testosterone were reported in male rats after a 7-day exposure to endosulfan using oral doses in the range of 7.5–10 mg/kg/day, but not at #5 mg/kg/day (Singh and Pandey 1989). However, results after a 15-day exposure were highly variable and frequently not dose-related, making interpretation of the significance of the study's results difficult. A subsequent study (Singh and Pandey 1990) indicated a dose-related decrease in testicular testosterone, plasma testosterone, luteinizing hormone (LH), and follicular stimulating hormone (FSH) in groups of male Wistar rats orally administered endosulfan at 0, 7.5, or 10 mg/kg/day for 15 or 30 days. In addition, activities of steriodogenic enzymes and testicular cytochrome P450-dependent monooxygenases were depressed after the 30-day exposure at $7.5 mg/kg/day. All of the effects from 30 days of exposure were reversible during a 7-day recovery period, except for decreased testicular testosterone, which remained depressed; no recovery period was utilized for the 15-day exposures.

Dermal Effects.   No studies were located regarding dermal effects in humans following oral exposure to endosulfan.

Only limited information was obtained regarding the effects of endosulfan on the skin in animals. Routine gross and microscopic examination of samples of skin obtained from dogs treated with 2.6 mg endosulfan/kg/day in the diet for 147 days revealed no adverse effects (Hoechst 1989c). Female, but no male, rats treated for 13 weeks with 4.6 mg endosulfan/kg/day in the diet exhibited hair loss in the dorsal scapular and cervical regions (Hoechst 1985a). Chronic treatment of rats, mice, or dogs with doses of approximately 2 mg endosulfan/kg/day caused no significant alterations in the skin (Hoechst 1988b, 1989a, 1989c).

Ocular Effects.   No studies were located regarding ocular effects in humans following oral exposure to endosulfan.

Only limited information was obtained regarding the effects of endosulfan on the eyes in animals. Routine gross and microscopic examination of samples of eyes obtained from rats, mice, and dogs in intermediate-duration (FMC 1965; Hoechst 1984b, 1985b, 1989c) and chronic-duration (Hoechst 1988b, 1989a, 1989c) studies revealed no adverse effects of endosulfan on these tissues. Also, ophthalmoscopy of the eyes revealed no treatment-related effects in rats that consumed doses of up to 23.41 mg/kg/day (males) and 27.17 mg/kg/day (females) for 13 weeks (Hoechst 1985a) or 2.9 mg/kg/day (males) and 3.8 mg/kg/day (females) for 2 years (Hack et al. 1995; Hoechst 1989a); in mice that consumed 3.7 mg/kg/day (males) and 4.6 mg/kg/day (females) for 42 days (Hoechst 1985b); or in dogs that consumed TWA doses of 2.9 mg/kg/day (males) and 2.6 mg/kg/day (females) for 146 days or 2 mg/kg/day (males) and 1.8 mg/kg/day (females) for 1 year (Hoechst 1989c).

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

Body weight was not significantly affected in rats treated with up to 6 mg endosulfan/kg/day for 7–8 days (Gupta and Gupta 1977a; Lakshmana and Raju 1994) or in mice treated with up to 15 mg technical endosulfan/kg in the food for 7 days (Wilson and LeBlanc 1998). However, rabbits treated once with 15.1 mg technical endosulfan/kg by gavage and followed for 35 days exhibited a 12% reduction in body weight (Ceron et al. 1995); the dose level was lethal in the rabbit study. No significant effects on body weight were obtained in intermediate-duration studies in which rats were administered 5 mg endosulfan/kg/day by gavage for 15 days (Gupta and Gupta 1977a), 1.5 mg endosulfan/kg/day by gavage for 30 days (Dikshith et al. 1984), or 5 mg endosulfan/kg/day in the diet for 30 days (Paul et al. 1995) or 9–18 weeks (Das and Garg 1981) or 10 mg endosulfan/kg by gavage in oil 5 days/week for 90 days (Sinha et al. 1997). Contradicting the results of Sinha et al. (1997), in a study by Gupta and Chandra (1977), rats treated with 10 mg endosulfan/kg/day by gavage in oil for 15 days gained 30% less weight than control; this dose also caused lethality. Also, decreased body weight gain was reported in dams treated with doses of 3.8 mg/kg/day for 84 days (Hoechst 1984a). A dose of 2 mg technical endosulfan/kg/day by gavage in water for 90 days was also reported to cause significant reduction in weight gain in rats (Paul et al. 1994); in this case, food intake was also suppressed. Body weight gain was significantly reduced in male, but not female mice treated in the diet with 2.5 mg endosulfan/kg/day for 24 months (Hack et al. 1995; Hoechst 1988b); the no-effect-level dose was 0.8 mg/kg/day. Both male

and female rats treated with 0.6–0.7 mg endosulfan/kg/day in the diet for 24 months also exhibited reduction in body weight gain in the range of 11–15% (Hack et al. 1995); dose levels between 3 and 3.5 mg/kg/day caused body weight gain reductions in the range of 21–29%. The no-effect-level dose was approximately 0.3 mg/kg/day. An additional chronic study also reported a significant decrease in weight gain in male rats fed a diet that provided approximately 20 mg of technical endosulfan/kg/day (NCI 1978). In this case, the treated animals were approximately 23% lighter than matched controls after 80 weeks on the experimental diet.

Metabolic Effects.   Severe metabolic acidosis with high anion gap and hyperglycemia was reported in humans after acute poisoning with endosulfan (Blanco-Coronado et al. 1992; Lo et al. 1995). In five of the six cases reported by Blanco-Coronado et al. (1992), the metabolic acidosis was corrected with gastric lavage with activated charcoal and intravenous sodium bicarbonate and diazepam. No further information regarding metabolic effects in humans after exposure to endosulfan was located.

Studies in animals indicate that this chemical may affect glucose metabolism and ion permeability of cells. Increased blood glucose and/or decreased hepatic glycogen levels have been observed following acute- and intermediate-duration oral exposure to endosulfan (Chatterjee et al. 1986; Garg et al. 1980; Kiran and Varma 1988). It should be noted that this has been observed in animals exhibiting frank neurotoxicity. Interestingly, the hyperglycemia and decreased hepatic glycogen levels reported by Kiran and Varma (1988) were much more marked in older rats than in younger animals; and older animal, but not younger ones showed frank neurotoxic effects. Decreased serum glucose levels and degranulation of the β-cells of the islets of Langerhans of the pancreas (indicating release of insulin) were observed following a single dose, but not multiple doses, of endosulfan (Barooah et al. 1980). The observation of increases in serum glucose in some studies but decreases in others may be due to the differences in the doses of endosulfan used in these studies. The doses at which increases in serum glucose were observed (12.5–70 mg/kg/day) were higher than those at which a decrease in serum glucose was observed (5 mg/kg/day).

Decreased serum calcium has also been observed following a 7-week oral exposure to 5 mg/kg/day of endosulfan (Garg et al. 1980).

Other Systemic Effects.   In a group of 7 rabbits treated with a single dose of 15.1 mg technical endosulfan/kg by gavage in oil, 2 that recovered from the severe initial neurotoxic effects decreased their food intake by 82% relative to controls during the following weeks after treatment (Ceron et al. 1995).

The remaining 5 rabbits died within hours of dosing. Rats treated for 90 days with daily doses of 2 mg technical endosulfan/kg by gavage in water also reduced their food intake throughout the study (Paul et al. 1994). On the average, the treated rats ate 22% less food than the controls. Although the treated rats did not exhibit severe neurotoxic effects, their spontaneous motor activity was increased relative to controls. Neither food nor water consumption was significantly altered in mice or rats administered technical endosulfan in the diet for 24 months (Hack et al. 1995). In spite of this finding, both mice and rats gained significantly less weight during the study than their matched controls.

2.2.2.3 Immunological and Lymphoreticular Effects

No lesions of the spleen were evident on autopsy of a man who ingested a dose of approximately 260 mg endosulfan/kg (Boereboom et al. 1998).

Studies in male rats indicate that both humoral and cellular immune responses are depressed by endosulfan at doses that do not induce any other overt signs of toxicity. In a series of experiments, Banerjee and Hussain (1986, 1987) administered endosulfan in the diet of male rats at concentrations ranging from 5 to 50 ppm (equivalent to 0.45–4.5 mg/kg/day) for 6–22 weeks. The animals were immunized with a subcutaneous injection of tetanus toxin with an equal volume of Freund's complete adjuvant approximately 20 days prior to sacrifice. The animals did not exhibit any overt signs of toxicity, and no changes in body weight or mortality were noted. Serum antibody titer (to tetanus toxin), serum immunoglobulin levels (IgM and IgG), and serum globulin fractions (α-, β-, and γ-globulin) were studied to evaluate humoral immune responses. Serum antibody titer to tetanus toxin, IgG, IgM, and γ-globulin levels were significantly decreased in rats exposed to 4.5 mg/kg/day of endosulfan for 6 weeks and in rats exposed to 0.9 mg/kg/day of endosulfan for longer periods. The effects of endosulfan on cell-mediated immune competence were evaluated with macrophage migration inhibition (MMI) and leukocyte migration inhibition (LMI) tests. The results of both tests indicated that the cell-mediated immune response was significantly depressed in a dose-related manner in animals administered 1.8, 2.7, and 4.5 mg/kg/day. Spleen and thymus weights were not affected by endosulfan treatment in animals treated for 6 weeks, but a significant decrease in spleen weight was observed at 22 weeks in the 1.8 mg/kg/day dose group. These rats also had a significantly increased albumin-to-globulin ratio at week 22. The authors concluded that these results indicate that endosulfan can suppress both humoral and cell-mediated immune responses in rats exposed to levels of endosulfan that induce no other signs of toxicity. This was an apparently well conducted study that measured sensitive indicators of both humoral and immune function using doses of endosulfan that have not been previously shown to cause toxicity. Male

mice exposed to 7.3 mg/kg/day for 13 weeks had significantly decreased spleen weights and decreased neutrophil counts (Hoechst 1984b), indicating that immune activity in mice may also be affected. An intermediate-duration oral MRL of 0.005 mg/kg/day was derived based on the NOAEL of 0.45 mg/kg/day for immunotoxicity identified in the Banerjee and Hussain (1986) study. In support of these positive findings, Khurana et al. (1998) observed decreased macrophage functionality, in the absence of any other apparent toxicological effects, in 1-day-old broiler chicks fed 30 ppm endosulfan in the diet for 4 or 8 weeks.

Other studies have examined the effects of endosulfan on immune function in rats and have not observed effects at higher doses; however, these other studies have examined the effects of endosulfan administration for shorter durations and did not evaluate many of the same end points that showed positive effects in the studies by Banerjee and Hussain (1986, 1987). For example, doses as high as 4.5 mg/kg/day given 2 days before and 10 days after infection with *Trichinella spiralis* larvae resulted in no effect on the number of worms found in the body at sacrifice, no effect on the thymus or spleen weights, and no effect on the percent lymphocytes or white blood cell count (Hoechst 1988c). Also, there were no or marginal effects on the weight and histopathology of the thymus, spleen, or mesenteric and popliteal lymph nodes, or on leukocyte or monocyte counts. Serum IgM and IgG were not affected by 3 weeks of exposure to 5 mg/kg/day (Vos et al. 1982).

Also, chronic-duration studies have not generally shown adverse effects on organs of the immune system. Routine gross and histopathologic examination of the lymph nodes and thymus of rats, mice, and dogs exposed to endosulfan for 2 years at doses of up to 2.9 mg/kg/day (Hoechst 1989a), 2.51 mg/kg/day (Hoechst 1988b), and 1 mg/kg/day (FMC 1967), respectively, revealed no adverse effects. However, these studies did not assess immune function directly.

These results demonstrate that immunotoxicity may be a sensitive end point of endosulfan-induced toxicity following exposure to low doses for sufficient durations. The highest NOAEL value and all reliable LOAEL values for immunological effects in each species in each duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

The most prominent signs of acute overexposure to endosulfan in both humans and animals are hyperactivity, tremors, decreased respiration, dyspnea, salivation, and tonic-clonic convulsions. Five

cases of acute lethal poisoning in humans resulting from accidental or intentional ingestion of Thiodan[®] were reported in an early study by Terziev et al. (1974). The ingested doses were not specified. Initial clinical signs observed in all cases included nervous system effects such as agitation, writhing, and loss of consciousness. Autopsies performed in three of the cases revealed brain edema. Central nervous system stimulation also characterized the clinical syndrome displayed by a 20-year-old man who attempted suicide by ingesting 200 mL of a 30% endosulfan formulation (Thionax[®]) (Shemesh et al. 1988). Although the patient's stomach contents were aspirated and he was given activated charcoal to reduce absorption, in the first 2 weeks following ingestion, the patient displayed recurrent convulsions. This stage was followed by a slow recovery phase, in which psychomotor function slowly returned. One year after his attempted suicide, his mental activity (presumably psychomotor activity) was still severely impaired, and he required medication to control his seizures. This case report demonstrates that long-term brain damage can occur following acute overexposure to endosulfan in humans. The brain damage may have been a result of a direct action of endosulfan on the brain tissue or the hypoxia that accompanied the recurring seizures and respiratory insufficiency seen within the first 2 weeks of ingestion. It is also unclear whether the effects observed may have been due, in part, to other ingredients in the Thionax[®].

Similarly, convulsive seizures and a sustained epileptic state persisted after stomach contents were pumped and activated charcoal and anticonvulsive medication were administered in a 43-year-old man who ingested approximately 260 mg/kg endosulfan (Boereboom et al. 1998). At 4 days after exposure, the man was pronounced brain dead, and autopsy revealed cerebral hernia from massive cerebral edema. Eight additional accidental and/or intentional cases of acute poisoning with endosulfan resulting in adverse neurological effects have been reported in more recent studies, six by Blanco-Coronado et al. (1992), one by Lo et al. (1995), and one by Pradhan et al. (1997); two out of the eight resulted in death. Tonic-clonic convulsions were seen in the Blanco-Coronado et al. (1992) cases, whereas Lo et al. (1995) reported the development of muscle fasciculations and episodes of convulsions in their case. In the case reported by Pradhan et al. (1997), the patient had consumed about 75 mL of liquid endosulfan (35% w/v). In this case, in addition to tonic-clonic seizures and myoclonic jerks, the patient developed psychosis, cortical blindness and limb rigidity. Magnetic resonance imaging showed reversible lesions of the basal ganglia and occipital cortex. The amount of endosulfan ingested in the Blanco-Coronado et al. (1992) and Lo et al. (1995) reports was unknown.

Central nervous system stimulation is the hallmark of acute overexposure to endosulfan in experimental animals. The spectrum of effects includes hyperexcitability, tremors, decreased respiration, tonic-clonic convulsions, and ultimately, death (Boyd and Dobos 1969; Boyd et al. 1970; Ceron et al. 1995; FMC

1958, 1959a, 1980a; Gilbert and Mack 1995; Hoechst 1970, 1975, 1984e; Kiran and Varma 1988; Terziev et al. 1974). Convulsions have been observed after single oral doses of 10 mg/kg in dogs (FMC 1959a), after a single dose of 5 mg/kg in rats (Gilbert and Mack 1995), after a single dose of 15.1 mg/kg in rabbits (Ceron et al. 1995), after 3 daily doses of 2.5 mg/kg/day in dogs (FMC 1959a), after 10 daily doses of 1.8 mg/kg/day in pregnant rabbits (FMC 1981), and after 14 daily doses of 10 mg/kg/day in pregnant rats (FMC 1980a). At 2.5 mg/kg/day for 14 days, pregnant rats displayed poor muscle tone and head swaying (FMC 1980a); and at 6 mg/kg/day for 14 days, pregnant rats displayed face rubbing, flaccidity, and hyperactivity (FMC 1980b). Cerebral congestion and edema are often observed at necropsy in animals that die following acute ingestion of endosulfan (Boyd and Dobos 1969; Boyd et al. 1970; Terziev et al. 1974). A study designed to test anticonvulsants for their effectiveness in reducing the lethality of endosulfan found that phenobarbital, administered following administration of a lethal dose of endosulfan (80 mg/kg), significantly decreased the mortality and signs of neurotoxicity (e.g., convulsions and spasms) (Hoechst 1984e).

Some of the severe central nervous system effects described above have not been described in some intermediate or chronic ingestion studies of endosulfan in experimental animals (FMC 1959a, 1965, 1967; Hoechst 1984b, 1988b, 1989a). For example, in rats given daily gavage doses of 5 mg/kg/day (males) and 1.5 mg/kg/day (females) of endosulfan for 30 days, signs of central nervous system stimulation were observed for the first 3–4 days only and subsided thereafter (Dikshith et al. 1984). However, dogs that ingested feed containing 30 ppm for 54 days, 45 ppm for 52 days, and 60 ppm for up to 40 days (a TWA dose of 2.9 mg/kg/day for males or 2.6 mg/kg/day for females) showed extreme sensitivity to noise, frightened reactions to optical stimuli, and tonic contractions of the muscles of the extremities, face, and jaw (Hoechst 1989c). Animals exhibiting these symptoms were sacrificed to prevent needless suffering. Prior to sacrifice, the reflexes of these animals were tested. The placing and righting reflexes were absent, but pupillary, flexor, patellar, oral, and cutaneous reflexes were unaffected. At autopsy, results of routine gross and microscopic examination of the cerebral cortex, brain stem, cerebellum, medulla, optic and sciatic nerves, and spinal cord were normal. At slightly lower doses in this study, approximately 2.5–6 hours after consuming 2 mg/kg/day (males) or 1.8 mg/kg/day (females), dogs showed convulsive spasms of the jaws and abdominal muscles without vomiting. Pathology of the gastrointestinal tract did not reveal any adverse effects on these tissues, suggesting that the nervous system may have been the cause of the spasms. However, no effects on reflexes were observed, and gross and microscopic examination of central nervous system tissue revealed no abnormalities. Thus, it is unclear whether the effects observed at this dose were centrally mediated or were responses to gastrointestinal disturbances. Increased brain weights were observed in female rats following consumption of doses of 4.59 mg/kg/day

for 13 weeks (Hoechst 1985a) and in F_0 parental females in a multigeneration reproduction study at doses of 0.75 mg/kg/day (Hoechst 1984a). However, similar results were not observed in other studies in rats at doses of 2.9 mg/kg/day (males) and 3.8 mg/kg/day (females) for up to 2 years (Hoechst 1989a) or in mice or dogs in intermediate- and chronic-duration studies (FMC 1959a, 1967; Hoechst 1984b, 1988b, 1989c). Thus, the significance of the increases in brain weight is unknown, but it could have been related to edema.

A series of experiments were conducted in male Long-Evans rats to (a) assess the generality of an increased and persistent susceptibility to seizures following endosulfan treatment, (b) test the bidirectionality of kindling transfer induced by chemical and electrical means, and (c) determine whether chemical kindling reflects cumulative endosulfan toxicity (Gilbert 1992; Gilbert and Mack 1995). The findings can be summarized as follows: (1) a single gavage dose of 2.5 mg/kg of endosulfan reduced the threshold for seizure activity by electrical stimulation in amygdala kindled rats; (2) previous electrical stimulation reduced the threshold for convulsions by a single endosulfan dose; (3) repeated pretreatment with endosulfan followed by a 2-week drug-free period reduced the threshold for seizures by a challenge dose of endosulfan, arguing against cumulative toxicity; and (4) repeated pretreatment with endosulfan reduced the threshold for seizures by electrical stimulation. The positive transfer to electrical kindling suggested a commonality in the mechanism between seizures induced by repeated administration of endosulfan and those produced by repeated electrical stimulation.

The effects of endosulfan on the concentration of neurotransmitter substances in various regions of the brain from rats has been examined (Lakshmana and Raju 1994). These authors found that, relative to controls, treatment of newborn rats by gavage with technical endosulfan (6 mg/kg) for 8 days resulted in changes (increases and decreases) in the levels of noradrenaline, dopamine, and serotonin in the areas of the central nervous system that were examined (olfactory bulb, hippocampus, visual cortex, brainstem, and cerebellum). Treatment for 23 days also resulted in changes in neurotransmitter levels, but either of different magnitude or different direction than those observed in the animals exposed for 8 days, indicating that duration of exposure is an important parameter to consider when dealing with very young animals. Lakshmana and Raju (1994) also conducted a behavioral test in the rats treated for 23 days and found that treated rats took 29% more time to learn a task than the matched controls. The neurobehavioral effects of endosulfan have also been examined by others. Treatment of immature male rats with 2 mg technical endosulfan/kg/day by gavage for 90 days resulted in inhibition of learning and memory processes, and increased spontaneous motor activity (Paul et al. 1994). Since motor coordination was not significantly altered, Paul et al. (1994) suggested that the impairment in memory and learning

was due to a motivation deficit rather than to motor impairment. The learning process, but not the memory process, was reinstated by a serotonin depletor, suggesting that endosulfan produced a learning deficit by increasing serotonergic activity. In a subsequent study by the same group of investigators, in which both male and female rats were tested, it was found that a 30-day treatment with endosulfan in the diet (3 mg/kg/day) increased spontaneous motor activity to a greater degree in males than in females, but there was no sex difference regarding the impairment in memory and learning processes (Paul et al. 1995). The authors (Paul et al. 1995) speculated that the more marked effect in males may have been due to males preferentially metabolizing endosulfan to a more lipophilic metabolite, endosulfan sulfate, which could have reached the central nervous system. However, other factors cannot be ruled out, in particular since based on the chemical properties described in Chapter 3, endosulfan sulfate does not appear to be significantly more lipophilic than the parent compound.

In summary, neurotoxic effects of endosulfan are usually apparent only after acute ingestion of relatively high doses. Cumulative neurotoxicity does not appear to be significant. If the animal survives the acute toxic effects, then no long-term neurotoxic effects are evident from behavioral, gross, and microscopic observations. However, some impairment may occur that can be detected only by specialized neurobehavioral testing.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive toxicity in humans after oral exposure to endosulfan.

Three studies examined the effects of endosulfan exposure on reproductive performance in rats. Consumption of estimated doses of endosulfan of up to 9 and 8 mg/kg/day by male and female rats, respectively, for 2 weeks prior to mating and continued consumption throughout gestation resulted in no adverse effect on mating performance, pregnancy rate, or gestation (Hoechst 1982). This study is limited in that the actual intake of test material was quantified only during the first 2 weeks of exposure, and a relatively small number of animals was used. Similarly, consumption of 5 mg/kg/day by male rats and 1.5 mg/kg/day by female rats for 30 days prior to mating had no adverse effects on fertility when the

matings of treated males with control females and treated females with control males were compared to the mating of control males and females (Dikshith et al. 1984). This study is limited in that only 5 males and 10 females per dose were tested. A two-generation reproduction study in rats detected no effect on the size, mortality, or sex ratio of the litters following consumption of doses as high as 3.75 mg/kg/day for 84 days prior to the F_0 mating and 98 days prior to the F_1 mating (Hoechst 1984a).

A number of studies that used dose levels comparable to those described above have not observed adverse effects on the reproductive organs of rats, mice, or dogs. For example, routine gross and histopatho-logical examination of the reproductive organs of male and female rats that ingested doses of endosulfan of 5 mg/kg/day for 15 days or 2 years revealed no adverse effects on these organs (FMC 1959b; Gupta and Gupta 1977a; Hack et al. 1995; Hoechst 1989a). Similarly, routine gross and histopathological examination of the reproductive organs of mice that consumed doses of 7.3 mg/kg/day (males) and 7.52 mg/kg/day (females) for 13 weeks (Hoechst 1984b) or 2.51 mg/kg/day (males) and 2.86 mg/kg/day (females) for 2 years (Hack et al. 1995; Hoechst 1988b; NCI 1978) revealed no toxic effects. Also, routine gross and microscopic examination of the reproductive organs of dogs that consumed doses of 2.9 mg/kg/day (TWA dose; males) and 2.6 mg/kg/day (TWA dose; females) for 146 days (Hoechst 1989c) or 2 mg/kg/day (males) and 1.8 mg/kg/day (females) for 1 or 2 years showed no adverse effects (FMC 1959a, 1967; Hoechst 1989c).

Other studies that conducted a more detailed examination of the reproductive organs of male animals have reported adverse reproductive effects. Reduced sperm count and altered testicular enzyme activities, indicating altered spermatogenesis, were reported in mature rats treated by gavage with 2.5 mg technical endosulfan/kg/day (the lowest dose tested), 5 days/week for 70 days (Sinha et al. 1995). Additional effects seen at higher doses (5 and 10 mg/kg/day) included reduced intratesticular spermatid count and daily sperm production, and increased incidence of abnormal sperm. All of these effects were also observed in young male rats (3 weeks old) treated by gavage with 2.5 mg technical endosulfan/kg/day (the lowest dose tested), 5 days/week for 90 days, suggesting that the younger animals were more sensitive than the older ones (Sinha et al. 1997). Altered spermatogenesis was also reported in male mice treated by gavage with 3 mg technical endosulfan/kg/day for 35 days (Khan and Sinha 1996). Similar results had been observed in earlier studies that tested higher doses of endosulfan. For example, male rats given oral doses of 10 mg/kg/day of endosulfan for 15 days had decreased weight of the testes with marked degenerative changes in the epithelium of the seminiferous tubules (Gupta and Chandra 1977). A limitation of the study is that high mortality of males was observed at 10 mg/kg/day. Similarly, male rats that consumed a TWA dose of 47.6 mg/kg/day for up to 74 weeks had testicular atrophy with

degeneration and necrosis of germinal cells lining the seminiferous tubules, multinucleated cells, and calcium deposition resulting in aspermatogenesis (NCI 1978; Reuber, 1981). This study is also limited due to the high mortality from kidney disease observed among the males at this dose.

Others reported effects on testosterone production in male rats after exposure to endosulfan doses in the range of 7.5–10 mg/kg/day, which may possibly lead to reproductive toxicity Singh and Pandey (1989). However, the results of this study were highly variable and frequently not dose related, making interpretation of the significance of the results difficult. A subsequent study (Singh and Pandey 1990) indicated a dose-related decrease in testicular testosterone, plasma testosterone, LH, and FSH in groups of male Wistar rats administered endosulfan at 0, 7.5, or 10 mg/kg/day for 15 or 30 days. Testicular microsomal cytochrome P450-dependent monooxygenases were also significantly inhibited at both dose levels after 30 days of exposure. All of the effects from 30 days of exposure were reversible during a 7-day recovery period, except for testicular testosterone, which remained depressed; no recovery period was utilized for the 15-day exposures. Singh and Pandey (1990) observed no significant effect on testis wet weight after 15 or 30 days of endosulfan administration at 7.5 or 15 mg/kg/day, while increased relative testes weight was observed following ingestion of 5 mg/kg/day by male rats for 30 days (Dikshith et al. 1984). However, the study is limited in that only five male rats were tested per dose.

In summary, although the available reproductive studies indicate endosulfan has no adverse effects on reproductive performance in animals, adverse effects on male reproductive organs have been seen in young rats and mice. The lack of effects seen in the studies that examined reproductive performance (specifically fertility rate) in treated males and females seems difficult to explain, given the finding of altered spermatogenesis in the more recent studies.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in rats, mice, and dogs for each duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No clear geographic association was observed between the level of pesticide use and the locations of homes of children who underwent surgical correction for cryptorchidism (failure of descent of testes) in the Granada region of Spain (Garcia-Rodriguez et al. 1996). Endosulfan exposure levels were unavailable, but another study reported endosulfan isomers and/or metabolites in adipose tissue of 20 of

50 children (40%) who were hospitalized in the Granada hospital for a variety of reasons (Olea et al. 1999), indicating that significant endosulfan exposures occurred in the region.

Developmental effects have been observed in rats following oral administration of endosulfan to pregnant dams during gestation. Daily administration of endosulfan at doses of 5 or 10 mg/kg/day during Gd 6–14 produced a statistically significant increase in the percentage of resorptions and skeletal variations in the fetuses (e.g., absent fifth sternebrae) (Gupta et al. 1978). A dose-related increase in maternal deaths was observed in both test groups. Thus, embryotoxic effects were observed at doses that also caused maternal toxicity. This study is limited in that dosing was not continued until day 15 and, therefore, did not include the entire period of organogenesis. No statistically significant effect on fetal weight, sex ratio, or skeletal, internal, or external development was observed following administration of doses of 1.5 mg/kg/day to pregnant rats during Gd 6–15 (FMC 1972). A slight increase in the incidence of nonossified sternebrae was observed but did not reach statistical significance. Statistically significant skeletal variations (e.g., bipartite and misaligned sternebrae) were observed in fetuses following daily administration of doses of 0.66 mg/kg/day to pregnant rats during Gd 6–19 (FMC 1980b). These variations did not, however, increase with dose, and the incidence observed at the highest dose tested (6 mg/kg/day) did not reach statistical significance. Thus, these effects cannot be used to set the LOAEL for the study. At 6 mg/kg/day, additional fetal toxicity was observed (e.g., decreased fetal weight and length and other skeletal variations). Therefore, 6 mg/kg/day was set as the LOAEL for developmental toxicity in this study. However, the observation of statistically significant changes at lower doses places some uncertainty on this LOAEL. Maternal toxicity (e.g., two deaths, decreased mean corrected body weight gain measured on Gd 20, face rubbing, flaccidity, and hyperactivity) was observed in the high-dose group (6 mg/kg/day) and to a lesser extent in the mid-dose group (2 mg/kg/day) (e.g., decreased mean corrected body weight gain measured on Gd 20 and face rubbing). Limitations of this study include a number of gavage errors and the unplanned addition of 10 more animals to the high-dose group and 5 more animals to the control group (mated at approximately 30 and 40 days after the initial mating). A range-finding study detected no developmental toxicity at doses as high as 10 mg/kg/day (FMC 1980a). However, this study used a small number of animals and effects on implantation and resorption were the only developmental end points examined.

Exposure of rabbits to endosulfan during Gd 6–28 produced no significant effects on the number of implants, litter size, sex ratio, fetal weight or length, or the percentage of live or resorbed fetuses at doses as high as 1.8 mg/kg/day (FMC 1981). However, dams treated with 1.8 mg/kg/day did exhibit neurotoxic signs (e.g., noisy and rapid breathing, hyperactivity, and convulsions) that were considered to be

treatment related. Such neurotoxic effects were not observed at 0.7 mg/kg/day. Animals from control groups, as well as all test groups developed ascites, and 6 rabbits were added to the 1.8-mg/kg/day dose group without concurrent controls. The occurrence of ascites in both control and treated animals indicates that a problem existed in the laboratory environment, and thus casts doubt on the credibility of the results from the FMC (1981) study.

In addition to the studies noted above that examined the effect of endosulfan administered only during the period of gestation, two studies have examined the effects of endosulfan on fetal development following administration prior to mating, as well as throughout gestation and lactation. Administration of endosulfan at doses as low as 6 mg/kg/day from 2 weeks prior to mating through weaning resulted in a significant decrease in mean litter weight during lactation (Hoechst 1982). At 8 mg/kg/day in this study, an increase in pup mortality was also observed. Maternal toxicity (e.g., decreased body weight and increased relative liver weight) was observed in females at 6 mg/kg/day and above. In the second study, consumption of 0.75 mg/kg/day and 3.75 mg/kg/day of endosulfan for 84 days prior to mating through weaning resulted in decreased litter weights of rats during lactation (Hoechst 1984a). At 3.75 mg/kg/day, increases in pituitary weights and uterine weights were also observed among the weanlings. Maternal toxicity (e.g., decreased body weight) was observed at 3.75 mg/kg/day. Both of these studies are limited in that insufficient information was provided regarding the intake of test material during gestation and lactation.

In summary, based on these studies, the evidence for endosulfan-induced adverse developmental effects in animals is inconclusive. The highest NOAEL value and all reliable LOAEL values for developmental effects in rats and rabbits for the acute- and intermediate-duration categories are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to endosulfan.

Genotoxicity studies in animals following oral exposure to endosulfan have yielded both positive and negative results. In male rats, acute exposure to doses of up to 22 mg/kg/day of endosulfan for 5 days did not induce chromosomal aberrations in either bone marrow (somatic) or spermatogonial (germinal) cells. The ratio of mitotic index and frequency of chromatid breaks in the two cell types had no correlation with the doses tested and were not significantly different from the control group (Dikshith and Datta 1978). In

mice, a statistically significant increase in chromosomal aberrations was observed 60 days after initial treatment with oral doses of 6.4 mg/kg/day of endosulfan for 5 days (Usha Rani and Reddy 1986). However, mice fed 21.7 mg/kg/day for 2 days did not show a statistically significant increase in the frequency of micronuclei in bone marrow erythrocytes 6 hours posttreatment (Usha Rani et al. 1980).

Oral administration of 11.6 mg/kg/day of endosulfan to rats for up to 30 days also failed to induce chromosomal damage in bone marrow and spermatogonial cell systems, but it is not known how soon after treatment the animals were killed. As shown in mouse studies (Usha Rani and Reddy 1986), a latency period of 60 days was required to see chromosomal aberrations in spermatogonia. However, relatively significant changes were observed for mitotic indices (Dikshith et al. 1978).

In summary, endosulfan was not shown to be genotoxic following oral exposure of rats, but the data are inconclusive. It induces chromosomal aberrations and gene mutations in mice and *Drosophila*. Further complicating analysis of this data, is the possibility that formulations of endosulfan used in these studies may have contained epichlorohydrin, a well documented genotoxic chemical, as a stabilizer (Hoechst 1990). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to endosulfan. Carcinogenic effects of endosulfan were investigated in a number of chronic animal bioassays with rats and mice; the available data provide no evidence that endosulfan is carcinogenic.

Carcinogenicity in rats was first assayed in Osborne-Mendel rats by NCI (1978). The assay was flawed because the female rats were given endosulfan for less than their entire lifetime (78 out of 110 weeks); high early mortality in the males caused the high- and low-dose males to be terminated at 74 and 82 weeks, respectively, while half of the control males continued on study until 110 weeks; and the doses were changed several times during the study. The poor survival in the male rats precluded drawing a conclusion regarding the carcinogenicity of endosulfan in males because insufficient numbers of animals were alive to demonstrate a risk from late-developing tumors. However, the authors concluded that under the conditions of the assay, endosulfan was not carcinogenic in female rats.

Histological sections from this study were reevaluated by Reuber (1981) who concluded that endosulfan was carcinogenic. By grouping tumors, Reuber identified statistically significant increases in the total

number of malignant tumors in both high-dose females (TWA dose, 22.3 mg/kg/day) and low-dose
females (TWA dose, 11.1 mg/kg/day), as well as in the total number of carcinomas and sarcomas in high-
dose females and lymphosarcomas in high-dose males (TWA dose, 47.6 mg/kg/day) and high-dose
females. No increases in tumor incidence were identified in any specific tissue, and Reuber's conclusions
were not independently confirmed by other scientists.

The carcinogenicity of technical endosulfan was reevaluated in Sprague-Dawley rats using lower doses of
endosulfan (Hoechst 1989a). Endosulfan was administered in the diet for 2 years, and no effect on
survival was observed in either sex at any dose. Under the conditions of this assay, dietary consumption
of doses as high as 3.8 mg/kg/day by females or 2.9 mg/kg/day by males did not result in an increase in
the incidence of any neoplastic lesions in these animals. The results from the Hoechst (1989a) bioassay
were subsequently published in the open literature (Hack et al. 1995). In an additional study, no increase
in neoplastic lesions was observed in Wistar rats that consumed doses of endosulfan as high as
5 mg/kg/day (males) or 1.5 mg/kg/day (females) for 2 years (FMC 1959b). However, this study is limited
in that relatively few rats were used (25/sex/dose), and histopathological evaluation was limited to
5 rats/sex/dose plus any grossly observed lesions.

Carcinogenicity has also been evaluated by NCI using mice (NCI 1968, 1978). Two strains of mice
(B6C3F$_1$ and B6AKF$_1$) were tested in the 1968 study. The B6C3F$_1$ mice are the product of mating
C57BL/6 females with C3H/Anf males. The B6AKF$_1$ mice are the product of mating C57BL/6 females
with AKR males. These hybrids were used because their susceptibility to carcinogenic stimuli was
expected to be high. Each treatment group, and each vehicle, positive and negative control group
consisted of 18 males and females of each strain. The animals were administered endosulfan in 0.5%
gelatin daily by gavage at doses of 1.0 and 2.15 mg/kg/day from 7 to 28 days after birth. From 28 days to
18 months they were given endosulfan in the diet *ad libitum*. Concentrations in the diet were calculated
so that the endosulfan doses consumed by the animals were the same as those given by gavage. However,
these calculations were based on starting body weights, and no adjustments were made to account for
growth and changes in food intake throughout the 18-month exposure period. A statistically significant
increase (p<0.05) in the incidence of total tumors and pulmonary adenomas was reported for endosulfan;
it appears, however, that the data for both strains and doses were combined to perform these statistical
analyses. Therefore, it is not possible to assess the validity of these conclusions. Furthermore, the
summary data sheets do not clearly indicate the dose, so it appears that the dose level with low survival
was not the same dose level that displayed an increase in tumor incidence. Because of the incomplete

reporting and the confusion regarding statistical analysis of tumor incidence data, these results cannot be considered adequate evidence of the carcinogenicity of endosulfan.

Carcinogenicity was reassayed by NCI (1978) in B6C3F$_1$ mice. Fifty mice per sex per dose were used. Male mice were given 0, 0.46, or 0.9 mg/kg/day (TWA doses). Female mice were given 0, 0.26, or 0.5 mg/kg/day for 78 weeks. Then mice of both sexes were observed for an additional 14 weeks. No statistically significant increases in tumor incidence were observed in female mice. Because mortality in male mice was high in all groups, a conclusion regarding carcinogenicity in males was not made. Reuber (1981) also reevaluated histological sections from this study and concluded that a significant increase in the incidence of hepatic carcinomas occurred in the low-dose female mice. However, he indicated that histological sections from the liver were inadequate, and his conclusions were not independently verified by other scientists.

The carcinogenicity of technical endosulfan was also evaluated in NMRI mice exposed through the diet to endosulfan for 2 years at doses as high as 2.51 mg/kg/day in males and 2.86 mg/kg/day in females (Hoechst 1988b). Sixty mice/sex/dose were used. No increase in the incidence of any neoplastic lesion was identified in either males or females at any dose. These results were later published in the open literature (Hack et al. 1995).

The ability of technical endosulfan (98.8% pure), α-endosulfan, and β-endosulfan to act as tumor promoters in a two-stage, altered hepatic foci bioassay was examined in male Sprague-Dawley rats (Fransson-Steen et al. 1992). The animals were initiated by intraperitoneal injection of nitroso-diethylamine followed by 2/3 partial hepatectomy. Five weeks later, they were transferred to a diet that provided approximately 1.5, 5, or 15 mg test material/kg/day for 20 weeks. Promoting activity was evaluated for the development of foci of gamma-glutamyltranspeptidase-positive hepatocytes (AHF). Of the three chemicals tested, the α-isomer exhibited the strongest promoting activity; in initiated rats it caused a significant and dose-related increase in both the volume fraction of liver occupied by AHF and the number of AHF/cm^3, and only the highest dose increased the mean foci volume. Technical endosulfan and the β-isomer increased the volume fraction of liver occupied by AHF and the number of AHF/cm^3, but the responses were not dose-related, and neither increased mean foci volume. Endosulfan, the α-isomer, and the β-isomer induced no or few AHF in rats that were not initiated.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to endosulfan. However, dermal exposure to endosulfan caused death in livestock and experimental animals. Nicholson and Cooper (1977) described the case of five calves that were "dusted liberally" in the late afternoon with endosulfan to remove lice. The dose was not specified. By 7:00 a.m. the next morning, one calf was dead, and the remaining four calves displayed signs of neurotoxicity: muscle tremors, twitching of the ears, snapping of the eyelids, hyperactivity, and tonic-clonic convulsions. By the end of the day, three more calves died, and the remaining calf recovered without complications. A necropsy performed on one of the calves revealed no gross lesions.

Lethality data from studies using experimental animals indicate that the lethal dose varies substantially depending on the species and the sex of the animal tested. The dermal LD_{50} obtained following a single dermal application of endosulfan to the backs of female rabbits was in the range of 167–182 mg/kg of endosulfan (Gupta and Chandra 1975). However, 2 out of 3 female rats died following exposure to 31.25 mg/kg/day β-endosulfan for 6 hours/day for 5 days (Hoechst 1989b). In contrast, exposure to 250 mg/kg/day during the same 5-day period was not lethal to male rats. At 500 mg/kg/day, 2 of 3 males died. This study is limited, however, by the small number of animals tested. Single dermal doses of 1,500 or 2,250 mg/kg applied to clipped skin of pregnant rats (number per exposure group was not clearly reported) on gestation day 1 resulted in death of at least two females, but no maternal deaths were reported at #1,000 mg/kg (EI Dupont deNemours & Co. 1973).

Similar differences in lethality were observed between different sexes and species during slightly longer exposure periods (Hoechst 1985c, 1985d). Exposure for a total of 21 days out of 30 for 6 hours/day, 5 days/week, resulted in deaths in males treated with doses of 81 mg/kg/day and in females treated with 27 mg/kg/day (Hoechst 1985c). In contrast, female guinea pigs appeared to be relatively resistant to endosulfan toxicity (Hoechst 1983b). Only 1 female out of 20 died when exposed to 587 mg/kg/day, for 6 hours/day, 3 days/week for 3 weeks, and it was unclear whether this death was treatment related. In the majority of these reports, the clinical signs observed prior to death (tremors, salivation, and convulsions) were similar to those seen following oral exposure to endosulfan (see Section 2.2.2.1).

All reliable LD_{50} and LOAEL values for death in each species and duration category are recorded in Table 2-3. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

2.2.3.2 Systemic Effects

The primary systemic targets of endosulfan toxicity in animals following dermal exposure are the liver and kidney. Adverse hematological effects have also been observed following dermal administration of endosulfan. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to endosulfan.

The highest NOAEL value and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

Respiratory Effects.   Increased occurrence of dyspnea and increased respiratory rate were noted in 18 agricultural workers in India who applied endosulfan without protective equipment (both dermal and inhalation exposures probably occurred) (Chugh et al. 1998).

Dyspnea and decreased respiration were observed in female rabbits prior to death following a single dermal application of 225 mg/kg of endosulfan (Gupta and Chandra 1975). It is unclear whether similar effects were observed at lower doses in this study. Irregular respiration was also observed in male and female rats as the result of 5 daily, 6-hour/day exposures of β-endosulfan at doses of 16 mg/kg/day (females) and 250 mg/kg/day (males) (Hoechst 1989b). These doses were the highest doses at which no deaths were observed. Acute congestion of the lungs with dilation of alveolar capillaries was observed at necropsy of animals that died as the result of exposure to doses of 31.25 mg/kg/day and above (females) and 500 mg/kg/day and above (males) in this study. Congestion of the lungs was also observed at necropsy of rats dying as the result of a 30-day, 6-hour/day, 5-day/week exposures to endosulfan at 81 mg/kg/day (males) and 27 mg/kg/day (females) (Hoechst 1985c). It is probable that these effects are a result of generalized effects on central nervous system activity and attendant sequelae.

