DRAFT
TOXICOLOGICAL PROFILE FOR
ENDOSULFAN

PUBLIC COMMENT PERIOD ENDS:
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

May 2013

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UPDATE STATEMENT

A Toxicological Profile for Endosulfan was released in 2000. This present edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences /
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30333

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FOREWORD

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

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 toxic 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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30333

Physical Mailing Address:
4770 Buford Highway
Building 106, 3rd floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

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

Robin M. Ikeda, MD, MPH
Acting Assistant Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Jessilynn Taylor, M.S., CDR USPHS
Hana R. Pohl, M.D., Ph.D.
Moiz Mumtaz, Ph.D.
Patricia Ruiz, Ph.D.
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Fernando Llados, Ph.D.
Catherine Rudisill, M.S.
Mario Citra, Ph.D.
SRC, Inc., North Syracuse, NY

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 Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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

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PEER REVIEW

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

1. Marilyn H. Silva, Ph.D. DABT, Department of Pesticide Regulation, Medical Toxicology Branch, Sacramento, California;

2. M. Eddleston MA, Ph.D., FRCP Edin, Scottish Senior Clinical Research Fellow, Clinical Pharmacology Unit, University of Edinburgh, Consultant Clinical Toxicologist and Director, National Poisons Information Service - Edinburgh, Royal Infirmary, Visiting Professor, University of Copenhagen, Department of International Health, Immunology and Microbiology, Edinburgh, Scotland;

3. Mark Gregory Robson, Ph.D., MPH, DrPH (hc), Dean of Agricultural and Urban Programs, Professor of Entomology, School of Environmental and Biological Sciences, Rutgers University, New Brunswick, New Jersey.

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

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

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

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1. PUBLIC HEALTH STATEMENT FOR ENDOSULFAN

Overview

We define a public health statement and show how it can help you learn about endosulfan.

Introduction

A public health statement summarizes information about a hazardous substance. The information is taken from a toxicological profile developed by ATSDR's Division of Toxicology and Human Health Sciences (DTHHS). A toxicological profile is a thorough review of a hazardous substance.

This toxicological profile examines endosulfan including the α-isomer, β-isomer, and the degradation product, endosulfan sulfate. This public health statement summarizes the DTHHS's findings on endosulfan, describes the effects of exposure to it, and describes what you can do to limit that exposure.

Endosulfan at hazardous waste sites

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. U.S. EPA then includes these sites the National Priorities List (NPL) and targets them for federal clean-up activities. U.S. EPA has found endosulfan in at least 176 of the 1,699 current or former NPL sites.

The total number of NPL sites evaluated for endosulfan is not known. But the possibility remains that as more sites are evaluated, the number of sites at which endosulfan is found may increase. This information is important; these future sites may be sources of exposure, and exposure to endosulfan may be harmful.

Why an endosulfan release can be harmful

When a contaminant 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. But such a release doesn't always lead to exposure. You can only be exposed to a contaminant when you come in contact with it. That contact—and therefore that exposure—can occur when you breathe, eat, or drink the contaminant, or when it touches your skin.

Even if you're exposed to endosulfan, you might not be harmed. Whether you are harmed will depend on such factors as the dose (how much), the duration (how long), and how you happen to contact it. Harm might also depend on whether you've been exposed to any other chemicals, as well as your age, sex, diet, family traits, lifestyle, and state of health.

A Closer Look at Endosulfan

Overview

This section describes endosulfan in detail and how you can be exposed to it.

What is endosulfan?

Endosulfan is a restricted-use pesticide that is particularly effective against aphids, fruit worms, beetles, leafhoppers, moth larvae, and white flies on a wide variety of crops. It is not approved for residential use. It 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. The use of endosulfan is being restricted to certain crops and is scheduled to be canceled for all uses by 2016.

How is endosulfan used?

Solid and liquid formulations are currently registered for active use in the United States. Dustable and wettable powders are recognized by the United Nations Food and Agriculture Organization (UN FAO), and may be available outside the United States. The restricted use classification requires that registered products may only be applied by a "certified pesticide applicator" or under the direct supervision of a certified pesticide applicator. Endosulfan is applied to crops by aerial or ground-level foliar spray.

Where is endosulfan found?

Endosulfan can be released into the air, water, and soil in areas where it is applied as a pesticide.