Table 2-3. Levels of Significant Exposure to Endosulfan - Dermal

| Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
Rat (CD-1)	once Gd 1				1500 F (lethal dose)	El DuPont Denemours & Co. 1973
Rat (Wistar)	5 d 6 hr/d				31 F (2/3 died)	Hoechst 1989b Beta
Rat (Wistar)	5 d 6 hr/d				500 M (3/3 died)	Hoechst 1989b Beta
Rabbit (albino)	1 d				167 (LD$_{50}$)	Gupta and Chandra 1975 Technical
Systemic						
Rat (Wistar)	5 d 6 hr/d	Resp		16 F (irregular respiration)	31 F (lungs filled with blood)	Hoechst 1989b Beta
		Gastro		16 F (diarrhea; mesenteric blood vessels distended)	31 F (small intestines filled with reddish fluid)	
		Hepatic		31 F (dark discoloration of the liver)		
		Dermal	31	62 F (slight to moderate erythema; slight edema)		
Rabbit (albino)	1 d	Hepatic			100 F (congestion; degeneration; necrosis)	Gupta and Chandra 1975 Technical
		Renal			100 F (shrunken glomerular tufts; necrosis of tubular epithelial cells)	
		Endocr			100 F (swollen adrenal cells with foamy cytoplasm and eccentric nuclei)	

Table 2-3. Levels of Significant Exposure to Endosulfan - Dermal (continued)

| Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | Reference Chemical Form |
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Rabbit	24 hr	Dermal		263 (mg/kg) (slight erythema)			Industria Prodotti Chimici 1975 Technical
Immunological/Lymphoreticular							
Rat (Wistar)	5 d 6 hr/d		500	1000 M (spleen reduced in size)			Hoechst 1989b Beta
Neurological							
Rat (Wistar)	5 d 6 hr/d				16 F (decreased activity; convulsions)		Hoechst 1989b Beta
Developmental							
Rat (CD-1)	once Gd 1		450		670 (exencephaly)		El DuPont Denemours & Co. 1973

Table 2-3. Levels of Significant Exposure to Endosulfan - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	

INTERMEDIATE EXPOSURE

Death

Species (Strain)	Exposure/Duration/Frequency	System	NOAEL	Less Serious	Serious	Reference Chemical Form
Rat (Wistar)	30 d 5 d/wk 6 hr/d				27 F (5/6 died)	Hoechst 1985c Technical
Rat (Wistar)	30 d 5 d/wk 6 hr/d				81 M (3/6 died)	Hoechst 1985c Technical
Rat (Wistar)	30 d 5 d/wk 6 hr/d				48 F (4/11 died)	Hoechst 1985d Technical
Rat (Wistar)	30 d 5 d/wk 6 hr/d				192 M (2/11 died)	Hoechst 1985d Technical

Systemic

Species (Strain)	Exposure/Duration/Frequency	System	NOAEL	Less Serious	Serious	Reference Chemical Form
Rat (Wistar)	30 d 1x/d	Hemato		19 M (decreased hemoglobin)		Dikshith et al. 1988 Technical
		Hepatic		10 F (decreased hepatic GOT and GPT; increase serum AP and LDH)		

Table 2-3. Levels of Significant Exposure to Endosulfan - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Rat (Wistar)	30 d 5 d/wk 6 hr/d	Resp	27 M		81 M (acute lung congestion; dilation of alveolar vessels)	Hoechst 1985c Technical
		Cardio	27 M		81 M (blood vessel congestion; cardiac ventricles filled with blood; acute heart and circulatory failure)	
		Gastro	81 M			
		Hemato	81 M			
		Musc/skel	81 M			
		Hepatic	81 M			
		Renal	81 M			
		Endocr	81 M			
		Dermal	81 M			
Rat (Wistar)	30 d 5 d/wk 6 hr/d	Resp	9		27 F (acute lung congestion; dilation of alveolar vessels)	Hoechst 1985c Technical
		Cardio	9		27 F (blood vessel congestion; cardiac ventricles filled with blood)	
		Gastro	27			
		Hemato	27			
		Hepatic	27			
		Renal	27			
		Endocr	27			
		Dermal	27			
Rat (Wistar)	30 d 5 d/wk 6 hr/d	Hemato	48	192 M (elevated serum protein; decreased serum cholinesterase)		Hoechst 1985d Technical
		Hepatic	48			
		Renal	48			
		Dermal	48			

Table 2-3. Levels of Significant Exposure to Endosulfan - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Gn pig (Pirbright-White)	3 wk 3 d/wk 6 hr/d	Dermal	587 (mg/kg) F			Hoechst 1983b Technical
Immunological/Lymphoreticular						
Gn pig (Pirbright-White)	3 wk 3 d/wk 6 hr/d		587 (mg/kg) F			Hoechst 1983b Technical
Neurological						
Rat (Wistar)	30 d 5 d/wk 6 hr/d			1 F (decreased brain cholinesterase)	81 (convulsions; diffuse brain edema)	Hoechst 1985c Technical
Rat (Wistar)	30 d 5 d/wk 6 hr/d			12 F (piloerection; slight lacrimation)	48 F (hypersalivation, tremors, convulsions)	Hoechst 1985d Technical

AP = alkaline phosphatase; ATPase = adenosine triphosphatase; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn pig = guinea pig; GOT = glutamic-oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase; Hemato = hematological; hr = hour(s); LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

Cardiovascular Effects. Both tachycardia and bradycardia were noted among 18 agricultural workers in India who applied endosulfan without protective equipment (both dermal and inhalation exposures probably occurred) (Chugh et al. 1998).

Blood vessels were congested and cardiac ventricles were distended with blood in rats that died as the result of a 6-hour/day, 5-day/week for 30-day exposure to 81 mg/kg/day (males) and 27 mg/kg/day (females) (Hoechst 1985c). However, it is unclear whether these effects were due to a direct action of endosulfan on the blood vessels and heart or were a result of a more general toxic insult (e.g., convulsions). The respective NOAELs for males and females were 27 and 9 mg/kg/day.

Gastrointestinal Effects. Abdominal discomfort after meals, nausea, and vomiting were noted in 18 agricultural workers in India who applied endosulfan without protective equipment (both dermal and inhalation exposures probably occurred) (Chugh et al. 1998). Another study reports gastrointestinal effects in 22 cases of acute poisoning of subjects spraying cotton and rice fields (Singh et al. 1992). Nausea, vomiting, pain in the abdomen, and diarrhea were among the signs and symptoms observed. Singh et al. (1992) assumed that exposure was mainly by the dermal route since subjects who sprayed the rice fields, and who suffered cuts over the legs with the sharp leaves of the rice plants exhibited the more severe toxicity.

Diarrhea was observed in rats exposed for 5 days, 6 hours/day to both lethal and sublethal doses of β-endosulfan ($250 mg/kg/day for males and $16 mg/kg/day for females) (Hoechst 1989b). Autopsy of animals from this study revealed that the mesenteric blood vessels of one of the surviving females exposed to 16 mg/kg/day were distended with blood, and that the small intestines of animals dying as a result of exposure were filled with a reddish fluid (500 mg/kg/day for males and 31.25 for mg/kg/day females). In contrast, no treatment-related effects were revealed by routine gross and histopathological examination of gastrointestinal tissues (stomach, small and large intestines, and pancreas) from rats exposed to doses of 27 mg/kg/day (females) and 81 mg/kg/day (males) for 30 days, 6 hours/day, 5 days/week (Hoechst 1985c).

Hematological Effects. Normal hemoglobin, hematocrit, white blood cell count, and differential and sedimentation rate were observed in a 35-year-old agricultural pilot approximately 8 hours after a 45-minute dermal exposure (with presumed concurrent inhalation exposure) when his clothing became soaked in endosulfan and methomyl (Cable and Doherty 1999).

Mixed results have been obtained in studies examining hematological effects of dermal exposure to endosulfan in rats. Although decreased hemoglobin was observed in male rats following daily application of doses of endosulfan of 18.75 mg/kg for 30 days (Dikshith et al. 1988), similar results have not been observed in female rats or in male rats at similar doses in other studies. For example, no hematological parameters were adversely affected following exposure of females to doses of 32 mg/kg/day for 30 days (Dikshith et al. 1988). In addition, no adverse effects on routine hematological parameters were observed following exposure of rats for 30 days for 6 hours/day, 5 days/week to doses of endosulfan ranging from 12 to 192 mg/kg/day (males) and from 3 to 48 mg/kg/day (females) (Hoechst 1985d). Similarly negative results were obtained in a comparable 30-day rat study using slightly lower endosulfan doses (Hoechst 1985c). Wistar rats were used in the studies by Dikshith et al. (1988) and Hoechst (1985c, 1985d); thus, the reason for the different results of these studies is unclear but may have been related to differences in the age of the rats or the application protocol.

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

Hepatic Effects.   Normal serum liver function tests (unspecified) were observed in a 35-year-old agricultural pilot approximately 8 hours after a 45-minute dermal exposure (with presumed concurrent inhalation exposure) when his clothing became soaked in endosulfan and methomyl (Cable and Doherty 1999).

Distinct hepatotoxicity has been observed in animal studies following acute-duration exposure to large dermal doses of endosulfan. The livers of female rabbits that survived a single dermal application of 100 mg/kg of endosulfan exhibited microscopic evidence of congestion, dilation of sinusoids, hepatocellular degeneration, hyperplastic Kupffer cells, focal necrosis, and portal tract and bile duct proliferation (Gupta and Chandra 1975). In addition, necropsy of rats that died following exposure for 5 days, 6 hours/day, to doses of endosulfan greater than or equal to 250 mg/kg/day (males) and 31.25 mg/kg/day (females) revealed darkly discolored livers (Hoechst 1989b).

Subchronic dermal exposures to slightly lower doses of endosulfan have been associated with more mild toxicity and adaptive changes. For example, histopathological examination of livers from male and female rats exposed to doses of 9 mg/kg/day 6 hours/day, 5 days/week for 30 days revealed slight fatty changes and an increased incidence of cellular hypertrophy and division (Hoechst 1985c). Similar changes were not observed in a repeat 30-day study at 12 or 192 mg/kg/day in males or at 48 mg/kg/day

in females (Hoechst 1985d). However, dermal administration of 18.75 mg/kg/day of endosulfan to male rats for 30 days resulted in decreases in hepatic levels of glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase and increases in serum levels of glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and alkaline phosphatase, but no changes in relative organ/body weight or other gross or histopathological evidence of liver damage (Dikshith et al. 1988). Effects in female rats at doses between 9.83 and 32 mg/kg/day were limited to decreases in hepatic glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase and increases in protein, hepatic alkaline phosphatase, and lactate dehydrogenase. The hepatic effects of long-term dermal exposure to endosulfan cannot be evaluated because of lack of data.

Renal Effects.   No studies were located regarding renal effects in humans after dermal exposure to endosulfan.

The kidneys of female rabbits given a single dermal application of 100 mg/kg of endosulfan exhibited shrunken glomerular tufts, thickened Bowman's capsules, and necrosis of the tubular epithelial cells (Gupta and Chandra 1975). However, daily application of up to 192 mg/kg/day (males) or 48 mg/kg/day (females) to the skin of rats for 30 days had no effect on kidney weight or histopathology (Dikshith et al. 1988; Hoechst 1985c, 1985d). The discrepancy may reflect species differences and/or differences in the application vehicle. The renal effects of long-term dermal exposure to endosulfan cannot be evaluated because of lack of data.

Endocrine Effects.   No studies were located regarding endocrine effects in humans after dermal exposure to endosulfan.

The adrenals of rabbits given a single dermal dose of 100 mg/kg of endosulfan exhibited microscopic changes, including swollen cells with foamy cytoplasm and eccentric nuclei (Gupta and Chandra 1975). Also, release of lipids from the adrenal cortex was observed in rats that died following daily application of 81 mg/kg/day (males) and 27 mg/kg/day (females) to the skin for 6 hours/day, 5 days/week for 30 days (Hoechst 1985c). However, daily application of up to 62.5 mg/kg/day (males) or 32 mg/kg/day (females) of endosulfan to the skin of rats for 30 days had no effect on adrenal weight or histopathology (Dikshith et al. 1988).

Dermal Effects.   No studies were located regarding dermal effects in humans after dermal exposure to endosulfan.

Mild dermal irritation has been observed in two studies following application of highly toxic amounts of endosulfan. A single 24-hour exposure of the skin of rabbits to 263 mg/kg of endosulfan resulted in only slight erythema (Industria Prodotti Chimici 1975). Daily application of β-endosulfan to rat skin for 6 hours/day for 5 days resulted in slight-to-moderate erythema, slight edema, and dry, rough, and scaling skin at 62.5 mg/kg/day in females and at 250 mg/kg/day in males (Hoechst 1989b). However, daily application of up to 48 mg/kg/day (females) or 192 mg/kg/day (males) to the skin of rats for 30 days (5 days/week, 6 hours/day) caused no apparent skin irritation (Hoechst 1985c, 1985d). Dermal application of 587 mg/kg/day of endosulfan 3 days/week, 6 hours/day for 3 weeks caused no erythema or edema in guinea pigs (Hoechst 1983b).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to endosulfan.

Limited information was available regarding ocular irritation by endosulfan. An unspecified amount of a 20% aqueous suspension of endosulfan instilled in the eyes of rabbits did not produce any ocular irritation or congestion (Gupta and Chandra 1975).

2.2.3.3 Immunological and Lymphoreticular Effects

The only study located regarding immunological effects in humans after dermal exposure to endosulfan was an account of the results of patch tests on the backs of 14 farm workers with work-related dermatitis and 8 controls who were not exposed to pesticides (Schuman and Dobson 1985). Skin sensitization was not observed in any of the subjects following a 48-hour, closed-patch exposure to an unspecified amount of 0.1% endosulfan in petrolatum.

Extremely limited information was available regarding immunological effects of endosulfan in animals following dermal exposures. No sensitization was observed after a challenge application of 587 mg/kg/day to female guinea pigs 16 days following a 6-hour/day, 3-day/week, 3-week exposure to this dose (Hoechst 1983b). In addition, no effect on thymus weight was reported following a 30-day (6 hours/day, 5 days/week) exposure to concentrations of up to 81 mg/kg/day in males and 27 mg/kg/day in females (Hoechst 1985c). However, one of the male rats that died following exposure to 1,000 mg/kg/day, 6 hours/day for 5 days had a spleen that was reduced in size (Hoechst 1989b); however, it is unclear whether the reduction in size was an immunotoxic effect or due to some other more generalized toxic insult.

The highest NOAEL and all reliable LOAEL values for immunological effects in rats or guinea pigs following acute- or intermediate-duration dermal exposures are recorded in Table 2-3. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

2.2.3.4 Neurological Effects

As indicated in the section on inhalation exposure, neurotoxicity is the primary effect observed in humans following occupational exposure to endosulfan. Since dermal exposures may comprise a substantial portion of occupational exposure to endosulfan, the results presented in Section 2.2.1.4 are repeated here, along with reports of human exposures that were primarily dermal. Convulsions were reported in nine individuals exposed to the endosulfan-containing insecticide, Thiodan®, during bagging (Ely et al. 1967). In addition, a case of long-term, possibly permanent brain damage in an industrial worker was attributed by Aleksandrowicz (1979) to endosulfan exposure. This worker was exposed while cleaning vats that contained residues of endosulfan solution. The acute phase of the poisoning was manifested by repeated convulsions and impaired consciousness. After recovery, the patient became disoriented and agitated. Two years later, he exhibited cognitive and emotional deterioration, memory impairment, and impairment of visual-motor coordination manifested by an inability to perform small tasks. However, modest alcohol consumption (1L of wine consumed per week) may have been a contributing factor directly on the brain or by decreasing metabolism of endosulfan in the liver. A 35-year-old male agricultural pilot experienced nausea, weakness, coldness, and blurred vision after 30 continuous minutes of dermal exposure when his clothes became soaked in endosulfan and methomyl, and tonic-clonic seizures 6 hours after a total of 45 minutes of dermal exposure (with presumed concurrent inhalation exposure) (Cable and Doherty 1999). Serum cholinesterase was within the normal range at 30 hours postexposure. A computed tomography (CT) scan showed no abnormalities, and the patient was discharged after 2 days of neurological observation, but three serial outpatient electroencephalographs (EEGs) showed a persistent nonspecific epileptic focus in the cerebral frontal lobes. In another study, dizziness, nausea, confusion and irritability, muscle twitching, tonic/clonic convulsions, and conduction defects were noted in 18 agricultural workers in India who applied endosulfan without protective equipment (both dermal and inhalation exposures probably occurred) (Chugh et al. 1998). Limitations associated with these reports include lack of quantitative exposure data, lack of data on the duration of exposure, the possibility of multiple routes of exposure (i.e., oral and dermal as well as inhalation), and possible concurrent exposure to other chemicals. Therefore, this information can only provide qualitative evidence of neurotoxicity associated with dermal exposure to endosulfan in humans.

Twenty-two cases of endosulfan poisoning were reported in people exposed while spraying cotton and rice fields; the dermal route of exposure was assumed to be the primary route of exposure (Singh et al. 1992). The assumption was based on the fact that those spraying rice fields, and who suffered cuts over the legs with the sharp leaves on the rice plants exhibited the more severe toxicity. Three out of the 22 cases exhibited tremors and 11 presented convulsions; all patients recovered.

Central nervous system stimulation similar to that reported for occupational exposure is seen following acute dermal exposure to endosulfan in experimental animals. The spectrum of effects includes hyperexcitability, tremors, decreased respiration, tonic-clonic convulsions, and ultimately death (Gupta and Chandra 1975; Hoechst 1989b; Nicholson and Cooper 1977). In rats, the lowest doses associated with these effects were 16 mg/kg/day in females and 250 mg/kg/day in males during a 6-hour/day, 5-day exposure regimen (Hoechst 1989b).

Similar signs of central nervous system stimulation were observed following exposure to doses of endosulfan as low as 48 mg/kg/day (females) and 81 mg/kg/day (males) during a 6-hour/day, 5-day/week, 30-day exposure period (Hoechst 1985c, 1985d). Diffuse edema was also observed in the brains of males at the 81-mg/kg/day exposure level. However, daily application of up to 62.5 mg/kg/day (males) or 32 mg/kg/day (females) of endosulfan to the skin of rats for 30 days had no effect on brain weight or histopathology (Dikshith et al. 1988). No information was found regarding neurological effects of long-term dermal exposure to endosulfan.

The highest NOAEL and all reliable LOAEL values for neurological effects in rats following acute- and intermediate-duration dermal exposures are recorded in Table 2-3. In some studies, only the α- or β-isomer of endosulfan was tested. In such cases, a notation regarding the specific isomer tested is included in the effect description.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to endosulfan.

Limited information was available regarding reproductive effects in animals following dermal exposures to endosulfan. No effects on the reproductive organs were observed during routine gross and histopatho-logical examination following exposure of rats to doses of 81 mg/kg/day (males) or 27 mg/kg/day (females) for 6 hours/day, 5 days/week for 30 days (Hoechst 1985c). Also, daily application of up to

62.5 mg/kg/day (males) or 32 mg/kg/day (females) to the skin of rats for 30 days had no effect on reproductive organ histopathology (Dikshith et al. 1988).

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to endosulfan.

An unspecified number of pregnant rats was administered a single dermal dose of 670 or 1,000 mg endosulfan/kg on clipped skin on gestation day 1, and exencephaly was observed in 5 and 3 pups, respectively (the total number of live pups at these dose levels was not clearly indicated) (EI Dupont deNemours & Co. 1973). Maternal death was reported at higher dose levels (1500 and 2250 mg/kg), no effects were reported at lower dose levels (0 and 450 mg/kg), and no increase in embryolethality was observed at any dose level. Further study details were not provided.

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to endosulfan.

2.3   TOXICOKINETICS

Data regarding toxicokinetics of endosulfan in humans are limited to information from cases of accidental or intentional ingestion of the chemical and cases of occupational exposure in the workplace where inhalation and/or dermal contact may have occurred. The evidence that humans absorb endosulfan by the inhalation and/or dermal routes of exposure is only indirect. Conclusive evidence exists regarding absorption through the gastrointestinal tract, although the extent of absorption is not known. Animals absorb endosulfan by the inhalation, oral, and dermal routes of exposure. Near 80% of the administered oral dose may be absorbed and near 20% or a dermal dose may be absorbed; the role of the administration vehicle has not been studied. Autopsy data in humans suggest that endosulfan may accumulate in the liver, kidney, and brain at least in the short-term. Data in animals also suggest that following initial distribution to adipose tissue, endosulfan accumulates in liver and kidney, and that the α-isomer

accumulates to a greater extent than the β-isomer. There is no information on the metabolism of
endosulfan in humans. In animals, endosulfan is metabolized predominantly to polar and nonpolar
metabolites by microsomal enzymes. Endosulfan and metabolites have been detected in the urine of
humans after ingestion of the chemical. In animals, the feces is the main route of excretion of unchanged
parent compound and metabolites. A physiologically based pharmacokinetic (PBPK) model for
endosulfan has not been developed.

2.3.1 Absorption

Health effects in humans and animals provide indirect evidence of absorption of endosulfan following
oral, inhalation, and dermal exposures. Endosulfan and metabolites have been detected in tissues of
humans and animals following various exposures to endosulfan, providing qualitative evidence that
endosulfan is absorbed. Endosulfan residues were found in fat of hospitalized Spanish children,
indicating that absorption occurs in children (Olea et al. 1999), but no studies were located regarding
known or suspected differences between children and adults with respect to endosulfan absorption.

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of endosulfan following inhalation in humans and
animals. However, Ely et al. (1967) described nine case reports of occupational exposure to endosulfan
resulting in neurological effects. Also, neurological effects have been observed in rats following
inhalation exposure to endosulfan (Hoechst 1983a). These studies describing the occurrence of
neurotoxicity following inhalation exposure to endosulfan provide indirect evidence that endosulfan is
absorbed by both humans and animals by this route of exposure.

2.3.1.2 Oral Exposure

Although no specific studies were located that quantified the absorption of endosulfan in animals or
humans, indirect evidence of toxic effects following ingestion of endosulfan suggests that the
gastrointestinal tract is a site of endosulfan absorption in humans and animals (Blanco-Coronado et al.
1992; Lo et al. 1995; Nath and Dikshith 1979; WHO 1984). Deaths occurred in humans within days after
ingestion of the toxic material. In two of these cases, endosulfan was the likely primary cause of toxicity,
although some synergism probably resulted from other chemicals present (e.g., alcohol, xylene). A third
case involved endosulfan ingestion that resulted in death, but because another more toxic material

(dimethoate) was present in the mixture, it is difficult to attribute the toxic effects observed to endosulfan itself. In addition, the two pesticides could have acted synergistically. Absorption of endosulfan was also evidenced by the appearance of endosulfan in samples of the liver and kidney obtained from poisoning victims at autopsy (Demeter and Heyndrickx 1978; Demeter et al. 1977). In the fatal cases reported by Blanco-Coronado et al. (1992) and Lo et al. (1995) there was little doubt that death was caused by effects triggered by endosulfan. In one fatality, the concentration in the blood was 2.85 mg/L, and this patient died 8 days after ingesting endosulfan accidentally mixed with food (Blanco-Coronado et al. 1992). In 5 cases who survived and eventually recovered, the concentration of endosulfan determined in the blood on admission to the hospital ranged from 0.29 to 0.67 mg/L (Blanco-Coronado et al. 1992). α-Endo-sulfan, β-endosulfan, and/or endosulfan sulfate were present in the blood and urine of a 43-year-old man for at least 91 hours after he intentionally ingested approximately 260 mg/kg endosulfan, and the stomach contents contained 3,540 and 1,390 µg/kg of α-endosulfan and β-endosulfan, respectively, upon autopsy 4 days after exposure, indicating that absorption from the gut can occur over a prolonged period after a single oral exposure (Boereboom et al. 1998).

Evidence of the absorption of endosulfan following oral exposure has also been found in animal studies. In metabolic studies with ^{14}C-endosulfan, approximately 65% of the administered radioactivity was recovered from the excreta and tissues of mice 24 hours after ingesting endosulfan in their diet (Deema et al. 1966). In descending order, the highest activities per gram of organ/excreta from two mice were as follows: feces, visceral fat, urine, tissues, respired air, and blood. In an experiment that involved cannulation of the bile duct, approximately 22, 13, and 47% of a 2-mg/kg oral dose of α-endosulfan, and 15, 10, and 29% of a 2 mg/kg oral dose of β-endosulfan were collected in the feces, urine, and bile, respectively, after 48 hours. This indicates that absorption could be as high as 78 and 85% for α- and β-endosulfan, respectively. The rats eliminated 88% of the α-endosulfan (75% in feces, 13% in urine) and 87% of the β-endosulfan (68% in feces, 19% in urine) within 5 days of oral administration (Dorough et al. 1978). A single oral dose of endosulfan given to sheep was almost completely excreted in the feces (50% of the radiolabel) or in the urine (40% of the radiolabel) within 22 days after administration (Gorbach et al. 1968). These studies indicate that absorption occurs in humans and animals following ingestion of endosulfan.

2.3.1.3 Dermal Exposure

Evidence suggesting that humans absorb endosulfan through the skin was presented by Singh et al. (1992) who briefly described 22 cases of acute poisoning among subjects spraying cotton and rice fields.

The assumption of dermal absorption was based on the fact that subjects who sprayed rice fields and who suffered cuts over the legs caused by the sharp leaves of the rice plants showed the most severe toxicity. In another case report, serum endosulfan was 4 µg/L at 30 hours after an agricultural pilot was exposed dermally (and probably also by inhalation) for approximately 45 minutes in clothing that was "heavily contaminated" with endosulfan and methomyl (Cable and Doherty 1999); the dermal exposure level was not estimated, and no other measures of tissue levels of endosulfan were obtained.

Indirect evidence indicates that dermal absorption occurs in animals. Calves dusted with a 4% dust formulation of endosulfan had neurological symptoms (tremors, twitching, convulsions) and died within a day after exposure (Nicholson and Cooper 1977). Neurological effects have also been reported in preclipped rabbits and rats after repeated application of endosulfan to the skin (Dikshith et al. 1988; Gupta and Chandra 1975). Dikshith et al. (1988) reported levels of α-, β-, and total endosulfan in liver, kidney, brain, testes, fatty tissue, and blood 30 days after dermal application of endosulfan.

One animal study provided direct evidence of absorption of endosulfan following dermal exposure by quantifying the rate and extent of dermal absorption in Sprague-Dawley rats (Hoechst 1986). A single dermal application of aqueous suspensions of 0.10, 0.76, and 10.13 mg/kg ^{14}C-endosulfan to male rats resulted in binding of approximately 80% of the test material to the skin at all three dose levels, with the amount bound proportional to the amount applied (Hoechst 1986). After 10 hours, approximately 72% of the applied dose was bound to the skin, and 8% of the applied dose was absorbed into the body. After 24 hours, approximately 25% of the bound material was absorbed into the body. Absorption rates were calculated, with the highest rates occurring within the first half hour after application. For the low-, middle-, and high-dose groups, the absorption rates at 0.5 hour were 2.8, 21.7, and 453.9 µg/cm^2 of skin/hour, respectively, with the rates being proportional to the amount of endosulfan applied to the skin. The absorption rates decreased with time for all three dose groups. By 24 hours, the absorption rates were 0.1, 0.7, and 6.3 µg/cm^2 of skin/hour for the low-, middle-, and high-dose groups, respectively (Hoechst 1986).

2.3.2 Distribution

Studies in animals and autopsy findings of endosulfan and metabolites in various tissues in humans suggest that absorbed endosulfan is most readily distributed to adipose and brain tissue, but that the liver and kidney may be longer-term repositories of endosulfan and its metabolites. Endosulfan residues were

found in fat of hospitalized Spanish children (Olea et al. 1999), but no studies were located regarding
known or suspected differences between children and adults with respect to endosulfan distribution.

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of endosulfan in humans and animals after inhalation
exposure to endosulfan.

2.3.2.2 Oral Exposure

α-Endosulfan, β-endosulfan, and the primary metabolite, endosulfan sulfate, have been detected in several
human autopsy samples following acute ingestion. In a man who had ingested endosulfan in a single oral
dose of approximately 260 mg/kg, postmortem tissue concentrations of α-endosulfan at 4-days
postexposure were 4,105, 80, and 59 µg/kg in the fat, brain, and kidney, respectively, the concentration of
β-endosulfan in the brain was 69 µg/kg, and the concentrations of endosulfan sulfate were 3,030, 1,350,
and 390 µg/kg in the liver, brain, and kidney, respectively (Boereboom et al. 1998). In 3 other suicides
cases, the following concentrations for combined isomers of endosulfan were found in autopsy
specimens: blood, 4–8 ppm; liver 0.8–1.4 ppm; kidney, 2.4–3.2 ppm; and brain, 0.25–0.30 ppm
(Coutselinis et al. 1978). No information was available on the amount of endosulfan ingested. It is
apparent that the highest concentrations were detected in the kidney, liver and blood. However, it was not
possible to determine the specific levels that elicited systemic toxicity prior to death. An autopsy was
performed on a 28-year-old man who ingested 20% endosulfan powder (12.4% α, 8.1% β) while drunk
and was dead on arrival at the hospital. The autopsy revealed α- and β-endosulfan in the following
concentrations: blood, 0.06 and 0.015 ppm; urine, 1.78 and 0.87 ppm; liver, 12.4 and 5.2 ppm; and
kidney, 2.48 and 1.8 ppm; respectively. In another case, endosulfan sulfate was found in the liver at a
concentration of 3.4 ppm (Demeter and Heyndrickx 1978; Demeter et al. 1977).

Endosulfan has been detected in breast milk of women environmentally exposed to a number of
contaminants in rural Kazakhstan (Lutter et al. 1998), indicating that transfer to children can occur during
lactation; the endosulfan concentration in the breast milk was not reported. Isomers and metabolites of
endosulfan were detected in the fat of 30–40% of children hospitalized in agricultural regions of Spain,
demonstrating that endosulfan accumulates in adipose tissue of children after presumably repeated dietary
exposure (Olea et al. 1999). Considering evidence from a study in rats indicating that endosulfan is
rapidly eliminated from fat tissues after cessation of dietary exposure (Dorough et al. 1978), it is probable

that the endosulfan residues in the fat tissues of the children do not represent long-term storage; rather, the residues probably represent recent exposures in children who were repeatedly exposed to endosulfan.

The distribution of radioactivity 24 hours after a single oral exposure to a food pellet treated with α- and β-^{14}C-endosulfan in male mice was as follows: feces > small intestine > urine > visceral fat > liver > kidney > expired carbon dioxide > blood (Deema et al. 1966). In a 14-day feeding study with 0.25 mg/kg/day of radiolabeled α- or β-endosulfan, female albino rats had the highest ^{14}C concentrations in liver and kidney (Dorough et al. 1978). The authors reported that endosulfan accumulated in fat tissues during the 14-day exposure period, then declined to undetectable levels by 7 days postexposure. Levels in the fat tissue never reached as high as those seen in the liver and kidney. Concentrations of α-endosulfan, β-endosulfan, and endosulfan sulfate in cattle fatally poisoned after a single exposure due to accidental ingestion of an unknown amount of endosulfan were reported by Braun and Lobb (1976). Total endosulfan residues (α-endosulfan, β-endosulfan, and endosulfan sulfate) were 0.083, 0.065, and 4.23 ppm in the liver; 0.04, 0.024, and 1.06 ppm in the kidney; 0.031, 0.024, and 0.61 ppm in muscle; and 720, 550, and 0.0 ppm in rumen contents, respectively. The surviving calf had 0.025 ppm endosulfan in its blood.

Rats exposed daily via gavage to 5 or 10 mg/kg/day of endosulfan in peanut oil had plasma levels of 2.26 and 0.46 µg/mL for the α- and β-isomers, respectively (Gupta 1978). These levels were measured on the day after the termination of a 15-day gavage dosing regimen. Fifteen days after the last treatment, the plasma concentration of α-endosulfan was 0.05 µg/L, while the β-isomer was not detected. Endosulfan levels were twice as high in fatty tissues as in liver and kidney following 30 days of exposure of male and female Wistar rats to endosulfan (Dikshith et al. 1984). Thirty days of exposure to 11 mg/kg/day produced the highest level in the kidney, while the fatty tissue had a slightly lower concentration (Nath and Dikshith 1979). Male rats exposed daily for 60 days to 2.5 or 3.75 mg/kg/day of endosulfan containing α- and β-isomers in a ratio of 2:1 produced somewhat different distribution patterns for the two isomers (Ansari et al. 1984). For both doses, the highest concentration of the α-isomer was detected in the kidney followed by the epididymis, ventral prostate or spleen, testes, brain, and liver. In descending order, the highest levels of the β-isomer were found in the seminal vesicle, epididymis, heart, ventral prostate, spleen, and liver. Overall, the greatest amounts of both α- and β-isomers of endosulfan were located in the kidney, seminal vesicle, and epididymis, with the liver having the least amount.

α-Endosulfan; β-endosulfan; and the endosulfan metabolites, endosulfan sulfate, endosulfan hydroxyether, endosulfan lactone, and endosulfan diol, were measured in blood, liver, and kidney from

male rats consuming 34 or 68 mg/kg/day of endosulfan over 4 weeks and from male rats given a 30-day recovery from exposure (Hoechst 1987). Only trace amounts of endosulfan and its metabolites were found in the blood. The predominant substances found in the liver were endosulfan sulfate and endosulfan lactone. Trace amounts of α- and β-endosulfan were measured in the liver; however, there was substantial accumulation of α-endosulfan in the kidneys. Approximately 200 times more α-endosulfan than β-endosulfan was found in the kidney. The predominant metabolites of endosulfan found in the kidney were endosulfan sulfate and endosulfan-lactone. Endosulfan-diol was also found, but at much lower concentrations. The amount of endosulfan found in the kidney decreased following a period free from exposure. By the end of the recovery period (4 weeks), α- and β-endosulfan and the endosulfan metabolites were reduced to trace levels in all organs (Hoechst 1987).

Information regarding transfer of endosulfan residues to offspring through breast milk is available from a study in lactating goats (Indraningsih et al. 1993). Goats were administered a daily dose of 1 mg/kg for 28 days and adults and kids were sacrificed at various times (days 1, 8, 15, 21 posttreatment) after treatment ceased. With the exception of the kidneys, the highest concentration of residues were recorded in the adults on day 1. In the kidneys, residues increased from day 1 to a maximum on day 8. On day 1, the concentration of residues in the kidneys, liver, and milk were 0.29, 0.20, and 0.02 mg/kg, respectively. No residues could be detected in milk on day 8. α-Endosulfan was the major residue in all tissues except for liver and fat which contained mainly endosulfan sulfate. No endosulfan residues were detected in the tissues of kids except for α-endosulfan in the liver at a concentration of 0.0011 mg/kg on day 1. These results suggest rapid elimination of residues from tissues and limited transfer to offspring through breast milk. Approximately 1% of the radiolabel from administration of a single oral dose of ^{14}C-endosulfan (65% α-isomer, 35% β-isomer) to milk sheep was recovered in the milk, primarily as endosulfan sulfate (Gorbach et al. 1968).

The distribution in animals after exposure to endosulfan indicates that the α-isomer of endosulfan accumulates throughout the body to a greater extent than the β-isomer (Ansari et al. 1984; Hoechst 1987). Endosulfan is distributed to the fatty tissues initially after exposure, while a greater accumulation of endosulfan reaches the kidney following prolonged exposure. Of all the metabolites of endosulfan, endosulfan sulfate appears to be the one that accumulates predominantly in the liver and kidneys (Hoechst 1987).

2.3.2.3 Dermal Exposure

Serum endosulfan was 4 µg/L at 30 hours after an agricultural pilot was exposed dermally (and probably also by inhalation) for approximately 45 minutes in clothing that was "heavily contaminated" with endosulfan and methomyl (Cable and Doherty 1999); the dermal exposure level was not estimated and no other measures of tissue levels of endosulfan were obtained. A study by Kazen et al. (1974) has identified endosulfan residues on the hands of workers after relatively long periods free from exposure. Endosulfan residues were identified on the hands of one worker approximately 30 days after exposure and on the hands of one worker who had not used endosulfan during the preceding season.

Three animal studies were located regarding distribution of endosulfan in animals following dermal exposure (Dikshith et al. 1988; Hoechst 1986; Nicholson and Cooper 1977). Endosulfan was detected in the brain (0.73 ppm), liver (3.78 ppm), and rumen contents (0.10 ppm) of calves that died after dermal exposure to a dust formulation of endosulfan (Nicholson and Cooper 1977). Following a single dermal application of aqueous suspensions of 0.1, 0.83, and 10.13 mg/kg ^{14}C-endosulfan to male Sprague-Dawley rats, low concentrations of endosulfan (ng/g levels) appeared in the blood and tissues (other than skin at and around the application site) after 1 hour (Hoechst 1986). The concentrations of endosulfan in the blood and tissues increased with the time of exposure and were proportional to the dose applied. The liver and kidney appeared to sequester radiolabel relative to the concentrations of radiolabel in the blood or fat. Endosulfan levels were approximately 10 times higher in the liver and kidney than in the fat, blood, and brain throughout the study (Hoechst 1986).

Tissue disposition of the α- and β-isomers has also been quantified in rats after intermediate-duration dermal application of technical-grade endosulfan for 30 days (Dikshith et al. 1988). Male rats were exposed to 18.8, 37.5, or 62.5 mg/kg/day; females were exposed to 9.8, 19.7, or 32.0 mg/kg/day. Fatty tissue contained the highest levels of both α- and β-isomers in both males and females. The levels (in ppb) of the α- and β-isomers, respectively, in animals exposed to the lowest doses was as follows: fatty tissue (0.26, 0.15) > kidney (0.16, 0.01) > blood (0.03, 0.015) > liver (0.02, 0.004) > brain (0.03, not detected) in male rats, and fatty tissue (2.4, 5.8) > liver (0.50, 1.2) > blood (0.56, 1.2) > kidney (0.65, 0.52) > brain (0.21, not detected) in female rats. Generally, these values increased with increased dose. The residue level of both isomers in fatty tissue was much higher in females (8.20–16.13 ng/g) than in males (0.42–0.62 ng/g).

## 2.3.2.4 Other Routes of Exposure

The distribution of endosulfan and endosulfan sulfate was evaluated in the brains of cats given a single intravenous injection of 3 mg/kg endosulfan (Khanna et al. 1979). Peak concentrations of endosulfan in the brain were found at the earliest time point examined (15 minutes after administration) and then decreased. When tissue levels were expressed per gram of tissue, little differential was observed in distribution among the brain areas studied. However, if endosulfan levels were expressed per gram of tissue lipid, higher initial levels were observed in the cerebral cortex and cerebellum than in the spinal cord and brainstem. Loss of endosulfan was most rapid from those areas low in lipid. Endosulfan sulfate levels peaked in the brain at 1 hour postadministration. In contrast, endosulfan sulfate levels in liver peaked within 15 minutes postadministration. The time course of neurotoxic effects observed in the animals in this study corresponded most closely with endosulfan levels in the central nervous system tissues examined.

2.3.3 Metabolism

No information is available on the metabolism of endosulfan in adult humans or children. Endosulfan is readily metabolized in animals following exposure (Deema et al. 1966; Dorough et al. 1978; Gorbach et al. 1968). It exists in two stable stereoisomeric forms, which can be converted to endosulfan sulfate and endosulfan diol (WHO 1984). These can be further metabolized to endosulfan lactone, hydroxyether, and ether. Figure 2-3 shows the pathway for the degradation of endosulfan. Dorough et al. (1978) indicated that the major portion of residues in the excreta and/or tissues consisted of unidentified polar metabolites that could not be extracted from the substrate, whereas the nonpolar metabolites, including sulfate, diol, α-hydroxyether, lactone, and ether derivatives of endosulfan, represented only minor amounts. Excretion data from an acute dermal study in rats showed that, after 24 hours, a dose-related decrease in excretion occurred at higher doses, suggesting saturation of the metabolic pathway of endosulfan (see Section 2.3.4.3) (Hoechst 1986).

High concentrations of endosulfan sulfate were found primarily in the liver, intestine, and visceral fat 24 hours after mice were exposed to a single dose of ^{14}C-endosulfan (Deema et al. 1966). Five days following a single oral administration of ^{14}C-endosulfan to rats, the diol, sulfate, lactone, and ether metabolites were detected in the feces (Dorough et al. 1978). In sheep, endosulfan sulfate was detected in the feces, and endosulfan alcohol and α-hydroxyether were detected in the urine (Gorbach et al. 1968).

2. HEALTH EFFECTS

Figure 2-3. Proposed Metabolic Pathway for Endosulfan
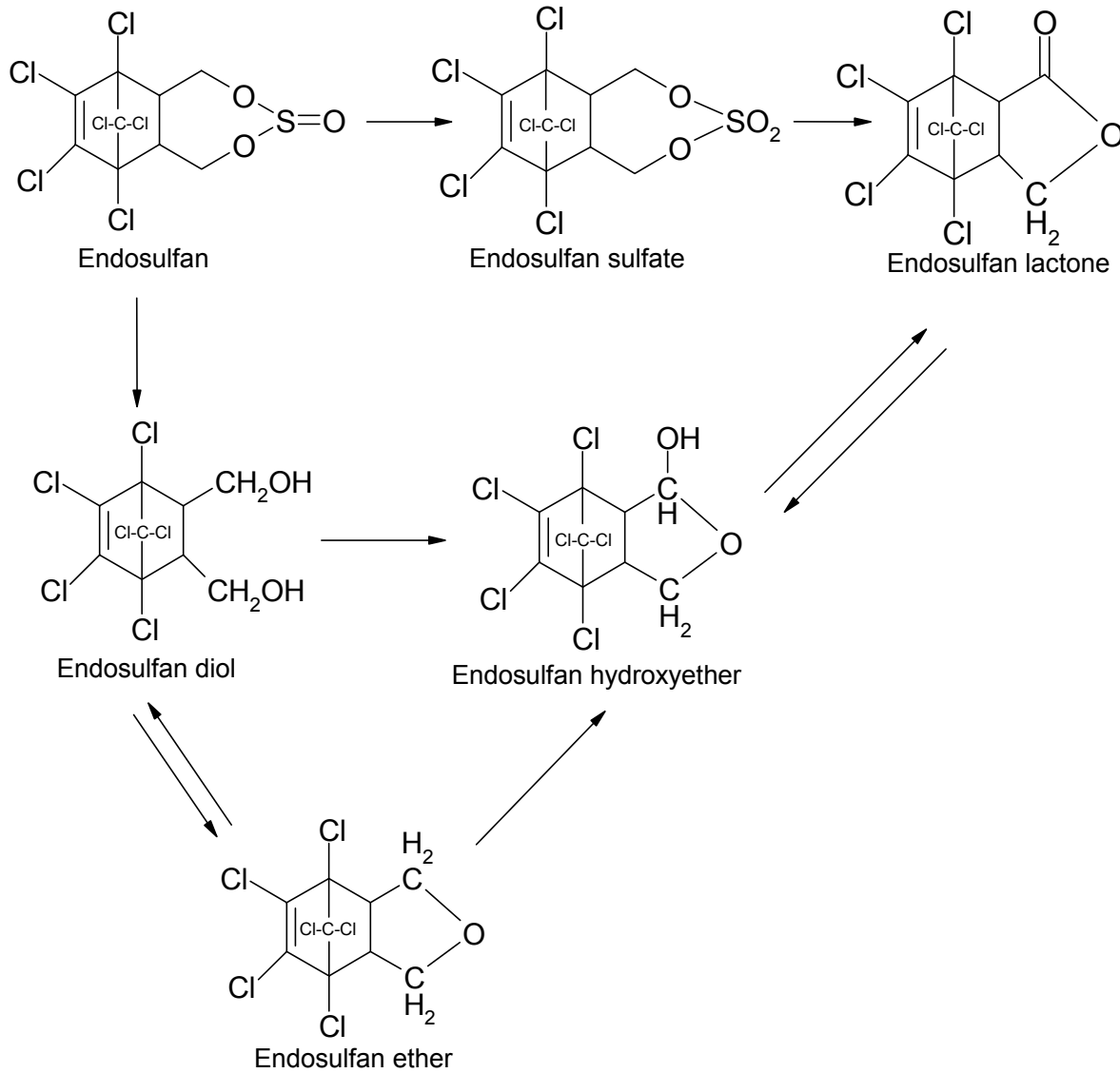
Adapted from:

Dorough et al. (1978)
Gorbach et al. (1968)

All the metabolism studies indicate that the parent compound was also found to a large degree in the tissues and excreta. Similar conclusions can be drawn from the work of Gupta and Ehrnebo (1979) who found that almost half of the parent compound was excreted unchanged in rabbits after endosulfan was injected intravenously. The metabolites (e.g., endosulfan sulfate, endosulfan diol) were reported in tissues and excreta following longer exposures to endosulfan (Deema et al. 1966; Dorough et al. 1978). Based on the rapid appearance of endosulfan sulfate in the liver following intravenous administration of endosulfan, it may be concluded that the liver is a site of high metabolic activity in the conversion of endosulfan to endosulfan sulfate (Khanna et al. 1979).

Results of a study in which male rats were fed 34 or 68 mg/kg/day endosulfan over 30 days suggest that metabolism of endosulfan occurs in the kidney (Hoechst 1987). This feeding study was initiated to clarify findings from a previous 13-week feeding study with endosulfan in which a yellow discoloration was observed in the kidneys of rats fed diets containing up to 360 ppm. The results of the 30-day feeding study showed that endosulfan accumulates predominantly in the kidney during exposure and that storage of endosulfan in the kidney is reversible upon removal from exposure (Hoechst 1987). Histological examination of the kidney revealed granular pigmentation and an increase in the number and size of lysosomes in the cells of the proximal convoluted tubules in the kidneys (Hoechst 1987). These changes diminished appreciably during the 30-day recovery period. These lysosomal changes may suggest storage or metabolism of endosulfan in the kidneys (Hoechst 1987). The lysosomal sequestration of endosulfan may account for the yellow pigment seen in the kidneys in a previous toxicity study. The diminishing pigmentation and decreasing endosulfan concentrations, which occurred during the 30-day recovery period, suggest metabolism of the compound in the kidney (Hoechst 1987).

Evidence suggests that endosulfan can induce microsomal enzyme activity. Increased liver microsomal cytochrome P-450 activity was observed in male and female rats after single and multiple administrations of endosulfan (Siddiqui et al. 1987a; Tyagi et al. 1984). Increased enzyme activity was observed in hepatic and extrahepatic tissues. Based on the increase in aminopyrine-*N*-demethylase and aniline hydroxylase activity, endosulfan has been shown to be a nonspecific inducer of drug metabolism (Agarwal et al. 1978).

The available evidence indicates that endosulfan can be metabolized in animals to other lipophilic compounds, which can rapidly enter tissues, and to more hydrophilic compounds that can be excreted.

2.3.4 Elimination and Excretion

Renal excretion is the most important endosulfan elimination route in humans and animals. Biliary
excretion has also been demonstrated to be important in animals. Estimated elimination half-lives ranged
between approximately 1 and 7 days in adult humans and animals. Endosulfan can also be eliminated via
the breast milk in lactating women and animals, although this is probably a relatively minor elimination
route. No studies were located regarding known or suspected differences between children and adults
with respect to endosulfan excretion.

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in animals after inhalation exposure to endosulfan.

The concentration of α- and β-endosulfan in the urine of a pest control worker who wore protective
equipment peaked at 0.2 days (approximately 5 hours) after completing a 25-minute application of
endosulfan in a greenhouse, declined to control levels by about 1.5 days postexposure, and remained at
levels comparable to controls until the end of sampling at 3-days postexposure (Arrebola et al. 1999).
Assuming first-order elimination, the urinary elimination half-life was estimated to be 0.94 days for
α-endosulfan and 1.16 days for β-endosulfan; no endosulfan metabolite was detected in any urine sample.

2.3.4.2 Oral Exposure

α-Endosulfan and endosulfan sulfate, but not β-endosulfan, were observed in the urine at 0–3.5 hours
after exposure, and endosulfan sulfate was also observed in the urine up to 91 hours after exposure in a
man who died from ingesting endosulfan in a single oral dose of approximately 260 mg/kg (Boereboom
et al. 1998); the terminal half-lives of α- and β-endosulfan in a two-compartment toxicokinetic model
were 24.3 and 60.4 hours, respectively. In another case report, endosulfan was quantified in the urine of
four patients who ingested endosulfan several hours earlier (Blanco-Coronado et al. 1992). Since the
amount ingested was not known, the percentage of the ingested dose that was excreted could not be
determined. It is also unknown whether the urine was the main route of excretion.

Endosulfan residues are rapidly eliminated from tissues as suggested by a half-life of approximately
7 days estimated in a 14-day oral study in female rats (Dorough et al. 1978). Rapid elimination was also

observed in a 28-day study in goats in which half-lives between 1.1 and 3.1 days were estimated for endosulfan residues in various organs and tissues (Indraningsih et al. 1993).

Orally administered endosulfan is eliminated in both the feces and the urine of mice and rats, with the feces containing most of the pesticide eliminated (Deema et al. 1966; Dorough et al. 1978). In a study using rats, endosulfan was orally administered as a single gavage dose (2 mg/kg) or in the diet (0.25 or 1.25 mg/kg/day) for 2 weeks (Dorough et al. 1978). The animals given the oral single dose eliminated 19 and 25% of the α- and β-isomer dose in the feces and the urine, respectively, in the form of the original compound and its metabolites 24 hours after exposure. After 120 hours, the percentages increased to 88 and 87%, respectively. The cumulative ratio of α-endosulfan eliminated in the feces compared with the urine after 120 hours was 5:1. The ratio for β-endosulfan was somewhat less than 7:2. These ratios are equivalent to excretion of 17% α-endosulfan and less than 22% β-endosulfan in the urine. The authors found that collection of bile from the rats caused a decrease in the elimination of endosulfan and its metabolites in the feces but had no effect on urinary excretion. Assuming little enterohepatic recirculation, data from bile duct cannulation indicate that about 65–70% of the amount in the feces was due to biliary excretion. Animals administered endosulfan in the diet for 2 weeks showed a similar elimination pattern. The total cumulative percentage of the radiocarbon eliminated from rats given the α- or β-isomers in the diet (5 ppm) was 64 and 65%, respectively. Ratios of the cumulative dose eliminated via the feces compared with the urine for both isomers were approximately 7:1. No major differences were noted in animals given 25 ppm endosulfan in the diet. Extraction and analysis of the feces showed that the residues consisted of the parent compound, five polar metabolites, and unidentified polar material. The urine and feces contained the diol, α-hydroxyether, and lactone of endosulfan. Furthermore, these authors indicated that 47% of the dose was eliminated from the liver via biliary secretion 48 hours following treatment. In mice, endosulfan sulfate and alcohol (diol) were the main metabolites detected, primarily in the feces (Deema et al. 1966). The ratio of radioactivity recovered per gram of excreta for feces and urine was 26:1; however, no corrections were made for quenching or self-absorption. Administration of a single oral dose of ^{14}C-endosulfan (65% α-isomer, 35% β-isomer) to milk sheep resulted in recovery of approximately 50% of the radiolabel in the feces, 4% in the urine, and 1% in the milk (Gorbach et al. 1968). Unmetabolized endosulfan was found in the feces but not in the urine. The main metabolites found in the urine were endosulfan diol and α-hydroxyendosulfan ether. Most of the ^{14}C activity in the milk of sheep was due to endosulfan sulfate. Although these studies suggest variations in the excretion patterns with different species, they do provide evidence that the excretion of endosulfan and its metabolites after oral exposure is rapid and occurs mainly through the fecal route.

Gavage dosing of male and female rats with endosulfan (65.3% α-endosulfan, 33.7% β-endosulfan) for 30 days resulted in a greater accumulation of endosulfan in fatty tissue from females than males (Dikshith et al. 1984). The authors speculated that the difference between males and females was a function of more rapid excretion of endosulfan by males than females, and that this could account for the higher sensitivity of female rats to endosulfan toxicity. However, excretion of endosulfan and its metabolites was not directly measured in this study; therefore, alternative explanations for the differences in residue content and toxicity cannot be discounted.

2.3.4.3 Dermal Exposure

Endosulfan and metabolites were observed in the urine of workers who had prepared and applied endosulfan for 2–5 hours either 1 day or 1 week prior to sampling, without using protective clothing or face mask (thus, exposure was probably both dermal and inhalation) (Vidal et al. 1998). Unchanged α- and β-endosulfan and endosulfan ether were the predominant chemicals excreted 1 day following exposure. One week after exposure, α-endosulfan was detected in urine of four of five workers, but β-endosulfan was detected in only one of five samples and endosulfan ether was not detected at all. Endosulfan sulfate was detected in only one of five samples at 1 week after exposure and in none of the four samples at 1 day postexposure. Endosulfan lactone was detected in one of four and one of five samples at 1 day and 1 week after exposure, respectively.

One study was located regarding excretion in animals after dermal exposure to endosulfan (Hoechst 1986). Following a single dermal application of an aqueous suspension of ^{14}C-endosulfan (at 0.1, 0.83, 10.13 mg/kg) to male Sprague-Dawley rats, limited excretion of radiolabel (0.5–1.0% of the applied dose) occurred during the first 10 hours of exposure and occurred primarily in the urine. However, between 10 and 24 hours, excretion increased to an average of 10% of the absorbed dose. Elimination was rapid once the endosulfan passed through the skin. Excretion was dose related (13.5% of the absorbed dose at the low dose; 12.4% at the middle dose; and 4.9% at the high dose), with the percentage excreted decreasing with increasing dose. Although excretion was greater in the urine than feces during the first 10 hours of exposure, by 24 hours, excretion in the feces was approximately two times greater than in the urine (Hoechst 1986).

2.3.4.4 Other Routes of Exposure

Intravenous administration of endosulfan (7:3 ratio of α- and β-isomers) in rabbits produced slower elimination of the α-isomer (Gupta and Ehrnebo 1979). Excretion of the two isomers occurred primarily via the urine (29%) with much less excreted via the feces (2%). Given the earlier evidence in rats and mice describing the principal route of elimination of endosulfan and its metabolite to be via the feces, the differences in the excretion pattern in this study may be attributable to differences in exposure routes, to species differences, or to both. Nevertheless, studies in laboratory animals suggest that both renal and hepatic excretory routes are important in eliminating endosulfan from the body. Elimination of small doses is essentially complete within a few days.

2.3.5 Physiologically based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen 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 sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

If PBPK models for endosulfan exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK modeling studies were located for endosulfan.

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance
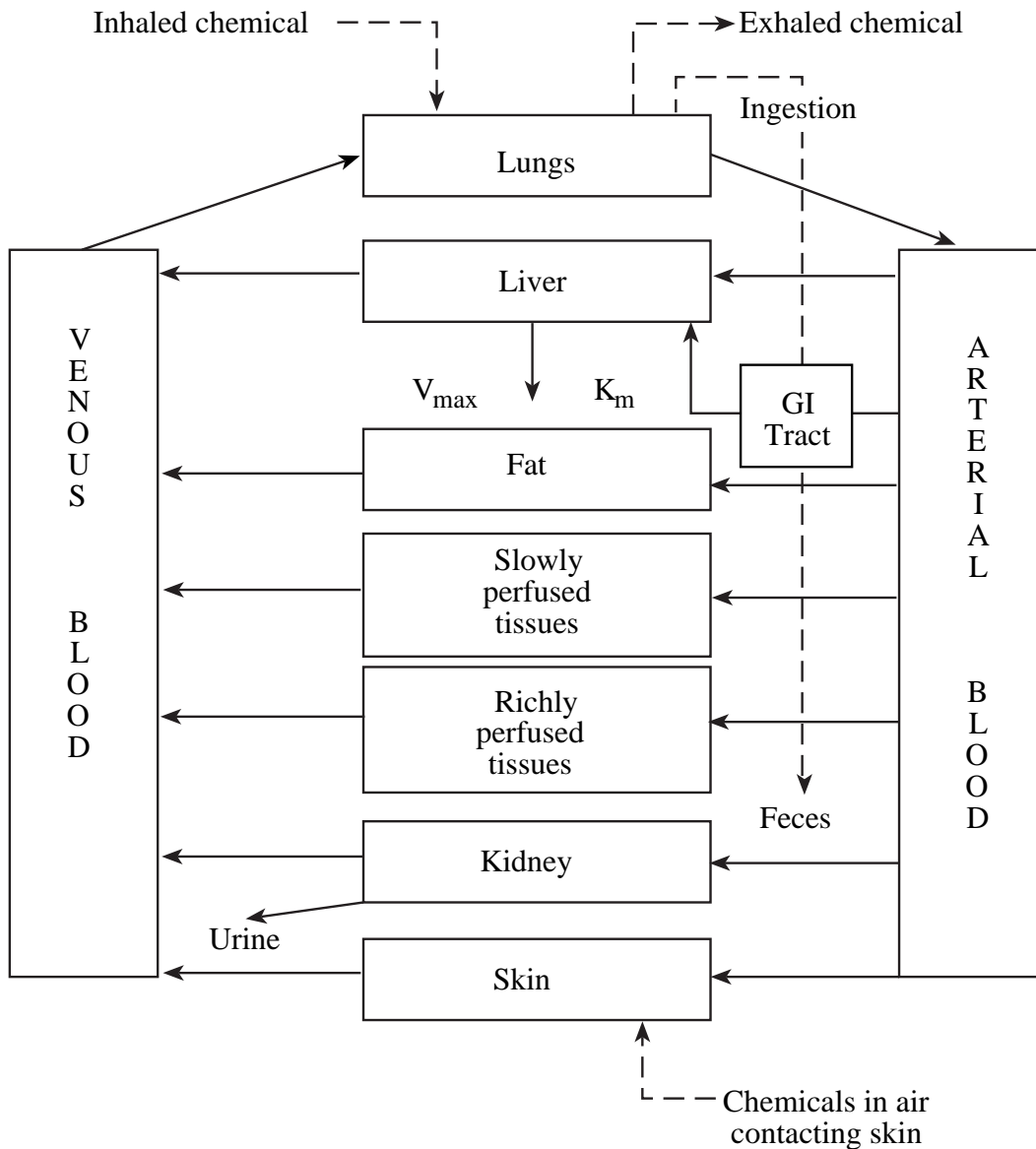
Source: adapted from Krishnan et al. 1994

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.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

No information was located regarding the mechanism of inhalation, oral, or dermal absorption of endosulfan in humans or animals; however, the lipophilic nature of endosulfan suggests that it is probably absorbed by passive diffusion. Also, no information was located regarding the mechanism by which endosulfan is transported in the blood. However, due to endosulfan's high solubility in lipids, it is reasonable to assume that in the blood it might be associated with a lipid fraction. Studies in animals suggest that endosulfan initially accumulates in fatty tissues and that relatively high amounts can be found in the liver and kidneys after exposure (Dorough et al. 1978; Gupta 1978; Hoechst 1987; Nath and Dikshith 1979). Rapid accumulation of endosulfan metabolites in the liver (Khanna et al. 1979) and increased lysozymal activity in the kidney (Hoechst 1987) suggest that these may be sites of endosulfan metabolism. Although endosulfan induces microsomal cytochrome P-450 in the liver (Siddiqui et al. 1987a; Tyagi et al. 1984), it is not clear whether endosulfan thereby induces its own metabolism. Results from a dermal study in rats suggested that the metabolism of endosulfan may be a saturable process (Hoechst 1986). In animals, biliary excretion of endosulfan and metabolites is a main route of elimination of this chemical and may contribute about two-thirds of the endosulfan found in the feces (Dorough et al. 1978). A minor proportion of endosulfan and metabolites is excreted in the urine.

2.4.2 Mechanisms of Toxicity

The neurotoxic effects of endosulfan are well documented in both humans and animals, and extensive research has been conducted in recent years aimed at elucidating its mechanism of neurotoxicity. Although serious neurotoxic effects, including death, generally occur after acute exposure to concentrations much higher than those commonly found in the environment, there is concern about the possibility of accidental exposure of those occupationally exposed such as agricultural workers who apply the pesticide in the fields. In addition to neurotoxicity, exposure to endosulfan in animals has induced a wide array of effects including liver and kidney toxicity, hematological effects, alterations in the immune system, and alterations in the reproductive organs of males. The possible mechanisms of the effects on organ or systems other than the nervous system have not been as well studied as the mechanism of neurotoxicity. Speculation in this section on the mechanism(s) of action involved in effects that have not been well characterized and/or have been seen inconsistently in animal studies seems inappropriate at this time. Yet, where possible explanations for some effects have been suggested by the investigators

conducting the research, these are presented in the appropriate subsections in Section 2.5. Therefore, this
section will focus mainly on the mechanism of neurotoxic effects of endosulfan.

Acute exposure to large amounts of endosulfan results in frank effects manifested as hyperactivity,
muscle tremors, ataxia, and convulsions. Possible mechanisms of toxicity include (a) alteration of
neurotransmitter levels in brain areas by affecting synthesis, degradation, and/or rates of release and re-
uptake, and/or (b) interference with the binding of those neurotransmitter to their receptors.

Several studies have reported changes in neurotransmitter levels following exposure to endosulfan. For
example, Gupta (1976) found that brain acetylcholinesterase activity was decreased following a single
intraperitoneal injection of endosulfan in rats and postulated that the decreased activity of this enzyme
resulted in an increase in brain levels of acetylcholine, which could, in turn, be responsible for the central
nervous system stimulation observed. However, brain cholinesterase was increased in female rats that
consumed 4.59 mg/kg/day and above for 13 weeks (Hoechst 1985a). Thus, it is unclear whether the
decrease in brain acetylcholinesterase observed by Gupta (1976) was a representative finding. Neither
Paul et al. (1994) nor Lakshmana and Raju (1994) found changes in the activity of acetylcholinesterase in
the brain of rats treated with 2 mg endosulfan/kg/day for 90 days or with 6 mg/kg/day for 23 days,
respectively. Ansari et al. (1987) also suggested that changes in neurotransmitter levels (specifically
serotonin, GABA, and dopamine) in the brain may be partly responsible for the neurotoxicity of
endosulfan in rats after observing hyperactivity, tremors, and convulsions following a single intra-
peritoneal injection of 40 mg/kg of endosulfan. More recently Paul et al. (1994) found significant
increases in serotonin concentration in the cerebrum and midbrain of rats after 90 days of treatment with
2 mg/kg/day endosulfan, and in this study, spontaneous motor activity was significantly increased in the
treated animals. Furthermore, Paul et al. (1994) also found a correlation between the increase in serotonin
and inhibition of a learning paradigm. Lakshmana and Raju (1994) also reported changes in the
concentrations of dopamine, noradrenaline, and serotonin in various brain areas of endosulfan-treated
rats. In this case, treated rats took 29% more time to learn a behavioral task; however, it was not
determined which neurotransmitter(s) change may have been responsible for the behavioral change.

Studies have also examined the role of neurotransmitter receptors in endosulfan-induced neurotoxic
effects. For instance, a single intraperitoneal dose of 3 mg/kg of endosulfan or administration of
1 mg/kg/day for 30-days had no effect on frontal cortical ^{3}H-serotonin binding or aggressive behavior in
adult rats, but 30 daily injections of 3 mg/kg/day caused a significant increase in ^{3}H-serotonin binding
affinity and foot-shock-induced fighting (Agrawal et al. 1983). Serotonin may also play a role in the

increase in aggressive behavior (foot-shock-induced fighting) observed in rats following multiple exposures to endosulfan (Agrawal et al. 1983; Zaidi et al. 1985). Rat pups injected with 1 mg/kg/day for 25 days showed a significant increase in frontal cortical ^{3}H-serotonin binding and exhibited a significant increase in foot-shock-induced fighting behavior (Zaidi et al. 1985). These effects were still observed 8 days after cessation of treatment. The authors concluded that endosulfan affects serotonergic function, which in turn induces neurotoxicity in both neonates and adults, as demonstrated by increased ^{3}H-serotonin binding to the frontal cortex and aggressive behavior. A correlation between ^{3}H-serotonin binding and aggressive behavior was also observed. These data also suggest that neonates show a greater sensitivity to endosulfan than adults.

The results from several studies suggest the involvement of GABA receptors in endosulfan-induced neurotoxicity. In a series of *in vitro* experiments using ^{3}H-dihydropicrotoxinin, Abalis et al. (1986), Cole and Casida (1986), Gant et al. (1987), and Ozoe and Matsumura (1986) showed that endosulfan acts as a noncompetitive GABA antagonist at the chloride channel within the GABA receptor in brain synapto-somes. Antagonism of GABAergic neurons within the central nervous system leads to generalized central nervous system stimulation. Binding of GABA to its receptor opens chloride-selective ion channels leading to influx of chloride into neurons through electrochemical gradient, resulting in hyperpolarization of the membrane and inhibition of cell firing. A reduced inhibitory drive translates into increased activity of the effector neurons. The studies mentioned above found that the ability of endosulfan to induce convulsions correlated with the potency to bind to this site and to inhibit GABA-induced chloride flux, thus providing good evidence for this mechanism of action. A more recent study showed that α-endosulfan blocked the chloride uptake induced by GABA in primary cultures of cortical neurones from 15-day old mice fetuses by interacting with the t-butylbicyclophosphorothionate (a GABA antagonist) binding site (Pomes et al. 1994). In a subsequent study, the same group of investigators found that α-endosulfan had relatively low cytotoxicity (assessed by disruption of cell membrane integrity) in primary neuronal cultures of cerebellar granule cells, and that it did not increase the formation of intracellular oxidative radicals (Rosa et al. 1996). It did, however, increased mitochondrial transmembrane potential which, according to Rosa et al. (1996), could be linked to a detoxification process of the cell. The authors further stated that their findings were consistent with the view that *in vivo* neurotoxicity is mediated mainly by inhibition of GABAergic function and that other effects detected *in vitro* are less important. Currently, the GABA-antagonism mechanism of toxicity is the most widely accepted hypothesis.

As summarized in Section 2.3.3 (Metabolism), the biotransformation of endosulfan can give rise to a number of both polar and nonpolar metabolites. There is little and inconclusive information on whether the toxicological properties of endosulfan are due to the parent compound or to any of its metabolites. One could assume that the more lipophilic substances will cross cell membranes more easily than polar metabolites, accumulate to a greater extent, and perhaps be the most neurotoxic. Differential toxicity could also be related to differential affinity for the GABA receptor. What is known from oral acute-lethality studies in rats and mice is that α-endosulfan is approximately 3 times more toxic than β-endosulfan (Dorough et al. 1978; Hoechst 1975, 1990; Maier-Bode 1968). In addition, in mice, the acute toxicity of endosulfan sulfate was comparable to that of α-endosulfan (Dorough et al. 1978). Also in mice, the metabolites endosulfan α-hydroxy ether, endosulfan lactone, and endosulfan ether had lethal doses 10–20 times higher than the α-or β-isomers; the lethal dose for endosulfandiol was two orders of magnitude higher than that of the α-or β-isomer (Dorough et al. 1978). Extrapolation of this information to possible potency differences in longer-term studies is clearly inappropriate since other factors, such as pharmacokinetics and possibly induction of biotransformation enzymes, play a role in longer-term studies.

Evidence from some oral studies in rats suggests that there is a difference in susceptibility to some effects of endosulfan between males and females. For example, the LD_{50} values in females were 3–4 times lower than in males (Hoechst 1990), and similar observations had been made by others (Gupta 1976; Gupta and Chandra 1977). Also, in a 30-day feeding study, 3 out 10 females, but no males, died during the study and the female survivors experienced more pronounced liver toxicity than the males (Paul et al. 1995). The higher sensitivity of females is thought to be due to a greater accumulation and slower elimination of endosulfan residues than the males (Dikshith et al. 1984, 1988). Paul et al. (1995) also conducted a series of motor and neurobehavioral tests in both sexes and found that although endosulfan increased spontaneous motor activity in both sexes, the increase was significantly greater in males. They speculated that males may produce more lipophilic metabolites, such as endosulfan sulfate, than females, which could be responsible for the more marked stimulation of spontaneous activity in males. If this were the case, then endosulfan residues other than the sulfate would be responsible for the adverse liver effects. No consistent differential sensitivity has been observed in species other than the rat.

Human data as well as studies in animals have provided negative evidence of carcinogenicity for endosulfan (Hack et al. 1995; Hoechst 1988b, 1989a). However, endosulfan promoted the development of altered hepatic foci in rats initiated with nitrosodiethylamine (Fransson-Steen et al. 1992). Although the mechanism of tumor promotion of endosulfan is not known, it has been suggested that it involves

inhibition of cellular communication (Kenne et al. 1994). A brief discussion of this topic is provided in
Section 2.5 under Cancer Effects.

2.4.3 Animal-to-Human Extrapolations

Almost all the information regarding the effects of endosulfan in humans is derived from cases of acute
exposure to high amounts of the chemical. Some of these cases resulted in death (Bernardelli and Gennari
1987; Blanco-Coronado et al. 1992; Demeter and Heyndrickx 1978; Lo et al. 1995; Terziev et al. 1974).
Postmortem examination revealed lesions to a variety of organs and tissues, and this is consistent with
findings in animals exposed to lethal doses of endosulfan. In both humans and animals, high doses of
endosulfan affect primarily the nervous system. However, whether effects seen in animals exposed to
lower doses of endosulfan for prolonged periods of time would also manifest in humans under similar
exposure conditions remains to be determined. Also, there is not enough information to predict whether
the metabolism and disposition of endosulfan by humans is similar to those in experimental animals.

2.5   RELEVANCE TO PUBLIC HEALTH

Overview.   Humans living in areas surrounding hazardous waste sites may be exposed to endosulfan
primarily via dermal contact with or ingestion of contaminated soils since this compound is found bound
to soil particles. Although endosulfan can be found in water as colloidal suspensions adsorbed to
particles, ingestion of contaminated finished drinking water is not expected to be a major route of
exposure since endosulfan is not very water soluble. Likewise, inhalation exposure to endosulfan via
volatilization from contaminated media is not a major route of exposure since endosulfan is not very
volatile. For the general population (including individuals not living in the vicinity of hazardous waste
sites), the most likely route of exposure to endosulfan is via ingestion of residues on contaminated food.
Issues relevant to children are explicitly discussed in 2.7 Children's Susceptibility and 5.6 Exposures of
Children.

The clinical signs common to both humans and animals after acute exposure to high doses of endosulfan
(e.g., hyperactivity, tremors, decreased respiration, dyspnea, salivation, tonic-clonic convulsions, and
death) point to the nervous system as the major target of toxicity. However, neurotoxic effects are
generally not seen following longer-term, low-dose exposure. Information regarding effects of
endosulfan in humans is derived mainly from studies of occupational exposure and cases of intentional or
accidental ingestion of endosulfan. The available occupational studies have limitations, including lack of

precise exposure data and presence of other compounds, as well as confounding factors. No information was located regarding immunological, reproductive, or developmental effects in humans exposed to endosulfan. No reports of cancer in humans associated with exposure to endosulfan were found. Endosulfan has not caused cancer in animals under the experimental conditions tested, but some found evidence of promotion activity. Target organs of endosulfan identified in experimental animals but not humans include the gastrointestinal tract, blood, liver, kidney, reproductive organs, and immune system. Developmental toxicity has also been noted in animals. There is conflicting evidence from animal studies as to whether young animals are more susceptible to the effects of endosulfan than older animals. Effects observed on the respiratory and cardiovascular systems are most likely secondary to effects of endosulfan on the central nervous system control of respiratory and cardiovascular function. Very few studies have examined the toxicity of endosulfan following inhalation or dermal exposure in humans or animals, but the effects reported (e.g., central nervous system stimulation and hepatic and renal effects) are similar to those seen after oral exposure. There is no evidence indicating that the effects of endosulfan are route-specific. A major metabolite of endosulfan, endosulfan sulfate, which is also found at some hazardous waste sites, is reported to have similar toxicity (WHO 1984).

Minimal Risk Levels for Endosulfan.

Inhalation MRLs.

Information regarding inhalation exposure to endosulfan by humans was inadequate for derivation of inhalation MRLs (Aleksandrowicz 1979; Ely et al. 1967). Limitations associated with these reports include lack of quantitative exposure data, lack of data on the duration of exposure, the possibility of multiple routes of exposure (i.e., oral and dermal, as well as inhalation), and possible concurrent exposure to other chemicals. Therefore, this information can only provide qualitative evidence of adverse effects associated with inhalation exposure to endosulfan in humans. No acute inhalation MRL was derived for endosulfan based on animal data because the most sensitive effects observed after acute inhalation exposure were trembling and ataxia in rats exposed to 3.6 mg/m^3 for 4 hours (Hoechst 1983a). These effects are considered by ATSDR to be serious effects, and MRLs are not derived using NOAELs or LOAELs for serious end points. No intermediate-duration inhalation MRL was derived because of a lack of suitable NOAELs or LOAELs. A study showed no observable systemic, immunologic, neurologic, or reproductive toxicity following inhalation exposure of rats to 2 mg/m^3 for 6 hours/day, 5 days/week for a total of 21 out of 29 days (Hoechst 1984c). However, in the absence of a body of data showing a continuum of effects at a range of doses, the use of a free-standing NOAEL for derivation of an MRL

value is not recommended. No chronic-duration inhalation MRL was derived because of a lack of studies
examining the effects of chronic-duration inhalation exposures.

Oral MRLs.

No acute-duration oral MRL was derived for endosulfan because no suitable end point was available
among the reliable acute-duration studies. The lowest LOAEL, 1.8 mg/kg/day, was for a serious end
point, convulsions in pregnant rabbits, appearing 10 days after the start of daily gavage dosing in the
FMC (1981) study. Because animals from both the control and the test groups developed ascites, and six
rabbits were added without concurrent controls, the reliability of these results is questionable.

- An MRL of 0.005 mg/kg/day has been derived for intermediate-duration (15–364 days) oral
  exposure to endosulfan.

The intermediate-duration oral MRL was derived based on the observation of decreases in humoral and
cell-mediated immune responses in rats consuming 0.9 mg/kg/day for 22 weeks (Banerjee and Hussain
1986). Choice of this end point is supported by the observation of similar effects in rats at higher doses
following ingestion for shorter periods (Banerjee and Hussain 1986, 1987) and decreased neutrophils and
spleen weight at slightly higher doses in mice (Hoechst 1984b). The absence of observed immunotoxicity
in the study by Vos et al. (1982) does not contradict these findings since not all of the same end points
were evaluated in the study by Vos et al. (1982), and a shorter period of exposure was used. In support of
the positive findings, Khurana et al. (1998) observed decreased macrophage functionality, in the absence
of any other apparent toxicological effects, in 1-day-old broiler chicks fed 30 ppm endosulfan in the diet
for 4 or 8 weeks. The intermediate-duration MRL of 0.005 mg/kg/day was derived by dividing the
NOAEL for immunotoxicity (0.45 mg/kg/day) by an uncertainty factor of 100 (10 for extrapolating from
animals to humans and 10 for human variability).

- An MRL of 0.002 mg/kg/day has been derived for chronic-duration (365 days or more) oral
  exposure to endosulfan.

The chronic-duration oral MRL was derived based on the observation of increased serum levels of
alkaline phosphatase (an indicator of hepatotoxicity) in dogs consuming 0.6 mg/kg/day for 1 year
(Hoechst 1989c). The choice of this end point is supported by the observation of hydropic hepatic cells in
rats that consumed 5 mg/kg/day for 2 years (FMC 1959b). The chronic-duration MRL of
0.002 mg/kg/day was derived by dividing the NOAEL for elevated serum alkaline phosphatase

(0.18 mg/kg/day) by an uncertainty factor of 100 (10 for extrapolating from animals to humans, and 10 for human variability).

No acute-, intermediate-, or chronic-duration dermal MRLs were derived for endosulfan because of the lack of an appropriate methodology for the development of dermal MRLs.

Death.   Endosulfan has been fatal to humans following accidental and intentional ingestion of concentrated endosulfan solutions (Bernardelli and Gennari 1987; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Demeter and Heyndrickx 1978; Lo et al. 1995; Terziev et al. 1974). Death has also been observed in animals following inhalation (Hoechst 1983a), oral (Boyd and Dobos 1969; Boyd et al. 1970; Chatterjee et al. 1986; FMC 1958, 1980a, 1980b; Gupta et al. 1978, 1981; Hoechst 1966a, 1966b, 1970, 1975, 1988a), and dermal (Gupta and Chandra 1975; Hoechst 1989b; Nicholson and Cooper 1977) exposure to endosulfan, but no such cases have been reported in humans following inhalation or dermal exposures. Death in humans and animals is generally attributed to respiratory arrest following convulsive seizures.

According to Blanco-Coronado et al. (1992), acute intoxication with endosulfan involves two stages: gastrointestinal symptoms, tonic-clonic convulsions, respiratory depression, metabolic acidosis, and hyperglycemia and hemodynamic instability appear within 4 hours of ingestion. Pulmonary edema and pulmonary aspiration, consumption coagulopathy with decreased platelets, elevated serum transaminases, and persistent hemodynamic instability can develop subsequently. A high blood endosulfan level and initial hypotension indicate poor prognosis. The doses required to produce death are relatively large, and reports of death in humans were found only in cases of accidental or intentional ingestion of large quantities of endosulfan-containing pesticides. Therefore, it is likely that the risk of death is very small under conditions of long-term, low-level exposure either from ingestion of contaminated food or water (endosulfan is not readily water soluble) or inhalation of endosulfan dusts or mists.

The oral LD_{50} values reported for technical-grade endosulfan vary depending on the species, sex, formulation tested, vehicle used, and nutritional status of the animal (Boyd and Dobos 1969; Boyd et al. 1970; Gupta 1976; Gupta and Gupta 1979; Hoechst 1990; WHO 1984). Outward signs of acute endosulfan toxicity are similar among species and are generally associated with endosulfan's effects on the central nervous system. Symptoms include hyperexcitability, dyspnea, decreased respiration, and fine tremors followed by tonic-clonic convulsions (Boyd and Dobos 1969; Boyd et al. 1970; Ceron et al. 1995; Gilbert and Mack 1995). Deaths have also been reported in rats after intermediate-duration

exposure (Gilbert 1992) and in female mice after chronic-duration exposure (Hack et al. 1995). Although the specific cause of death was not discussed in the Hack et al. (1995) study, it does not appear that neurological effects played any role. Mice generally appear to be more sensitive to the lethal effects of endosulfan than rats (Gupta 1976; Gupta et al. 1981). Female rats are more sensitive to the lethal effects of endosulfan than male rats (Gupta 1976; Hoechst 1990).

Protein deficiency enhances the lethal effects of endosulfan in Wistar rats (Boyd and Dobos 1969; Boyd et al. 1970). Thus, humans consuming protein-deficient diets may represent a sensitive subpopulation (see Section 2.9).

Systemic Effects.

Respiratory Effects. No reports were located indicating that endosulfan is a significant respiratory irritant. However, respiratory effects (e.g., hypoxia, dyspnea, and cyanosis) have been observed in humans and animals following acute, high-level exposure to endosulfan (Blanco-Coronado et al. 1992; FMC 1958; Gupta and Chandra 1975; Hoechst 1970, 1983a, 1989b; Shemesh et al. 1988; Terziev et al. 1974). Since these respiratory effects have been reported only at doses that produce marked neurotoxicity and/or were lethal, it is likely that the effects observed in humans and animals following acute, high-level exposure are a result of disruption of the central nervous system control of respiratory activity. The possibility that endosulfan has a direct toxic effect on the respiratory tissues at these high doses cannot, however, be ruled out. It is not likely that humans exposed to low levels of endosulfan will experience adverse respiratory effects.

Cardiovascular Effects. Cardiovascular effects, such as tachycardia and hypertension, followed by cardiogenic shock, increased cardiac output, and an increase in total peripheral resistance, have been observed in humans and animals following acute, high-level exposure to endosulfan (Anand et al. 1980b, 1981; Shemesh et al. 1988). A more recent study reported severe hypotension followed by disseminated intravascular coagulation and cardiogenic shock in a woman who eventually died after ingesting endosulfan (Blanco-Coronado et al. 1992). Lo et al. (1995) reported that autopsy of a man who died after ingesting endosulfan showed cardiomegaly with congestive heart failure. In addition, systemic congestion consistent with acute heart failure has been observed in short-term, high-dose studies in animals (Gupta and Chandra 1977; Hoechst 1970). Histopathological changes in the hearts of animals have been observed in acute-duration, high-level exposures to endosulfan (Hoechst 1985c; Terziev et al. 1974). Also, calcification of the heart and blood vessels as a result of parathyroid hyperplasia secondary

to kidney disease was observed in male rats in a chronic duration study that used relatively high doses of endosulfan (NCI 1978). The available information does not suggest that endosulfan has a direct toxic effect on the cardiovascular system. These effects are only seen at doses that evoke convulsions, indicating that the cardiovascular effects are a result of increased central sympathetic nervous system activity. Therefore, it is not likely that humans exposed to low levels of endosulfan will experience adverse cardiovascular effects.

Gastrointestinal Effects. Nausea, gagging, vomiting, and/or diarrhea in humans and animals have been reported following acute, high-level oral exposure to endosulfan (Blanco-Coronado et al. 1992; Ceron et al. 1995; FMC 1958, 1959a; Hoechst 1989b; Singh et al. 1992; Terziev et al. 1974). Gross pathologic examination of gastrointestinal tissues from several studies have shown adverse effects (Boyd et al. 1970; FMC 1958; Hoechst 1970, 1989b) indicating that endosulfan may have a direct toxic effect on these tissues. However, a neurologic component of the emesis and diarrhea cannot be eliminated. Because these effects have been observed only following acute-duration, high-level exposures to endosulfan, it is unlikely that humans exposed to low levels of endosulfan will experience adverse gastrointestinal effects. Long-term studies in animals have provided no evidence of adverse gastrointestinal effects in rats, mice, or dogs (FMC 1959a, 1959b, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989a, 1989c).

Hematological Effects. Adverse hematological effects were reported in a group of six subjects who acutely accidentally or purposely consumed unknown, but assumed high, amounts of endosulfan (Blanco-Coronado et al. 1992). Five patients showed diminution of the platelets in circulating blood, consistent with consumption coagulopathy. One woman, who eventually died, developed disseminated intravascular coagulation along with thrombi of multiple vessels, including the aorta and the pulmonary artery system.

In animals, treatment-related effects on the hematopoietic system (decreases in hemoglobin, red cell count, mean corpuscular hemoglobin concentration, and/or packed cell volume) have been noted in a few studies following oral exposure to endosulfan (Ceron et al. 1995; Das and Garg 1981; Hoechst 1985a; Siddiqui et al. 1987b). In two cases, the effects on the hematopoietic system were observed following acute-duration, high-level exposure to endosulfan (Ceron et al. 1995; Siddiqui et al. 1987b), and in another study, the effects were observed at very low doses only following a pretreatment period of protein depletion (Das and Garg 1981). Only one study showed effects consistent with anemia following longer-duration oral exposure to moderate levels of endosulfan (Hoechst 1985a). However, several studies were located that do not indicate significant changes in these parameters following intermediate- or chronic-

duration oral exposure to endosulfan (Das and Garg 1981; FMC 1959a, 1959b, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989a, 1989c). In addition, one study indicated an increase in red cell count (Dikshith et al. 1984). Mixed results were also obtained in studies examining the effects of dermal exposure to endosulfan (Dikshith et al. 1988; Hoechst 1985c, 1985d). Thus, the available studies suggest that endosulfan can induce adverse hematological effects if sufficiently high doses are consumed. Protein deficiency or other unidentified stressors may enhance the anemia-inducing effect of endosulfan.

In vitro studies support the ability of endosulfan to adversely affect the red blood cell. Marked damage to human red blood cell membranes has been reported to occur *in vitro* at endosulfan concentrations as low as 1 ppb (in the medium) (Daniel et al. 1986). Fresh red blood cells were suspended in 1% normal saline and incubated for 60 minutes with various concentrations of endosulfan in ethanol. The red blood cells were examined immediately after incubation. The effects observed included crenation, threading, pitting of the surface, and loss of cellular outline and cell fusion. Cellular damage and altered cell morphology were accompanied by increased cell membrane permeability, as evidenced by the release of plasma hemoglobin into the test media. In addition, α-endosulfan, but not the β-isomer, was a strong inhibitor of the calcium transport ATPase of human erythrocyte membranes, suggesting that the chemical may be incorporated into membranes, thus impairing enzyme activity (Janik and Wolf 1992). Increased fragility and permeability of red blood cell membranes have also been observed in red blood cells obtained from cats that received a single intravenous dose of 3 mg/kg (Misra et al. 1982). Decreased erythrocyte Na^+, K^+-ATPase activity was observed by Kiran and Varma (1988) following acute oral administration of 12.5 mg/kg/day of endosulfan to rats, suggesting that endosulfan may alter cellular ion permeability by decreasing the activity of this enzyme.

Musculoskeletal Effects. Very limited data were available regarding the effects of endosulfan on the musculoskeletal system. However, the available animal data did not indicate that this system is adversely affected following either inhalation or oral exposure to endosulfan (FMC 1965, 1967; Hoechst 1984b, 1984c, 1988b, 1989a, 1989c). Thus, persons exposed to endosulfan would not be expected to experience adverse effects on the musculoskeletal system.

Hepatic Effects. Elevated serum transaminases (AST, ALT) were seen in a patient two days after ingesting an unknown amount of endosulfan mixed in with food (Blanco-Coronado et al. 1992). Eight days after admission to the hospital, the patient died, and postmortem examination revealed dilation and congestion of hepatic sinusoids. In another fatal case, postmortem examination revealed centrilobular congestion and slight prominence of the bile canaliculi (Lo et al. 1995). Studies using experimental

animals indicate that endosulfan affects the liver following oral, dermal, and parenteral exposure. The effects seen include an increase in liver weight and/or induction of microsomal enzymes (Anand et al. 1980b; Ansari et al. 1984; Banerjee and Hussain 1986, 1987; Das and Garg 1981; Den Tonkelaar and Van Esch 1974; Dikshith et al. 1984; Gupta and Chandra 1977; Gupta and Gupta 1977a; Hoechst 1984a; Kiran and Varma 1988; Misra et al. 1980; Siddiqui et al. 1987a). Although histopathological changes have generally not been reported to accompany the enzyme induction and increase in liver weight discussed above, Gupta and Chandra (1977) observed hepatic lesions that included moderate-to-severe inflammation, dilation of the sinusoids, necrosis, and Kupffer cell hyperplasia in rats administered 5 or 10 mg/kg/day of endosulfan by gavage for 15 days. Increased serum and liver transaminases activities, suggestive of liver damage, were reported in rabbits after a single endosulfan dose of 15.1 mg/kg (Ceron et al. 1995) and in rats after doses of 3 mg/kg/day in the food for 30 days (Paul et al. 1995). Based on results from *in vitro* studies, some have suggested that the cytotoxic effects of endosulfan in the liver are related to its ability to uncouple oxidative phosphorylation and inhibit electron transport (Dubey et al. 1984; Narayan et al. 1985a, 1985b).

The biological significance of the adaptive changes discussed above is not known since these effects have not been observed in most chronic studies (FMC 1959a, 1967; Hack et al. 1995; Hoechst 1988b, 1989a; NCI 1978). However, increased serum alkaline phosphatase in dogs consuming endosulfan for 1 year in the absence of detectable effects on liver weight, function, or microscopic damage (Hoechst 1989c) and an increased incidence of hydropic hepatic cells in rats consuming endosulfan for 2 years (FMC 1959b) have been observed in chronic-duration studies. Therefore, the potential exists for adverse hepatic effects in humans following long-term exposure to sufficiently high levels of endosulfan. A chronic-duration oral MRL was derived based on the observation of increased serum alkaline phosphatase in dogs (Hoechst 1989c). Also, as seen in the cases reported by Blanco-Coronado et al. (1992), short-term exposure to very high levels of endosulfan may cause adverse effects on the livers of humans.

Renal Effects. Hemorrhage of the medullary layer of the kidneys was observed in an early report of three fatal cases of acute oral poisoning with endosulfan (Terziev et al. 1974). More recent studies have reported acute renal failure after ingestion of endosulfan as a major contributing cause of death in two individuals; in both cases, postmortem examination showed extensive tubular necrosis (Blanco-Coronado et al. 1992; Lo et al. 1995). Neither case discussed the possible mechanism of endosulfan-induced acute renal failure, but in one case, the authors of the report indicate that the renal lesions may relate to sepsis and shock (Blanco-Coronado et al. 1992). Ingested doses were not determined in any of these cases, and

it is not totally clear that the effects observed at autopsy were a direct result of endosulfan exposure, although based on results from acute animal studies, it seems likely.

There have been no reports of renal toxicity associated with acute inhalation exposure to endosulfan in laboratory animals. However, acute oral and dermal exposure to endosulfan has been reported to cause damage to the kidneys of rats, rabbits, and dogs (FMC 1958, 1980a; Gupta and Chandra 1975; Hoechst 1970; Terziev et al. 1974). This is consistent with acute oral exposure in humans. Intermediate-duration ingestion of endosulfan by rats has also been reported to result in renal changes (Dikshith et al. 1984; Gupta and Chandra 1977; Hoechst 1984a, 1985a). Some of these changes are manifestations of renal toxicity, whereas for others, it is unclear whether the effects observed represent a toxic effect. For example, clearly toxic responses included congestion, shrunken glomerular tufts, thickened Bowman's capsules, focal degeneration or necrosis of the epithelial lining of the kidney tubules, protein aggregates in the lumen of renal tubules, and eosinophilic droplets in cells of the proximal convoluted tubules (Gupta and Chandra 1975, 1977; Hoechst 1985a). In contrast, yellowish discoloration of the cells of the proximal convoluted tubules and granular/clumped pigment in the cells of the straight portions and/or proximal convoluted tubules may either represent storage of endosulfan in the kidney or renal pathology. Although the Hoechst (1987) study indicated that the yellow discoloration and increases in kidney weight may be a reflection of lysosomal sequestration of endosulfan in the cells of the renal tubules, tests assessing renal performance were not conducted. Thus, the significance of these changes remains unclear. Chronic ingestion of endosulfan has also resulted in renal toxicity in male rats (FMC 1959b; Hack et al. 1995; Hoechst 1989a; NCI 1978). Thus, individuals exposed to sufficiently high levels of endosulfan for either acute, intermediate, or chronic durations may be at risk for compromised renal function and possible injury.

Endocrine Effects. No information was located regarding endocrine effects in humans following exposure to endosulfan. In animals, with one exception, routine and/or microscopic examination of endocrine glands following inhalation (Hoechst 1984c) or oral exposure (FMC 1965, 1967; Gupta and Gupta 1977a; Hoechst 1984a, 1988b, 1989a, 1989c) to endosulfan for various durations revealed no significant treatment-related effects. The exception is the observation of degranulation of the β-cells of the islets of Langerhans of the pancreas in rats administered a single oral dose of 1 mg of endosulfan/kg (Barooah et al. 1980). This effect, however, was not observed after the same dose was administered daily for five days. Both administration protocols caused dilation of the blood vessels of the islets of Langerhans. Microscopic alterations of the adrenals were observed in rabbits (Gupta and Chandra 1975) and rats (Hoechst 1985c) after dermal application of endosulfan; however, these were lethal or near-lethal

dermal doses of endosulfan. Adverse endocrine effects secondary to chronic renal failure were observed in rats treated chronically with endosulfan in the diet (NCI 1978). The effects consisted of parathyroid hyperplasia and calcification of tissues.

In recent years, concern has been raised that many industrial chemicals, endosulfan among them, are endocrine-active compounds capable of having widespread adverse effects on reproductive health of humans and wildlife (Daston et al. 1997; Safe et al. 1997). Numerous studies have examined the possibility that endosulfan might be an endocrine-disrupter. The overall evidence is mixed. A variety of *in vitro* assays indicate that endosulfan has weakly estrogenic properties at exposure levels of approximately 5–50 µM (the estrogenic effect of endosulfan treatment was approximately 30–85% of that seen after treatment with approximately 0.01 µM 17β-estradiol) and is generally cytotoxic at about 100 µM (Andersen et al. 1999; Legler et al. 1999; Ramamoorthy et al. 1997; Soto et al. 1994, 1995; Vonier et al. 1996; Wade et al. 1997), while other *in vitro* assays apparently contradict these findings, showing no endocrine disruptive activity at similar exposure levels (Andersen et al. 1999; Arcaro et al. 1998; Hsu et al. 1998; Shelby et al. 1996). Endosulfan was not estrogenic in female animals as indicated by lack of changes in relative uterine weight in the following three *in vivo* assays: ovariectomized female rats orally administered 1.5 mg/kg/day for 30 days (Raizada et al. 1991); immature female rats administered 3 mg/kg/day by intraperitoneal injection for 3 days (Wade et al. 1997); immature female mice acutely exposed by subcutaneous injection for 3 days at up to 10 mg/kg/day (Shelby et al. 1996). However, in male rats, altered testicular testosterone was seen after both acute- and intermediate-duration oral exposures to $7.5 mg/kg/day (Singh and Pandey 1989, 1990). Further details of studies that evaluate whether endosulfan is an endocrine disrupter are provided in Section 2.6 (Endocrine Disruption). Overall, there is only weak evidence to suggest that levels in the environment to which the general population is exposed could induce adverse endocrine effects.

Dermal Effects. There have been no reports of adverse dermal effects associated with exposure to endosulfan in humans. When tested in farmers, endosulfan did not cause contact dermatitis (Schuman and Dobson 1985). Studies in experimental animals have shown that dermal exposure to endosulfan is only slightly to moderately irritating at relatively high doses (Hoechst 1983b, 1985c, 1985d, 1989b; Industria Prodotti Chimici 1975).