Possible Sources	Environmental Fate
Air: Levels of endosulfan in air samples are highly variable depending on location. Remote Arctic air concentrations range from 3.3 to 8.3 picograms per cubic meter [pg/m^3]. Rural areas tend to have higher reported concentrations (18–82 pg/m^3), with spikes reported during growing seasons.	In the air, α- and β-endosulfan may be broken down by chemical reactions, but are not expected to be broken down by direct sunlight. Endosulfan sulfate may be broken down by sunlight, but data are conflicting. Endosulfan can be transported long distances in the air to remote locations.
Water: Levels of endosulfan in drinking water sources are regularly monitored through federal and state government programs. Endosulfan generally has low rates of detection in groundwater. Surface water concentrations are highly variable, but are generally highest in water bodies that drain areas of high agricultural use (0.21–54 nanograms/liter [ng/L] for α-endosulfan).	α-Endosulfan and β-endosulfan will transform in water into the less toxic endosulfan diol. Endosulfan sulfate is more difficult to break down in water.

Soil: Endosulfan is applied directly to plants and soil during its use as pesticide.	In soil, endosulfan attaches to soil particles and is not expected to move from soil to groundwater. α-Endosulfan and β-endosulfan are expected to break down in soil, but endosulfan sulfate is more resistant. Movement of α- and β-endosulfan from soil surfaces to air may be significant.
Food: Endosulfan residues can be present in food; the highest concentrations reported were in fresh and frozen vegetables (0.011–0.037 parts per million [ppm]).	Dietary intake is expected to be the main source of endosulfan exposure to the general population.

How Endosulfan Can Affect Your Health

Overview

This section looks at how endosulfan enters your body and potential endosulfan health effects found in human and animal studies.

How endosulfan enters your body

Endosulfan can enter your body from water, food, or soil.

Possible Sources	Possible Exposure Pathway
Water	If you drink water containing endosulfan, some will enter your body through the digestive tract, but we do not know how much.
Food	If you eat food contaminated with endosulfan, most of it will probably rapidly enter your body through the digestive tract.
Soil and vegetation	If you touch soil contaminated with endosulfan or fruits or plants that have been sprayed with it, some small amount of endosulfan will probably enter the body through the skin.

How endosulfan leaves your body

Endosulfan has been detected in the urine of exposed people. In animals, endosulfan and breakdown products leave the body mainly in the feces within a few days or weeks.

Introduction to endosulfan health effects

The health effects of endosulfan depend on how much endosulfan you are exposed to and the length of that exposure. Environmental monitoring data suggest that any endosulfan levels the public might encounter through contact, through water, soil, or food are generally much lower than animal-study levels.

Short-term exposure effects

People who ingested endosulfan either intentionally or in contaminated food, or who were exposed during spraying fields suffered tremors and seizures and some died.

The same types of effects have been observed in animals exposed briefly to high levels of endosulfan.

Long-term exposure effects

There are no studies of people exposed to low levels of endosulfan for long periods of time (i.e., years). Animal studies have shown that swallowing endosulfan in contaminated food over long periods affects mainly the kidneys.

Endosulfan and cancer

Studies of occupational and environmental exposure of humans did not provide conclusive evidence that endosulfan can cause cancer. Endosulfan did not cause cancer in animal studies.

Some cancer findings by government and other agencies

The U.S. Department of Health and Human Services (DHHS), the U.S. EPA, and the International Agency for Research on Cancer (IARC) have not classified endosulfan as to its ability to cause cancer.

See Chapters 2 and 3 for more information on endosulfan health effects.

Children and Endosulfan

Overview

This section discusses potential health effects of endosulfan exposure in humans from when they're first conceived to 18 years of age, and how you might protect against such effects.

Exposure effects for children generally

Children who accidentally ate endosulfan or received applications of endosulfan onto the skin to remove lice developed seizures, the same effect seen in adults exposed to high amounts of endosulfan.

What about birth defects and other effects?

We do not know whether endosulfan can produce birth defects in children.

Studies have examined possible associations between maternal exposure to endosulfan and autism, thyroid function, and development of the nervous system in newborn children. Studies also have examined potential associations between direct

exposure of children to endosulfan and blood cancer and sexual maturation in males. In all cases, the results were suggestive but not conclusive due to study limitations.

Effects in animals

Exposure of pregnant animals to endosulfan can produce abnormalities in the skeleton and organs in the offspring and reduced pup weight during lactation. This often occurred with doses that were also toxic to the mothers.

Some studies showed that exposure of pregnant rats to endosulfan resulted in decrease in sperm in the male offspring when they reached adulthood. Other studies did not find this effect.