Ocular Effects. An aqueous solution of endosulfan was found to be nonirritating to the eyes of rabbits (Gupta and Chandra 1975), and ophthalmologic examination of the eyes of rats, mice, and dogs following intermediate- or chronic-duration oral exposure revealed no adverse effects (Hack et al. 1995; Hoechst

1984b, 1985a, 1985b, 1988b, 1989a, 1989b, 1989c). However, it has been reported that chronic intraperitoneal administration of endosulfan to rabbits induced widespread damage to the ocular tissues (Anand et al. 1987). The authors hypothesized that the ocular effects associated with endosulfan may be a result of prolonged hypertension (although no data on blood pressure were presented, and there is no other information to indicate that chronically administered endosulfan induces hypertension) or an endosulfan-induced vitamin A deficiency (which was observed in this study). Although the rabbit may represent a uniquely sensitive species, the possibility that long-term exposure of persons at hazardous waste sites to endosulfan may result in adverse effects on ocular tissues cannot be eliminated.

Body Weight Effects. No information was located regarding body weight effects in humans following exposure to endosulfan. One study in rats reported decreased body weight gain following intermediate-duration nose-only exposure to 2 mg/m^3 aerosolized technical endosulfan (Hoechst 1984c). Numerous studies monitored body weight in animals following oral exposure. It is apparent that doses of endosulfan that decreased survival and/or caused frank toxicity also decreased body weight gain. This was demonstrated in an acute-duration study in rabbits (Ceron et al. 1995) and an intermediate-duration study in rats (Gupta and Chandra 1977) and in a chronic study in rats (NCI 1978). Food consumption was significantly depressed in the study in rabbits, but no information was provided in the rat studies. Interestingly, in a 24-month feeding study in rats and mice, body weight gain was significantly reduced in male mice and in male and female rats even though the authors reported that food and water consumption were not significantly altered in either species (Hack et al. 1995). No explanation was provided for this finding, and its significance for human health is unknown.

Metabolic Effects. Severe metabolic acidosis with high anion gap and hyperglycemia were reported in humans acutely poisoned by ingestion of endosulfan (Blanco-Coronado et al. 1992; Lo et al. 1995). In the cases reported by Blanco-Coronado et al. (1992), mitigation of the initial convulsive activity also corrected the metabolic acidosis, which according to the authors suggested that anoxia due to convulsions may be the primary cause of the metabolic acidosis. Studies in rats suggest opposing effects on circulating glucose levels depending on dose. After a single moderate dose of endosulfan, degranulation of the β-cells of the islets of Langerhans of the pancreas (indicating release of insulin) and decreased serum glucose have been observed (Barooah et al. 1980). After higher doses of endosulfan, decreased hepatic glycogen and increased serum glucose have been observed (Chatterjee et al. 1986; Garg et al. 1980; Kiran and Varma 1988). It should also be noted that the studies that reported hyperglycemia and decreased hepatic glycogen also reported frank neurotoxicity manifested as convulsive activity. It may well be, as pointed out by Kiran and Varma (1988), that the hyperglycemia is due to the mobilization of

glucose from store sites (like the liver) triggered by the energy demands of a drastic increase in muscle activity that follow high doses of endosulfan. The limited information available suggests that exposure of persons to endosulfan in dosages high enough to cause muscle tremor or seizures, may result in metabolic acidosis and hyperglycemia. Daily exposure of the general population to levels of endosulfan commonly found in food stuff is not expected to induced adverse metabolic effects.

Other Systemic Effects. Decreased food consumption has been reported in acute- and intermediate-duration oral studies in animals administered technical endosulfan by gavage. However, in the acute-duration study in rabbits endosulfan caused frank toxicity, including seizure activity, and was lethal to 5 of 7 rabbits (Ceron et al. 1995). In the study in rats (Paul et al. 1994), while there were no severe neurotoxic effects, spontaneous motor activity was significantly increased in the treated animals, and this may have contributed to the reduced food intake. In one chronic-duration feeding study in rats and mice treatment with endosulfan did not result in significant alterations in food or water consumption, but body weight gain was reduced in the animals (Hack et al. 1995). Whether this suggests altered food utilization remains unclear, and its significance to human health is unknown.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological effects in humans after exposure to endosulfan. However, studies in rats indicate that both humoral and cellular immune responses (e.g., serum antibody titer to tetanus toxin; IgG, IgM, and γ-globulin levels; MMI and LMI) are depressed by oral exposure to endosulfan at doses that do not induce any other overt signs of toxicity (Banerjee and Hussain 1986, 1987). Based on the observation of depressed cellular and humoral responses following oral exposure of rats to 0.9 mg/kg/day for 22 weeks and the absence of this effect at 0.45 mg/kg/day (Banerjee and Hussain 1986), an intermediate-duration MRL of 0.005 mg/kg/day was derived. Mice administered daily intraperitoneal injections of approximately 0.8 mg/kg/day in 10 administrations over a period of 30 days (daily dose level was ambiguously reported) also showed impaired humoral (bovine serum albumin antibody titre) and cell-mediated (LMI and phagocytic activity) immune responses (Bhatia et al. 1998). These results demonstrate that immunotoxicity may be a more sensitive end point of endosulfan-induced toxicity than other end points (e.g., neurotoxicity) and that humans may be at risk for adverse immune effects following exposure to endosulfan.

The observed immunosuppressive effect could be due either to a general effect on the animal's physiological condition, hormonal function, nutritional status, or hepatic metabolism of other endogenous and immunoregulatory substances or an effect on lymphoid cells, lymphoid cell distribution,

immunoglobulin metabolism, T-cell/B-cell-macrophage cooperation, or macromolecular biosynthesis (Banarjee and Hussain 1986).   Serum complement (a group of serum proteins believed to be involved in immunopathology and immunoregulation) may be involved in some immunological alterations induced by endosulfan, as proposed by Das et al. (1988). They found that endosulfan activated serum complement *in vitro* by the alternative pathway. Complement activation has been shown to occur in association with many pathological conditions, including allergic diseases. In summary, sensitive indicators of both humoral and immune function have suggested altered immunocompetence at doses of endosulfan that have not been previously shown to cause toxicity.

Neurological Effects.   The most prominent signs of acute exposure to high concentrations of endosulfan in humans are hyperactivity, tremors, decreased respiration, dyspnea, salivation, and tonic-clonic convulsions. These effects have been observed in cases of occupational exposure as well as following intentional or accidental ingestion of large amounts of endosulfan. Autopsies performed in three cases of lethal exposure to endosulfan in humans revealed brain edema (Terziev et al. 1974), but a more recent study found no hemorrhagic areas in the brain of a patient who also died after ingestion of endosulfan (Blanco-Coronado et al. 1992). One year after an attempted suicide by ingestion of an endosulfan-containing pesticide, the mental activity (presumably psychomotor function) of a 20-year-old man was still severely impaired, and he required medication to control his seizures (Shemesh et al. 1988). Long-term brain damage has also been associated with occupational endosulfan intoxication (Aleksandrowicz 1979). These case reports suggest that long-term brain damage can occur following exposure to high concentrations of endosulfan in humans. The brain damage may have been a result of a direct action of endosulfan on the brain tissue or the hypoxia that accompanied seizures. However, interpretation of these studies is difficult because limited information was presented regarding neuropsychiatric status before exposure to endosulfan. It is possible that not all of the defects observed post-ingestion are attributable to the pesticide.

Signs of acute endosulfan intoxication similar to those reported in humans have been observed in animals. Also, cerebral congestion and edema is often observed at necropsy in animals that die following acute ingestion of endosulfan (Boyd and Dobos 1969; Boyd et al. 1970; Terziev et al. 1974). The severe central nervous system effects described above have not been described in many intermediate or chronic-duration ingestion studies of endosulfan in experimental animals. This may reflect lack of careful observation of the animals, administration of relatively low doses of endosulfan, or increased tolerance to endosulfan.

Perhaps one of the most important findings in animal studies in recent years regarding the neurological effects of endosulfan is that low doses of endosulfan reduced the threshold for seizures produced by electrical stimulation in kindled animals (Gilbert and Mack 1995). Also, the increase in seizure susceptibility was long-lasting and transferred positively to electrical kindling up to 1 month following cessation of treatment. Keeping in mind that the endosulfan doses administered to the animals in these studies are well above those typically found in the environment, these results indicate that humans with a predisposition to seizure disorders through hereditary or environmental causes may be at higher risk to the adverse effects of endosulfan and related chemicals (Gilbert and Mack 1995). Recent studies in animals have also found that administration of endosulfan can induce changes in the levels of various neurotransmitter in different brain areas (Lakshmana and Raju 1994) and alter learning and memory processes (Paul et al. 1994, 1995). The possible mechanisms by which endosulfan can induce some of the neurotoxic effects that have been observed are briefly discussed in Section 2.4.2.

In summary, the frank neurotoxic effects of endosulfan are apparent only after acute ingestion of relatively high doses in animals. However, long-term decreased psychomotor function, possibly resulting from acute endosulfan exposure, have been reported by two authors (Aleksandrowicz 1979; Shemesh et al. 1988). Such effects cannot be easily measured in animals. Hence, the fact that long-term neurotoxic effects have not been observed in animals does not mean that such effects cannot occur in humans. However, no information was located that indicated that persons exposed to low levels of endosulfan might experience any neurotoxicity.

Reproductive Effects.   No studies were located regarding reproductive effects in humans after exposure to endosulfan. Three studies were available regarding the effects of oral endosulfan exposure on reproductive performance in animals, and all yielded negative results (Dikshith et al. 1984; Hoechst 1982, 1984a). In contrast, studies that evaluated the toxicity of endosulfan on reproductive organs rather than on reproductive function showed evidence of the ability of endosulfan to adversely affect male reproductive organs (Gupta and Gupta 1977a; Khan and Sinha 1996; NCI 1978; Singh and Pandey 1989; Singh and Pandey 1990; Sinha et al. 1997). Male mice showed a significant reduction in sperm counts after 35 days of treatment with 3 mg/kg/day (Khan and Sinha 1996), and similar effects were seen adult male rats treated with 5 mg/kg/day for 70 days (Sinha et al. 1995) or in young male rats treated for 90 days (Sinha et al. 1997). Neither one of these two studies examined reproductive performance. In the Khan and Sinha (1996) study, simultaneous intraperitoneal administration of different doses of vitamin C reduced the effects of endosulfan in a dose-related manner. A higher-dose study showed that male rats given 10 mg/kg/day for 15 days had increased weight of the testes with marked degenerative changes in

the seminiferous epithelium of the tubules, but no examinations were conducted on spermatozoa production or the reproductive performance of the animals (Gupta and Gupta 1977a). Singh and Pandey (1989, 1990) reported effects on testosterone production in male rats after exposure to endosulfan (at approximately 7.5–10 mg/kg/day), which may possibly lead to reproductive toxicity. Wilson and LeBlanc (1998) recently showed that short-term administration of endosulfan to female mice increased the clearance of testosterone, but this was associated with only a small, nonsignificant decrease in serum testosterone levels. Histopathological effects (a dose-related atrophy characterized by testicular degeneration and necrosis) were noted in the reproductive organs of male rats fed a diet that provided approximately 48 mg endosulfan/kg/day for 74 weeks (NCI 1978); the no-effect-level in that study was 20 mg/kg/day. Chronic-duration exposure studies in rats and mice with doses <5 mg/kg/day provided no evidence of gross or microscopic alterations in the reproductive organs, but the scope of the microscopical evaluation was not provided (Hack et al. 1995). A recent study with human sperm *in vitro* showed that concentrations of technical endosulfan as low as 0.1 nM strongly inhibited the acrosome reaction (AR, an essential fertilization event) initiated by glycine; 1 nM also inhibited the acrosomal reaction initiated by progesterone (Turner et al. 1997). Chloride channels activated by GABA are involved in the AR. Turner et al. (1997) pointed out that although their results were striking because of the low concentration of endosulfan at which the inhibition occurred, there is yet no established link between human or wildlife infertility, the AR inhibitory levels of endosulfan, and the levels of endosulfan found in the environment. *In vitro* cultures of preimplantation hybrid mouse embryos showed significantly increased incidence of mice with altered preimplantation development after cultivation in serum of rats that had been exposed intraperitoneally with 10 mg/kg of the powder or 200 mg/kg in microcapsular form (Popov et al. 1998a).

In summary, although the available reproductive studies indicate that endosulfan has no adverse effects on reproductive performance in animals, severe adverse effects on male reproductive organs have been seen in rats and mice. This apparent discrepancy needs to be resolved with further research. Endosulfan may potentially cause reproductive toxicity in humans.

As discussed in the Endocrine Effects section, endosulfan has shown weak estrogenic properties in some *in vitro* assays, but no such properties could be confirmed in studies *in vivo*.

Developmental Effects.   No studies were located regarding developmental toxicity in humans after exposure to endosulfan. In animals, the evidence is inconclusive. Studies of gestational exposure found increased skeletal variations and resorptions at endosulfan doses of 5 mg/kg/day or greater, which also caused maternal death (Gupta et al. 1978). Another study found increased skeletal variations and

decreased birth weight and length at doses of 6 mg/kg/day, which also induced maternal toxicity (FMC 1980b). Furthermore, in the FMC (1980b) study, replacement of animals during and after the study made it difficult to interpret the data (IRIS 2000).

A study of exposure of rats to endosulfan prior to and during gestation, as well as during lactation, reported fetal toxicity (decreased litter weights during lactation), but only in the presence of maternal toxicity (Hoechst 1982). A similar subsequent study showed lower fetal weights during lactation in the absence of observed maternal toxicity (Hoechst 1984a), but because there was no corroborative finding of a decrease in the number of pups per litter or in pup weight, the decrease in litter weight was not considered to be treatment-related (IRIS 2000).

A study conducted in rat pups in which the animals were treated intraperitoneally with 1 mg of technical endosulfan/kg/day for 25 days beginning at 1 day of age found a significant increase in the binding of serotonin to frontal cortical membranes (Zaidi et al. 1985). This increase correlated well with an increase in aggressive behavior. In contrast, exposure of adults to 1 mg/kg for 30 consecutive days or 3 mg/kg for 15 days did not induce significant changes in the binding or in aggressive behavior (Seth et al. 1986). Without further elaboration, Seth et al. (1986) suggested that neonates are more sensitive because serotonergic receptors develop postnatally (see also Section 2.6). Based on data from existing studies in animals, there is inconclusive evidence to characterize endosulfan as a potential developmental toxicant in humans. *In vitro* cultures of postimplantation rat embryos showed significantly increased incidences of embryolethality and developmental abnormalities both after direct exposure to endosulfan in powder or microcapsular form, and after cultivation in serum of rats that had been exposed intraperitoneally with either the powder or microcapsular form (Popov et al. 1998a).

Genotoxic Effects.   Endosulfan has been evaluated for genotoxicity in a variety of *in vivo* and *in vitro* assays. As summarized in Tables 2-4 and 2-5, the results of these assays have been positive and negative, but the majority of mutagenicity tests reported positive results. Certain studies were unsatisfactory, as indicated below.

DNA damage in mononuclear leukocytes was significantly increased in agricultural workers after occupational exposure to a pesticide mixture including endosulfan, although the contribution of endosulfan to the observed effect is uncertain (Lebailly et al. 1998). Both positive (Falck et al. 1999) and negative (Scarpato et al. 1996a, 1996b; Venegas et al. 1998) results were obtained in peripheral

Table 2-4. Genotoxicity of Endosulfan *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells: Mouse spermatogonial cells	Chromosomal aberrations	+	Usha Rani and Reddy 1986
Rat spermatogonial cells	Chromosomal aberrations	–	Dikshith and Datta 1978; Dikshith et al. 1978
Rat spermatogonial cells	Aberrant metaphases	+	Dikshith et al. 1978
Rat bone marrow cells	Chromosomal aberrations	–	Dikshith and Datta 1978; Dikshith et al. 1978
Rat bone marrow cells	Aberrant metaphases	+	Dikshith et al. 1978
Mouse bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei	–	Usha Rani et al. 1980
Mouse bone marrow	Chromosomal aberrations	+	Kurinnyi et al. 1982
Hamster bone marrow	Chromosomal aberrations	+	Dzwonkowska and Hubner 1986
Mouse bone marrow	Aberrant metaphases	+	L'Vova 1984
Insect systems: *Drosophila melanogaster* (sex-linked recessive lethal test)	Recessive lethal mutation	+	Velazquez et al. 1984
D. melanogaster	Sex-chromosome loss	+	Velazquez et al. 1984

+ = positive results; – = negative results

Table 2-5. Genotoxicity of Endosulfan *In Vitro*

Species (test system)	End point	Results With activation	Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100	Gene mutation	–	–	Pednekar et al. 1987
S. typhimurium TA89, TA100, TA1535, TA1537, TA1538	Gene mutation	No data	–	Moriya et al. 1983
S. typhimurium TA98, TA100, TA1535, TA1978	Spot test	No data	No data	Dorough et al. 1978
S. typhimurium TA 1535/pSK 1002	umu gene expression	No data	+	Chaudhuri et al. 1999
Escherichia coli WP hcr	Gene mutation	No data	–	Moriya et al. 1983
E. coli K12	Gene mutation	No data	+	Chaudhuri et al. 1999
E. coli WP2s	prophage λ induction	No data	+	Chaudhuri et al. 1999
Eukaryotic organisms:				
Saccharomyces cervisiae	Miotic cross over	No data	–	Yadav et al. 1982
S. cerevisiae D7	Reverse mutation	No data	+	Yadav et al. 1982
S. cerevisiae D7	Mitotic gene conversion	No data	+	Yadav et al. 1982
S. cerevisiae D7	Aberrant colonies	No data	+	Yadav et al. 1982
S. cerevisiae D7	Mitotic gene conversion	No data	–	L'Vova 1984
S. cerevisiae T2 (PG-155)	Mitotic recombination	No data	+	L'Vova 1984
Mammalian cells: Cultured human lymphocytes	Mitotic recombination Aberrant metaphases	No data	–	L'Vova 1984
Cultured human lymphocytes	Sister chromatid exchange	+	+	Sobti et al. 1983
Human liver hepatoblastoma	DNA adducts	+	No data	Dubois et al. 1996

Table 2-5. Genotoxicity of Endosulfan *In Vitro (continued)*

Species (test system)	End point	Results With activation	Without activation	Reference
Fetal rat hepatocytes	DNA adducts	+	No data	Dubois et al. 1996
Rat hepatocyte culture	Unscheduled DNA synthesis	No data	–	Hoechst 1984c

+ = positive results; – = negative results; DNA = deoxyribonucleic acid

lymphocyte micronucleus studies in workers who applied various pesticides, including endosulfan. No increase in chromosomal aberrations or sister chromatid exchanges was seen in greenhouse workers in Italy who were exposed to complex mixtures of pesticides that included endosulfan (Scarpato et al. 1996a, 1996b, 1997). The mixed results in human genotoxicity assays should be treated with caution because coexposure to a variety of other chemicals occurred in each study and the exposure levels of endosulfan were not reported.

The induction of genotoxic effects in animals following *in vivo* exposure to endosulfan has been evaluated in the chromosomal aberration test in somatic and germinal cell systems with rats (Dikshith et al. 1978), mice (Kurinnyi et al. 1982; Usha Rani and Reddy 1986), and hamsters (Dzwonkowska and Hubner 1986), as well as in the bone marrow micronucleus test with mice (Usha Rani et al. 1980), and in the sex-linked recessive lethal mutation test with *Drosophila* (Velazquez et al. 1984). Endosulfan enhanced chromosomal aberrations in mouse spermatocytes 60 days posttreatment (Usha Rani and Reddy 1986), in mouse bone marrow (Kurinnyi et al. 1982) and in hamster bone marrow (Dzwonkowska and Hubner 1986), but the pesticide failed to induce chromosomal aberrations in the bone marrow and spermatogonial cells of rats (Dikshith and Datta 1978; Dikshith et al. 1978). However, it is not known how soon after treatment the animals were killed, and as shown in the mouse studies (Usha Rani and Reddy 1986), a latency period of 60 days was required to see chromosomal aberrations in spermatogonia. Endosulfan also increased the cytogenetic activity (aberrant metaphases) of mouse bone marrow (L'Vova 1984). In rats, relatively significant changes in mitotic indices (decreased metaphases) in bone marrow and spermatogonial cells have been observed (Dikshith et al. 1978). Endosulfan did not induce micronuclei in mice (Usha Rani et al. 1980). Endosulfan was positive *in vivo* for the induction of sex-linked recessive lethals and sex-chromosome loss, which indicates that endosulfan is an efficient mutagen in *Drosophila* (Velazquez et al. 1984). The incidence of *in vitro* sister chromatid exchanges was increased at least 5-fold compared to controls in cultured postimplantation rat embryos both after direct exposure to endosulfan in powder or microcapsular form, and after cultivation in serum of rats that had been exposed intraperitoneally with either the powder or microcapsulated endosulfan (Popov et al. 1998a).

Endosulfan is toxic to yeast but is also mutagenic without activation (Yadav et al. 1982). *In vitro*, endosulfan induced reverse mutations and mitotic gene conversion and increased the percentage of aberrant colonies in *Saccharomyces cerevisiae* but did not induce mitotic cross-overs (Yadav et al. 1982). This indicates that endosulfan is capable of inducing chromosome breakage and loss. Endosulfan also

induced cytotoxic activity (significant increase in the number of crossover colonies) in the yeast strain *S. cerevisiae* T2 (deficient in repair system), but not in *S. cerevisiae* T1 (L'Vova 1984).

No mutagenic activity was demonstrated for the *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535, TA1537, TA1538 without activation (Moriya et al. 1983; Pednekar et al. 1987) or for *Escherichia coli* WP2 without activation (Moriya et al. 1983). Endosulfan also tested negative in the *Salmonella* mutagenicity test with or without activation with S9 liver homogenate (Dorough et al. 1978). A forward mutation assay in *E. coli* K12 showed an endosulfan-induced increase in mutations from ampicillin-sensitive to ampicillin-resistant (Chaudhuri et al. 1999). Prophage λ was also induced by endosulfan in *E. coli*, and *umu* gene expression was induced by endosulfan exposure in *S. typhimurium* (Chaudhuri et al. 1999).

In cultured mammalian cells, endosulfan was reported positive in sister chromatid exchanges in human lymphoid cells exposed both with and without activation (Sobti et al. 1983) and in forward locus mutations in mouse lymphoma cells in the absence of S9 mix (McGregor et al. 1988). Endosulfan did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes (Hoechst 1984d). Negative results were also reported for UDS in human lung carcinoma (A 549) cells using liquid scintillation counting (Hoechst 1988d), but the study was inconclusive because the author did not present any evidence that DNA synthesis was inhibited, and high background levels compromised the sensitivity of the assay. In a more recent study, endosulfan was found to induce the formation of DNA adducts in both fetal rat hepatocytes and Hep G2 (human liver hepatoblastoma) cells (Dubois et al. 1996); this activity strongly correlated with high induction of CYP3A gene expression.

In summary, genotoxicity studies of endosulfan have provided evidence that this compound is mutagenic and clastogenic, and that it induces effects on cell cycle kinetics in two different mammalian species. However, some of these data may be suspect because some formulations of endosulfan have contained epichlorohydrin, a known genotoxic chemical, as a stabilizer (Hoechst 1990). It should be noted that humans may also be exposed to epichlorohydrin along with endosulfan.

Cancer. No reports of cancer in humans associated with exposure to endosulfan have been found. The carcinogenicity of endosulfan has been studied in chronic oral bioassays using rats (FMC 1959b; Hack et al. 1995; Hoechst 1989a; NCI 1978) and mice (Hack et al. 1995; Hoechst 1988b; NCI 1968, 1978). While early studies in experimental animals have limitations (e.g., poor survival, less-than-lifetime exposures, inadequate reporting of data, use of only one dose level, and use of doses that were possibly

less than the maximum tolerated dose) that render them inadequate for drawing definitive conclusions
regarding the carcinogenicity of endosulfan, the later studies by Hack et al. (1995) and earlier ones by
Hoechst (1988b, 1989a) show no evidence of increased neoplasms in rats or mice chronically exposed to
endosulfan. Consumption of 3.8 mg/kg/day (females) or 2.9 mg/kg/day (males) by Sprague-Dawley rats
for 2 years did not result in an increased incidence of any neoplastic lesion (Hack et al. 1995; Hoechst
1989a). Similarly, consumption of 2.86 mg/kg/day (females) or 2.51 mg/kg/day (males) by NMRI mice
for 2 years resulted in no increase in neoplastic lesions in these animals (Hack et al. 1995; Hoechst
1988b).

Technical endosulfan as well as the α- and β-isomers showed promoting activity in a two-stage, altered
hepatic foci bioassay in male rats; of the three compounds, α-endosulfan had the strongest promoting
activity (Fransson-Steen et al. 1992). Because both the phenobarbital and methylcholanthrene-inducible
forms of hepatic cytochrome P450-dependent monooxygenases were marginally induced by the
chemicals, an involvement of cytochrome P450 in the tumor promoting activity of these chemicals was
considered unlikely (Fransson-Steen et al. 1992). Instead, the authors suggested that endosulfan is a
tumor-promoting agent acting by clonal expansion of initiated cells. One possible mechanism of tumor
promotion is the inhibition of gap junctional intercellular communication and the possibility that
endosulfan exhibits such property has been studied *in vitro*. Results from studies by Fransson-Steen and
Warngard (1992) showed that in primary rat hepatocytes β-endosulfan is a more potent inhibitor of
intercellular communication than α-endosulfan, but the two isomers had similar inhibitory potency in
WB-Fischer 344 rat liver epithelial cells. The mechanism of inhibition of intercellular communication by
endosulfan has not been elucidated, but results from studies in IAR 20 rat liver epithelial cells have
suggested an effect on connexin 43, the main gap junction protein in this cell line (Kenne et al. 1994).
Phosphorylation of connexins is one posttranslational alteration involved in regulation of gap junctional
communication (Musil et al. 1990). In the IAR 20 cell line, endosulfan was found to increase slightly
phosphorylation of connexin 43 initially during the assay, but longer exposure periods led to
hypophosphorylation (Kenne et al. 1994). While these *in vitro* assays are useful in short-term detection
of tumor promoters, the general biological significance of gap junctional intercellular communication in
tumor promotion needs further clarification (Fransson-Steen and Warngard 1992).

2.6   ENDOCRINE DISRUPTION

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, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997a). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of 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 endosulfan.

In vivo studies in animals suggest that endosulfan may disrupt normal reproductive hormone levels in male animals, but that it is not an endocrine disrupter in females. Persistent depressed testicular testosterone was seen in male rats after intermediate duration oral exposures to endosulfan. In ovariectomized female rats, orally administered endosulfan did not induce normal development of female reproductive tissues, and in female mice and immature female rats, acute parenteral exposure to endosulfan did not affect several endocrine-related end points. *In vitro* studies have evaluated endosulfan for estrogen receptor (ER) and cytosolic protein binding affinity, ER-mediated reporter gene expression, estrogenic induction of cell proliferation, and alteration of relative abundance of active estradiol metabolites. Overall, *in vitro* evidence in favor of endosulfan estrogenicity indicates relatively weak potency compared to 17β-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.

Significantly increased serum testosterone and decreased testicular testosterone were reported in male rats after a 7-day exposure to endosulfan using oral doses in the range of 7.5–10 mg/kg/day, but not at #5 mg/kg/day (Singh and Pandey 1989). However, results after a 15-day exposure were highly variable and frequently not dose-related, making interpretation of the significance of the study's results difficult. A subsequent study (Singh and Pandey 1990) indicated a dose-related decrease in testicular testosterone, and plasma testosterone, LH, and FSH in groups of male Wistar rats orally administered endosulfan at 0, 7.5, or 10 mg/kg/day for 15 or 30 days. In addition, activities of steriodogenic enzymes and testicular cytochrome P450-dependent monooxygenases were depressed after the 30-day exposure at $7.5 mg/kg/day. All of the effects from 30 days of exposure were reversible during a 7-day recovery period, except for decreased testicular testosterone, which remained depressed; no recovery period was utilized for the 15-day exposures.

In ovariectomized female rats, gavage administration of 1.5 mg endosulfan/kg/day for 30 days did not influence the relative weights or histology of the uterus, cervix, or vagina compared to ovariectomized control rats that did not receive endosulfan (Raizada et al. 1991). Rats in a positive control group received intraperitoneal injections of estradiol (dose not reported) and showed increased relative organ weights and normal development of female reproductive tissues compared to the untreated ovariect-omized control rats. Organ weights and tissue development in rats administered both endosulfan and estradiol were not significantly different from those seen in rats that received estradiol alone. The Raizada et al. (1991) study results indicate that endosulfan was neither estrogenic nor anti-estrogenic with respect to the end points evaluated and under the conditions of this assay. Immature female rats intraperitoneally administered technical grade endosulfan at 3 mg/kg/day for 3 days showed no changes with respect to relative uterine and pituitary weights, uterine peroxidase activity, circulating thyroxine levels, or to levels of FSH, LH, TSH, prolactin, and growth hormone in the pituitary gland (Wade et al. 1997). As an extension of the same assay, endosulfan did not alter relative levels of ER or progesterone receptors compared to controls in crude uterine cytosol prepared from uterine tissue of the rats dosed intraperitoneally. Uterine weight in female mice was not affected by acute subcutaneous administration of technical grade endosulfan at up to 10 mg/kg/day for 3 days, whereas 17β-estradiol at up to 4 mg/kg/day gave a strong positive response (Shelby et al. 1996).

Catfish (*Clarias batrachus*) plasma vitellogenin levels were significantly decreased after $48 hours of exposure to 0.0015 mg/L of commercial-grade endosulfan (Chakravorty et al. 1992). Levels did not recover substantially with injections of various hormones, including estradiol. In rainbow trout,

endosulfan did not induce vitellogenin production at 9 days after a single intraperitoneal injection of 5 mg/kg in peanut oil (Andersen et al. 1999).

In vitro direct binding affinity of endosulfan for human ER was approximately 12,000-fold lower than 17β-estradiol and negligible for rabbit uterus ER. Endosulfan (60% α-isomer and 38% β-isomer) at 300 µM had approximately 20 times lower *in vitro* binding affinity for oviductal cytosolic binding proteins of yellow-bellied turtle (*Trachemys scripta*) and American alligator (*Alligator mississippiensis*) compared to 17β-estradiol at 1 µM (Crain et al. 1998). The results of these studies suggest that the relatively low binding affinity of endosulfan for ER may be somewhat offset by a relatively lower binding affinity for cytosolic proteins, producing a relatively greater bioavailability for interacting with intracellular steroid receptors than estradiol. Indeed, in a competitive ER-binding assay, endosulfan significantly inhibited both [3H]17β-estradiol binding to the estrogen receptor and progestin [3H]R5020 binding to the progesterone receptor using receptors prepared from alligator oviduct tissue (Vonier et al. 1996). However, in another competitive binding assay, neither of the endosulfan isomers either singly or in combination with dieldrin inhibited 17β-estradiol binding either to recombinant human ER at concentrations up to 10 µM (Arcaro et al. 1998) or to mouse uterine receptor (Shelby et al. 1996). Similarly, 17β-estradiol-induced foci formation in MCF-7 human breast cancer cells was neither inhibited nor stimulated by cotreatment with endosulfan (Arcaro et al. 1998).

ER-mediated reporter gene expression was related to endosulfan incubation concentration; in general, 100 µM induced gene expression, while mixed results were obtained at lower concentrations. Endosulfan induced human ER-mediated β-galactosidase (β-gal) activity at 100 µM in an estrogen-responsive reporter system in yeast, but not at #10 µM (Ramamoorthy et al. 1997). The endosulfan-induced yeast β-gal activity was about 32% of that induced by estradiol at 0.01 µM. Endosulfan was the only pesticide (among endosulfan, chlordane, toxaphene, and dieldrin) to induce β-gal activity above background; binary mixtures of endosulfan with the other pesticides induced significantly less activity than endosulfan alone.

The test system was considerably less sensitive to endosulfan when mouse ER, rather than human ER, was used to mediate β-gal activity (Ramamoorthy et al. 1997). In similar assays, endosulfan at 10 µM had no effect on β-gal activity in yeast (*Saccharomyces*) transfected with either the human or rainbow trout ER (Andersen et al. 1999). In addition, no effect was observed on transcriptional activation of HeLa cells transfected with plasmids containing an estrogen receptor as a responsive element (Shelby et al. 1996). Endosulfan also did not induce transient reporter gene expression in MCF-7 human breast cancer

cells at an incubation concentration of 2.5 µM (Andersen et al. 1999). Maximum endosulfan-induced
ER-mediated luciferase reporter gene expression occurred *in vitro* in a T47D human breast
adenocarcinoma cell line at approximately 10 µM, while 50% expression of luciferase occurred at about
5.9 µM; the maximum expression was approximately 59% of the effect from exposure to 0.03 nM
estradiol (0.00003 µM) (Legler et al. 1999). Luciferase expression from combined treatment with
endosulfan and dieldrin was additive over concentrations ranging from 3 to 8 µM.

Endosulfan at 10 µM induced *in vitro* proliferation of MCF-7 human breast cancer cells to between 2- and
5-fold higher than that seen in hormone-free cells, but appeared to be cytotoxic at approximately 100 µM
(Andersen et al. 1999). A similar study showed that endosulfan (technical grade) induced cell
proliferation in the MCF-7 human breast cancer cell line at exposure levels of 10 and 50 µM between
2 and 4 times control levels, but not at #2 µM (Wade et al. 1997). Soto et al. (1994, 1995) also
demonstrated MCF-7 proliferation at a dose level of 10–25 µM endosulfan, with the maximum cell
growth induced by endosulfan achieving 86% of that induced by estradiol, and cytotoxicity occurring at
higher exposure levels. In apparent contradiction of these positive findings, endosulfan (isomeric
composition not reported) did not substantially affect the growth of either ER-positive (MCF-7) or
ER-negative (SK-BR-3) cultured human breast cancer cell lines at concentrations of #35 µM. Endosulfan
did severely inhibit cell growth at higher concentrations, and this growth inhibition was synergistic when
cultures were incubated with either dieldrin or chlordane (Hsu et al. 1998). In another *in vitro* assay, both
α- and β-endosulfan were weakly estrogenic in inducing foci in MCF-7 cultures at 10 µM (but not at
lower concentrations), and showed no estrogenic synergism when incubated in combination with dieldrin
(Arcaro et al. 1998). In addition to inducing cell proliferation, endosulfan induced proliferation of the
progesterone receptor, which is another estrogen-mimicking effect (Soto et al. 1995).

α- and β-Endosulfan each altered the relative quantities of estradiol metabolites *in vitro* in ER-positive
MCF-7 human breast cancer cells. The amount of a genotoxic estradiol metabolite, 16α-hydroxyesterone
(16α-OHE1), was increased relative to controls and the metabolite 2-hydroxyestrone (2-OHE1), which
inhibits breast cell proliferation, was decreased relative to controls (Bradlow et al. 1995), resulting in a
slight increase in the 16α-OHE1/2-OHE1 ratio. The authors hypothesized that by producing an increase
in the 16α-OHE1/2-OHE1 ratio, endosulfan may increase the risk of estradiol-induced abnormal cell
growth in ER-positive tissues such as breast tissue.

The overall evidence indicates that endosulfan administered *in vivo* may be disruptive of reproductive
hormone levels in male animals. On the other hand, endosulfan is neither estrogenic nor disruptive of

thyroid or pituitary hormone levels in females *in vivo*, despite its weak estrogenicity in several *in vitro* test systems.

2.7   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 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the

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

Certain characteristics of the developing human may increase exposure or susceptibility while 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).

The effects of endosulfan have not been studied in children, but they would likely experience the same health effects seen in adults exposed to endosulfan. Data in adults, mostly derived from cases of accidental or intentional acute exposure (ingestion) to large amounts of endosulfan, indicate that the primary target of endosulfan toxicity is the nervous system. The effects are manifested as hyperactivity and convulsions and in some cases have resulted in death (Aleksandrowicz 1979; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Cable and Doherty 1999; Lo et al. 1995; Terziev et al. 1974). These effects have been reproduced in experimental animals.

Results from a few animal studies suggest that, for some end points, young and older animals exhibit different susceptibility. For example, a study conducted in rat pups in which the animals were treated intraperitoneally with 1 mg of technical endosulfan/kg/day for 25 days beginning at 1 day of age found a significant increase in the binding of serotonin to frontal cortical membranes (Zaidi et al. 1985). This increase correlated well with an increase in aggressive behavior. In contrast, exposure of adults to 1 mg/kg for 30 consecutive days did not induce significant changes in the binding or in aggressive behavior (Seth et al. 1986). Without further elaboration, Seth et al. (1986) suggested that the increased sensitivity showed by the pups may be due to the fact that serotonergic receptors develop postnatally. Kiran and Varma (1988) administered endosulfan orally for 4 days at 12.5 mg/kg/day to rats of four different ages (15, 30, 70, and 365 days old) and found that in older animals, endosulfan produced body tremors and muscular contractions, as well as hyperglycemia and reduction in liver glycogen content. None of these effects were observed in the 15-day-old pups, but endosulfan did reduce the activity of

erythrocyte Na^+-K^+-ATPase in this age group. No explanation was offered for this differential effect. If, as discussed in Section 2.4.2, endosulfan-induced convulsive activity is caused by inhibition of GABAergic systems, an immature GABAergic system in the 15-day-old pups may have been responsible for the lack of such activity. The results from these studies suggest that the determination of whether young animals are more susceptible than older ones or vice versa is influenced by the specific neurological response that is affected. The neurological response, in turn, depends on the degree of maturation of the neurotransmitter system(s) responsible for that response.

An additional study reported age-dependent effects. Lakshmana and Raju (1994) found that oral treatment of rat pups with endosulfan from postnatal days 2–10 resulted in changes in the concentration of noradrenalin, dopamine, and serotonin in various brain areas that differed either in magnitude or direction from changes seen in pups treated from postnatal days 2–23. While the results from this study do not necessarily indicate that neonates are more sensitive to the toxic effects of endosulfan, they do show that the duration of exposure in neonates is an important parameter to consider.

Differential susceptibility between young and older animals has also been found regarding other end points. Studies by Sinha et al. (1995, 1997) found that oral treatment of 3-week-old male rats with endosulfan for 90 days resulted in reduced intratesticular spermatid count and increased percent of abnormal sperm at doses lower than those that caused similar effects in 3-month-old rats treated for 70 days. This led the authors to conclude that exposure during a period of testicular maturation when spermatogenesis is in progress may result in disturbed spermatogenesis at sexual maturity.

Results from studies in animals exposed to endosulfan during gestation have provided inconclusive evidence of adverse developmental effects in the offspring. Some effects reported included an increased percentage of resorptions and skeletal variations in the fetuses (Gupta et al. 1978) and decreased fetal weight and length and increased skeletal variations (FMC 1980b). However, the dose levels at which these effects were observed also caused maternal toxicity, suggesting that may have been only secondary to the poor health condition of the mother. Studies in which administration of endosulfan included a period prior to mating as well as through gestation and lactation reported effects such as decrease in mean litter weight also at maternally toxic dose levels (Hoechst 1982). An additional study also reported decreased mean litter weight (Hoechst 1984a), but upon further analysis of the data, the effect was not considered treatment-related (IRIS 2000). Endosulfan was not estrogenic in *in vivo* assays in immature female rats (Raizada et al. 1991; Wade et al. 1997) or mice (Shelby et al. 1996), and exhibited mixed

positive and negative results with respect to estrogenic properties in various *in vitro* assays (see further details in 2.6 Endocrine Disruption).

There is no information regarding pharmacokinetics of endosulfan in children or regarding nutritional factors that may influence absorption of endosulfan. Based on the results from the studies mentioned above, there is no evidence that endosulfan or its metabolites cross the placenta. On the other hand, there is no apparent reason why they would not do so. Endosulfan was detected in the breast milk of rural Khazakhstan women who were environmentally exposed (Lutter et al. 1998). In a study in which lactating goats were administered endosulfan for 28 days, only trace amounts of endosulfan residues were transferred to the nursing kids (Indraningsih et al. 1993). In milk sheep, approximately 1% of radio-activity administered in a single oral dose of ^{14}C-endosulfan was recovered in the milk as endosulfan sulfate at approximately 1 day postdosing; the concentration in the milk declined to very low levels by 8 days postexposure, but was still detectable in milk at 2 ppb at 22 days postexposure (the end of the study) (Gorbach et al. 1968). There is no information on the metabolism of endosulfan in children. Because endosulfan is rapidly eliminated from the body after exposure, there is little likelihood that the chemical from preconception exposures in women would be present in the body during pregnancy or lactation. Although there is evidence that endosulfan induces microsomal cytochrome P-450 in animals (Siddiqui et al. 1987a; Tyagi et al. 1984), the specific mechanism of endosulfan metabolism is not known, and therefore no conclusion about developmental regulation can be drawn. There are no PBPK models for endosulfan.

There are no biomarkers of exposure or effect for endosulfan that have been validated in children or adults exposed as children. Isomers and metabolites of endosulfan were detected in the fat of 30–40% of children hospitalized in agricultural regions of Spain (Olea et al. 1999). The adipose endosulfan was presumably from recent dietary exposure in the light of evidence in a rat study (Dorough et al. 1978), indicating that endosulfan is rapidly eliminated from fat tissues after cessation of dietary exposure. However, methods for obtaining samples of fat are relatively invasive, so adipose endosulfan may not be practicable as a routine biomarker of recent exposure in children. No studies were located regarding interactions of endosulfan with other chemicals in children. Information regarding interactions of endosulfan with other chemicals in humans are limited to anecdotic reports, and inference to what might occur in children based on those reports might be inappropriate.

No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to endosulfan, reducing body burden, or interfering with the mechanism of action for toxic

effects. Also, no data were located regarding whether methods for reducing toxic effects of endosulfan used in adults might be contraindicated in children. No data were available on whether methods for reducing toxic effects of endosulfan used in adults have been validated in children.

There is no information regarding possible transgenerational effects of endosulfan exposure in humans and the limited data in animals are insufficient to establish whether such effects might occur. For example, a statistically significant increase in chromosomal aberrations was observed in mouse spermatocytes 60 days after initial treatment with oral doses of endosulfan of 6.4 mg/kg/day for 5 days (Usha Rani and Reddy 1986). In male rats, acute exposure to doses of up to 22 mg/kg/day of endosulfan for 5 days did not induce chromosomal aberrations in spermatogonial cells (Dikshith and Datta 1978). The ratios of mitotic index and frequency of chromatid breaks in the two cell types had no correlation with the doses tested and were not significantly different from the control group. Oral administration of 11.6 mg/kg/day of endosulfan to rats for up to 30 days also failed to induce chromosomal damage in spermatogonial cell systems, but it is not known how soon after treatment the animals were killed, and as shown in mouse studies (Usha Rani and Reddy 1986), a latency period of 60 days was required to see chromosomal aberrations in spermatogonia. However, relatively significant changes were observed for mitotic indices (Dikshith et al. 1978).

2.8   BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the

body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to endosulfan are discussed in Section 2.8.1.

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 endosulfan are discussed in Section 2.8.2.

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 2.10 "Populations That Are Unusually Susceptible".

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Endosulfan

The primary biomarkers for endosulfan exposure include tissue and excreta concentrations of endosulfan, or its metabolite, endosulfan sulfate. Other metabolites that can be detected include endosulfan diol, hydroxyether, and endosulfan lactone (Hayes 1982; WHO 1984). In animals, the metabolites appear in the tissues and excreta following prolonged exposure to endosulfan (Deema et al. 1966; Dorough et al. 1978). These water-soluble metabolites are rapidly formed and excreted in the urine and feces. Elevated levels of both α- and β-endosulfan, but not endosulfan metabolites, were detected in the urine of a pest control worker (who wore protective equipment) after a single 25-minute exposure to endosulfan in a greenhouse application. Urinary endosulfan declined to control levels by about 1.5 days postexposure (Arrebola et al. 1999). α- and β-Endosulfan were detected in the urine of workers who had applied endosulfan on the day prior to urine sampling, and were at lower levels in workers who had been occupationally exposed 1 week prior to sampling (Vidal et al. 1998). Metabolites (endosulfan ether, endosulfan sulfate, and endosulfan lactone) were either infrequently detected or occurred at relatively low levels in the urine. Endosulfan was detected in the serum of an agricultural pilot 30 hours after his

clothes became soaked with endosulfan and methomyl (Cable and Doherty 1999). Endosulfan has been detected in breast milk of rural Khazakhstan women exposed environmentally to endosulfan (Lutter et al. 1998), and endosulfan sulfate has been detected in sheep breast milk following consumption of large oral doses (Gorbach et al. 1968). Isomers and metabolites of endosulfan were detected in the fat of 30–40% of children hospitalized in agricultural regions of Spain, demonstrating that endosulfan accumulates in adipose tissue of young humans after repeated dietary exposure (Olea et al. 1999). No other biomarkers of exposure were identified in the available literature. No studies were located that quantified the concentrations of endosulfan or its metabolites in relation to specific environmental exposure concentrations.

Since endosulfan is a cytochrome P450-dependent monooxygenase inducer, the quantification of specific enzyme activities (e.g., aminopyrine-*N*-demethylase, aniline hydroxylase) may indicate that exposure to endosulfan has occurred (Agarwal et al. 1978). Because numerous chemicals and drugs found at hazardous waste sites and elsewhere also induce hepatic enzymes, these measurements are nonspecific and are not necessarily an indicator solely of endosulfan exposure. However, these enzyme levels can be useful indicators of exposure, together with the detection of endosulfan isomers or the sulfate metabolite in the tissues or excreta.

Evidence of anemia may also be used as a nonspecific biomarker for endosulfan exposure. There is evidence to suggest that endosulfan at levels as low as 1 ppb causes damage to human red blood cell membranes *in vitro* (Daniel et al. 1986) and that it produces other hematologic effects (reduced red blood cells, hemoglobin concentrations, and packed cell volume) in animals following oral exposure to levels ranging from 0.5 to 360 ppm (Das and Garg 1981; Hoechst 1985a; Siddiqui et al. 1987b). However, these effects are not specific enough to be used as biomarkers for exposure to endosulfan *in vivo*.

More recent studies have focused on developing sensitive *in vitro* assays that can serve as biomarkers for chemicals possessing estrogenic activity. Sonnenschein et al. (1995) described a procedure to extract and separate xenoestrogens from ovarian estrogens in human serum followed by determination of their concentration in *in vitro* gene expression assays in MCF-7 breast cancer cells. Such a biomarker seems more discriminative than those discussed above. However, one reservation about the assay, as stated by Sonnenschein et al. (1995), is that estrogen-inducible genes could also be induced by nonestrogenic substances.

2.8.2 Biomarkers Used to Characterize Effects Caused by Endosulfan

Acute clinical signs of neurotoxicity, manifested by hyperexcitability, dyspnea, decreased respiration, tremors, and convulsions, were identified in the available literature as effects caused by high doses of endosulfan. Exposure to high levels of endosulfan in humans may possibly be associated with permanent brain damage as manifested by cognitive and emotional deterioration, memory impairment, and impairment of visual-motor coordination (e.g., inability to perform small tasks) (Aleksandrowicz 1979; Shemesh et al. 1988). The organs most sensitive to longer-term endosulfan exposure appear to be the liver, kidney, and testes. Histopathological and degenerative changes in liver and kidney cells and increased hepatic enzyme activities (aminopyrine, *N*-demethylase, and aniline hydroxylase) have been observed following long-term treatment with low doses of endosulfan. Decay curves for aminopyrine in plasma, which are semiquantitative indices of liver enzyme induction, have been used successfully to demonstrate enzyme induction in pesticide-exposed workers. Decreased red blood cells, hemoglobin, packed cell volume, and IgG, IgM, and γ-globulin levels in the blood have also been detected in animals following exposure to endosulfan (Banerjee and Hussain 1986, 1987; Das and Garg 1981; Hoechst 1985a; Siddiqui et al. 1987b) and thus can be considered as other nonspecific biomarkers of effects. Rats exposed to endosulfan levels as low as 60 ppm were shown to have darker urine and marginal increases in protein and ketone levels in the urine than control animals (Hoechst 1985a). Degenerative effects on reproductive organs and histopathological effects in the kidneys of animals have also been associated with chronic administration of endosulfan. All parameters mentioned are generally nonspecific for endosulfan exposure as numerous other chemicals elicit changes in these end points. See Section 2.2 for other effects caused by endosulfan.

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

2.9 INTERACTIONS WITH OTHER CHEMICALS

The results of two human cases suggest that endosulfan and alcohol might act synergistically to cause death (Demeter et al. 1977). In one death, the blood alcohol concentration was 1.81 g/L (which is not considered lethal), and the quantity of endosulfan consumed (although the exact quantity was not reported) was also unlikely to be fatal when ingested alone. Thus, the authors suggested that the endosulfan and alcohol acted synergistically to result in death. It is also likely that alcohol interfered with

the metabolism of endosulfan in the liver and, therefore, delayed endosulfan elimination. A second fatal

outcome was reportedly caused by ingestion of alcohol and Posidor (20% endosulfan and 30%

dimethoate in xylene). Dimethoate is an organophosphate insecticide and a potent inhibitor of the

cholinesterase; it was considered by the authors to be much more acutely toxic than endosulfan (Demeter

et al. 1978). It is likely that the dimethoate and endosulfan acted synergistically. Because of the

limitations of these reports, such as multiple chemical exposure and unquantified doses, they provide only

suggestive evidence of an interaction.

Endosulfan has been documented to be an enzyme inducer of the cytochrome P450-dependent

monooxygenase system in several studies with experimental animals (Agarwal et al. 1978; Den Tonkelaar

and Van Esch 1974; Gupta and Gupta 1977a; Kiran and Varma 1988; Siddiqui et al. 1987a; Sriram and

Misra 1983). Vitamin A was found to inhibit the activity of cytochrome P450-dependent monooxygenase

systems induced by endosulfan. Specific parameters included microsomal protein and cytochrome P-450

contents and the activities of NADPH-cytochrome c reductase, aminopyrine *N*-demethylase, and aniline

hydroxylase (Sriram and Misra 1983). Endosulfan and pentobarbital have also demonstrated an

interactive effect. Endosulfan reduced the sleeping time induced in male rats by the administration of

sodium pentobarbitone (Balasubramamian et al. 1996). The induction of hepatic microsomal enzyme

activity and the enhanced metabolism of the pentobarbitone caused by endosulfan are the probable

mechanisms, as evidenced by reduced pentobarbitone concentrations in the blood and brain of

endosulfan-treated rats (Balasubramamian et al. 1996; Den Tonkelaar and Van Esch 1974; Gupta and

Gupta 1977a).

Phenobarbital has a mitigating effect on endosulfan toxicity in rats (Hoechst 1984e). The acute lethal

toxicity and neurotoxicity of endosulfan were decreased when phenobarbital (50–70 mg/kg) was given

following the appearance of toxic signs. In contrast, diazepam (2–60 mg/kg) delayed death but did not

prevent it. It is possible that phenobarbital-induced microsomal enzymes increased the metabolism of

endosulfan. In a more recent study, it was found that endosulfan promoted the hypnotic effects of

diazepam by prolonging the duration of the loss of righting reflex (Balasubramamian et al. 1996). The

authors speculated that endosulfan increased the potency of diazepam by increasing the binding sites for

diazepam in the brain synaptic membranes and/or promoted its biotransformation to a longer-acting

metabolite, oxazepam (Balasubramamian et al. 1996). In the same study, endosulfan promoted the

convulsant action of picrotoxin by shortening the convulsion latency and increasing convulsion

frequency. This was thought to have been due to endosulfan increasing the picrotoxin biotransformation

into the active compound (Balasubramamian et al. 1996). It is also possible that endosulfan enhanced the convulsant activity of picrotoxin because both compounds act at the GABA receptor.

Other studies have reported negative findings following the investigation of possible interactions between endosulfan and various compounds. In rats, treatment with endosulfan did not potentiate or aggravate the adverse liver effects induced by pretreatment with carbon tetrachloride (Dikshith and Raizada 1983). The *in vitro* estrogenic effects of endosulfan and dieldrin were found to be additive but not synergistic (Wade et al. 1997). Endosulfan estrogenicity in transfected yeast was inhibited by coexposure with other pesticides. Endosulfan induced human ER-mediated β-galactosidase (β-gal) activity at 100 µM in an estrogen-responsive reporter system in yeast, but did not induce human ER-mediated β-gal activity at #10 µM exposure levels (Ramamoorthy et al. 1997). Binary mixtures of endosulfan with chlordane, toxaphene, and dieldrin induced significantly less activity than endosulfan alone. No additive, antagonistic, or potentiating effects were observed in rats treated with endosulfan and metepa (a chemosterilant used to control insect vectors) (Nath et al. 1978).

Cytotoxic synergism between endosulfan and other organochlorine pesticides was demonstrated in an *in vitro* assay of growth inhibition of ER-negative SK-BR-3 human breast cancer cells, but was not demonstrated in a parallel assay using ER-positive MCF-7 cells (Hsu et al. 1998). The concentration at which 50% growth inhibition (IC_{50}) was achieved in SK-BR-3 cells was approximately 35 µM for endosulfan and dieldrin individually, but the IC_{50} was 0.1 µM for the mixture of the two pesticides. Similarly, the IC_{50} value for chlordane alone was 3.5 µM, but in combination with endosulfan, the IC_{50} was 0.2 µM. A lack of synergism between α- or β-endosulfan and dieldrin was also seen in a foci-induction assay with MCF-7 cells, in which the endosulfan isomers individually were weak inducers of foci at 10 µM (Arcaro et al. 1998).

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to endosulfan than will most persons exposed to the same level of endosulfan 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 endosulfan, or compromised function of organs affected by endosulfan. Populations who are at greater risk due to their unusually high exposure to endosulfan are discussed in Section 5.7, Populations With Potentially High Exposures.

The limited toxicity data available for endosulfan suggest that several subgroups of the population may be more susceptible to endosulfan exposure than the general population. These subgroups include the unborn and neonates; the elderly; and people with liver, kidney, or neurological diseases, - effects that have been better characterized in animal studies.

People in the general population with underlying or overt liver or kidney disease, may be at increased risk of adverse health effects following exposure to endosulfan. Evidence from animal studies suggests that endosulfan induces microsomal enzymes and causes histopathological changes in the liver (Dikshith et al. 1984; Gupta and Chandra 1977; Hoechst 1985a). Individuals with liver dysfunction may be more sensitive to the liver toxicity of endosulfan because they cannot detoxify endosulfan as efficiently as individuals with normal liver function. The observation of marked congestion and focal degenerative changes in the kidneys of animals who ingested endosulfan suggests that individuals with renal disease may be more susceptible to the toxic effects of this chemical (Gupta and Chandra 1977; Hack et al. 1995; NCI 1978). Although immunological effects of endosulfan have not been well characterized in animals studies, and altered immunocompetence was reported only in the Banerjee and Hussain (1986, 1987) studies, evidence from studies with other chemicals suggest that immunosupression is a sensitive end point in rodents and other animal species. Therefore, individuals with compromised immune systems such as AIDS patients, infants, and elderly people (who often exhibit a deficiency in immune response because of aging factors) may be more sensitive to endosulfan-induced immunotoxicity than members of the general population (Calabrese 1978). Limited data from animal studies indicate that hematologic effects may result from endosulfan exposure (Das and Garg 1981; Hoechst 1985a; Siddiqui et al. 1987b); therefore, individuals with preexisting anemia or other hematologic disorders may experience intensified systemic toxicity.

The central nervous system is a major target of endosulfan-induced toxicity in both humans and animals (Blanco-Coronado et al. 1992; Boyd and Dobos 1969; Boyd et al. 1970; Garg et al. 1980; Kiran and Varma 1988; Terziev et al. 1974). Therefore, individuals with seizure disorders, such as epilepsy, may be particularly susceptible because exposure to endosulfan may reduce the threshold for tremors, seizures, and other forms of neurotoxicity, as demonstrated in studies in rats (Gilbert and Mack 1995; Gilbert 1992).

Several studies conducted in experimental animals have demonstrated that diets deficient in protein exacerbate the oral toxicity of endosulfan (Boyd 1972; Boyd et al. 1970; Das and Garg 1981). These results suggest that people who consume low-protein diets, such as chronic alcoholics, dieters, food

faddists, various cults, some ethnic groups, the elderly, and some people living in depressed areas or underdeveloped countries, may be more susceptible to the toxic effects of endosulfan.

A detailed discussion of children's susceptibility can be found in Section 2.7, Children's Susceptibility.

2.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to endosulfan. 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 endosulfan. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to endosulfan:

> Ellenhorn, M.J. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. (2nd ed). Williams and Wilkins, Baltimore. 2047 pp.

2.11.1   Reducing Peak Absorption Following Exposure

Procedures that have been used in an acute exposure situation to limit absorption of endosulfan include the following. In inhalation and dermal exposures, the exposed person is first removed from the source of exposure. Endosulfan rapidly binds to the skin (Hoechst 1986); however, washing the skin thoroughly with mild soap and water may remove any unabsorbed material (Bronstein and Currance 1988; Howland 1990). Since leather absorbs pesticides, it is recommended that leather not be worn in the presence of pesticides and all contaminated leather should be discarded (HSDB 1999). After acute high-dose oral exposures, absorption from the gastrointestinal tract is limited by gastric lavage followed by administration of activated charcoal to adsorb residual endosulfan present in the gut (Blanco-Coronado et al. 1992; Chugh et al. 1998; Howland 1990; Shemesh et al. 1988). Gastric lavage may be indicated in patients who are comatose or at risk of convulsing (HSDB 1999). Oil-based cathartics may facilitate gastrointestinal absorption and, therefore, are not used (Haddad and Winchester 1990; Howland 1990).

2.11.2   Reducing Body Burden

The only relevant information located was that administration of cholestyramine resin may increase fecal excretion of endosulfan trapped in the enterohepatic circulation (Dreisbach and Robertson 1987; Howland 1990; HSDB 1999).

2.11.3   Interfering with the Mechanism of Action for Toxic Effects

The primary life-threatening effect produced following exposure to high levels of endosulfan is respiratory paralysis resulting from the development of seizures. Diazepam (Aleksandrowicz 1979; Blanco-Coronado et al. 1992), midazolam followed by a 30-minute loading dose of phenytoin (Cable and Doherty 1999), and phenobarbitone (Chugh et al. 1998) have been used to control tonic-clonic seizures following massive endosulfan exposures. Lorazepam has also been recommended (HSDB 1999). It is important to control seizures because the anoxia due to convulsions may be the primary cause of severe metabolic acidosis that occurs following acute poisoning (Blanco-Coronado et al. 1992). Fosphenytoin has been suggested if seizures are uncontrollable or recur after diazepam (HSDB 1999). A study using rats showed that phenobarbital is substantially more effective in reducing the neurotoxicity and mortality of endosulfan than is diazepam (Hoechst 1984e). Thus, phenobarbital may be more effective in cases of human exposure as well.

No treatment strategies were located for chronic low-level exposures to endosulfan.

2.12 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 endosulfan 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 endosulfan.

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.

2.12.1 Existing Information on Health Effects of Endosulfan

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to endosulfan are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of endosulfan. 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* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Most of the literature reviewed concerning the health effects of endosulfan in humans described case reports of occupational exposure and accidental or intentional ingestion of endosulfan. The cases of occupational exposure to endosulfan concerned exposures of acute-to-intermediate durations, and the cases of oral exposure were exclusively acute-duration exposure situations. The predominant route of exposure in the occupational case reports is believed to be inhalation, but the possibility of some degree of dermal exposure cannot be ruled out. The information on human exposure is limited because the possibility of concurrent exposure to other pesticides or other toxic substances cannot be excluded. In addition, the precise duration and level of exposure to endosulfan generally cannot be quantified from the information presented in these reports.

The database for the health effects of endosulfan following ingestion in experimental animals is substantial. However, as can be seen in Figure 2-5, somewhat less information is available on the effects of inhalation and dermal exposure to endosulfan in animals. Furthermore, the health effects associated with acute- and intermediate-duration inhalation and dermal exposure are more fully characterized than those associated with chronic inhalation or dermal exposure. There is no evidence suggesting that the toxicity of endosulfan is route-specific. However, ingested endosulfan should reach the liver sooner.

People living near hazardous waste sites may be exposed to endosulfan primarily via dermal contact with or ingestion of contaminated soils since endosulfan is found bound to soil particles. Another possible

Figure 2-5. Existing Information on Health Effects of Endosulfan

Human

Animal

● Existing Studies

mechanism for oral exposure to endosulfan is the ingestion of pesticide-laden dust from a waste site or treated field carried by the wind and deposited on garden crops. Ingestion of contaminated water is not expected to be a significant route of exposure since endosulfan is not very water soluble and is generally not found in groundwater. Likewise, inhalation exposure to endosulfan via volatilization from contaminated media is not a major route of exposure since endosulfan is not very volatile. For the general population, the primary route of exposure to endosulfan is via ingestion of residues on contaminated foods. Therefore, information on the toxicity of endosulfan following ingestion and dermal exposure is most relevant for individuals living in the vicinity of hazardous waste sites.

2.12.2   Identification of Data Needs

Acute-Duration Exposure.   Information is available regarding the effects of acute-duration exposure in humans following inhalation, oral, and dermal exposure to high levels of endosulfan (Aleksandrowicz 1979; Bernardelli and Gennari 1987; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Demeter and Heyndrickx 1978; Ely et al. 1967; Lo et al. 1995; Schuman and Dobson 1985; Shemesh et al. 1988; Singh et al. 1992; Terziev et al. 1974). In animals, information is available following exposures by all three routes (Boyd and Dobos 1969; Boyd et al. 1970; Den Tonkelaar and Van Esch 1974; FMC 1958, 1959a, 1972, 1980a, 1980b; Gilbert and Mack 1995; Gupta and Chandra 1975; Gupta and Gupta 1977a; Gupta et al. 1978, 1981; Hoechst 1966a, 1966b, 1970, 1975, 1983a, 1984e, 1988c, 1989b; Industria Prodotti Chimici 1975; Kiran and Varma 1988; Lakshmana and Raju 1994; Lindquist and Dahm 1957; Misra et al. 1980; Nicholson and Cooper 1977; Siddiqui et al. 1987b; Terziev et al. 1974; Wilson and LeBlanc 1998). Endosulfan may be lethal to humans and animals by all routes of exposure studied, depending on dose (Bernardelli and Gennari 1987; Boereboom et al. 1998; Blanco-Coronado et al. 1992; Boyd and Dobos 1969; Boyd et al. 1970; Demeter and Heyndrickx 1978; FMC 1980a; Gupta and Chandra 1975; Gupta et al. 1978, 1981; Hoechst 1966a, 1966b, 1975, 1983a, 1989b; Lindquist and Dahm 1957; Lo et al. 1995; Nicholson and Cooper 1977; Terziev et al. 1974). The main target of toxicity in humans and animals following acute, high-level exposure by any route is the central nervous system (Aleksandrowicz 1979; Boereboom et al. 1998; Boyd and Dobos 1969; Boyd et al. 1970; Cable and Doherty 1999; Ceron et al. 1995; Chugh et al. 1998; Ely et al. 1967; FMC 1958, 1959a, 1980a, 1981; Gilbert and Mack 1995; Gupta and Chandra 1975; Hoechst 1970, 1975, 1983a, 1984e, 1989b; Kiran and Varma 1988; Nicholson and Cooper 1977; Shemesh et al. 1988; Terziev et al. 1974). Limited information regarding adverse systemic effects has been reported in humans (Blanco-Coronado et al. 1992; Boereboom et al. 1998; Cable and Doherty 1999; Chugh et al. 1998; Demeter and Heyndrickx 1978; Shemesh et al. 1988; Terziev et al. 1974). However, the liver and kidney also appear to be targets of endosulfan toxicity following acute

exposure in experimental animals (with effects on the respiratory and cardiovascular systems that are most likely secondary to central nervous system toxicity) (Boyd et al. 1970; Den Tonkelaar and Van Esch 1974; FMC 1958, 1959a, 1972, 1980a; Gupta and Chandra 1975; Gupta and Gupta 1977a; Hoechst 1970, 1983a, 1989b; Industria Prodotti Chimici 1975; Kiran and Varma 1988; Misra et al. 1980; Siddiqui et al. 1987b; Terziev et al. 1974). No conclusive evidence of developmental toxicity has been presented, mainly because of the questionable quality of the studies available and/or observations of developmental toxicity at maternally toxic doses of endosulfan (FMC 1980b, 1981; Gupta et al. 1978; Hoechst 1982, 1984a).

The data in animals are insufficient to derive an acute inhalation MRL because serious effects were observed at the lowest dose tested (Hoechst 1983a). No acute oral MRL was derived for the same reason. The available toxicokinetic data are not adequate to predict the behavior of endosulfan across routes of exposure. However, the limited toxicity information available does indicate that similar effects are observed (i.e., death, neurotoxicity) in both animals and humans across all routes of exposure, but the concentrations that cause these effects may not be predictable for all routes. Most of the acute effects of endosulfan have been well characterized following exposure via the inhalation, oral, and dermal routes in experimental animals, and additional information on the acute effects of endosulfan does not appear necessary. However, further well conducted developmental studies may clarify whether this chemical causes adverse developmental effects.

Intermediate-Duration Exposure. No information is available on the toxicity of endosulfan to humans following intermediate-duration exposure by the oral route. Only very limited information is available regarding intermediate-duration occupational exposure (Aleksandrowicz 1979). Information is available regarding the effects of intermediate-duration exposure in animals following inhalation, oral, and dermal exposure (Banerjee and Hussain 1986, 1987; Das and Garg 1981; Dikshith et al. 1984, 1988; Garg et al. 1980; Gupta and Chandra 1977; Gupta and Gupta 1977a; Hoechst 1982, 1983b, 1984a, 1984b, 1984c, 1985a, 1985b, 1985c, 1985d, 1987, 1989c; Vos et al. 1982). The targets of toxicity in animals following intermediate exposure by any route appear to be the liver, kidney, reproductive (testes), immune systems, and nervous system (Das and Garg 1981; Dikshith et al. 1984, 1988; Gilbert 1992; Gupta and Chandra 1977; Gupta and Gupta 1977a; Hoechst 1983b, 1984b, 1985a, 1985b, 1985c, 1985d, 1987, 1989c; Lakshmana and Raju 1994; Paul et al. 1995; Sinha et al. 1997; Vos et al. 1982). The data in animals are not sufficient to derive an intermediate-duration inhalation MRL. However, sufficient data were available to derive an intermediate-duration oral MRL. The intermediate-duration oral MRL of 0.005 mg/kg/day was based on immunotoxicity in rats (Banerjee and Hussain 1986). The available

toxicokinetic data are not adequate to predict the behavior of endosulfan across routes of exposure. However, the limited toxicity information available does indicate that similar effects are observed (i.e., hepatic, neurological) in animals across all routes of exposure, but the concentrations that cause these effects may not be possible to predict for all routes. Since the effects of intermediate-duration exposure to endosulfan have been well characterized in experimental animals, additional information on the effects of intermediate-duration exposure to endosulfan is not necessary.

Chronic-Duration Exposure and Cancer.   No information is available on the toxicity of endosulfan to humans following chronic-duration exposure by any route. Also no information is available regarding chronic-duration inhalation or dermal exposure in experimental animals. Information is, however, available regarding the effects of chronic-duration exposure in animals following oral exposure (FMC 1959a, 1959b, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989a, 1989c; NCI 1978). The targets of toxicity in animals following chronic oral exposure appear to be the liver and kidney. A chronic-duration oral MRL of 0.002 mg/kg/day was based on increased serum alkaline phosphatase in dogs consuming endosulfan in the diet for 1 year (Hoechst 1989c). Since no data are available for the inhalation route of exposure, a chronic inhalation MRL could not be derived. The available toxicokinetic data are not adequate to predict the behavior of endosulfan across routes of exposure. However, the limited toxicity information available for acute- and intermediate-duration exposures does indicate that similar effects are observed in animals, but the concentrations that cause these effects may not be possible to predict for all routes. Since the effects (or lack thereof) of chronic-duration oral exposure to endosulfan have been well characterized in experimental animals, and since inhalation is not expected to be a major route of exposure for individuals living in the vicinity of hazardous waste sites because of endosulfan's low volatility, additional information on the effects of chronic-duration oral exposure to endosulfan is not necessary. However, a chronic-duration dermal study might be useful to identify more accurately the end points of toxicity and the concentrations at which these effects are observed.

No studies or reports of cancer in humans associated with exposure to endosulfan by any route have been found. The carcinogenicity of endosulfan has been studied in chronic oral bioassays using rats (FMC 1959b; Hack et al. 1995; Hoechst 1989a; NCI 1978) and mice (Hack et al. 1995; Hoechst 1988b; NCI 1968, 1978). The available data in experimental animals were negative or inconclusive. The limited information available on the toxic effects of dermally administered endosulfan suggests that this chemical behaves similarly across both the oral and dermal routes of exposure. However, a study assessing the neoplastic potential of chronic-duration dermal exposure to endosulfan might be valuable.

Genotoxicity.   No reliable data on humans exist to indicate whether endosulfan may act by a genotoxic mechanism. The results from available *in vivo* animal studies and *in vitro* studies are mixed, but generally provide evidence that this compound is mutagenic, clastogenic, and induces effects on cell cycle kinetics in two different mammalian species (Dikshith and Datta 1978; Dikshith et al. 1978; Dorough et al. 1978; Dubois et al. 1996; Dzwonkowska and Hubner 1986; Hoechst 1984d, 1988d; Kurinnyi et al. 1982; L'Vova 1984; McGregor et al. 1988; Moriya et al. 1983; Pednekar et al. 1987; Sobti et al. 1983; Usha Rani and Reddy 1986; Usha Rani et al. 1980; Velazquez et al. 1984; Yadav et al. 1982). Some positive results may be suspect, however, because some endosulfan formulations contained epichlorohydrin, a known genotoxic chemical, as a stabilizer. Thus, additional testing verifying the positive results reported by Dikshith and Datta (1978), Dikshith et al. (1978), Dzwonkowska and Hubner (1986), Kurinnyi et al. (1982), L'Vova (1984), Usha Rani and Reddy (1986), Usha Rani et al. (1980), and Velazquez et al. (1984) would be valuable. Also, *in vivo* tests of chromosomal aberrations in exposed human populations would provide valuable information on the genotoxic potential of endosulfan in humans.

Reproductive Toxicity.   No information is available on humans to indicate that endosulfan affects reproductive function. Studies have reported that oral endosulfan had no effect on reproductive performance in rats (Dikshith et al. 1984; Hoechst 1982, 1984a). At higher doses than those used in these studies, adverse effects on the testes were observed in male rats that ingested endosulfan, but no assessment of reproductive performance was made (Gupta and Gupta 1977a; NCI 1978). More recent studies that looked at possible effects of endosulfan on spermatogenesis found reduced sperm counts and sperm abnormalities in rats and mice in intermediate-duration studies (Khan and Sinha 1996; Sinha et al. 1995, 1997). Testicular atrophy was observed in rats treated with relatively high doses of endosulfan in the diet for up to 82 weeks (NCI 1978). No information is available on effects on reproductive performance of inhaled or dermally administered endosulfan. Although the available reproductive studies indicate that endosulfan has no adverse effects on reproductive performance in animals following oral exposure, further studies are necessary to clarify the issue, since this apparently contradicts the more recent findings of altered spermatogenesis at comparable dose levels. The oral route of exposure is chosen for further testing because it is most relevant for humans living in the vicinity of hazardous waste sites, adverse testicular effects have been observed following oral exposure. The limited information available on the toxic effects of dermally administered endosulfan suggests that this chemical behaves similarly across both routes of exposure.

Developmental Toxicity.   No information is available regarding the effects of endosulfan on human fetal development. No conclusive evidence of developmental toxicity has been presented, mainly because of the questionable quality of the studies available and/or observations of developmental toxicity at maternally toxic doses of endosulfan (FMC 1980b, 1981; Gupta et al. 1978; Hoechst 1982, 1984a). Further testing would be helpful to verify the effects that have been observed and to delineate clearly the doses at which these effects may be expected to occur. Any further testing should be by the oral route of exposure because it is the most relevant for humans living in the vicinity of hazardous waste sites, adverse developmental effects have been observed following oral exposure, and the limited information available on the toxic effects of dermally administered endosulfan suggests that this chemical behaves similarly across both routes of exposure. There is no information about postnatal exposures and any associated postnatal developmental effects.

Immunotoxicity.   Limited information is available regarding the effects of endosulfan on the human immune system. However, specially designed studies using rats indicate that both humoral and cellular immune responses are depressed by ingested endosulfan at doses that do not induce any overt signs of toxicity (Banerjee and Hussain 1986, 1987). *In vitro* studies support the possibility that endosulfan affects immune system function (Das et al. 1988). These results demonstrate that immunotoxicity may be a more sensitive end point of endosulfan-induced toxicity than other end points, and humans may be at risk for adverse immune effects following exposure to endosulfan. An intermediate-duration oral MRL was derived based on the observation of depressed immune responses (Banerjee and Hussain 1987). Since the limited information available on the effects of dermally administered endosulfan suggests that this chemical behaves similarly across both routes of exposure and that adverse effects on immune function end points have also been observed *in vitro*, there is no reason to suspect that the immunotoxic effects observed following oral exposure are route-specific. Tests of immunologic function in exposed human populations would provide information as to whether immunosuppression also occurs in humans or whether this effect may be species-specific. Further studies investigating the mechanism of endosulfan-induced immunotoxicity would be helpful since this information may help identify special populations at risk for such effects. In addition, a determination of the threshold dose at which immunotoxic effects occur would be helpful in assessing the risk posed to humans exposed to endosulfan.

Neurotoxicity.   Information indicates that the central nervous system is the major target of endosulfan-induced toxicity in humans and animals following acute exposure by any route (Aleksandrowicz 1979; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Boyd and Dobos 1969; Boyd et al. 1970; Cable and Doherty 1999; Chugh et al. 1998; Ely et al. 1967; FMC 1958, 1959a, 1980a; Gilbert and Mack 1995;

Gupta and Chandra 1975; Hoechst 1970, 1975, 1983a, 1984e, 1989b; Kiran and Varma 1988; Lakshmana and Raju 1994; Lo et al. 1995; Nicholson and Cooper 1977; Pradhan et al. 1997; Shemesh et al. 1988; Terziev et al. 1974). The most prominent signs of acute exposure to endosulfan in humans (oral and occupational) and animals (by all routes) are hyperactivity, tremors, decreased respiration, dyspnea, salivation, and tonic-clonic convulsions, which can lead to death. Neurotoxic effects are not always seen following intermediate- or chronic-duration exposure; however, chronic effects were observed in dogs (Hoechst 1989c). Also, two reports indicated that persistent cognitive brain damage may result following acute exposure (Aleksandrowicz 1979; Shemesh et al. 1988). More recent studies in animals have shown changes in neurotransmitter levels and alterations in neurobehavioral processes after exposure to endosulfan (Lakshmana and Raju 1994; Paul et al. 1995). Since the limited information available on the effects of dermally administered endosulfan suggests that this chemical behaves similarly across both routes of exposure, and neurotoxicity has been observed following inhalation exposure as well, there is no reason to suspect that the neurological effects observed following oral exposure are route-specific. Further studies investigating the mechanism for endosulfan-induced neurotoxicity would be helpful since this information might help identify special populations at risk for such effects. Furthermore, although neurotoxic effects have not generally been observed in intermediate- or chronic-duration animal studies, sensitive neurological functional end points (e.g., various reflexes, grip strength, sensory function, motor activity, or nerve conduction velocity), extensive histologic neuropathological evaluations of brain, spinal cord, and peripheral nerves, or evaluations of higher functions such as learning and memory have not been done for long-term exposures to endosulfan. This information would be useful to assess the potential for this chemical to cause permanent neurological damage.

Epidemiological and Human Dosimetry Studies.   Most of the literature reviewed concerning the health effects of endosulfan in humans described case reports of occupational exposure or accidental or intentional ingestion of endosulfan (Aleksandrowicz 1979; Bernardelli and Gennari 1987; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Cable and Doherty 1999; Chugh et al. 1998; Demeter and Heyndrickx 1978; Ely et al. 1967; Lo et al. 1995; Shemesh et al. 1988; Terziev et al. 1974). In one case-control study of the relation between occupational exposures to various suspected estrogenic chemicals and the occurrence of breast cancer, the breast cancer odds ratio was not significantly elevated above unity (OR=1.3; 95% CI=0.2–1.2) for occupational exposure to endosulfan compared to unexposed controls (Aschengrau et al. 1998). However, the study was limited by very small sample sizes, and coexposure to other unreported chemicals also occurred. The predominant routes of exposure in the occupational studies are believed to be inhalation and dermal (workers involved in pesticide manufacture, formulation, and application). The information on human exposure is limited because of the possibility of

concurrent exposure to other pesticides or other toxic substances, and the duration and level of exposure to endosulfan generally cannot be quantified from the information presented in these reports. The most likely identifiable subpopulation exposed to endosulfan is pesticide applicators or individuals involved in the production and formulation of endosulfan. Well designed epidemiological studies of these exposed workers, specifically examining the effects of endosulfan on the liver, kidney, reproductive organ of males, and immune system would be useful. Results may show whether these organs and/or systems are adversely affected in humans since they appear to be the major end points of toxicity in experimental animals. Absorption of endosulfan by the subjects of such a study should be confirmed by analysis of blood and urine for endosulfan isomers and endosulfan sulfate. If endosulfan causes adverse effects in any of these target organs or systems, then these end points may be useful tools to monitor endosulfan exposure in individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect.

Exposure. Known biomarkers of exposure to endosulfan include the measurement of endosulfan or its metabolites in tissue and excreta (Deema et al. 1966; Dorough et al. 1978; Gorbach et al. 1968); these measurements can indicate whether absorption of endosulfan has occurred. The presence of the parent compound and its metabolites are specific biomarkers for endosulfan exposure. However, no studies are available that quantify the concentrations of endosulfan or its metabolites in relation to specific environmental exposure levels. Since endosulfan induces cytochrome P450-dependent monooxygenases (Agarwal et al. 1978), the quantification of these specific enzymes may indicate that exposure to endosulfan has occurred. Blood tests, such as decay curves for aminopyrine in plasma, which are semiquantitative indices of liver enzyme induction, have been used successfully in the past to demonstrate enzyme induction in pesticide-exposed workers. Because numerous chemicals found at hazardous waste sites also induce these hepatic enzymes, these measurements are not specific for endosulfan exposure. However, measurements of enzyme activity, together with the detection of the parent compound or its metabolites in tissue or excreta, can be useful indicators of exposure. All of these potential biomarkers require further verification in epidemiological studies. Further studies with focus on the development of methods to separate and measure the estrogenicity of endosulfan in *in vitro* assays would be valuable since these assays are more sensitive and discriminative than other conventional biomarkers. Preliminary results have been presented by Sonnenschein et al. (1995).

Effect. Histopathological and degenerative changes in liver and kidney cells, increased hepatic enzyme activities (aminopyrine *N*-demethylase and aniline hydroxylase), and decreased red blood cells,

hemoglobin, packed cell volume, IgG, IgM, and γ-globulin levels have been detected in animals
following exposure to endosulfan and thus may be considered biomarkers of effects (Banerjee and
Hussain 1986, 1987; Das and Garg 1981; Hoechst 1985a; Misra et al. 1980; Siddiqui et al. 1987a, 1987b).
These parameters can be measured in liver tissue, kidney tissue, and serum. They are generally
nonspecific for endosulfan exposure, because numerous other chemicals elicit changes in these end
points. All of the endpoints are useful for measuring short- or intermediate-duration exposure, but only
kidney effects have been seen following long-term exposure in animals (FMC 1959b; Hack et al. 1995;
Hoechst 1989a; NCI 1978). Therefore, there is no need for additional biomarkers of effects for
endosulfan, although development of specific, easily measured biomarkers of exposure would be useful to
monitor the endosulfan levels in the human population following long-term exposure to endosulfan.

Absorption, Distribution, Metabolism, and Excretion.   Indirect evidence describing the
occurrence of toxic effects following exposure to endosulfan by all three routes (inhalation, oral, and
dermal) indicates that this compound is absorbed by both humans and animals (Bernardelli and Gennari
1987; Boereboom et al. 1998; Blanco-Coronado et al. 1992; Cable and Doherty 1999; Chugh et al. 1998;
Deema et al. 1966; Demeter and Heyndrickx 1978; Dorough et al. 1978; Ely et al. 1967; Gorbach et al.
1968; Gupta and Gupta 1979; Nath and Dikshith 1979; Nicholson and Cooper 1977; WHO 1984). No
information is available to assess the relative rates and extent of endosulfan absorption following
inhalation or oral exposure in humans or animals or dermal exposure in humans. Limited data are
available that assess the relative rates and extent of endosulfan absorption following dermal exposure in
animals (Hoechst 1986). The data indicate that endosulfan binds to the skin of rats and is only slowly
absorbed in the body, with absorption rates decreasing with time. Only about 25% of the bound material
was absorbed into the body by 24 hours (Hoechst 1986). Quantitative information that describes the rate
and extent of endosulfan absorption following inhalation, oral, and dermal exposure in humans and/or
animals would be useful to assess more fully the hazard presented by exposure to endosulfan at various
levels from these different routes. In addition, studies investigating the efficiency of endosulfan
absorption from dust particles in the gut would be helpful in estimating the hazard posed by this major
route of exposure.

Limited information from case reports is available regarding the distribution of endosulfan in humans
following oral exposure (Boereboom et al. 1998; Coutselinis et al. 1978; Demeter and Heyndrickx 1978;
Demeter et al. 1977). Isomers and metabolites of endosulfan were detected in the fat of 30–40% of
children hospitalized in agricultural regions of Spain, demonstrating that endosulfan accumulates in
adipose tissue of children after presumably repeated dietary exposure (Olea et al. 1999). Animal studies

describe the distribution of endosulfan following both short-term and long-term oral exposure (Ansari et al. 1984; Braun and Lobb 1976; Dikshith et al. 1984; Gupta 1978; Hoechst 1987; Nath and Dikshith 1979). The available evidence indicates that endosulfan tends to distribute initially to the fatty tissues but accumulates in the kidney with prolonged exposure. No quantitative information is available on the distribution of endosulfan following inhalation exposure, and three studies are available that describe the distribution of endosulfan in animals after dermal exposure (Dikshith et al. 1984; Hoechst 1986; Nicholson and Cooper 1977). Although limited data are available on the rate and extent of endosulfan distribution, the available information indicates the kidney appears to be the organ with the greatest tissue accumulations following both short- and long-term exposure. However, more information on the distribution of endosulfan in humans and animals following exposure to all three routes would be useful in ascertaining whether there are differences across routes of exposure with respect to distribution.

No information is available regarding the metabolism of endosulfan in humans. However, the metabolic pathway of this chemical has been well characterized in several species of experimental animals (Deema et al. 1966; Dorough et al. 1978; Gorbach et al. 1968; WHO 1984). The data indicate that metabolism of endosulfan occurs in both the liver and kidney (Agarwal et al. 1978; Deema et al. 1966; Hoechst 1987; Siddiqui et al. 1987a; Tyagi et al. 1984). Limited data from an acute dermal study showing a dose-related decrease in excretion with increasing dose indicate that the metabolism of endosulfan is saturable (Hoechst 1986).

Information is available regarding excretion of endosulfan and metabolites in humans. Blanco-Coronado et al. (1992) measured total endosulfan in the urine of poisoned individuals shortly after poisoning occurred. However, it could not be ascertained whether the urine was a major or minor excretion route. α-Endosulfan, β-endosulfan, and/or metabolites were present in the urine of humans after intentional oral exposure (Boerebomm et al. 1998) and after occupational exposure either with (Arrebola et al. 1999) or without (Vidal et al. 1998) protective clothing.

No information was located regarding excretion of endosulfan residues in animals following inhalation exposure. Limited data were located regarding excretion in animals following dermal exposure (Hoechst 1986). The routes and extent of endosulfan excretion following oral exposure in animals have been characterized (Deema et al. 1966; Dorough et al. 1978; Gorbach et al. 1968). More data are needed regarding the characterization of the metabolites and the extent of endosulfan excretion following inhalation and dermal exposure in both humans and animals.

Practically all toxicokinetic properties reported were based on results from acute exposure studies. Generally, no information was available regarding intermediate or chronic exposure to endosulfan. Since endosulfan is an enzyme inducer (Siddiqui et al. 1987a; Tyagi et al. 1984), the kinetics of metabolism during chronic exposure probably differ from those seen during acute exposure. Similarly, excretion kinetics may differ with time and dose. Thus, additional studies on the metabolism and excretion of endosulfan during intermediate or chronic exposure would be useful to assess the potential for toxicity following longer-duration exposures. No PBPK models have been developed for endosulfan.

Comparative Toxicokinetics.   Most of the reliable data available on the toxicity of endosulfan in humans are from acute exposures where neurotoxicity is the end point of concern (Aleksandrowicz 1979; Ely et al. 1967; Shemesh et al. 1988; Terziev et al. 1974). The same spectrum of effects is seen in animals after acute exposure (Boyd and Dobos 1969; Boyd et al. 1970; Ceron et al. 1995; FMC 1958, 1959a, 1980a; Gilbert and Mack 1995; Gupta and Chandra 1975; Hoechst 1970, 1975, 1983a, 1984e, 1989b; Kiran and Varma 1988; Nicholson and Cooper 1977; Terziev et al. 1974). However, effects on the gastrointestinal tract, liver, kidney, testes, and hematopoietic and immune systems have also been observed in animals (Banerjee and Hussain 1986, 1987; Boyd et al. 1970; Das and Garg 1981; Den Tonkelaar and Van Esch 1974; Dikshith et al. 1984; FMC 1958, 1959a, 1959b, 1980a; Gupta and Chandra 1977; Gupta and Gupta 1977a; Hoechst 1970, 1985a, 1989a, 1989c; Misra et al. 1980; NCI 1978; Siddiqui et al. 1987b; Terziev et al. 1974), and these effects have generally not been observed (or studied) in humans. No toxicokinetic studies have been performed in humans, but there is information on some toxicokinetic aspects of endosulfan in several species of experimental animals (rats, mice, rabbits, and sheep), and there appears to be little difference between the species (Ansari et al. 1984; Braun and Lobb 1976; Dikshith et al. 1984; Deema et al. 1966; Dorough et al. 1978; Gorbach et al. 1968; Gupta 1978; Nath and Dikshith 1979; Nicholson and Cooper 1977; WHO 1984). However, substantial differences exist in the doses required to produce toxicity in male and female rats in acute- (Hoechst 1985c, 1985d, 1990) and intermediate-duration studies (Paul et al. 1995). Differences in the rates of excretion were proposed to account for the differences in sensitivity of male and female rats (Dikshith et al. 1984), but excretion was not directly studied by these authors. Therefore, further studies evaluating the reason for this difference may provide valuable information for estimating acutely toxic doses in humans.

Methods for Reducing Toxic Effects.   There is good information on the procedures that may be used to limit absorption of endosulfan following ingestion (Dreisbach and Robertson 1987; Howland 1990). However, limited information exists for removing endosulfan that has bound to the skin

(Bronstein and Currance 1988; Howland 1990). Animal studies indicate that although endosulfan rapidly binds to the skin, its absorption into the bloodstream from the skin is much slower (Hoechst 1986). The slow rate of entry into the bloodstream could provide a good opportunity to limit toxic effects resulting from dermal exposure if a method to remove endosulfan from the skin were found. Earlier data in rats suggested that phenobarbital may be more effective at reducing the acute neurotoxicity and lethality of endosulfan than diazepam (Hoechst 1984e). A more recent 90-day study found that endosulfan increased the potency of diazepam, possibly by increasing the binding sites for diazepam of brain synaptic membranes or by promoting its biotransformation to a longer acting metabolite, oxazepam (Balasubramaniam et al. 1996). Therefore, additional information regarding differences in the effectiveness of these therapies in human exposure situations would also be valuable. In cases of acute intoxication it is critical to control the convulsive activity since this may lead to severe metabolic acidosis and hyperglycemia (Blanco-Coronado et al. 1992). Additional information on the mitigation of the long-term effects of endosulfan (i.e., renal and hepatic toxicity) would also be valuable.

Children's Susceptibility.   The information on health effects of endosulfan 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. No reports of adverse effects in endosulfan-exposed children were found, but it is reasonable to assume that children will exhibit similar signs and symptoms to those in adults under similar exposure conditions. Some studies in animals have provided evidence that young animals respond to endosulfan differently than adult animals (Kiran and Varma 1988; Lakshmana and Raju 1994; Sinha et al. 1995, 1997; Zaidi et al. 1985), 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 endosulfan either prenatally or postnatally. Studies in animals have provided inconclusive evidence (FMC 1980b, 1981; Gupta et al. 1978; Hoechst 1982, 1984a), and further well-conducted research would be helpful to clarify this issue.

No data were located concerning whether pharmacokinetics of endosulfan in children are different from adults. There are no adequate data to determine whether endosulfan or its metabolites can cross the placenta. Studies in animals addressing these issues would provide valuable information. Although endosulfan has been detected in human milk (Lutter et al. 1998), studies in animals showed very little accumulation of endosulfan residues in breast milk (Gorbach et al. 1968; Indraningsih et al. 1993), which

is consistent with the rapid elimination of endosulfan from tissues and subsequent excretion via feces and urine. There are no PBPK models for endosulfan in either adults or children. There is no information to evaluate whether absorption, distribution, metabolism, or excretion of endosulfan in children is different than in adults.

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

Child health data needs relating to exposure are discussed in 5.8.1, Identification of Data Needs: Exposures of Children.

2.12.3   Ongoing Studies

The following ongoing research project was identified in FEDRIP (1999).

Dr. John E. Casida from the University of California Berkeley is investigating the fundamental basis for the selective toxicity of insecticides, including endosulfan, acting at the gamma-aminobutyric acid (GABA) receptor of mammals and insects. The research is sponsored by the National Institute of Environmental Health Sciences.

Dr. G. A. LeBlanc of North Carolina State University is evaluating effects of potentially endocrine-disrupting chemicals, including endosulfan, on steroid hormone biotransformation/elimination processes in daphnids, fish, and mice, and is constructing models of the processes. The work is being funded by the U.S. Department of Agriculture.

Dr. D.E. Woolley from the University of California, Davis, is conducting research aimed at determining the immediate and long-term effects of exposure to environmental toxicants, especially insecticides, in order to obtain basic toxicological data important for determining mechanisms of action in the intact animal, to evaluate the hazard posed by these agents for the health of man and other nontarget mammalian species. The effects of several organochlorine and other insecticides (endosulfan among them) on physiological, neurological, neurochemical and behavioral end points will be determined in rats, as an

example of a mammalian nontarget species. Dr. Woolley's research is sponsored by the U.S. Department
of Agriculture.

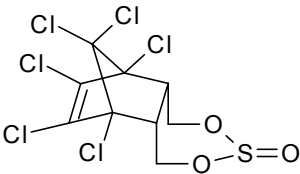# 3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Technical-grade endosulfan contains at least 94% of two pure isomers, α- and β-endosulfan (Maier-Bode 1968; NRCC 1975). The α- and β-isomers of endosulfan are present in the ratio of 7:3, respectively. Technical-grade endosulfan may also contain up to 2% endosulfan alcohol and 1% endosulfan ether. Endosulfan sulfate is a reaction product found in technical endosulfan; it is also found in the environment due to photolysis and in organisms as a result of oxidation by biotransformation (EPA 1979; Coleman and Dolinger 1982). The chemical formula, structure, synonyms, and identification numbers for endosulfan, α-endosulfan, β-endosulfan, and endosulfan sulfate are listed in Tables 3-1, 3-2, 3-3, and 3-4, respectively.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of endosulfan, α-endosulfan, β-endosulfan, and endosulfan sulfate are listed in Tables 3-5, 3-6, 3-7, and 3-8, respectively. It should be noted that β-endosulfan is slowly converted to α-endosulfan (Hapeman et al. 1997; Rice et al. 1997).
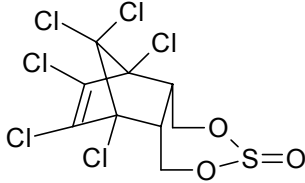
Table 3-1. Chemical Identity of Endosulfan

Characteristic	Information	Reference
Chemical name	Endosulfan	Budavari 1996
Synonym(s)	6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzo(e)-dioxathiepin-3-oxide; Endosulfan technical; 5-Norbornene-2,3-dimethanol-1,4,5,6,7,7-hexachlorocyclic sulfite	HSDB 1999; IRIS 2000; Budavari 1996
Registered trade name(s)	Thiodan; Thionex; Thionate Malix; HOE 2671; FMC 5462; Cyclodan; Thifor; Beosit; Chlorthiepin; Endocide; Endosulphan	IRIS 1999; Suntio et al. 1988; Tomlin 1994; Budavari 1996
Chemical formula	$C_9H_6Cl_6O_3S$	Budavari 1996
Chemical structure		EPA 1984

Identification numbers:

CAS registry	115-29-7	Budavari 1996
NIOSH RTECS	RB9275000	HSDB 1999
EPA hazardous waste	P050	HSDB 1999
OHM/TADS	7216559	HSDB 1999
DOT/UN/NA/IMCO shipping	2761	HCDB 1986
HSDB	390	HSDB 1999
NCI	C00566	HSDB 1999

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 Substance 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

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Chemical Identity of α-Endosulfan

Characteristic	Information	Reference
Chemical name	α-Endosulfan	Tomlin 1994
Synonym(s)	Endosulfan I; Endosulfan A; 6,9-Methano-2,4,3-benzodioxathiepin, 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-, 3-oxide (3α, 5a β, 6α, 9a α, 9β)-	RTECS 1989; Tomlin 1994
Registered trade name(s)	α-Benzoepin; α-Thiodan; Thionex	RTECS 1989
Chemical formula	$C_9H_6Cl_6O_3S$	HSDB 1999
Chemical structure		EPA 1984

Identification numbers:

CAS registry	959-98-8	Tomlin 1994
NIOSH RTECS	RB9275100	NIOSH 1997
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	

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 Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-3. Chemical Identity of β-Endosulfan

Characteristic	Information	Reference
Chemical name	β-Endosulfan	Tomlin 1994
Synonym(s)	Endosulfan II; Endosulfan B; 6,7,9,10,10-Hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodiozathiepin-3-oxide, (3α, 5aα, 6β, 9β, 9aα)-	CHEMLINE 1989; Tomlin 1994
Registered trade name(s)	α-Benzoepin; α-Thiodan; Thionex	CHEMLINE 1989
Chemical formula	$C_9H_6Cl_6O_3S$	HSDB 1999
Chemical structure		EPA 1984

Identification numbers:		
CAS registry	33213-65-9	Tomlin 1994
NIOSH RTECS	No data	
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	

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 Substance 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
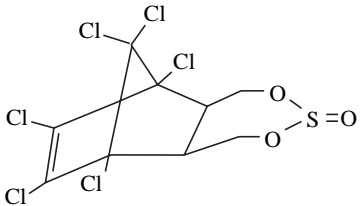
3. CHEMICAL AND PHYSICAL INFORMATION
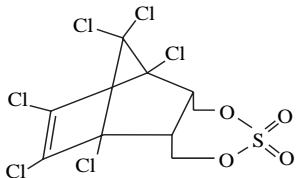
Table 3-4. Chemical Identity of Endosulfan Sulfate

Characteristic	Information	Reference
Chemical name	Endosulfan sulfate	Budavari 1996
Synonym(s)	6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-hexahydro-,6,9-methano-2,4,3-benzodiozathiepin-3,3-dioxide	HSDB 1999
Registered trade name(s)	No data	
Chemical formula	$C_9H_6Cl_6O_4S$	HSDB 1999
Chemical structure		EPA 1984
Identification numbers:		
CAS registry	1031-07-8	HSDB 1999
NIOSH RTECS	RB9150000	RTECS 1989
EPA hazardous waste	No data	
OHM/TADS	8300205	OHM/TADS 1989
DOT/UN/NA/IMCO shipping	No data	
HSDB	6180	HSDB 1999
NCI	No data	

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

Table 3-5. Physical and Chemical Properties of Endosulfan

Property	Information	Reference
Molecular weight	406.95	Budavari 1996
Color	Cream to brown; mostly beige	Tomlin 1994
Physical state	Crystalline solid; Waxy solid	Budavari 1996; NIOSH 1997
Melting point		
Pure	106 $^\circ$C	Budavari 1996
Technical	70–100 $^\circ$C	Budavari 1996
Boiling point	No data	
Density at 20/4 $^\circ$C	1.735 g/mL	HSDB 1999
Density for vapor	14	HCDB 1986
Odor		
α-Endosulfan	Terpene-like	HSDB 1999
Decomposition products	May have a slight odor of sulfur dioxide	HSDB 1999
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25 $^\circ$C	60–100 µg/L	Sittig 1980
Organic solvents at 20 $^\circ$C		
Dichloromethane	65 g/L	Coleman and Dolinger 1982; HSDB 1999; Maier-Bode 1968
Ethanol	65 g/L	
Ethyl acetate	200 g/L	
Hexane	24 g/L	
Toluene	200 g/L	
Acetone	262 g/L	
Benzene	333 g/L	
Carbon tetrachloride	460 g/L	
Chloroform	746 g/L	
Ethanol	40 g/L	
Kerosene	164 g/L	
Methanol	89 g/L	
Xylene	388 g/L	
Partition coefficients:		
Log K_{ow}	3.55 and 3.62	HSDB 1999
Log K_{oc}	3.5	EPA 1987b
Vapor pressure at 25 $^\circ$C	1×10^{-5} mmHg	Coleman and Dolinger 1982; Mabey et al. 1982

Table 3-5. Physical and Chemical Properties of Endosulfan *(continued)*

Property	Information	Reference
Vapor pressure at 20 °C	0.83 mPa	Tomlin 1997
Vapor pressure at 880 °C	9×10^{-3} mmHg	Maier-Bode 1968; NRCC 1975
Henry's law constant at 24.8 °C	1×10^{-5} atm m^3/mol 1.01×10^{-4} atm m^3/mol	Suntio et al. 1988 Montgomery 1993
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data	
Reactivity	Both isomers are slowly hydrolysed by aqueous acids and alkalis, with the formation of the diol and sulfur dioxide	Tomlin 1994
	α and β isomers are rapidly oxidized by peroxides or permanganate to endosulfan sulfate	HSDB 1999
	The β form is slowly converted to the more stable α form at high temperatures	Hapeman et al. 1997; Rice et al. 1997
	Both isomers slowly oxidize in air to endosulfan sulfate	Metcalf RL 1995
	Corrosive to iron	HSDB 1999
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 °C	1 ppm=0.0601 mg/m^3	Verschueren 1977
mg/m^3 to ppm (v/v) in air at 25 °C	1 mg/m^3=16.64 ppm	Verschueren 1977
Explosive limits	No data	

Table 3-6. Physical and Chemical Properties of α-Endosulfan

Property	Information	Reference
Molecular weight	406.93	Budavari 1996
Color:		Tomlin 1994
Pure	Colorless	
Technical	Cream to brown, mostly beige	
Physical state	Crystalline solid	Tomlin 1994
Melting point	108–110 EC	Budavari 1996
Boiling point	No data	
Density at 20/4 EC	No data	
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 22 EC (pH 7.2)	0.15 mg/L	HSDB 1999
	0.32 mg/L	Tomlin 1994
Water at 25 EC	0.53 mg/L	EPA 1982c; Weil et al. 1974
Organic solvents at 20 EC	No data	
Partition coefficients:		
Log K_{ow}	3.83	Hansch et al. 1995
Log K_{oc}	3.55	HSDB 1999
Vapor pressure at 25 EC	1×10^{-5} mmHg	EPA 1982c
Henry's law constant at 25 EC	1×10^{-5} atm m^3/mol	EPA 1982c
	1.01×10^{-4} atm m^3/mol	Montgomery 1993
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data	

Conversion factors:
  ppm (v/v) to mg/m^3
  in air at 25 EC
	1 ppm=0.0601 mg/m^3	Verschueren 1977

mg/m^3 to ppm (v/v) in air at 25 EC	1 mg/m^3=16.64 ppm	Verschueren 1977
Explosive limits	No data	

Table 3-7. Physical and Chemical Properties of β-Endosulfan

Property	Information	Reference
Molecular weight	406.93	Budavari 1996
Color	Cream or tan	Tomlin 1994
Physical state	Crystalline solid	Budavari 1996
Melting point	207–209 EC 208–210 EC 212 EC	EPA 1979; Coleman and Dolinger 1982; EPA 1982c; Budavari 1996
Boiling point	No data	
Density at 20/4 EC	No data	
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 22 EC (pH 7.2)	0.33	Tomlin 1994
Water at 25 EC	0.28	EPA 1982c; Weil et al. 1974
Organic solvents at 20 EC	Soluble in most organic solvents	Budavari 1996
Partition coefficients:		
Log K_{ow}	3.52	Hansch and Leo 1995
Log K_{oc}	No data	
Vapor pressure at 25 EC	1×10^{-5} mmHg	EPA 1982c
Henry's law constant at 25 EC	1.91×10^{-5} atm m^3/mol	EPA 1982c
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data	
Reactivity	Both isomers are slowly hydrolysed by aqueous acids and alkalis, with the formation of the diol and sulfur dioxide	Tomlin 1994
	The β form is slowly converted to the more stable α form at high temperatures	Hapeman et al. 1997; Rice et al. 1997

Table 3-7. Physical and Chemical Properties of β-Endosulfan (*continued*)

Property	Information	Reference
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 EC	1 ppm=0.0601 mg/m^3	Verschueren 1977
mg/m^3 to ppm (v/v) in air at 25 EC	1 mg/m^3=16.64 ppm	
Explosive limits	No data	

Table 3-8. Physical and Chemical Properties of Endosulfan Sulfate

Property	Information	Reference
Molecular weight	422.9	EPA 1982c
Color	Brown	HSDB 1999
Physical state	Crystalline solid	HSDB 1999
Melting point	181 EC 198–201EC	EPA 1982c; White-Stevens 1971
Boiling point	No data	
Density at 20/4 EC	No data	
Odor	Pungent	HSDB 1999
Odor threshold: Water Air	 No data No data	
Solubility: Water at 22 EC (pH 7.2) Water at 25 EC Organic solvents at 20 EC	 0.22 0.117; 0.22 No data	 EPA 1982c; NRCC 1975; OHM/TADS 1989
Partition coefficients: Log K_{ow} Log K_{oc}	 3.66 No data	 EPA 1979
Vapor pressure at 25 EC	1×10^{-5} mmHg	EPA 1979; EPA 1982c
Henry's law constant at 25 EC	2.61×10^{-5} atm m^3/mol	EPA 1982c
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data	
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 EC	1 ppm=0.058 mg/m^3	Verschueren 1977
mg/m^3 to ppm (v/v) in air at 25 EC	1 mg/m^3=17.29 ppm	Verschueren 1977
Explosive limits	No data	

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

4.1 PRODUCTION

Endosulfan was first introduced into the United States in 1954 by Farbwerke Hoechst A.G. under the registered trademark, "Thiodan®" (Maier-Bode 1968). The main method of production involves the Diels-Alder addition of hexachlorocyclopentadiene and cis-butene-1,4-diol in xylene. This step is followed by a hydrolysis of the adduct to the cis-diol or dialcohol (Melnikov 1971). The endosulfan end product is then obtained by treating this bicyclic dialcohol with thionyl chloride ($SOCl_2$) (NRCC 1975; Sittig 1980). Pure endosulfan may be found as two different conformations, α and β. Technical-grade endosulfan, which must contain 94% endosulfan according to the specifications of the Food and Agricultural Organization of the United Nations (FAO), consists mainly of the α- and β-isomers in approximately a 7:3 ratio, as well as a few impurities or degradation products including endosulfan-ether, -alcohol, and -sulfate (Maier-Bode 1968; NRCC 1975). Technical endosulfan may also contain but not exceed concentrations of 2% endosulfan alcohol and 1% endosulfan ether. One degradation or reaction product, endosulfan sulfate, has chemical properties similar to the pure substance and is formed from photolysis (in solid or gas phase), biotransformation, or oxidation of endosulfan (EPA 1979). In the environment, both isomers of endosulfan can be metabolized to endosulfan sulfate by a variety of organisms (Maier-Bode 1968).

Several formulations containing endosulfan are presently on the market, and pesticide manufacturers make use of various inert ingredients (such as alcohol solvent emulsifiers; petroleum distillate emulsifiers; suspension agents, water, clay, and wetting agents; and talc) to produce these formulations (NRCC 1975). Formulated (processed) endosulfan exists in several forms (most of which are registered under the name "Thiodan®"). The main forms are the following: wettable powder with 17.5, 35, or 50% active ingredient (technical) with clay and wetting agents as inert ingredients; and emulsifiable concentrate with 17.5 or 35% active agent mixed with petroleum distillates or alcohol plus emulsifiers (as inert ingredients) (Coleman and Dolinger 1982).

Epichlorohydrin was reported to have been used in technical-grade endosulfan at one time as a stabilizer (Hoechst 1990). However, it is unclear when this practice was discontinued.

Few details are available on endosulfan's production volume. In 1974, the annual production of endosulfan in the United States was estimated at 3 million pounds (Sittig 1980). However, domestic

production was near 5,000 pounds in 1977 (HSDB 1999). The major U.S. manufacturer of endosulfan was FMC Corporation, formerly called the Niagara Chemical Division of Food and Machinery Corporation. FMC Corporation's annual production of endosulfan active ingredient for 1971 was estimated at about 2 million pounds (EPA 1972). According to Coleman and Dolinger (1982), however, this figure may be a low estimate. Endosulfan has not been produced in the United States since 1982 (HSDB 1999); therefore, worldwide production volumes listed after 1982 do not include data for the United States. Worldwide production of endosulfan in 1984 was estimated at 10,000 metric tons (WHO 1984). Current estimates of worldwide production or domestic formulation were not located.

Although endosulfan is no longer produced in the United States, it is still used in chemical formulations. Formulation sites for endosulfan around the United States include FMC Corporation, Chemical Group, Agricultural Chemical Division, Fresno, California and Jacksonville, Florida (SRI 1989); Drexel Chemical Company, Memphis, Tennessee (CIS 1988); and SureCo, Inc. (formerly known as Security Chemical Company), Fort Valley, Georgia (SRI 1989). Several corporations around the world continue to produce endosulfan, including All India Medical Corporation, Bombay, India; Bharat Pulverizing Mills Pvt., Ltd., Bombay, India; Dupont Conid S.P.A., Amonn Fitichimica Division, Bolzano, Italy; Excel Industries, Ltd., Bombay, India; FBC Limited, Cambridge, Great Britain; Krishi Rasayan, Calcutta, India; Makhteshim Chemical Works, Ltd., Beer-Sheva, Israel; Mewar Oil and General Mills, Ltd., Udaipur, India; Mictonion Industries Corporation, Taipei, Taiwan; and Productos Químicos de Chihuahua, S.A., Chihuahua, Mexico (CIS 1988). Farbwerke Hoechst A.G. in Frankfurt, West Germany, is a major producer worldwide (Coleman and Dolinger 1982). No production volume data were available for these companies. From the available information, it is unclear whether these sites represent producers of technical-grade endosulfan or manufacturers of endosulfan formulations.

There is currently only one facility that produces or processes endosulfan in the United States (SRI 1997).

4.2 IMPORT/EXPORT

Little is known about import volumes of endosulfan, but they are assumed to be substantial. Imports of endosulfan for 1982 were estimated at 182,000 kg (HSDB 1999).

Technical endosulfan is no longer produced in the United States; therefore, it is no longer exported. Data on export of formulated products containing endosulfan were not located.

4.3   USE

Endosulfan is registered in the United States as a contact and stomach insecticide for over 60 food and
nonfood crops. It is applied to crops to control over 100 different insect pests (EPA 1980b). It is
particularly effective against the Colorado potato beetle, the peach tree borer, the cabbage worm, the
tarnished plant bug, the leafhopper, and various aphids including the woolly apple aphid. Endosulfan
exhibits low toxicity to bees. The pesticide is applied on crops before harvest as soon as insects appear;
repeated applications follow if necessary (FAO/WHO 1975a; NRCC 1975). It is most often applied using
air-blast equipment or boom sprayers (HSDB 1999). Minimum intervals observed after spraying and
harvest vary according to crop (FAO/WHO 1975a). Worldwide, endosulfan is used on food crops such as
tea, vegetables, and deciduous fruits (and nuts), as well as nonfood crops such as tobacco and cotton.
This pesticide is also used on forage crops such as alfalfa (Coleman and Dolinger 1982).

Endosulfan formulations are used in commercial agriculture and home gardening (Coleman and Dolinger
1982). They are also used for wood preservation (HSDB 1999).

In the United States, endosulfan is mainly applied to tobacco and fruit crops. In the state of California,
however, spraying of lettuce, tomatoes, and artichokes accounts for half of the total use. The six major
crops protected by endosulfan in California, according to 1977 figures, are tomatoes, cotton, lettuce,
strawberries, pears, and grapes in decreasing order of amount of endosulfan used for each crop. Grapes,
strawberries, and pears account for most of the endosulfan used on fruit, and alfalfa accounts for most of
its use on forage in California. Use of endosulfan in California has decreased from 1,077,711 pounds in
1971 to 718,593 pounds in 1977 with the use levels dropping to 401,298 pounds in 1976 (Coleman and
Dolinger 1982).

4.4   DISPOSAL

Endosulfan is listed as a toxic substance under Section 313 of the Emergency Planning and Community
Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act
(SARA) (EPA 1995c). Disposal of wastes containing endosulfan is controlled by a number of federal
regulations (see Chapter 7).

According to EPA (1974), pesticides such as endosulfan should be destroyed at high temperature in an
approved incinerator with a hydrochloric acid scrubber, if available. Any sludges or solid residues

generated from this process are to be disposed of in a manner approved by all applicable federal, state, and local pollution control requirements. EPA strongly recommends that if incineration of excess pesticides is not possible, organic pesticides should be buried in a designated landfill site.

It has also been suggested that remaining endosulfan residues may be emptied in diluted form into a deep pit avoiding groundwaters (FAO/WHO 1975a). EPA, however, does not recommend well injection unless all other reasonable alternatives, including biodegradation and temporary storage, have been explored (EPA 1974). Moreover, pesticide residues and contaminated soil should be packaged in 17H epoxy-lined drums and disposed of at an EPA-approved chemical waste landfill (OHM/TADS 1989). Local toxic waste disposal and regulatory officials should be informed of the disposal process (OHM/TADS 1989).

Other methods of endosulfan disposal have previously been suggested by the Working Group on Pesticides (1970). The group outlined six possible methods for ground disposal of pesticides, their residues, spillage, and contaminated containers. The first method proposed for pesticide disposal was deep-well, given the wells are located far below freshwater aquifers and are separated from them by impervious geologic strata. Thorough geologic and hydrologic studies usually precede construction of deep wells to determine whether the location is sound. A sanitary landfill was another option for underground disposal of hazardous pesticides presented by the Working Group on Pesticides (1970). Pesticide wastes are placed in the landfill (which is usually located away from underground water sources), compacted, and covered with a layer of soil to prevent dispersal of dangerous residues. Disposal pits or dumps were a third alternative for pesticide waste removal. When this method has been used, no immediate efforts have been made to cover waste materials in the pits with earth (it is not clear whether the pits were located near local groundwater sources). A fourth suggested method of disposing of liquid formulations was by impounding waste materials in a lagoon, which is a shallow excavation or natural depression in the earth. Pesticides are allowed to oxidize, biodegrade, or evaporate in the open. Solids settle to the bottom during this process. Where especially hazardous chemicals are involved, an effort may be made to line the sides and bottom of the lagoon with cement, bentonite clay, asphalt, or bitumen. Ground surface disposal offered another alternative; wastes are spread out on a soil surface thereby taking advantage of natural processes of microbial metabolism, photochemical transformation, and aerobic oxidation of pesticides. Disposal via the city sewage system was the final alternative. Homeowners, home gardeners, businesses, and operators of small nurseries usually have taken advantage of this simple method of disposal, which poses a serious hazard to the surface water. Generally, EPA

does not recommend water dumping of pesticides (e.g., disposal through the city sewage system) (EPA 1974).

Spills of endosulfan, according to FAO/WHO (1975a), should be cleaned up by first washing with 5% sodium hydroxide solution and then rinsing with large quantities of water. In addition, empty containers that held endosulfan residues should be rinsed two or three times with water while the sides are scrubbed, and once with 5% sodium hydroxide solution. Thus decontaminated, the empty containers can be recycled and used by pesticide manufacturers to package a chemical similar to endosulfan if the containers remain in good condition and if such reuse is not prohibited by federal, state, or local laws. No food or beverages should be packaged in such a decontaminated container. If the empty, decontaminated containers are damaged, they should first be punctured and then incinerated or transported to a designated landfill for scrap burial (EPA 1974; FAO/WHO 1975a; HSDB 1999).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1   OVERVIEW

Endosulfan is released to the environment mainly as the result of its use as an insecticide. Significant
contamination is limited to areas where endosulfan is manufactured, formulated, applied, or disposed of.
The compound partitions to the atmosphere and to soils and sediments. Endosulfan can be transported
over long distances in the atmosphere, but the compound is relatively immobile in soils. It is transformed
by hydrolysis to the diol and by microorganisms to a number of different metabolites. It is
bioconcentrated only to low levels and does not biomagnify in terrestrial or aquatic food chains.

The most important routes of exposure to endosulfan for the general population are ingestion of food and
the use of tobacco products with endosulfan residues remaining after treatment. Farmers, pesticide
applicators, and individuals living in the vicinity of hazardous waste disposal sites contaminated with
endosulfan may receive additional exposure through dermal contact and inhalation.

Endosulfan has been identified in at least 164 of the 1,577 hazardous waste sites that have been proposed
for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites
evaluated for endosulfan is not known. The frequency of these sites can be seen in Figure 5-1. Of these
sites, 87 are located in the United States, one is located in Guam, and one is located in the Virgin Islands
(not shown).

5.2   RELEASES TO THE ENVIRONMENT

Endosulfan (one or both of its isomers) has been identified in a variety of environmental media (air,
surface water, groundwater, soil, and sediment) collected at 164 of the 1,577 NPL hazardous waste sites
(HazDat 2000).

Endosulfan has been released to the environment mainly as a result of its use as an insecticide. There are
no known natural sources of the compound. Endosulfan and endosulfan sulfate are not contained in the
list of chemicals for which releases are required to be reported to EPA for the SARA Section 313 Toxic
Release Inventory (TRI) (EPA 1997a).

Figure 5-1. Frequency of NPL Sites with Endosulfan Contamination
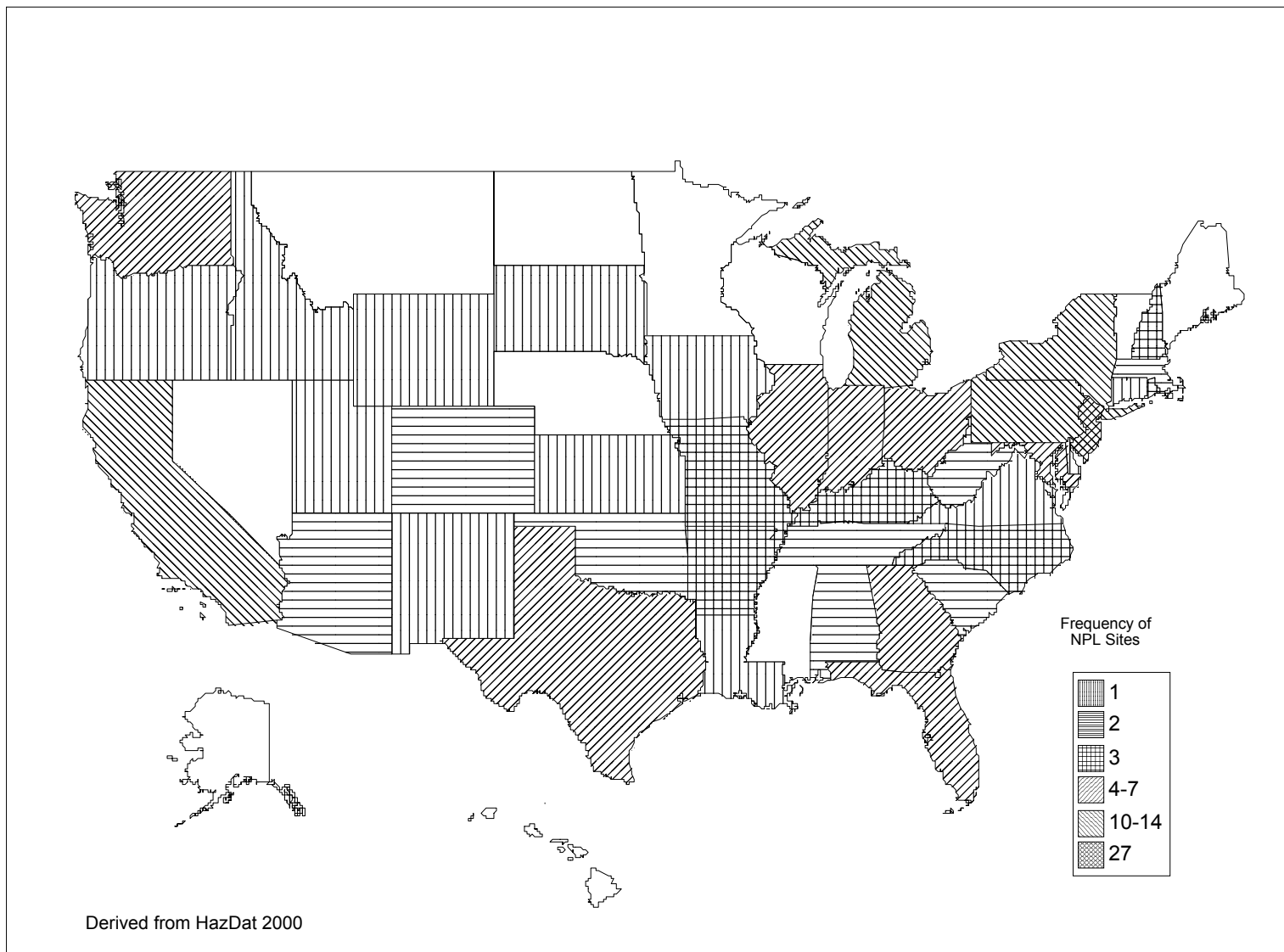
Frequency of
NPL Sites

▦	1
▤	2
▦	3
▨	4-7
▧	10-14
▦	27

Derived from HazDat 2000

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

5.2.1 Air

Endosulfan (one or both of its isomers) has been identified in air samples collected at only 4 of the 164 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

As a result of its use as an insecticide on fruit trees, vegetables, and other crops, endosulfan is released directly to the atmosphere during application. The compound is applied principally by air-blast equipment or boom sprayers (WHO 1984). No information was found in the available literature regarding atmospheric releases from manufacturing or formulation operations, or occurrence of the compound in air samples collected at NPL sites.

5.2.2 Water

Endosulfan (one or both of its isomers) has been identified in 24 surface water and 103 groundwater samples collected from 164 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

Effluents from manufacturing and formulating facilities and surface runoff from treated croplands are sources of releases of the compound to surface waters. Endosulfan has been detected in rivers draining industrial areas where manufacturers or formulators of the compound are located (WHO 1984) and in streams adjacent to treated fields (NRCC 1975). For example, about 0.6% of the 5.6 kg/hectare of endosulfan applied to soybean fields in Mississippi was lost from the fields in runoff. Endosulfan residues were detected up to 3.5 kilometers (km) downstream from the treatment area for about 3 weeks following the last application of the compound (Willis et al. 1987).

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

5.2.3 Soil

Endosulfan has been identified in 162 soil and 45 sediment samples collected at 131 of the 164 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

The main routes of release of endosulfan to soils are application of the compound to crops and land disposal of unused formulated pesticide products containing the compound.

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

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Spray drift from aerial application of endosulfan is often the source of contamination of adjacent untreated croplands and streams (NRCC 1975). However, endosulfan released to the atmosphere may also be transported for long distances before being removed in wet and dry deposition. For example, endosulfan was detected in rainfall samples collected in 1976 and 1977 in Canada at sites inland from the Great Lakes and remote from any nearby industrial or urban contamination. Mean rainfall concentrations of 1–2 ng/L for the α-isomer and 4–5 ng/L for the β-isomer were associated with particulate deposition during rainfall events. A seasonal pattern was observed in the rainfall concentrations; endosulfan was detected in spring and summer rainfall samples but not in fall and winter samples (Strachan et al. 1980). α-Endosulfan was detected at concentrations of 0.1–1.34 ng/L in snowpack samples collected from 12 sites widely distributed throughout the Canadian Arctic in the spring of 1986 (Gregor and Gummer 1989). The source of the contamination was reported to be long-range atmospheric transport and subsequent deposition in snowfall The environmental distribution of organic chemicals in air has been characterized in terms of persistence and spatial range (Scheringer 1997). The model shows endosulfan to have a limited spatial range (approximately 15% of the earth's perimeter) and a persistence of less than 10 days. Spatial range is predicted to increase with increased sorption of the compound to particulate matter, a condition hypothesized to preclude the fast reaction of semivolatile compounds with OH radicals.

Endosulfan is also released to the atmosphere as the result of volatilization from treated plant surfaces and surface waters. The volatilization half-life from surface waters is greater than 11 days and possibly greater than 1 year (EPA 1979). The vapor pressure ($1x10^{-5}$ mmHg at 25 EC; 0.83 mPa at 20EC) and Henry's law constant ($1x10^{-5}$–$2.6x10^{-5}$ atm m^3/mol at 25 EC) values for endosulfan isomers and endosulfan sulfate presented in Tables 3-5 through 3-8 also suggest limited volatilization from surface waters. However, it has been reported that substantial volatilization losses from aqueous surfaces in seawater/sediment microcosm tests occur (Cotham and Bidleman 1989). The α-isomer volatilized to a much greater extent than the β-isomer during the initial 72 hours following introduction of the compounds to the test chambers. Air/water partitioning of endosulfan has a major influence on the fate of the material in the atmospheric compartment. The air/water distribution of the endosulfan isomers was determined using a wetted-wall-column apparatus.

When pure β-endosulfan was allowed to equilibrate in the apparatus, the ratio of the β-isomer to the α-isomer in the gas phase became 8:92 at 20 EC, suggesting that the β-isomer converts to the α-isomer (Rice et al. 1997). Several investigators have reported rapid initial losses of endosulfan residues from treated plant surfaces due to volatilization (Archer 1973; Terranova and Ware 1963; Ware 1967). One research group (Willis et al. 1987) attributed the limited runoff losses found in soybean fields treated with endosulfan to early losses of the compound during application and to volatilization/degradation of the compound from plant surfaces. Air sampling performed in a wind tunnel under defined conditions (20 EC; air velocity 1 m/sec; relative humidity 40–60%) showed that 60% of the initial dose of endosulfan is volatilized from French bean surfaces after 24 hours (Rudel 1997). Influences of various pesticide application formulations were not tested.

The results of several laboratory and greenhouse studies indicate that α- and β-endosulfan are strongly adsorbed to soil. In standard glass-column elution tests, both isomers were found to adsorb tightly to loamy sand, sandy loam, sandy clay loam, and sandy clay soils (Bowman et al. 1965; El Beit et al. 1981c). In model soil evaporation beds constructed to test the feasibility of treating pesticide wastes, endosulfan exhibited no movement in loamy sand soil beds up to 54 weeks after the start of the tests (Hodapp and Winterlin 1989). In air sampling studies done in a wind tunnel, 12% of the initial endosulfan application volatilized from a silty sand soil after 24 hours, as compared to 60% from plant surfaces in 24 hours (Rudel 1997). Endosulfan did not leach from sandy loam soil following incorporation of 6.7 kg/hectare of the compound (Stewart and Cairns 1974). After sampling periods of 503–828 days, 90% of the residues were found in the top 0–15 cm of soil, 9% at 15–30 cm, and 1% at 30–45 cm. In one report, an estimated K_{oc} of 2000 was determined for endosulfan suggesting that

mobility in soil is expected to be slight (State of California 1991). The K_{oc} values of α- and β-endosulfan in marine sediment were measured to be 3,981 and 19,953, respectively (Peterson & Batley 1993). Adsorption of α- and β-endosulfan to soil particulates is predicted based on the relationship between the octanol/water partition coefficient, K_{ow} and K_{oc}. Using a regression-derived equation found in Lyman (1990) and the reported log K_{ow} values found in Tables 3-6 and 3-7, the K_{oc} values for α- and β-endosulfan can be estimated to be 2,887 and 1,958, respectively.

Adsorption is also important in aquatic systems. For example, 82–85% of the endosulfan residues in water samples taken from the Rhine River (0.2–0.6 ppb) were associated with the particulate phase (Greve and Wit 1971).

Endosulfan does not bioaccumulate to high concentrations in terrestrial or aquatic ecosystems. In aquatic ecosystems, residue levels in fish generally peak within 7 days to 2 weeks of continuous exposure to endosulfan. Maximum bioconcentration factors (BCFs) are usually less than 3,000, and residues are eliminated within 2 weeks of transfer to clean water (NRCC 1975). A maximum BCF of 600 was reported for α-endosulfan in mussel tissue (Ernst 1977). In a similar study, endosulfan, isomers not specified, had a measured BCF of 22.5 in mussel tissue (Roberts 1972). Tissue concentrations of α-endosulfan fell rapidly upon transfer of the organisms to fresh seawater; for example, a depuration half-life of 34 hours (Ernst 1977). Higher BCFs were reported for whole-body and edible tissues of striped mullet (maximum BCF=2,755) after 28 days of exposure to endosulfan in seawater (Schimmel et al. 1977). However, tissue concentrations decreased to undetectable levels 48 hours after the organisms were transferred to uncontaminated seawater. Similarly, a BCF of 2,650 was obtained for zebra fish exposed to 0.3 µg/L of endosulfan for 21 days in a flow-through aquarium (Toledo and Jonsson 1992). It was noted that endosulfan depuration by fish was rapid, with approximately 81% total endosulfan eliminated within 120 hours when the fish were placed in a tank of water containing no endosulfan.

In freshwater studies, mosquito fish, catfish, and freshwater eels were exposed to endosulfan in static tests. Maximum tissue concentrations in mosquito fish (933 µg/kg; α-isomer) were found in fish exposed to 16 µg technical-grade endosulfan/L for 24 hours. The maximum tissue concentrations in fish exposed to 2 µg technical-grade endosulfan/L for 7 days was 143 µg α-isomer/kg. Mean endosulfan residues in catfish were 61.3 µg/kg (α-isomer) following 7 days of exposure to 0.7 µg technical-grade endosulfan/L. After 43 hours of exposure to 1 µg technical-grade endosulfan/L, mean residues in freshwater eels were 0.145 µg/kg α-isomer, 0.138 µg/kg for the β-isomer, and 0.117 µg/kg for endosulfan sulfate (Novak and Ahmad 1989).

Plant tissue residues are usually the result of surface deposition of the compound (EPA 1992c). Very
limited data indicate that endosulfan and its metabolites are translocated in plants. In one study, the
above-soil portion of bean and sugar beet plants were immersed in a water solution containing endosulfan
and then allowed to dry under both laboratory controlled and semi-controlled greenhouse conditions
(Beard and Ware 1969). Both α- and β-endosulfan and its metabolites (endosulfan diol, ether, and
sulfate) were found to penetrate plant tissue and were translocated from the leaves to the roots of both
bean and sugar beet plants. Translocation occurred at a higher rate in greenhouse plants than in
laboratory plants. Under semi-controlled greenhouse conditions for both beets and beans, the highest
residues were found in the plant extracts (indicating penetration of the material), with lower
concentrations deposited on leaves, and with the lowest levels in the roots. The residue levels on both the
plant surface and in tissue extracts decreased during the course of the experiment, while the levels in the
roots increased. In bean plant roots, translocation (day 4) was as follows: isomer β (0.28 ppm) > ether
(0.18 ppm) > sulfate (0.08 ppm). No residue of the α-isomer or the diol appeared in bean roots by day 4.
In sugar beet roots, residue levels were as follows: α-isomer (2.8 ppm) > β-isomer (0.5 ppm) > ether
(0.1 ppm), sulfate (0.1 ppm) > diol (0 ppm) (Beard and Ware 1969).

The results of metabolism studies with laboratory animals and livestock indicate that endosulfan does not
bioconcentrate in fatty tissues and milk. Lactating sheep administered radiolabeled endosulfan produced
milk containing less than 2% of the label. Endosulfan sulfate was the major metabolite in milk (Gorbach
et al. 1968). A half-life of about 4 days was reported for endosulfan metabolites in milk from survivors of
a dairy herd accidentally exposed to acutely toxic concentrations of endosulfan; endosulfan sulfate
accounted for the bulk of the residues detected in the milk (Braun and Lobb 1976). No endosulfan
residues were detected in the fatty tissue of beef cattle grazed on endosulfan-treated pastures for
31–36 days (detection limits of 10 ppm for endosulfan, 40 ppm for endosulfan diol); the animals began
grazing 7 days after treatment of the pastures. Some residues were detected in the fatty tissue of one
animal administered 1.1 mg/kg/day of endosulfan in the diet for 60 days. No endosulfan residues were
detected in milk from cows fed silage containing 0.41–2.35 ppm endosulfan for 21 days (Beck et
al. 1966).

In field trials following multiple aerial applications of endosulfan for tsetse fly control in Africa over a
3-month period, residues of the compound in fish tissues decreased to low concentrations within 3 months
after spraying. The fish tissue residues were still detectable after 12 months. Residue concentrations in
fish-eating birds and crocodiles were similar to fish tissue residue levels; endosulfan did not biomagnify
in the food chain (HSDB 1999).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The α- and β-isomers of endosulfan undergo photolysis in laboratory tests after irradiation in polar
solvents and upon exposure to sunlight on plant leaves. The α-isomer also undergoes isomerization to the
β-isomer, which is relatively more stable (Dureja and Mukerjee 1982). A photolytic half-life of about
7 days was reported for endosulfan by EPA (1982c). The primary photolysis product is endosulfan diol,
which is subsequently photodegraded to endosulfan α-hydroxyether. Endosulfan sulfate is stable to direct
photolysis at light wavelengths of >300 nm; however, the compound reacts with hydroxy radicals, with
an estimated atmospheric half-life of 1.23 hours (HSDB 1999).

5.3.2.2 Water

Endosulfan undergoes hydrolysis to endosulfan diol in surface water and groundwater. The rate of
hydrolysis is influenced by pH. Half-life values reported in the literature vary somewhat. The chemical
degradation of α- and β-endosulfan was studied under both anaerobic and aerobic environments. Under
aerobic conditions, both hydrolysis and oxidation of endosulfan can occur, while under anaerobic
conditions, only hydrolysis can occur. The hydrolytic half-lives for α- and β-endosulfan under anaerobic
conditions at pH 7 were 35 and 37 days, respectively (Greve and Wit 1971). At pH 5.5 the half-lives
were 151 and 187 days, respectively. Under aerobic conditions, the half-lives decreased. At pH 7, the
half-lives of the chemical degradation (hydrolysis and oxidation) of both α- and β-endosulfan were 23 and
25 days, respectively, while at pH 5, the half-lives were 54 and 51 days, respectively. At T=20 EC and
pHs of 5.5 and 8.0, the half-lives of α-endosulfan in distilled water were 11.3 and 5.3 days, respectively
(Kaur et al. 1998). The half-lives at pH 7.23 and 69.5 EC for α- and β-endosulfan were 1.2 and
0.96 hours, respectively (EPA 1987f). Losses of endosulfan, at an initial concentration of 0.5 mg/L, from
natural lake water and tap water were 89 and 69%, respectively (Ferrando et al. 1992). The natural water
was more alkaline than the tap water; this finding is in agreement with other studies. The half-life of the
pesticide in the tap water was approximately 68 hours.

Endosulfan in aqueous solutions is also expected to undergo biodegradation. In laboratory tests at pH 7
and 20 EC, *Pseudomonas* bacteria degraded endosulfan (isomers not specified) under aerobic conditions
with a half-life of about 1 week (Greve and Wit 1971). Biotic and abiotic transformations of endosulfan
in seawater/sediment microcosms have been reported (Cotham and Bidleman 1989). In biotic tests, half-

lives for the α- and β-isomers in seawater-only microcosms (pH$8) were about 5 and 2 days, respectively. In seawater-only microcosms under sterile conditions at a pH of 8 or higher, the half-life for the α-isomer was 2–3 days, whereas the half-life for the β-isomer was 1–2 days. Half-lives were longer in seawater/ sediment microcosms, possibly because of the lower pHs (7.3–7.7) in these test systems; half-lives were 22 and 8.3 days for the α- and β-isomers, respectively. Endosulfan diol was the main metabolite identified.

5.3.2.3 Sediment and Soil

Endosulfan released to soil is most likely subjected to photolysis (on soil surfaces), hydrolysis (under alkaline conditions), or biodegradation. Endosulfan has been shown to be biodegraded by a wide variety of soil microorganisms in numerous studies. Sixteen of 28 species of fungi, 15 of 49 species of soil bacteria, and 3 of 10 species of actinomycetes metabolized radiolabeled endosulfan in a laboratory study under aerobic conditions (Martens 1976). Endosulfan sulfate was the major product of the fungal metabolism, whereas the bacterial transformation produced endosulfan diol. Degradation of endosulfan by soil fungi and bacteria has also been reported (El Beit et al. 1981b). Biotransformation occurs under both aerobic and anaerobic conditions. Aerobic incubation of soil with endosulfan yielded mainly endosulfan sulfate (30–60%), some endosulfan diol (2.6%), and endosulfan lactone (1.2%) (Martens 1977). Flooded (anaerobic) incubation produced mainly endosulfan diol (2–18%), endosulfan sulfate (3–8%), and endosulfan hydroxyether (2–4%). In aqueous nutrient media (20EC) containing a mixed culture of microorganisms isolated from a sandy loam soil, endosulfan was reported to be transformed to endosulfan diol with half-lives of about 1.1 and 2.2 weeks for the α- and β-isomers, respectively (Miles and Moy 1979).

A two-membered bacterial coculture was found to aerobically degrade α- and β-endosulfan efficiently without accumulating any of its metabolites. However, the degradation of soil-bound endosulfan was slower by 4-fold than in culture media; only 50% of the material (initially at 50 ppm) was degraded in 4 weeks (Awasthi et al. 1997). A field study report stated that endosulfan was transformed to endosulfan sulfate following incorporation of 6.7 kg/hectare of the pesticide into sandy loam soil (Stewart and Cairns 1974). The half-lives for the α- and β-isomers were reported to be 60 and 800 days, respectively. *Pseudomonad* microbes have been reported to isomerize β-endosulfan to α-endosulfan and biodegrade both isomers to endosulfan alcohol and endosulfan ether (U.S. Department of Interior 1978). In a field study conducted from 1989–1990 in northern India, dissipation of endosulfan in sandy loam soil was examined (Kathpal et al. 1997). It was found that α-endosulfan could be detected up to 14 and 28 days in

two different soil plots, while β-endosulfan could be detected up to 70 and 238 days. An overall half-life

for endosulfan degradation ranged from 39.5 to 42.1 days. Endosulfan residues dissipated to an extent of

92–97% in the first 4-week period of application and by about 99% in 238 days. A residue half-life of

15 days for endosulfan (unspecified isomer) has been reported in Australian black soil when incubated at

30 EC at field capacity moisture level (Kathpal et al. 1997). Fate and movement of endosulfan isomers

and endosulfan sulfate under field application conditions have been studied (Antonious and Byers 1997).

New modes of cultivation showed reduced runoff water and sediment loss and reduced endosulfan

movement from the site of application to the surface water runoff. Results indicated vertical movement of

the pesticide through the vadose zone at a concentration of 0.63 µg/L. Soil core data shows endosulfan

leaches from 23 to 46 cm into the soil (Antonious and Byers 1997).

On plant surfaces, as in soils, numerous studies have demonstrated that endosulfan is oxidized to

endosulfan sulfate. Initial residues of endosulfan on treated vegetables generally range from 1 to

100 mg/kg. However, residue levels typically decrease to less than 20% of initial levels within 1 week

after treatment (NRCC 1975). Residues of endosulfan isomers are generally negligible after 2–3 weeks;

the α-isomer is much less persistent than the β-isomer. In most plant residue studies, endosulfan sulfate

residue levels tend to increase relative to the parent isomers and other metabolites and appear to be very

persistent (Coleman and Dolinger 1982).

5.4   LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to endosulfan depends in part on the reliability of

supporting analytical data from environmental samples and biological specimens. In reviewing data on

endosulfan levels monitored or estimated in the environment, it should also be noted that the amount of

chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1   Air

Endosulfan has been detected in only a limited number of ambient air samples taken in the United States.

As part of EPA's National Pesticide Monitoring Program conducted between 1970 and 1972, in 1970,

only 6.6 and 1% of the ambient air samples collected at selected sites in 14 states contained α- and

β-endosulfan, respectively. Mean concentrations for the positive samples were 112 ng/m^3 for the

α-isomer (maximum 2,257 ng/m^3) and 22 ng/m^3 for the β-isomer (maximum 55 ng/m^3). Sampling sites

were selected for their potentially high concentrations of pesticides in ambient air. Endosulfan was not

detected in any of the ambient air samples collected from sites in 16 states in 1971 or 1972 (Kutz et al. 1976). α-Endosulfan was detected at a mean concentration of 0.078 ng/m^3 in ambient air samples collected in Columbia, South Carolina from June to mid-August 1978 (Bidleman 1981). Air samples obtained at a rural site near Egbert, Ontario, Canada in 1988–1989 contained an average of 3.7 ng/m^3 of the local and regionally used pesticide, endosulfan (Hoff et al. 1992). The average air concentration of α-endosulfan over a 14-month period in 1991–1992 in Bloomington, Indiana, was 86 pg/m^3 (0.086 ng/m^3) (Burgoyne 1993). Diurnal variations in ambient air concentrations of endosulfan were noted for samples taken in September 1994 near Bloomington, Indiana (Wallace and Hites 1996). Air samples taken over a 6-hour period in the morning had twice the concentration (0.031 ng/m^3) than those collected at midnight.

Rainfall samples collected in the Great Lakes area of Canada in 1976 and 1977 contained mean concentrations of 1–2 ng/L (parts per trillion) α-endosulfan and 4–5 ng/L β-endosulfan. Endosulfan was detected in spring and summer rainfall samples but not in samples collected during the fall and winter (Strachan et al. 1980). α-Endosulfan has also been detected in snowpack samples obtained from widely distributed sites in the Canadian Arctic. Endosulfan concentrations in samples collected in the spring of 1986 ranged from 0.1 to 1.34 ng/L (Gregor and Gummer 1989).

5.4.2 Water

Although endosulfan and endosulfan sulfate have been found at low concentrations in a few surface water and groundwater samples collected at hazardous waste sites (see Section 5.2.2), no information was found in the available literature regarding current concentrations of endosulfan or endosulfan sulfate in domestic surface waters not associated with these sites. The World Health Organization (WHO) reported that although endosulfan has been detected in agricultural runoff and in surface waters draining industrialized areas, contamination of surface waters with this compound does not appear to be widespread (WHO 1984). EPA (1982c) stated that endosulfan concentrations in surface water are generally <1 ppb.

In a survey of streams in the western United States conducted by the U.S. Geological Survey (USGS) from 1968 to 1971, endosulfan was detected in only 1 of the 546 surface water samples collected, at a concentration of 0.02 μg/L (EPA 1980a). α-Endosulfan was detected in water samples collected in 1980 from Inner Harbor Navigation Canal of Lake Pontchartrain (New Orleans, Louisiana). At ebb and flood tide, it was found at levels of 0.8 ppt (1.5 m ebb tide), 0.9 ppt (1.5 m flood tide), and 3 ppt (10 m flood tide) (McFall et al. 1985). Detection limits were not reported. α-Endosulfan was determined in the surface microlayer and suspended solids at 3 of 5 stations along the Niagara River in 1981 at levels

ranging from 0 to 0.0204 µg/L and from 0 to 0.025 mg/kg, respectively (level of detection, 0.0001 µg/L
in water and 0.001 mg/kg in suspended solids) (Maguire et al. 1983). α-Endosulfan was not detected in
subsurface water at any of the stations. Concentrations of β-endosulfan in the surface microlayer,
subsurface water, and suspended solids were below the detection limits, except at one station where
β-endosulfan was found at a level of 0.021 mg/kg in suspended solids (Maguire et al. 1983).

Rain samples collected from around the Great Lakes contained both α- and β-endosulfan (Strachan and
Huneault 1979). Mean concentrations of α-endosulfan in rain samples from the Great Lakes ranged from
0.1 ng/L (n=13) to 3.8 ng/L (n=16). Mean concentrations of β-endosulfan in rain samples ranged from
1 (n=14) to 12 ng/L (n=16). The endosulfans were not found to any significant extent in snow-core
samples (Strachan and Huneault 1979). Detection limits were not reported.

Runoff waters from agricultural areas have been found to contain low concentrations of endosulfan in the
aqueous phase and higher concentrations in the particulate phase of the runoff. For example, runoff from
a soybean field in Mississippi treated with 5.6 kg endosulfan/hectare was reported to contain maximum
concentrations of 0.019 mg/L and 8.7 mg/kg (α- and β-isomers) in the aqueous and suspended sediment
phases, respectively (Willis et al. 1987). The samples were collected within 3 weeks of the last
application of the compound. Samples taken from runoff ditches from an agricultural area near Lake Erie
in Ontario, Canada, contained endosulfan residue (unspecified isomer/sulfate content) concentrations of
<0.002–0.18 µg/L in runoff water and 1–62 µg/kg in bottom mud. Soils from a farm located near the
runoff ditch contained 640 µg endosulfan residues/kg (Miles and Harris 1971). Endosulfan was detected
in stream waters collected from 11 agricultural watersheds in Ontario from 1975 to 1977 (Frank et al.
1982). The overall mean for all 11 watersheds was 3.7 ng/L in 1975–1976 and 2.0 ng/L in 1976–1977.
Detection limits were not reported. Endosulfan exceeded the water quality criteria of 3.0 ng/L established
by the International Joint Commission for lake and stream waters entering the Great Lakes in 14% of the
samples. Endosulfan appeared in water samples throughout the year (outside the spray season); it entered
water with storm runoff throughout the season because of its persistence in soil (Frank et al. 1982). In the
early 1990s, endosulfan was found in the waters and sediment of the canals of South Florida (Miles and
Pfeuffer 1997). α-Endosulfan and endosulfan sulfate residues as high as 0.22 and 0.45 µg/L, respectively,
were observed in confined surface waters in the Homestead area. Such values exceed the Florida water
quality criterion.

From February 1995 to June 1997, endosulfan concentrations (isomers not specified) in river, well,
lagoon, and spring water samples were studied from the greater Cholutecan River Basin of Honduras

(Kammerbauer and Moncada 1998). Endosulfan was found predominantly in Choluteca well water and in Yeguare river water at approximately 0.06 mg/kg. It was also found in Choluteca river water, Zamorano well/lagoon water, and La Lima well/lagoon water at concentrations ranging from 0.01 to 0.02 mg/kg. In a study of water samples collected from the Segre river basin in Spain from May–June 1995, endosulfan (isomers not specified) was detected in four of six samples at approximately 0.01 µg/L (Planas et al. 1997).

Three out of nine groundwater samples extracted from Dobrich in northeastern Bulgaria contained endosulfan (isomers not specified) ranging from 0.020 to 0.025 µg/L in March 1996 (Pulido-Bosch et al. 1999). The suspected source of this pollution was from agricultural practices in the region.

5.4.3 Sediment and Soil

Endosulfan has been detected in only a limited number of urban and agricultural soils in the United States. The National Soils Monitoring Program conducted in 1972 included the collection of 1,483 soil samples from 37 states. The α- and β-isomers of endosulfan and endosulfan sulfate were each detected in only one sample at <0.01 ppm (Carey et al. 1979a). Endosulfan was not detected (method detection limit of 1 µg/kg) in sediments collected from the Central Columbia plateau of the United States (Munn and Gruber 1997). In soil samples collected from five metropolitan areas in the United States as part of the Urban Soils Monitoring Program, endosulfan sulfate was detected in samples from two cities: Macon, Georgia (in 1 of 43 samples) and Baltimore, Maryland (in 1 of 156 samples) at concentrations of <0.01 ppm (Carey et al. 1979b). Surveys of agricultural soils in North America have determined that endosulfan residue levels (α- and β-isomers and endosulfan sulfate) are typically less than 1 mg/kg (WHO 1984).

From February 1995 to June 1997, endosulfan concentrations (isomers not specified) in soil samples were studied from the greater Cholutecan River Basin of Honduras (Kammerbauer and Moncada 1998). Endosulfan was found in Choluteca and La Lima soil at concentrations ranging from 0.01 to 0.02 mg/kg.

Soils sampled at two sites in creek beds and drainage ditches in an agricultural area in the Point Mugu watershed near Oxnard, California, contained endosulfan at concentrations between 20 and 30 ppm. The majority of the other sites had much lower concentrations (Leung et al. 1998).

5.4.4 Other Environmental Media

Levels of endosulfan and endosulfan sulfate in domestic foodstuffs have been determined as part of
FDA's Total Diet Studies series. The FDA's 1995 pesticide residue monitoring program found
81 instances of detection of endosulfan in 3 market baskets consisting of 783 items (FDA 1995). In the
1980–1982 survey of 27 cities (Gartrell et al. 1986), individual food items were separated into food
groups, and foods in each group were blended in amounts proportional to weights consumed to yield
homogeneous composites. α-Endosulfan, β-endosulfan, and endosulfan sulfate were detected only in the
leafy vegetable, garden fruit, and fruit food groups. The isomers and the breakdown product were not
found in the following food groups included in the survey: dairy products; meat, fish, and poultry; grain
and cereal products; potatoes (α- and β-isomers); legume vegetables; root vegetables; oils and fats; sugar
and adjuncts; or beverages.

Domestic and imported pears and tomatoes were collected and analyzed for pesticide residues from July
1992–July 1993 (Roy et al 1995). Endosulfan (both isomers) was found in 471 of 1,219 domestic tomato
samples at a maximum concentration of 0.2 mg/kg and in 80 of 144 imported tomato samples at a
maximum concentration of 0.55 mg/kg. In pears, endosulfan was found in 144 of 710 domestic samples
at a maximum concentration of 1.1 mg/kg, and in 4 of 949 imported samples at a maximum concentration
of 0.13 mg/kg.

Studies of carrot and tomato crops sprayed with endosulfan 2 to 8 days prior to harvest showed that more
pesticide remains in the pulp than in the juices of these vegetables. Washing and peeling the vegetables
lowered the endosulfan concentration considerably (Burchat et al. 1998).

Neither endosulfan nor endosulfan sulfate was detected in surveys of the milk supply of the southern
region of Ontario, Canada conducted in 1970–1971 and 1973 (Frank et al. 1975). In Burley tobacco,
when the crop was harvested immediately after treatment with 0.5 pound/acre of endosulfan, the total
endosulfan residue levels (isomers and sulfate) were reported to average 23.2 ppm after curing for
4 months. Average total residues decreased to 2.2 ppm when the time between treatment and harvest was
increased to 28 days (Dorough et al. 1973).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The main route of exposure to endosulfan for the general population is ingestion of food containing residues of endosulfan as a result of application or bioconcentration. Levels of endosulfan and endosulfan sulfate in domestic foodstuffs have been determined as part of FDA's Total Diet Studies series. The FDA's 1995 pesticide residue monitoring program found 81 instances of detection of endosulfan in 3 market baskets consisting of 783 items (FDA 1995). A total diet study conducted by the FDA from June 1984 to April 1986 studied the dietary intake of various pesticides by different age groups in the population (Gunderson 1995b). The mean daily intakes per unit of body weight (mg/kg body weight/day) for α-endosulfan were 1.3×10^{-6} for ages 14–16 years, 1.8×10^{-6} for ages 25–30 years and 2.0×10^{-6} for ages 60–65 years while for β-endosulfan, the mean daily intakes were 2.1×10^{-6} for ages 14–16 years, 2.5×10^{-6} for ages 25–30 years, and 2.9×10^{-6} for ages 60–65. In the same type of study conducted from July 1986 to April 1991, the mean daily intakes per unit body weight (mg/kg body weight/day) for α-endosulfan were 2.3×10^{-6} for ages 14–16 years, 3.0×10^{-6} for ages 25–30 years, and 3.8×10^{-6} for ages 60–65 years, while for β-endosulfan, the mean daily intakes were 6.5×10^{-6} for ages 14–16 years, 6.8×10^{-6} for ages 25–30 years, and 9.9×10^{-6} for ages 60–65 years (Gunderson 1995a). Studies of foods in India have identified endosulfan in okra at an average concentration of 0.22 µg/g (Mukherjee and Gopal 1996). Dietary characterization of food and beverages were made during a study of human exposure in the lower Rio Grande valley (Berry et al. 1997). A total of 30 different pesticides were detected in 54 local food samples; endosulfan was one of the most commonly found residues. Endosulfan sulfate, α-endosulfan, and β-endosulfan residues were found in 4–6 foods sampled in the spring at concentrations ranging from 0.005 to 0.072, 0.007 to 0.050, and 0.002 to 0.095 µg/g, respectively (Berry et al. 1997). Howard (1991) has estimated an average daily intake of endosulfan via food at 1.18 µg by averaging the average daily intake values for the years 1971–1976.

In Hsinchu, Taiwan, the dietary intake of α- and β-endosulfan was studied from June 1996 to April 1997 (Doong and Lee 1999). β-Endosulfan was not detected in any of the 14 different foods studied, including fruits, meats, seafood, and cereal, and α-endosulfan, by contrast, was found in 78 of 149 samples at an average concentration of 2.76 ng/g wet weight. Based on the average Taiwanese diet, the estimated daily intake of α-endosulfan was 6.24×10^{-4} mg body weight/day.

Exposure to endosulfan residues in tobacco products could be another important source of general population exposure. Endosulfan residues in tobacco leaves and finished tobacco products were reviewed by EPA (1982a). For example, auction market tobacco had a mean residue of <0.2–14 ppm endosulfan

and endosulfan sulfate in the early 1970s, and cigarettes sold in 1973 contained a mean residue of 0.83 ppm endosulfan. No information was found in the available literature regarding endosulfan concentrations in cigarette smoke.

In occupational settings, exposure to endosulfan is mainly via the dermal and inhalation routes. Although workers involved in the manufacture and formulation of pesticide products containing endosulfan are potentially exposed to high concentrations of the compound, actual exposure is probably limited by the use of engineering controls and personal protection equipment. The highest documented dermal and inhalation exposures have been reported for agricultural workers involved in the spray application of endosulfan products. Among these individuals, mixers and applicators have the highest potential for direct exposure. For example, during spray application of endosulfan on fruit orchards using air-blast equipment, a mean dermal exposure of 24.7 mg/hour (range, 0.6–95.3 mg/hour) and a mean inhalation exposure of 0.02 ng/hour (range, 0.01–0.05 ng/hour) were estimated in one study (Wolfe et al. 1972). In another study in which endosulfan was applied to fruit orchards using air blast equipment, total exposures of 0.27–2.2 mg/hour were reported during mixing operations, and 4.1–9.3 µg/hour were reported during spraying operations (Oudbier et al. 1974). Estimates of mean dermal exposure of workers who apply endosulfan to fields of tobacco in Kentucky have been made (Lonsway et al. 1997). The mean dermal exposures to mixers and sprayers of endosulfan via a tractor mounted boom sprayer and highboy were 16.18 and 8.06 mg/kg/day, respectively. Not using protective measures when spraying endosulfan can lead to poisoning. In the Punjab area, 8.6% of poisonings of all types admitted to the hospital in 1989 were due to endosulfan (Singh et al. 1992). Singh cautions that applications of oil to body surfaces before beginning work in the fields will increase the absorption of endosulfan. Furthermore, the presence of cuts on the legs or hands facilitates entry of pesticides to the body's circulatory system. Studies of pesticide penetration through protective clothing (Archibald et al. 1994a) indicated that rubber or tyvek provided the best protection.

In one study, the exposure of an individual involved in spraying the compound, while wearing protective overalls, gloves and breathing mask, was examined (Arrebola et al. 1999). The individual applied 300L of an endosulfan mixture to plants and later gave 10 urine samples over the course of 3 days. The study found that the highest concentrations occurred 4.3 hours after exposure with concentrations for α- and β-endosulfan reaching 4,289 and 1,079 pg/mL, respectively. The half-lives for the excretion of α- and β-endosulfan were determined to be 23 and 27 hours, respectively. Between October 1995 and September 1997, 18 cases of endosulfan poisoning by accidental overexposure during spray applications were reported at the medical center in Haryana, India (Chugh et al. 1998). Ten fatal cases of endosulfan

exposure were reported in a survey of pesticide poisoning incidents in Spain from 1991 to 1996 (Garcia-Repetto et al. 1998).

Endosulfan is a popular pesticide with greenhouse chrysanthemum producers. Surveys of usage patterns and potential exposure were conducted in Ontario (Archibald et al. 1994b). Collection and analysis of α- and β-endosulfan and endosulfan sulfate in greenhouse air have been described (Vidal et al. 1997). Results indicate that 7.5% of the initial concentration of endosulfan remained in the greenhouse atmosphere 24 hours after application.

The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, estimated that 3,205 workers in the agricultural services industry were exposed to endosulfan in the workplace in 1980 (NIOSH 1984). The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any chemicals; the survey provides only estimates of the number of workers potentially exposed to chemicals in the workplace.

5.6   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 2.7 Children's Susceptibility.

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

Infants are particularly sensitive to endosulfan due to their higher intestinal permeability and immature detoxification system. In a study of human breast milk conducted in the country of Kazakhstan in 1994, the concentration of various contaminants, including endosulfan, were determined (Lutter et al. 1998). Of the 91 samples of breast milk analyzed, only 2 had detectable quantities of endosulfan (concentrations not specified). In another study, the transfer of endosulfan and its metabolites were studied in breast milk of

lactating goats (Indraningsih et al. 1993). Endosulfan residues in milk of goats administered a daily dose of 1 mg/kg for 28 days reached 0.02 mg/kg on day 1. However, by day 8, no residues or metabolites could be detected. Likewise, no endosulfan residues could be detected in the tissues of kids except for α-endosulfan in the liver at a concentration of 0.0011 mg/kg. Analysis of milk from cows which ingested potentially poisonous amounts of endosulfan revealed a level of >1 ppm endosulfan immediately following the intoxication (Braun and Lobb 1976). This level decreased to 1 ppb at the end of 35 days with a half-life of about 4 days in milk. No endosulfan residues were detected (detection limit= 0.01 mg/L) in milk from cows fed silage containing 0.41–2.35 ppm endosulfan for 21 days (Beck et al. 1966).

The FDA pesticide residue monitoring program analyzes selected baby foods for endosulfan under its Total Diet Study. In the period 1991–1995, 29 incidences of detectable amounts of endosulfan were reported from analyses of 276 items purchased in 12 separate collections (FDA 1995).

A total diet study conducted by the FDA from June 1984 to April 1986 studied the dietary intake of various pesticides by different age groups (Gunderson 1995b). The mean daily intakes per unit of body weight (mg/kg body weight/day) for α-endosulfan were 2.6×10^{-6} for children 6–11 months of age and 4.5×10^{-6} for children 2 years of age, while for β-endosulfan the mean daily intakes were 5.4×10^{-6} for children 6–11 months of age and 8.1×10^{-6} for children 2 years of age. In the same type of study conducted from July 1986 to April 1991, the mean daily intakes per unit body weight (mg/kg body weight/day) for α-endosulfan were 3.2×10^{-6} for children 6–11 months of age and 7.6×10^{-6} for children 2 years of age, while for β-endosulfan, the mean daily intakes were 1.69×10^{-5} for children 6–11 months of age and 2.38×10^{-5} for children 2 years of age (Gunderson 1995a). From October 1984 through September 1991, 27 market basket samples of foods eaten by infants and children were collected and analyzed for pesticide residues (Yess et al. 1993). These foods included fruits/fruit juices, baked goods, cereals, combination meat/poultry dinners, desserts, infant formulas, and vegetables. Concentrations of endosulfan (both isomers) found in foods eaten by infants were 0.001 mg/kg in 1 sample of desserts; 0.004 mg/kg (maximum) in 5 samples of applesauce; 0.0007 mg/kg in 1 sample of strained orange/orange pineapple juice; 0.010 mg/kg (maximum) in 3 samples of peaches; 0.053 mg/kg (maximum) in 20 samples of pears/pineapples; 0.002 mg/kg in 1 sample of prunes/plums; and 0.004 mg/kg (maximum) in 2 samples of green beans. Concentrations of endosulfan (both isomers) found in foods eaten by both infants and children were 0.046 mg/kg (maximum) in 25 samples of apples and 0.041 mg/kg (maximum) in 20 samples of raw pears.

5. POTENTIAL FOR HUMAN EXPOSURE

A similar survey conducted in 1977–1978 in 10 cities focused on infant and toddler diets (Podrebarac 1984a). Of 11 food groups included in that survey, β-endosulfan was found in the vegetables and fruit/ fruit juices food groups for the toddler diet at 0.001–0.004 ppm. Endosulfan sulfate was found in the potato and sugar and adjunct groups in the infant diet at 0.001–0.004 ppm and in the vegetable and potato groups in the toddler diet at 0.004–0.005 ppm. The compounds were not detected in the following food groups included in the survey: drinking water; fresh whole milk; other dairy products; meat, fish and poultry; grain and cereal products; oils and fats; or beverages. In a total of 98 infant diet composite samples, β-endosulfan was detected in 1 composite and endosulfan sulfate was found in 2 composites. Out of a total of 110 toddler diet composite samples, the α-isomer, β-isomer, and sulfate forms were detected in 1, 2, and 2 composites, respectively.

Although child exposure to endosulfan through inhalation has not been studied, it is anticipated that exposure through this route is extremely low. The vapor pressure of endosulfan is negligible (1.0x10^{-5} mmHg at 25 EC) (Coleman and Dolinger 1982), suggesting that an extremely small amount is expected to exist in the vapor phase at environmental conditions (Bidleman 1988). Although the vapor density is reported as 14 (HCDB 1986), suggesting that vapor-phase endosulfan is heavier than air, inhalation exposure is not expected to be significant to children due to the extremely small amount of endosulfan that will exist in the vapor-phase at environmental conditions.

Since young children spend more time outdoors and have a tendency to ingest soil, it is important to examine child exposure through ingestion. Although no studies have been conducted concerning this subject, exposure through ingestion of soil is not expected to be significant. Endosulfan undergoes many degradative processes in the environment, such as hydrolysis, photolysis, oxidation, and biodegradation, that will reduce its concentration in soil. Degradation half-lives for the combined effects of hydrolysis and oxidation in moist soils range from 23 to 54 days depending on pH (Greve and Wit 1971). Photolysis on soil surfaces is expected to occur as well. The photolytic half-life of endosulfan on plant leaves was reported to be 7 days (EPA 1982a). Endosulfan has also been shown to be biodegraded by both bacteria and fungi in the soil environment (El Beit et al. 1981b; Martens 1976). Both abiotic and biotic processes are therefore expected to decrease endosulfan concentrations in soil environments. However, children may potentially be exposed to endosulfan from oral/dermal exposure if they play in the soil of contaminated areas such as hazardous waste sites. Based on degradation of endosulfan in the environment, child exposures to endosulfan through soil ingestion is not expected to be very significant.

No studies could be located discussing exposure of children to endosulfan after household use by parents. Likewise, no exposure studies could be located concerning the exposure of children whose parent(s) work with endosulfan on a daily basis. However, many studies suggest that pesticides used in the workplace can be brought home through contaminated clothing, shoes, and other materials (NIOSH 1995). Although no documented cases could be located, the possibility exists that endosulfan used in a work setting may be brought home by working parents. It is uncertain what amount of endosulfan exposure a child may encounter under these situations.

5.7   POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Farmers and pesticide applicators using endosulfan to control insects on crops appear to be the only workers currently exposed to potentially high concentrations of the compound. Members of the general population with potentially high exposure to endosulfan or endosulfan sulfate include people living near the 164 NPL sites currently known to be contaminated with these compounds. Exposure of the general population to higher concentrations of endosulfan may result from chemical contact with or ingestion of contaminated hazardous waste site media, principally soils. The size of these populations and the concentrations of endosulfan in the contaminated media to which these people would potentially be exposed have not been adequately characterized.

In addition to individuals who are occupationally exposed to endosulfan (see Section 5.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to endosulfan. These populations include individuals living in proximity to sites where endosulfan was produced or sites where endosulfan was disposed of, and individuals living near one of the 164 NPL hazardous waste sites where endosulfan has been detected in some environmental media (HazDat 2000).

5.8   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 endosulfan 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 endosulfan.

 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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties.   The physical/chemical properties of endosulfan are
sufficiently well characterized to enable assessment of the environmental fate of the compound (Budavari
1996; Coleman and Dolinger 1982; EPA 1982c, 1987b; Hansch and Leo 1995; HSDB 1999; Metcalf
1995; NIOSH 1997; Sittig 1980; Suntio et al. 1988; Tomlin 1997). The relative persistence of the two
isomers and the potential for conversion from one isomer to another may also deserve further study.

Production, Import/Export, Use, Release, and Disposal.   Endosulfan is distributed in the
environment as a result of its use as an insecticide (Gregor and Gummer 1989; NRCC 1975; Strachan et
al. 1980). Humans may be exposed through the ingestion or use of contaminated food (Gartrell et al.
1986; Podrebarac 1984a) or tobacco products (EPA 1982a), contact with media from contaminated
hazardous waste sites (principally soils), or insecticide application (Oudbier et al. 1974; Wolfe et al.
1972).

Although endosulfan is currently produced for use as an insecticide, information on the current
production, import, and export of endosulfan by the United States is limited. Annual production volumes
in the United States were 3 million pounds in 1980 (Sittig 1980), and 10,000 metric tons (approximately
22 million pounds) worldwide were reported in 1984 (WHO 1984). However, as of 1982, endosulfan was
no longer produced in the United States (HSDB 1999). Although U.S. imports of endosulfan are
reportedly substantial, the most recent import information (182,000 kg) was for the year 1982 (HSDB
1999). Additional information on the production/formulation, import, and export volumes for endosulfan
would be useful in assessing the extent to which, and conditions under which, humans may be exposed to
endosulfan or endosulfan sulfate.

Releases of the compound as an insecticide are typically to the atmosphere and land (WHO 1984). The
medium of most importance to human exposure appears to be contaminated foods (Gartrell et al. 1986).

Methods suggested for the disposal of endosulfan, or more generally, pesticides, their residues and spillage, and contaminated containers include ground surface disposal, incineration, lagooning, and disposal in deep wells, sanitary landfills, and disposal pits (EPA 1974; FAO/WHO 1975a; Working Group on Pesticides 1970). However, no data on the amounts disposed of by each method were available. Regulations pertaining to the disposal of endosulfan include the requirement that containers contaminated with endosulfan residues be emptied, decontaminated, and either recycled or disposed of in landfills, depending on their condition (EPA 1974; FAO/WHO 1975a; HSDB 1999). Current information on disposal practices for endosulfan would be useful in evaluating the potential for exposure to endosulfan and endosulfan sulfate.

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 Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate.   Endosulfan partitions to the atmosphere and soils and sediments. It is transported in the atmosphere (Gregor and Gummer 1989; Strachan et al. 1980), but it is immobile in soils (Bowman et al. 1965; El Beit et al. 1981c; Hodapp and Winterlin 1989; Stewart and Cairns 1974). It is transformed in surface waters and soils via hydrolysis (Greve and Wit 1971; Schoetteger 1970) and biodegradation (Cotham and Bidleman 1989; El Beit et al. 1981c; Greve and Wit 1971; Martens 1976; Miles and Moy 1979; Stewart and Cairns 1974). Endosulfan sulfate persists in soils (Coleman and Dolinger 1982). Additional information is needed on the extent to which the compound undergoes photochemical oxidation in the atmosphere. This information would be helpful in establishing the atmospheric half-life of the compound.

Bioavailability from Environmental Media.   Endosulfan can be absorbed following inhalation of contaminated workplace air and ingestion of insecticide-contaminated food (Ely et al. 1967). Dermal contact with or ingestion of endosulfan that is tightly bound to soil particles is an exposure route of concern at hazardous waste sites. No information is available on the absorption of endosulfan in either adults or children following ingestion or dermal contact with contaminated soils. Therefore, additional information is needed on the uptake of endosulfan from contaminated soil following ingestion or dermal contact. This information would be useful in determining the bioavailability of soil-bound endosulfan.

5. POTENTIAL FOR HUMAN EXPOSURE

Food Chain Bioaccumulation.   Endosulfan is bioconcentrated by aquatic organisms (Ernst 1977; Novak and Ahmad 1989; NRCC 1975; Roberts 1972; Schimmel et al. 1977) but not by plants or animals (EPA 1982a). The compound is metabolized by terrestrial (Coleman and Dolinger 1982; El Beit et al. 1981c; Martens 1977; NRCC 1975) and aquatic organisms (Cotham and Bidleman 1989), and it does not biomagnify to any great extent in terrestrial or aquatic food chains (HSDB 1999). No additional information on the bioaccumulation of endosulfan is needed at this time.

Exposure Levels in Environmental Media.   Endosulfan and endosulfan sulfate have been detected in ambient air (Bidleman 1981; Kutz et al. 1976), surface water (EPA 1980b, 1982c; Frank et al. 1982b; Maguire et al. 1983; McFall et al. 1985; Miles and Harris 1971; Willis et al. 1987), rain water (Strachan and Huneault 1979), cropland soils (Carey et al. 1979a, 1979b), and some foodstuffs (Gartrell et al. 1986; Podrebarac 1984a). However, with the exception of the food concentrations, the data are not current. Estimates of human intake of endosulfan or endosulfan sulfate are limited to ingestion of contaminated foodstuffs. Additional information is needed on the current levels of these compounds in ambient air, surface water, and soils, particularly at the 162 NPL hazardous waste sites known to be contaminated with these compounds. This information would be helpful in estimating human exposure to these compounds via contact with contaminated media.

Reliable monitoring data for the levels of endosulfan in contaminated media at hazardous waste sites are needed. This information could be used in combination with the known body burdens of endosulfan to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans.   Endosulfan and endosulfan sulfate can be measured in human blood, urine, and tissues following exposure to high levels in workplace environments or following accidental or intentional ingestion of insecticides containing endosulfan (Coutselinis et al. 1978; Demeter and Heyndrickx 1978; Demeter et al. 1977). However, no monitoring studies are available in which human fluids or tissues were used to assess occupational or general population exposure to endosulfan. Additional data on levels in human blood and urine are needed following occupational and general population exposure, particularly exposure at hazardous waste sites, in order to correlate concentrations in these media with those in environmental media and the subsequent development of health effects, if any.

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

Exposures of Children.   Data need to be developed to properly assess the exposure of infants who eat processed baby foods containing residues of pesticides such as endosulfan. Several studies have estimated exposure based on endosulfan concentration found in foods typically eaten by infants; however, no studies that directly studied infant exposure could be located. Attention should also be given to infant formulas and to the tap water used to prepare infant formulas from condensed or powdered forms. More data are also required to properly assess endosulfan exposure to children who live, play, or attend school near farmlands that are treated with endosulfan. Maps that catalog endosulfan use on crops and present average application rates would better allow an assessment of the potential for children in farming communities to be exposed. The possibility that farming parents' work clothes and shoes may carry endosulfan residues into the home also should be studied. In addition, home use of endosulfan, which may result in exposure of children, needs to be investigated.

Child health data needs relating to susceptibility are discussed in 2.1.2.2 Identification of Data Needs: Children's Susceptibility.

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

The compound 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 the exposure to this compound.

Information is particularly needed on the size of the populations potentially exposed to endosulfan 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 endosulfan. 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 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.

5.8.2 Ongoing Studies

No ongoing studies regarding release, bioavailability, bioaccumulation or exposure registries were located. However, several ongoing studies regarding the fate and transport, disposal, and human exposure of endosulfan were located. Researchers from the University of Nevada are examining the atmospheric transport and deposition of endosulfan and its input to the Sierra Nevada mountains (FEDRIP 1999). At the University of California at Davis, researchers are examining an integrated approach to the bioremediation of pesticides at hazardous waste sites (FEDRIP 1999). This approach involves the use of flooded plots and rice plants to enhance degradation. In another study, researchers from Kentucky State University are analyzing the fate of endosulfan under field conditions in an artificial wetlands environment (FEDRIP 1999). They are studying the influence of landscape features and soil amendments on runoff and infiltration of water quality as well as the fate of pesticides found along the edge of fields. In New South Wales, a group of researchers are examining the impact of endosulfan on natural water systems as a result of industrial activity (FEDRIP 1999). At the Beltsville Agricultural Research Center, the atmospheric and surface interactions of endosulfan and its fate and transport are being studied (FEDRIP 1999).

6. ANALYTICAL METHODS

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

6.1   BIOLOGICAL SAMPLES

Endosulfan in its pure form is a crystalline substance consisting of α- and β-isomers in the ratio of approximately 7:3. It is an organochlorine pesticide, and analysis of biological and environmental samples for endosulfan commonly results in the detection of other organochlorine pesticides and polychlorinated biphenyls. These can interfere with the determination of endosulfan unless adequate cleaning and separation techniques are used. Detection of low levels of endosulfan typically involves extraction of samples with organic solvents, a clean-up step to remove lipids and other materials that may interfere with analysis, high-resolution gas chromatography (HRGC) to separate endosulfan from other compounds in the extract, and confirmation of endosulfan by electron capture detector (ECD) or mass spectroscopy (MS). Method blanks and control samples should be used to verify method performance and to ensure that the reagents and glassware are not introducing contaminants that might interfere with the determination of endosulfan isomers or endosulfan sulfate.

The method of choice for the determination of α- and β-endosulfan in blood, urine, liver, kidney, brain, and adipose tissue is gas chromatography equipped with an electron capture detector (GC/ECD) (Coutselinis et al. 1976; Demeter and Heyndrickx 1979; Demeter et al. 1977; Le Bel and Williams 1986). This is because GC/ECD is relatively inexpensive, simple to operate, and offers a high sensitivity for halogens (Griffith and Blanke 1974). After fractionation of adipose tissue extracts using gel permeation chromatography, detection limits of low-ppb (1.2 ng/g) were achieved for endosulfan and other chlorinated pesticides using GC/ECD (Le Bel and Williams 1986).

A new technique has been developed to analyze α- and β-endosulfan concentrations in human urine (Vidal et al. 1998). Samples are mixed with a buffer solution and then passed through solid phase extraction cartridges for analysis using gas chromatography-tandem mass spectrometry (GC-MS-MS).

β-Endosulfan has also been measured in hand rinsings using GC/ECD (Kazen et al. 1974). Sample preparation involves hand rinses with hexane followed by concentration, fractionation, and clean-up with Florisil®. Sensitivity, recovery, and precision data were not reported.

Positive identification of low-ppb (µg/L) levels of endosulfan in human blood has been achieved by GC equipped with a microcoulometric detector (GC/MC) (Griffith and Blanke 1974). Although GC/MC is specific and nearly as sensitive as GC/ECD for detecting endosulfan in blood, GC/MC is more difficult to operate. Both isomers of endosulfan can be measured in blood using a method described by Guardino et al. (1996). According to the authors, endosulfan can be recovered and measured with an approximate limit of quantitation (LOQ) of 0.2 µg/L (sub-ppb).

GC/MS has been employed by Demeter et al. (1978) to quantitatively detect low-ppb levels of α- and β-endosulfan in human serum, urine, and liver. This technique could not separate α- and β-isomers, and limited sensitivity confined its use to toxicological analysis following exposures to high levels of endosulfan. More recently, Le Bel and Williams (1986) and Williams et al. (1988) employed GC/MS to confirm qualitatively the presence of α-endosulfan in adipose tissue previously analyzed quantitatively by GC/ECD. These studies indicate that GC/MS is not as sensitive as GC/ECD. Mariani et al. (1995) have used GC in conjunction with negative ion chemical ionization mass spectrometry to determine alpha- and beta-endosulfan in plasma and brain samples with limits of detection reported to be 5 ppb in each matrix. Details of commonly used analytical methods for several types of biological media are presented in Table 6-1.

6.2 ENVIRONMENTAL SAMPLES

Reliable analysis of endosulfan residue concentrations in environmental samples usually involves detection of the α- and β-isomers plus endosulfan sulfate (a degradation product of endosulfan). GC/ECD has been the most widely used analytical technique for determining low-ppb to parts-per-trillion (ppt) levels of α- and β-endosulfan and endosulfan sulfate in air, water, waste water, sediment, soil, fish, and various foods (Bennett et al. 1997; Chopra and Mahfouz 1977a; EPA 1988a, 1997a, 1997b, 1997c, 1992a; FDA 1994; Fisk 1986; Fukuhara et al. 1977; Giabbai et al. 1983; Goebel et al. 1982; Kutz et al.

Table 6-1. Analytical Methods for Determining Endosulfan in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Acidification of blood sample and extraction with ether; evaporation of extract to dryness and dissolution of residue in hexane	GC/ECD	No data	65–68	Coutselinis et al. 1976
Blood	Addition of H_2SO_4 to blood sample, extraction with hexane, acetone (9:1) and extract concentration	GC/MC	10–20 μg/L (ppb)	50	Griffith and Blanke 1974
Blood	Homogenization of sample followed by extraction with methanol and centrifugation; isolation of pesticides using SPE	GC/ECD	Approximately 0.2 µg/L (ppb)	No data	Guardino et al. 1996
Blood (serum) and urine	Extraction of sample with benzene and concentration; clean-up using HPLC	GC/MS	Low/μg/L (ppb) levels	99–103% (generally 1–14% RSD; worst for serum)	Demeter et al. 1978
Plasma, brain (alpha and beta)	Brain: homogenization with ethanol, centrifugation, phase separation and evaporation of ethanol and addition of internal stardard. Plasma: extraction with hexane and then as for brain samples	GC/NICI MS	5 ng/mL for plasma (ppb); 5 ng/g (ppb) for brain; 8–31% RSD	85–93	Mariani et al. 1995
Liver, kidney, and brain	Homogenization and addition of hexane to tissue sample; evaporation of extract to dryness; dissolution of residue in hexane	GC/ECD	No data	65–68	Coutselinis et al. 1976

Table 6-1. Analytical Methods for Determining Endosulfan in Biological Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver	Addition of water to sample followed by homogenization; extraction with benzene, clean-up on silica column and HPLC	GC/ECD	No data	No data	Demeter and Heyndrickx 1979
Liver	Addition of water to sample followed by homogenization an dextraction with benzene; clean-up extract on HPLC	GC/MS	Low μg/L (ppb) levels	No data	Demeter et al. 1978
Adipose tissue	Addition of acetone: hexane (15:88) to tissue followed by homogenization; clean-up extract on gel permeation and Florisil® columns	GC/ECD and GC/MS	0.0012 μg/L (ppb)	96.5 (at 0.01 μg/L)	Le Bel and Williams 1986
Hand rinsings	Rinsing of hands twice with hexane; solvent volume reduction; fractionation and clean-up on Florisal®	GC/ECD	No data	No data	Kazen et al. 1974

ECD = electron capture detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; MC = microcoulometric detector; MS = mass spectrometry; NICI = negative ion chemical ionization; RSD = relative standard deviation; SPE = solid phase extraction

1976; Marsden et al. 1986; Mitchell 1976; Musial et al. 1976; Noroozian et al. 1987; Pokharker and Dethe 1981; Woodrow et al. 1986; Zoun et al. 1987). Both GC and high performance liquid chromatography (HPLC) have been used to separate endosulfan and its major metabolites endosulfan ether, endosulfan sulfate, endosulfan lactone, and endosulfan diol (Kaur et al. 1997).

Solid phase micro extraction (SPME) is a techniques in which a silica fiber coated with a thin film of polymer is brought into contact with an aqueous matrix where the organics in solution partition onto the fiber. The fiber is subsequently placed into the injector of a GC where the heat causes the release of analyte onto the column. This has been applied to endosulfan (α- and β-) and endosulfan sulfate in water with limits of detection of less than 0.3 µg/L reported (Magdic and Pawliszyn 1996).

Measurements of endosulfan in air are made on samples forced through a collection device. The sample is extracted with an organic solvent, followed by clean-up using column chromatography. GC, GC/MS, and GC/ECD have been used to analyze endosulfan in air samples. Method TO-4 (EPA 1988a) uses the adsorption of the pesticides onto polyurethane foam in a high-volume sampler with subsequent extraction and analysis using GC/ECD. Sensitivities on the order of 1 ng/m^3 were reported. Kutz et al. (1976) used a polyethylene glycol impinger for sample collection of ambient air from several sites throughout the U.S. Extraction and clean-up were followed by quantitative analysis by GC/ECD. The lower limit of detection using this method was 0.001–0.01 µg/m^3.

GC/ECD or a halogen-specific detector (HSD) (Method 8080) is the technique recommended by EPA's Office of Solid Waste and Emergency Response for determining α- and β-endosulfan and endosulfan sulfate in water and waste water at low-ppb levels (EPA 1986a). At these low concentrations, identification of endosulfan residues can be hampered by the presence of a variety of other pesticides. Consequently, sample clean-up on a Florisil® column is usually required prior to analysis (EPA 1986a).

Methods 508, 508.1, and 525.2 (EPA 1997a, 1997b, 1997c) are applicable to drinking water and ground-water and can determine α- and β-endosulfan and endosulfan sulphate at concentrations as low as 7 ppt using liquid solid extraction (LSE) and GC/ECD.

GC/ECD and GC/MS (EPA Method 608) are the methods recommended for determining α-endosulfan, β-endosulfan, and endosulfan sulfate in municipal and industrial discharges (EPA 1991a). Sample clean-up on Florisil® column and an elemental sulfur removal procedure are used to reduce or eliminate interferences. Sensitivity is in the sub-ppb range. Recoveries and precision are good.

A procedure has been developed for the analysis of α- and β-endosulfan and endosulfan sulfate in fish, water, and sediments (Chau and Terry 1972; Musial et al. 1976). This procedure involves the acetylation of endosulfan residues into their diacetates and subsequent quantification by GC/ECD. Detection limits of low-ppb levels of endosulfan were reported. This approach is rapid and simple, and minimum sample preparation is required (Chau and Terry 1972; Musial et al. 1976).

Numerous methods have also been reported for foods, including milk (Bennett et al. 1997), chili fruits (Pokharkar and Dethe 1981), fruits and vegetables (Mitchell 1976), and the multiresidue methods for fatty and non-fatty foods (fruits, vegetables, seeds, dairy, eggs, meats) published by FDA (FDA 1994). Limits of detection are generally in the sub-ppm to ppb range.

Dreher and Podratzki (1988) developed an enzyme immunoassay technique for detecting endosulfan and its degradation products (i.e., endosulfan diol, endosulfan sulfate, endosulfan ether, and endosulfan lactone) in aqueous media. The enzyme immunoassay technique is based on detecting antibodies raised against the diol of endosulfan by immunizing rabbits with an endosulfan-hemocyanin conjugate. Minor problems were encountered with coupling of the detecting enzyme (peroxidase) to the conjugate and with cross-reactivity with the pesticide endrin. Although the enzyme immunoassay technique does not require sample extraction, and it is rapid and inexpensive, it is not yet in common use in environmental residue analysis. A detection limit of 3 μg/endosulfan/L of sample was achieved (Dreher and Podratzki 1988; Frevert et al. 1988). Immunoassays have also been reported for endosulfan (both isomers), endosulfan sulfate, and endosulfan diol in water and soil (Lee et al. 1997a, 1997b) with limits of detection reported to be 0.2 μg/L for water and 20 μg/kg in soil. Details of commonly used analytical methods for various environmental media are presented in Table 6-2.

6.3   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 endosulfan 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 endosulfan.

Table 6-2. Analytical Methods for Determining Endosulfan in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Pumping of air through glass fiber filter and polyurethane foam plugs for collection; extraction of plugs with petroleum ether and filters with dichloromethane followed by hexane reflux; clean-up on either Florisil/ alumina or silicic acid column	GC and GC/MS	No data	No data	Bidleman 1981
Air	Collection on polyethylene glycol impinger and extraction with hexane; clean-up on Florisil column	GC/ECD	0.001–0.01 µg/m^3	No data	Kutz et al. 1976
Air	Collection of pesticide onto polyurethane foam using high volume sampler; extraction of PUF using 5% ether in hexane; extract volume reduction; column clean-up	GC/ECD	Approximately 1 ng/m^3	>75%	EPA 1988a (Method TO-4)
Drinking water	Extraction of water with methylene chloride, removal of water from extract, volume reduction to 5 mL after solvent exchange to methyl-t-butyl ether	GC/ECD	α-endosulfan: 0.015 µg/L (ppb); β-endosulfan: 0.024 µg/L; endosulfan sulfate: 0.015 µg/L	α: 87 (10% RSD) β: 92 (11% RSD) sulfate: 102 (15% RSD)	EPA 1997d (Method 508)
Drinking water	Extraction of water using C$_{18}$ extraction disks (LSE); elution using ethyl acetate and methylene chloride; volume reduction	GC/ECD	< 0.007 µg/L (α, β, and sulfate)	88–106, (12–29% RSD) at 0.03 µg/L	EPA 1997e (Method 508.1)
Drinking water	Extraction of sample using LSE; solvent elution; volume reduction	GC/MS	0.07 to 0.11 µg/L using ITMS (α, β, and sulfate)	116–128	EPA 1997f (Method 525.2)
Water	Passage of samples through XAD-4 resin column and extraction with methylene chloride; clean-up extract with HPLC	GC/ECD	0.00001 µg/L	65.5 (at 0.01 µg/L	Woodrow et al. 1986
Water	Extraction of sample with methylene chloride	GC/MS	10 µg/L	87 (α-endosulfan); 107 (β-endosulfan II); 71 (endosulfan sulfate)	Eichelberger et al. 1983

Table 6-2. Analytical Methods for Determining Endosulfan in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Extract ion of sample with toluene	GC/ECD	0.5 µg/L (α-endo-sulfan); 0.5 µg/L (β-endosulfan); 25 µg/L (endosulfan sulfate)	99 (α-endosulfan); 99 (β-endosulfan); no data (endosulfan sulfate)	Zoun et al. 1987
Water	Adjustment of pH of sample to near neutral and extraction with methylene chloride; volume reduction; clean-up sample on Florisil column	GC/ECD	0.5 µg/L (α-endo-sulfan); 0.1 µg/L (β-endosulfan); 0.1 µg/L (endosulfan sulfate)	No data	Marsden et al. 1986
Water	Development of antibodies against the diol of endosulfan and its degradation products	EIA	3 µg/L	No data	Dreher and Podratzki 1988; Frevert et al. 1988
Water	SPME of water; thermal transfer to GC	GC/ECD	α: 0.3 µg/L (ppb) β: 0.4 µg/L (ppb) Sulfate: 0.05 µg/L (ppb)	No data	Magdic and Pawliszyn 1996
Water, soil	Analysis of water directly; extraction of soil with methanol followed by dilution of extract with water	Immunoassay (Total endosulfan including endosulfan sulfate and endosulfan diol)	water: 0.2 µg/L (ppb) soil: 20 µg/kg (ppb)	No data	Lee et al. 1997a, 1997b
Water; waste water	Extraction of sample with methylene chloride and clean-up on Florisil column	GC/ECD	0.49 µg/L (α-endo-sulfan); 6.1 µg/L (β-endosulfan); 2.7 µg/l (endosulfan sulfate)	No data	EPA 1986c (Method 8080)
Municipal and industrial discharge	Extraction of sample with methylene chloride; water removal; exchange to hexane; volume reduction; clean-up on Florisil column and removal of elemental sulfur	GC/ECD; GC/MS	0.014 µg/L (α-endo-sulfan); 0.004 µg/L (β-endosulfan); 0.066 µg/L (endosulfan sulfate)	97 (α-endosulfan); 93 (β-endosulfan); 89 (endosulfan sulfate)	EPA 1991b (Method 608)

Table 6-2. Analytical Methods for Determining Endosulfan in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Municipal and industrial wastewater; sludge	Extraction with methylene chloride or acetonitrile and methylene chloride (depending on solids content); volume reduction and clean-up using GPC, column chromatography, or SPE; sulfur removal if needed	GC/ECD	α: 11 ng/L β: 8 ng/L sulfate: 7 ng/L	18–158	EPA 1992a (Method 1656)
Water; fish	Extraction of sample with organic solvents; derivatize to the diacetate and analyze	GC/ECD	0.005 µg/L	60–65	Chau and Terry 1972
Fish	Grinding of sample and extraction with toluene; clean-up extract on alumina column	GC/ECD	0.005 µg/L (α-endo-sulfan); 0.005 µg/L (β-endosulfan); 0.025 µg/L (endosulfan sulfate)	84 (α-endosulfan); 79 (β-endosulfan); 86 (endosulfan sulfate)	Zoun et al. 1987
Sediment	Extraction of sample with organic solvent; derivatize extract to the diacetate	GC/ECD	0.005–0.01 µg/g (ppm)	No data	Musial et al. 1976
Sediment; soil	Extract of sample with methylene chloride: acetone (1:1); clean-up extract using Florisil column	GC/ECD	0.002 µg/g (ppm) (α-endosulfan); 0.004 µg/g (β-endo-sulfan); 0.004 µg/g (endosulfan sulfate)	No data	Marsden et al. 1986
Non-fatty foods (<2% fat, > 75% water)	Extraction with acetone and removal of water with Hydromatrix; cleanup using Florisil	GC/ECD	No data	>85% (α, β, sulfate)	FDA 1994 (PAM Method 302)
Non-fatty foods (<2% fat, <75% water)	Extraction with acetonitrile, partition into petroleum ether; cleanup using Florisil	GC/ECD	No data	>85% (α, β, sulfate)	FDA 1994 (PAM Method 303)
Fatty foods (>2% fat)	Extraction of fat using sodium sulfate, petroleum ether, by filtering, or by solvents; cleanup using solvent partitioning, Florisil	GC/ECD	No data	>85% (α, β, sulfate)	FDA 1994 (PAM Method 304)

Table 6-2. Analytical Methods for Determining Endosulfan in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Milk	Extraction of milk with ethanol-ethyl acetate (9: 95, v/v) with sodium sulfate; centrifugation and volume reduction	GC/ELCD	α: 0.9 µg/kg (ppb) β: 0.9 µg/kg Sulfate: 1.8 µg/kg	α: 90 (5% RSD) β: 91 (11% RSD) Sulfate: 88 (11% RSD)	Bennett et al. 1997
Chili fruits	Homogenization of sample with benzene:isopropanol (3:1); clean-up extract using carbon:celite (1:1)	GC/ECD	0.005 µg per sample	96.4 (α-endosulfan); 97 (β-endosulfan); 96.2 (endosulfan sulfate)	Pokharkar and Dethe 1981
Fruits; vegetables	Homogenization of sample with acetonitrile and clean-up on Florisil column	GC/ECD	<1 ppm (mg/kg)	101.5–103.6 (α-endo-sulfan); 100–102 (β-endo-sulfan); 92.9 (endosulfan sulfate)	Mitchell 1976

GC = gas chromatography; ECD = electron capture detector; EIA = enzyme-immunoassay; GPC = gel permeation chromatography; HPLC = high-performance liquid chromatography; ITMS = ion trap mass spectrometer; LSE = liquid solid extraction; MS = mass spectrometry; RSD = relative standard deviation; SPE = solid phase extraction

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.

6.3.1   Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.   GC/ECD, GC/MS, and GC/MC are analytical techniques used for measuring endosulfan in blood, urine, hand rinses, and various biological tissues and excreta at low- and sub-ppb levels (Coutselinis et al. 1976; Demeter and Heyndrickx 1978; Demeter et al. 1977; Griffith and Blanke 1974; Guardino et al. 1996; Kazen et al. 1974; Le Bel and Williams 1986; Mariani et al. 1995; Williams et al. 1988). These techniques are sensitive for measuring background levels of endosulfan in the population and levels of endosulfan at which health effects might begin to occur. However, it should be noted that because endosulfan is used in tobacco farming, background levels of endosulfan in the population may vary considerably, especially between smokers and nonsmokers (Coleman and Dolinger 1982; WHO 1984). Although accurate and reliable methods are available for analysis of endosulfan in biological tissues and fluids, insufficient data have been collected using these techniques to correlate the concentrations of endosulfan in biological materials with environmental exposure and health effects (see Chapter 2).

Sensitive, reliable biochemical assays have been used for measuring changes in enzyme activities (e.g., aminopyrine-*N*-demethylase, aniline hydroxylase) as an indication of exposure to endosulfan in animals (Agarwal et al. 1978). Decreased red blood cells, hemoglobin, and IgG and IgM levels have also been detected in animals following exposure to endosulfan (Banerjee and Hussain 1986, 1987; Das and Garg 1981; Hoechst 1985a; Siddiqui et al. 1987b). While well documented methods exist to monitor these parameters, they are not specific for endosulfan exposure (see Chapter 2). However, if used in combination with measurements of endosulfan and its metabolites in biological tissues and excreta, one or more of these enzymatic and blood changes may prove to be useful biomarkers of exposure and effect. There is a need for further research to correlate specific levels of endosulfan in biological media with known biochemical changes that occur on exposure to endosulfan.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media.   GC/ECD is the most prevalent analytical method for measuring low levels of α- and

β-endosulfan and endosulfan sulfate in water, waste water, soil, sediment, and foods (Bennett et al. 1997;
Chopra and Mahfouz 1977a; EPA 1986a, 1988a, 1991a, 1992; FDA 1994; Fisk 1986; Fukuhara et
al. 1977; Giabbai et al. 1983; Goebel et al. 1982; Kutz et al. 1976; Marsden et al. 1986; Mitchell 1976;
Noroozian et al. 1987; Pokharker and Dethe 1981; Woodrow et al. 1986; Zoun et al. 1987). This
technique is sensitive for measuring background levels of endosulfan in foods and water (media of most
concern for potential human exposure to endosulfan) and levels of endosulfan at which health effects
might begin to occur. The chronic oral MRL is 0.002 mg/kg/day, which translates to a required LOD of
0.07 mg/L, and these methods easily meet that need. GC/ECD or HSD is the method (Method 8080)
recommended by EPA (1986a) for detecting α- and β-endosulfan and endosulfan sulfate in water and
waste water at low-ppb levels. GC/ECD has also been used to detect low-ppb levels of α- and
β-endosulfan and endosulfan sulfate in foodstuffs, soil, and sediment.

An enzyme immunoassay technique has been employed for measuring endosulfan and its degradation
products (i.e., endosulfan diol, endosulfan sulfate, endosulfan ether, and endosulfan lactone) in water at
3 ppb (Chau and Terry 1972; Musial et al. 1976). However, this technique is not currently in use in
environmental residue analysis. Further research into this technique could produce a rapid, reliable, and
sensitive method for identifying contaminated areas posing a risk to human health. No additional
methods for detecting endosulfan in environmental media appear to be necessary at this time. However,
methods for the determination of endosulfan degradation products are needed.

6.3.2 Ongoing Studies

Researchers at the University of Florida Department of Food Science and Nutrition are evaluating the use
of liquid solid extraction for the determination of endosulfan and other pesticides in seawater and fish
(FEDRIP 1999). At the U.S. Department of Agriculture in Beltsville, Maryland, scientists are studying
the transport, deposition, and degradation of pesticides, including endosulfan. They stress the importance
of measuring both the α-and β-isomers because of the transformations (FEDRIP 1999). A technique
using solid phase extraction to sample water for endosulfan concentrations is being developed by the
University of Florida (FEDRIP 1999). The storage stability and transportability of endosulfan absorbed
by the disks will be studied to determine analytical efficiency. The Eastern Regional Research Center in
Wyndmoor Pennsylvania is developing advanced technologies for the analysis of endosulfan in meat,
poultry and eggs (FEDRIP 1999). This technique will include the use of a supercritical fluid extractor in
order to reduce the amount of organic solvent use and to speed up extraction times.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines pertaining to endosulfan and its metabolites in air, water, and other media are summarized in Table 7-1.

ATSDR has derived an intermediate-duration oral MRL of 0.005 mg/kg/day for endosulfan based on a NOAEL for immunological effects in rats (Banerjee and Hussain 1986).

ATSDR has derived a chronic-duration oral MRL of 0.002 mg/kg/day for endosulfan based on a NOAEL for hepatic effects in dogs (Hoechst 1989c).

EPA's Integrated Risk Information System (IRIS) lists an oral reference dose (RfD) of 0.006 mg/kg/day for endosulfan (IRIS 2000). No reference concentration (RfC) for chronic inhalation exposures to endosulfan was reported.

The U.S. EPA and the International Agency for Research on Cancer (IARC) have not classified endosulfan as to its carcinogenicity (IARC 1987, 1998). Studies conducted by the National Toxicology Program (NTP) using rats and mice indicated inadequate and negative evidence, respectively, for carcinogenic effect from endosulfan (NTP 1991). No data were available for studies conducted for the metabolites of endosulfan.

Endosulfan, α-endosulfan, and β-endosulfan have been designated as a hazardous substances pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1995a, 1996b). The statutory source for this designation for the alpha- and beta- compounds is Section 307 of the Clean Water Act (CWA). In addition to Section 307 of the CWA, the designation for endosulfan is based on section 311(b)(4) of the CWA, and section 3001 of the Resource Conservation and Recovery Act (RCRA) (EPA 1995a). The owner and operator of any facility that produces, uses, or stores a CERCLA hazardous substance in an amount exceeding the "threshold planning quantity" are required to immediately report any release to any environmental media, if the amount released is equal to or exceeds the specified "reportable quantity" assigned to the substance. As a hazardous substance that is formulated as a solid, endosulfan is subject to either of two threshold planning quantities (EPA 1996b). If a solid hazardous substance exits in powdered form and has a particle size less than 100 microns, then it is subject to the lower number. If the solid does not meet this criteria, then it is subject to the higher number. The threshold reporting quantities for endosulfan are 10 and 10,000 pounds (4.54 and 4,540 kg)

Table 7-1. Regulations and Guidelines Applicable to Endosulfan

Agency	Description	Information	References
INTERNATIONAL Guidelines:			
IARC	Cancer Classification	None	IARC 1987
WHO	Drinking-water guideline values for health-related organics	None	WHO 1984
NATIONAL Regulations and Guidelines:			
a. Air:			
ACGIH	TLV-TWA (skin)	0.1 mg/m^3	ACGIH 1999
NIOSH	REL TWA (skin)	0.1 mg/m^3	NIOSH 1999

OSHA	PEL 8-hr TWA
	    Current
	    Vacated[a]
		
		None
		0.1 mg/m^3
			
			OSHA 1989a
			OSHA 1993

	OSHA Standards for Shipyard Employment–endosulfan	0.1 mg/m^3	29 CFR 1915.1000, OSHA 1999a
	TLV for Construction Workers–endosulfan	0.1 mg/m^3	29 CFR 1926.55, OSHA 1999b
b. Water			

EPA	Ambient water quality criteria for protection of human health for alpha-, beta-endosulfan and endosulfan sulfate[b]:
	    water and organisms
	    organisms only
		
		110 µg/L
		240 µg/L
			EPA 1999c

	Ambient water quality criteria for protection of aquatic life for alpha-, beta-endosulfan and endosulfan sulfate[b]:
	    Freshwater
	    Saltwater
		
		0.22 µg/L
		0.034 µg/L
			EPA 1999c

	Universal treatment standards
	    alpha-endosulfan
	    beta-endosulfan
	    endosulfan sulfate
	
	    alpha-endosulfan
	    beta-endosulfan
	    endosulfan sulfate
		Waste water
		0.023 mg/L
		0.029 mg/L
		0.029 mg/L
		
		Non-waste water
		0.066 mg/L
		0.13 mg/L
		0.13 mg/L
			40 CFR 268.48, EPA 1999b

Table 7-1. Regulations and Guidelines Applicable to Endosulfan *(continued)*

Agency	Description	Information	References
NATIONAL (contd)			
	Water Quality Guidance for the Great Lakes System—Pollutants that are bioaccumulative	Yes	40 CFR 132, EPA 1995d
c. Food:			
	Pesticide Classification for endosulfan and endosulfan sulfate	Chlorinated organic pesticide	40 CFR 180.3 EPA 1998g
	Tolerances for endosulfan and endosulfan sulfate residues in or on raw agricultural commodities	0.1–2.0 ppm range for 79 commodities	40 CFR 180.182, EPA 1998h
	Pesticide Tolerances in Food– endouslfan and endosulfan sulfate residue in or on dried tea	24 ppm	40 CFR 185.2600 EPA 1998k
d. Other:			
ACGIH	Cancer Classification	A4[c]	ACGIH 1999
ATSDR	Minimal Risk Level		
	intermediate-duration oral	0.005 mg/kg/day	Banerjee and Hussain 1986
	chronic-duration oral	0.002 mg/kg/day	Hoechst 1989c
EPA	RfD (Oral) Carcinogenic classification Oral slope factor	6×10^{-3} mg/kg/day No data No data	IRIS 1999
	Reportable quantities of hazardous substances		40 CFR 302.4, EPA 1999d
	Endosulfan - designated CERCLA hazardous substance under sections 311(b)(4), and 307(a), of the Clean Water Act and RCRA section 3001	1 pound (0.454 kg)	
	Alpha-endosulfan - designated CERCLA hazardous under section 307(a) of the Clean Water Act	1 pound (0.454 kg)	
	Beta-endosulfan - designated CERCLA hazardous under section 307(a) of the Clean Water Act	1 pound (0.454 kg)	

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Endosulfan *(continued)*

Agency	Description	Information	References
NATIONAL (contd)			
	Endosulfan sulfate - designated CERCLA hazardous under section 307(a) of the Clean Water Act	1 pound (0.454 kg)	
	Statutory source for designation as a CERCLA Hazardous Substance	Yes	Clean Water Act, U.S. Congress 1977
	Designated hazardous substance in accordance with section 311(b)(2)(a) of the Act	Yes	40 CFR 116.4 EPA 1998l
	Toxic chemical release reporting; community right-to-know list	Not included	40 CFR 372.65, EPA 1998j
	Included in the list of organic pesticide active ingredients	Yes	40 CFR 455.67, EPA 1998e
	Identification and Listing of endosulfan as a Hazardous Waste	Yes	40 CFR 261.33, EPA 1999a
	Designated toxic pollutant under Section 307(a)(1) of the Act– endosulfan and its metabolites	Yes	40 CFR 401.15 EPA 1998m
STATE Regulations and Guidelines:			
a. Air:			
Arizona	Average acceptable ambient air concentrations[d] (1 hour) (24 hours)	2.4 µg/m^3 0.8 µg/m^3	NATICH 1992
Connecticut	Average acceptable ambient air concentrations[d]— (8 hours)	2 µg/m^3	
Florida (Pinella)	Average acceptable ambient air concentrations[d] (8 hours) (24 hours) (1 year)	1 µg/m^3 0.24 µg/m^3 0.05 µg/m^3	
Idaho	Acceptable concentration Occupational exposure level	0.005 mg/m^3 0.1 mg/m^3	Idaho Department of Health and Welfare 1999
Kansas	Average acceptable ambient air concentrations[d]— (1 year)	0.238 µg/m^3	NATICH 1992
Nevada	Average acceptable ambient air concentrations[d]— (8 hours)	0.002 µg/m^3	
North Dakota	Average acceptable ambient air concentrations[d]— (8 hours)	1x10^{-3} µg/m^3	
Oklahoma	Average acceptable ambient air concentrations[d]— (24 hours)	1.0 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Endosulfan *(continued)*

Agency	Description	Information	References
STATE (contd)			
Pennsylvania	Average acceptable ambient air concentrations[d]— (1 year)	2.4 µg/m^3	
Texas	Average acceptable ambient air concentrations[d]		
	(30 minutes)	1 µg/m^3	
	(1 year)	0.1 µg/m^3	
Virginia	Average acceptable ambient air concentrations[d]— (24 hours)	1.7 µg/m^3	
Washington	Average acceptable ambient air concentrations[d]— (24 hours)	0.3 µg/m^3	
Wisconsin	Acceptable emission levels		Wisconsin Department Natural Resources 1997
	<25 feet	8.4x10^{-3} lbs/hr	
	25 feet	3.4x10^{-2} lbs/hr	
b. Water:			
Alabama	Aquatic life:	acute	chronic	BNA 1998
	Freshwater–alpha-endosulfan and beta-endosulfan	(µg/L) (µg/L) 0.22 0.56	
	Marine alpha-endosulfan and beta-endosulfan	acute chronic (µg/L) (µg/L) 0.34 8.7x10^{-3}	
	Aquatic Life Criteria for alpha-, and beta-endosulfan:		Alabama Department of Environmental Management 1998
	Freshwater acute	0.22 µg/L	
	Freshwater chronic	5.6x10^{-2} µg/L	
	Marine acute	3.4x10^{-2} µg/L	
	Marine chronic	8.7x10^{-3} µg/L	
	Human health criteria for alpha- and beta-endosulfan and endosulfan sulfate[e]:		
	water and fish	3.5X10^{-4} mg/L	
	water only	4.3X10^{-4} mg/L	
Arizona	Drinking water quality guidelines for Endosulfan	74 µg/L	FSTRAC 1995
	Human health based guidance levels (HBGLS)for ingestion of contaminents in drinking water		Arizona Department of Health Services 1999
	Oral HBGL	42 ug/L	
Colorado	Aquatic life based criteria for surface waters— endosulfan		Colorado Department of Public Health and Environment 1999
	Acute	0.11 µg/L	
	Chronic	0.056 µg/L	
	Human health based for surface water— endosulfan sulfate		
	water and organism		
	water only	110 µg/L Not given	

Table 7-1. Regulations and Guidelines Applicable to Endosulfan *(continued)*

Agency	Description	Information	References
STATE (contd)			

Hawaii	Health guidelines applicable to all water:
	    Freshwater
	        acute
	        chronic
	    Saltwater
	        acute
	        chronic
	    Fish consumption
		
		0.22 µg/L
		0.056 µg/L
		
		0.034 µg/L
		0.0087 µg/L
		52 µg/L
			Hawaii Department of Health 1999

Kansas	Surface water quality standards for aquatic life for endosulfan, and alpha- and beta-endosulfan
	    acute
	    chronic
		
		0.22 mg/L
		0.056 mg/L
			Kansas State Health and Environment 1998

New Jersey	Ground water quality for endosulfan, alpha- and beta-endosulfan, and endosulfan sulfate	0.4 µg/L	New Jersey Dept of Environmental Protection 1993

[a]Since June 27, 1974, OSHA had promulgated permissible exposure limits (PELs) for approximately 264 toxic substances. On January 18, 1989, OSHA promulgated more protective PELs for approximately 376 toxic substances. In July 1992, the 11th Circuit Court Appeals rescinded the 1989 promulgation. On March 23, 1993, OSHA resumed enforcing the air contaminant exposure limits that were in effect prior to the issuance of the new limits in 1989 (i.e., OSHA 1974 PELs). Prior to the 1989 promulgation, OSHA had not established a PEL for endosulfan. On June 30, 1993, OSHA published in the Federal Register a final rule announcing the revocation of the 1989 exposure limits.

[b]This criterion is based on 304(a) aquatic life criterion issued in 1980 and was also issued in EPA 440/5-80-046, EPA 1980a. The values are different as they are derived differently.

[c]Not classifiable as a human carcinogen

[d]The values listed in NATICH 1992 as "acceptable ambient concentrations guidelines or standards" may not be referred to as such by certain States and localities. For example, the values listed for Connecticut are referred to as "hazard limiting values"

[e]The following equations were used to calculate the values as given in the Alabama State laws:
    Consumption of water and fish: Concentration (mg/L) = (HBW X RfD) / [(FCR X BCF) + WCR]
    Consumption of water only: Concentration (mg/L) = (HBW X RfD) / (FCR X BCF)
        HBW = human body weight, set at 70 kg
        RfD = reference dose, 0.00005 mg/(kg-day) for alpha-, beta-endosulfan, and endosulfan sulfate
        FCR = fish consumption rate, set at 0.030 kg/day
        BCF = bioconcentration factor, 270 L/kg for alpha-, beta-endosulfan, and endosulfan sulfate
        WCR = water consumption rate, set at 2 L/day

ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = code of federal regulations; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance committee; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; REL = recommended exposure limit; RfD = oral reference dose; TLV= threshold limit value; TWA = time-weighted average; WHO = World Health Organization

(EPA 1996b). The reportable quantity for endosulfan and its metabolites is 1 pound (0.454 kg) (EPA 1995a). Endosulfan and its metabolites do not appear on the list of toxic chemicals subject to Section 313 of the Emergency Planning and Community Right-to-Know-Act of 1986 (EPA 1995c).

Endosulfan and its metabolite, endosulfan sulfate, are classified as a chlorinated organic pesticides. The EPA regulates endosulfan and endosulfan sulfate as pesticide chemicals and has established tolerance limits for their residues in or on raw agricultural commodities. Tolerances for "total residue" for each of these insecticides ranging from 0.1 (negligible residue) ppm to 2 ppm have been established for approximately 79 commodities (EPA 1982a). Many pesticide chemicals within the chlorinated organic pesticide class have pharmacological effects related to other classes of pesticides. For example, pesticide chemicals in the chlorinated organics, arsenic-containing, metallic dithiocarbamates, and the cholinesterase-inhibiting classes have related pharmacological effects. When applied to agricultural commodities, and there is no contrary evidence, pesticide chemicals that cause related pharmacological effects are regarded as having an additive deleterious action (EPA 1993b). Tolerances established for such related pesticide chemicals may limit the amount of common component (e.g., As_2O_3) that may be present, the amount of biological activity (e.g., cholinesterase inhibition), or the total amount of related pesticide chemical that may be present (EPA 1993b). The EPA has established a tolerance limit of 24 ppm for endosulfan residues in or on dried tea. When endosulfan is applied to growing tea this limit reflects a residue level of 0.1 ppm in beverage tea (EPA 1988d).

Between June 27, 1974 and January 18, 1989, the Occupational Safety and Health Administration (OSHA) had promulgated protective, permissible exposure limits (PELs) for approximately 264 toxic substances (OSHA 1993). The OSHA PELs were established to protect workers against adverse health effects resulting from exposure to hazardous substances. The PELs determined for hazardous substances are enforceable, regulatory limits on allowable indoor air concentrations. OSHA requires employers of workers who are occupationally exposed to these hazardous air contaminants to institute engineering controls and work practices to reduce and maintain employee exposure at or below PELs. An employer must ensure that an employee's exposure in any 8-hour work shift of a 40-hour week does not exceed the 8-hour time-weighted average (TWA) established for the air contaminant (OSHA 1993). On January 18, 1989, OSHA promulgated more protective PELs for approximately 376 toxic substances. Endosulfan was included among 164 toxic substances not previously regulated (OSHA 1989b). The newly established PEL for endosulfan was set at 0.1 mg/m^3 (OSHA 1989a). OSHA also provided a "skin designation" for endosulfan. The skin designation would indicate a potential for dermal absorption and the need for employers to implement the use of good work practices including providing workers with

gloves, coveralls, goggles, and other appropriate equipment in order to prevent skin exposures (NIOSH 1997). Because the 1989 promulgation was rescinded by the 11th Circuit Court Appeals in July 1992, only those PELs in place prior to the 1989 rule are currently enforced by OSHA. On June 30, 1993, OSHA published in the Federal Register a final rule announcing the revocation of the 1989 exposure limits, including the newly established limits for endosulfan (OSHA 1993). Currently, there is no OSHA PEL for endosulfan. However, the National Institute for Occupational Safety and Health (NIOSH) and several states adopted the 0.1 mg/m^3 exposure limit for endosulfan that was initially promulgated by OSHA (NIOSH 1992, 1997). In the construction industry, exposure of employees to endosulfan through inhalation, ingestion, skin absorption, or contact should not exceed the "Threshold Limit Values(TLVs) of Airborne Contaminants for 1970" established by the American Conference of Governmental Industrial Hygienists (ACGIH) (OSHA 1997a). The ACGIH exposure limit for endosulfan is 0.1 mg/m^3 (ACGIH 1998a; OSHA 1997a, 1997b).

Endosulfan and its metabolites are included on the list of toxic pollutants regulated by the Effluent Guidelines and Standards provided in Subchapter N of Title 40 of the Code of Federal Regulations (40 CFR) (EPA 1992c). Pursuant to the Clean Water Act (CWA) these regulations prescribe effluent limitations guidelines for existing sources, standards of performance for new sources, and pretreatment standards for new and existing sources (EPA 1992c). The point source categories for which endosulfan sulfate is a regulated toxic pollutant are the electroplating (EPA 1986a), steam electric power generating (EPA 1992d), and metal finishing (EPA 1986b).

Endosulfan is regulated as a waste water pollutant in discharges from new and existing facilities that formulate, package, and repackage pesticide products. Facilities of this type make up two subcategories of the Pesticide Chemicals Point Source Category—Subcategory C: Pesticide Formulating, Packaging and Repackaging, which includes facilities that also manufacture pesticide active ingredients (PAIs), and Subcategory E: Repackaging of Agricultural Pesticides Performed at Refilling Establishments (EPA 1996a). As of January 6, 1997, the regulatory limit for Subcategory C facilities on the discharge of waste water pollutants into navigable waters and into publicly owned treatment works (POTWs) is a choice between zero discharge or compliance with the pollution prevention alternative provided in Table 8 of 40 CFR 455 (EPA 1996a). Subcategory E facilities are required to achieve the "zero" criterion for discharge of waste water pollutants (EPA 1996a). Some of the PAIs to which these effluent guidelines and standards do not apply are sanitizers, including pool chemicals; microorganisms, such as *Bacillus thuringiensis;* and certain liquid chemical sterilants that are used on critical or semi-critical medical devices (EPA 1996a). Complete listings of PAIs that are not required to meet the Subcategory C

and E guidelines and standards can be found in 40 CFR 455.40 and 40 CFR 455.60, respectively. Endosulfan sulfate is regulated and monitored along with other toxic organic compounds as total toxic organics (TTO) in the discharges from the aluminum forming point source category (EPA 1988b). The term total toxic organic means the sum of the masses or concentrations of all toxic organic compounds found in the discharge at a concentration greater than 0.010 mg/L (EPA 1988b).

In terms of toxicity, NIOSH recommends that endosulfan be recognized as a Group 1 Pesticide (NIOSH 1992). Pesticides in Group 1 pose a significant risk of adverse acute health effects at low concentrations or carcinogenic, teratogenic, neurotoxic, or reproductive effects (NIOSH 1992).

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9. GLOSSARY

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

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by 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)—is 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—is 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—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.

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.

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.

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.

Immunological Effects—are functional changes in the immune response.

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

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$_{(50)}$ (LC$_{50}$)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

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

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

Lethal Time$_{(50)}$ (LT$_{50}$)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) —An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

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

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio—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—is 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—is 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—is 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 describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study--a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) 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.

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 casual 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 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

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

Toxicokinetic—The 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; 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.

Vadose —Refers to the region between the ground surface and the water table.

Xenobiotic—any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Endosulfan
CAS Number: 115-29-7
Date: April 6, 2000
Profile Status: Third Draft Post Public
Route: [ ] Inhalation   [X] Oral
Duration: [ ] Acute   [X] Intermediate   [ ] Chronic
Graph Key: 66r
Species: Rat

Minimal Risk Level: 0.005   [X] mg/kg/day   [ ] ppm

Reference: Banerjee BD, Hussain QZ. 1986. Effect of sub-chronic endosulfan exposure on humoral and cell-mediated immune responses in albino rats. Arch Toxicol 59:279-284.

Experimental design: Groups of male Wistar (10–12/group) (85–90 g body weight) received technical grade endosulfan (α- and β-endosulfan in the ratio of 7:3) in their diets at dietary levels of 0, 5, 10, or 20 ppm (equivalent to 0, 0.45, 0.9, and 1.8 mg/kg/day, using the EPA [1988d] food factor for male Wistar rats, subchronic duration). Test diets were prepared by dissolving the endosulfan in groundnut oil and mixing this into standard laboratory diet. Samples analyzed from each batch of diet indicated that the actual levels of endosulfan in the diet were within 10% of the desired levels. Control animals received a diet with an equal amount of groundnut oil mixed in. Rats were randomly allocated to groups and were caged 4 to a stainless steel, mesh-bottom cage. Food and water were available to these rats on "as needed" basis for between 8 and 22 weeks. At weeks 8, 12, 18, and 22, between 10 and 12 rats were selected from each group and sacrificed. Twenty days before sacrifice, the rats were immunized by injecting 0.2 mL of tetanus toxin mixed with an equal volume of Freund's adjuvant subcutaneously. An additional group of 10–12 rats per dose were sacrificed at the time periods indicated, but these rats were not immunized with the tetanus toxin and adjuvant. At the time of sacrifice, the liver, spleen, and thymus were removed and weighed, blood samples were collected by cardiac puncture, and peritoneal exudate was collected by washing the peritoneal cavity with between 10 and 15 mL of RMPI medium.

The antibody titer to tetanus toxin was estimated using an indirect hemagglutination technique. Briefly, a suspension of sheep red blood cells was treated with tannic acid (1:20,000 dilution) and used for antigen coating. Tetanus toxin was then mixed with the treated sheep red blood cell and antibody titers were determined using the first dilution where no visible agglutination was observed. Serum proteins were determined using zone electrophoresis. Quantitation of serum levels of IgG and IgM was performed using radial immunodiffusion in agarose containing either anti IgG or anti IgM. The leukocyte migration inhibition test was performed using leukocytes isolated from rat blood by sequential centrifugation and washing. Migration from micro capillary tubes was measured using a camera lucida and migration into control medium was compared with migration into medium containing tetanus toxin. The macrophage migration inhibition test was performed using microphages isolated from the peritoneal exudate by sequential centrifugation and washing. Migration was measured as described above for the leukocytes.

<u>Effects noted in study and corresponding doses</u>: No difference between the controls and rats given diets containing 5 ppm endosulfan was observed in any of the parameters measured. Rats consuming diets containing 10 ppm endosulfan and treated with tetanus toxin had significantly decreased serum IgG levels at weeks 12, 18, and 22. These rats also had significantly decreased antibody titer to tetanus toxin at weeks 8, 12, 18, and 22. Leukocyte and macrophage migration was also significantly inhibited at weeks 8, 12, 18, and 22. The magnitude of the differences between the 10 ppm rats and the controls increased at each later time point. These rats also had a significantly increased albumin to globulin ratio at week 22. Rats consuming diets containing 20 ppm showed all of the same changes as the rats at 10 ppm but to a greater degree. In addition, at weeks 2, 18, and 22, these rats showed a significantly increased albumin to globulin ratio, and at 22 weeks, these rats showed a significant decrease in relative spleen weight. No effect on the relative thymus weight was observed at any dose at any of the times tested.

<u>Dose and end point used for MRL derivation</u>: 0.45 mg/kg/day; depressed immune response.

[X] NOAEL   [] LOAEL

<u>Uncertainty Factors used in MRL derivation</u>:

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

<u>Was a conversion factor used from ppm in food or water to a mg/body weight dose?</u>
Yes, 0.45 mg/kg/day was calculated by multiplying the dietary level of 5 ppm (5 mg endosulfan/kg diet) by the food factor for male Wistar rats in a subchronic study of 0.09 kg diet/ kg body weight/day (EPA 1988d).

<u>If an inhalation study in animals, list conversion factors used in determining human equivalent dose:</u>
Not applicable

<u>Was a conversion used from intermittent to continuous exposure?</u>
No.

<u>Other additional studies or pertinent information that lend support to this MRL:</u> Choice of this immunological end point as the basis for derivation of the intermediate-duration oral MRL is supported by the observation of similar effects in rats following ingestion of higher doses of endosulfan for shorter periods of time (Banerjee and Hussain 1986, 1987). Additional support of the positive findings is provided in Khurana et al. (1998) in which decreased macrophage functionality was observed, in the absence of any other apparent toxicological effects, in 1-day-old broiler chicks fed 30 ppm endosulfan in the diet for 4 or 8 weeks. The absence of observed immunotoxicity in the study by Vos et al. (1982) in rats does not contradict these findings since not all of the same immunological parameters were evaluated in the by Vos et al. (1982) and a shorter period of exposure was used. The only other intermediate-duration study that reported effects at relatively low doses of endosulfan is that by Hoechst (1984a) in which a decrease in litter weight was observed in F1B pups during the lactation to weaning period at an endosulfan dose level of 0.8 mg/kg/day. However, EPA review the study and because there was no corroborative finding of a decrease in the number of pups per litter or in pup weight, the decrease in litter weight was not considered to be treatment-related (IRIS 2000).

<u>Agency Contact (Chemical Manager):</u> Lori L. Miller, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Endosulfan
CAS Number: 115-29-7
Date: April 6, 2000
Profile Status: Final
Route: [ ] Inhalation   [X] Oral
Duration: [ ] Acute   [ ] Intermediate   [X] Chronic
Graph Key: 103d
Species: Dog

Minimal Risk Level: 0.002   [X] mg/kg/day   [ ] ppm

Reference: Hoechst. 1989c. Endosulfan - substance technical (code HOE 02671 OI ZD96 0002): Testing for toxicity by repeated oral administration (1-year feeding study) to Beagle dogs. Conducted for Hoechst Aktiengesellschaft, Frankfurt, Germany. Project no. 87.0643.

Experimental design: Male and female beagle dogs (6/sex/dose) were fed diets containing endosulfan at dietary concentrations of 0, 3, 10, and 30 ppm for 1 year. An additional group was fed diets containing endosulfan at concentrations of 30 ppm for 54 days, 45 ppm for 52 days, and 60 ppm for up to 40 days, but this group is considered separately since all surviving animals were sacrificed by day 147. When multiplied by estimated food factors of 0.067 and 0.060 kg food/kg body weight/day for males and females, respectively, these dietary concentrations are equivalent to 0, 0.2, 0.67, and 2 mg/kg/day for males and 0, 0.18, 0.6, and 1.8 mg/kg/day for females. The food factors were calculated based upon the actual average body weight and food consumption data from the study. Test diets were prepared daily immediately before feeding from endosulfan-containing cornmeal premixes which were mixed into the daily feed ration of 1 kg (males) and 0.8 kg (females) wet diet. Control animals received the basal diet containing the same proportion of cornmeal as the 30/45/60 ppm group's diet. Dogs were randomly allocated to dose groups and were housed in separate kennels.

Animals were observed twice daily for deaths and behavioral abnormalities. General health and food consumption were checked only daily and body weights were checked once weekly. Tests for hepatic function (bromsulphthalein) and renal function (phenosulphthalein), tests for reflexes and righting reactions, ophthalmological exams, hearing tests, and dental inspections for all dogs were performed before the start of the study and before termination. In addition, the two highest dose groups were tested after 6 weeks and every 3 months. Hematology, clinical chemistry, and urinalysis were performed at the start and at termination of the study, after 6 weeks, and again every 3 months. At termination, all dogs were examined grossly, the weighs of the major organs were determined, and a wide spectrum of tissues were examined microscopically.

Effects noted in study and corresponding doses: Because the highest dose group (30/45/60 ppm) was sacrificed before 6 months, this group is not discussed here. No effects were observed in the dogs receiving diets containing 3 ppm endosulfan. No deaths occurred during the study that could be directly attributed to consumption of diets containing endosulfan. One male in the 30 ppm dietary group was sacrificed in extremis and necropsy revealed severe inflammation of the mediastinum (origin unknown). Approximately 2.5–6 hours after consuming test diets containing 30 ppm endosulfan, three males and two females exhibited convulsive spasms of the abdominal muscles and jaws without vomiting. It is not clear whether this effect was neurological or gastrointestinal in origin. Routine histopathological examination of the central and peripheral nervous system and eyes revealed no adverse effects. No abnormalities were detected in animal's pupillary or blink reflexes; flexor patellar, anal, or cutaneous reflexes; or extensor postural thrust reaction, placing reaction, or righting abilities. Cholinesterase activities were also not

affected by treatment with endosulfan. Serum alkaline phosphatase was significantly elevated in males at 10 and 30 ppm at most test intervals and in females at early intervals at 10 ppm and at most intervals at 30 ppm, indicating some form of tissue damage. In dogs, alkaline phosphatase is primarily of hepatic origin, but gross and microscopic pathology was unremarkable. Lactate dehydrogenase was also elevated in males and females from the 10 ppm group at 9 months and at 30 ppm at 12 months. Routine and gross histopathological examination of the major organs and tissues including skin, reproductive organs, lymphoreticular organs, and endocrine and exocrine glands revealed no adverse effects. In addition, ophthalmology, hematology, urinalysis, and renal function tests revealed no adverse effects of endosulfan consumption.

Dose and end point used for MRL derivation: 0.18 mg/kg/day; for increase in serum alkaline phosphatase activity.

[X] NOAEL   [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Yes, 0.18 mg/kg/day was calculated by multiplying the dietary level of 3 ppm (3 mg endosulfan/kg diet) by food factors of 0.067 and 0.06 kg food/kg body weight/day for males and females, respectively, derived from food consumption and body weight data provided in the study. The female food factor (0.06 kg food/kg body weight/day) was used because this yielded the most conservative dose estimate.

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

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

Other additional studies or pertinent information that lend support to this MRL: The choice of this end point (hepatic toxicity as evidenced by increased serum alkaline phosphatase activity) is supported by the observation of hydropic hepatic cells in male rats that consumed a diet that provided a dose of endosulfan of approximately 5 mg/kg/day for 2 years (FMC 1959b). The hepatic NOAEL in that study was approximately 1 mg/kg/day. In another 2-year dietary study in rats it was observed that male and female rats that received doses of endosulfan of approximately 0.6–0.6 mg/kg/day gained 11–15% less weight (estimated as the difference between starting weight and final weight) than the controls; however, the biological significance of this observation is unclear (Hack et al. 1995).

Agency Contact (Chemical Manager): Lori L. Miller, M.P.H.

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 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 2-1

(1)   <u>Route of Exposure</u> 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 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

APPENDIX B

(2)   <u>Exposure Period</u> 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)   <u>Health Effect</u> 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)   <u>Key to Figure</u> 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 2-1).

(5)   <u>Species</u> The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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)   <u>Exposure Frequency/Duration</u> 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)   <u>System</u> 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.

(8)   <u>NOAEL</u> 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)   <u>LOAEL</u> 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 endpoint 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) <u>Reference</u> The complete reference citation is given in chapter 8 of the profile.

(11) <u>CEL</u> 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) <u>Footnotes</u> 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 2-1

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) <u>Exposure Period</u> 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) <u>Health Effect</u> These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) <u>Levels of Exposure</u> concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) <u>NOAEL</u> In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) <u>CEL</u> 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.

(18) <u>Estimated Upper-Bound Human Cancer Risk Levels</u> 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) <u>Key to LSE Figure</u> The Key explains the abbreviations and symbols used in the figure.

SAMPLE

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
Systemic	9	9	9	9	9		9
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE						11	
Cancer						9	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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

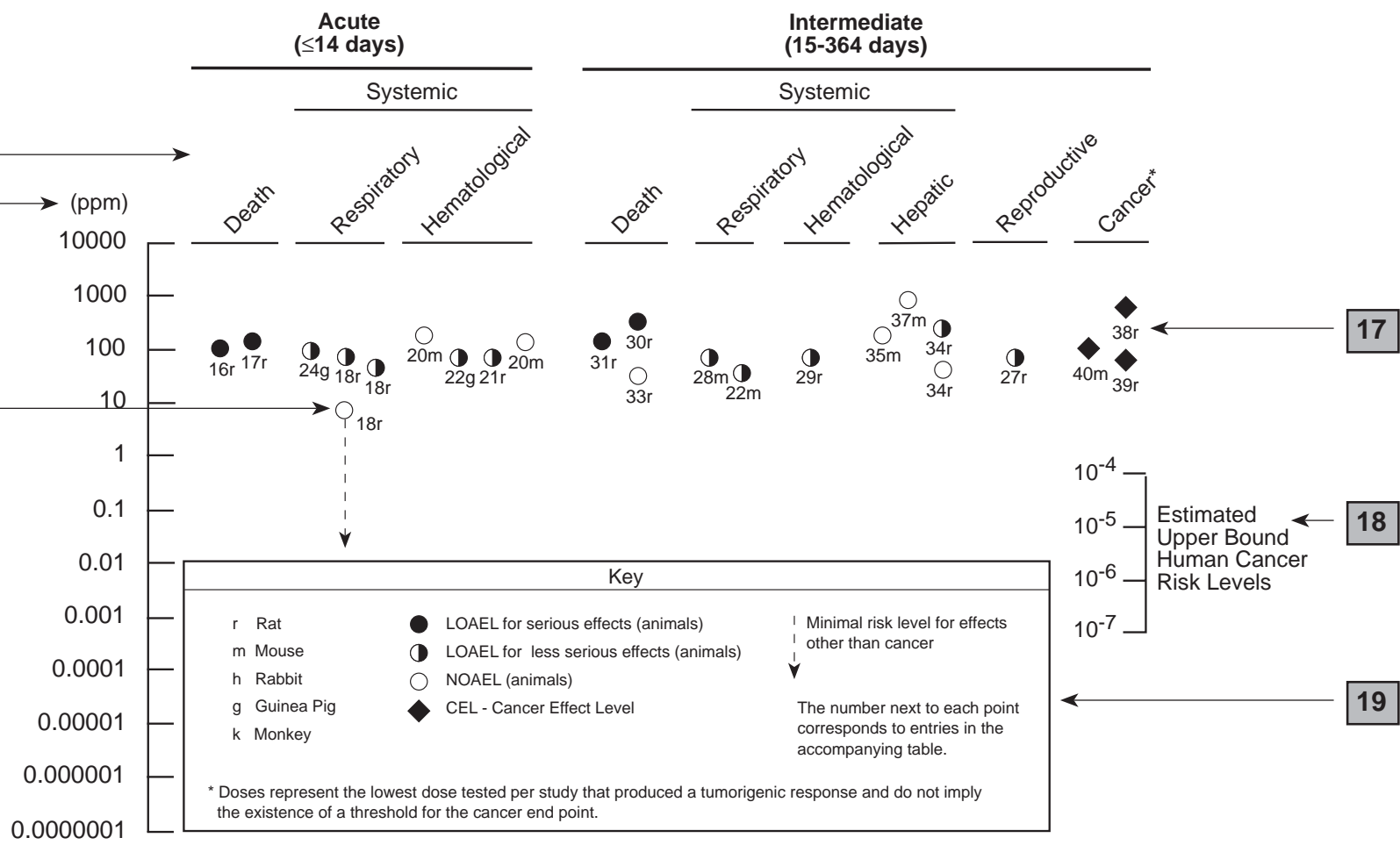Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section 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 section. 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 Data Needs section.

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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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).

APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	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

APPENDIX C

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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

APPENDIX C

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
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
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

APPENDIX C

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
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
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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 Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
>	greater than
$\geq$	greater than or equal to
=	equal to
<	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer

APPENDIX C

μg	microgram
q_1^*	cancer slope factor
−	negative
+	positive
(+)	weakly positive result
(−)	weakly negative result