Breast milk

Endosulfan has been found in human breast milk, which means that mothers can transfer this chemical to their babies by nursing.

Medical Tests to Determine Endosulfan Exposure

Overview

We identify medical tests that can detect whether endosulfan is in your body, and we recommend safe toxic-substance practices.

Endosulfan can be measured in blood and urine

Endosulfan and its breakdown products (metabolites) can be measured in blood, urine, fat tissue, and breast milk. However, the detection of endosulfan does not necessarily mean that you will suffer adverse health effects. Because endosulfan and its metabolites leave the body fairly rapidly (within days), the tests need to be conducted within a few days after exposure.

For more information on the different substances formed by endosulfan breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

Federal Government Recommendations to Protect Human Health

Overview

One way the federal government promotes public health is by regulating toxic substances or recommending ways to handle or to avoid toxic substances.

The federal government regulates toxic substances

Regulations are enforceable by law. The U.S. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that have adopted toxic substances regulations.

The federal government recommends safe toxic substance practices

ATSDR and the National Institute for Occupational Safety and Health (NIOSH) have made recommendations about toxic substances. Unlike enforceable regulations, these recommendations are advisory only.

Toxic substance regulations

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Check for regulation updates

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

Some regulations and recommendations for endosulfan include

Federal Organization	Regulation or Recommendation
U.S. Environmental Protection Agency (EPA)	The U.S. EPA recommends that the amount of endosulfan sulfate in lakes, rivers, and streams should not be more than 62 micrograms per liter (µg/L). 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.
Occupational Safety and Health Administration (OSHA)	OSHA has not set a legal limit of endosulfan in air for an 8-hour work day.
National Institute for Occupational Safety and Health (NIOSH)	NIOSH recommends a limit of 0.1 milligram per cubic meter (mg/m^3) of endosulfan in air averaged over a 10-hour work day.

Additional Information

Overview

Where to find more information about endosulfan

Whom to contact first

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

Additional information from ATSDR

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

Where to obtain toxicological profile copies

Toxicological profiles are also available online at www.atsdr.cdc.gov and on CD-ROM. Request a copy of the ATSDR ToxProfiles™ CD-ROM by

- Calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636),
- E-mailing cdcinfo@cdc.gov, or
- Writing to

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
1600 Clifton Road NE
Mailstop F-57
Atlanta, GA 30333
Fax: 1-770-488-4178

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ENDOSULFAN IN THE UNITED STATES

The manufacture and use of endosulfan as a broad spectrum contact insecticide and acaricide applied to a wide variety of fruits, vegetables, grains, etc. has led to its direct release into the environment. Technical-grade endosulfan contains at least 94% of two pure isomers, α- and β-endosulfan. The α- and β-isomers of endosulfan are present in the ratio of 7:3, respectively. Endosulfan sulfate is a reaction product found in technical endosulfan; it is also found in the environment due to oxidation by biotransformation. Beginning on July 31, 2012, a voluntary cancellation and phase-out of endosulfan began and all uses of this product are scheduled to end by July 31, 2016. The phase-out will be executed in six phases over this 4-year period. During these phases, use of endosulfan on certain types of crops and products are scheduled to end.

After its release to the environment, endosulfan undergoes a variety of transformation and transport processes. In soil, endosulfan sulfate is the major degradation product from the biodegradation of endosulfan and is considered to be more persistent than the parent compound. Neither endosulfan nor its biodegradation products are expected to be mobile in soil. In an aerobic soil metabolism study using five different soils, half-lives of α-endosulfan ranged from 35 to 67 days and half-lives of β-endosulfan ranged from 104 to 265 days with endosulfan sulfate as the major metabolite. Soil erosion, run-off, spray drift and atmospheric deposition contribute to releases of endosulfan to aquatic ecosystems. Endosulfan transported to water is expected to eventually partition to sediment. In water, endosulfan is hydrolyzed to the less toxic endosulfan diol with a half-life of approximately 1 month at pH 7. Endosulfan has a relatively high potential to bioaccumulate in fish and other aquatic organisms. Volatilization from soil, water, or plant surfaces may occur over time for endosulfan.

Due to its potential for long-range transport, endosulfan is detected in air at both source and non-source locations. Remote Arctic air concentrations range from 3.3 to 8.3 pg/m^3. Rural source areas where endosulfan may be used tend to have higher reported concentrations (18–82 pg/m^3), with spikes reported during growing seasons. Data obtained from the U.S. Geological Survey (USGS) National-Water Quality Assessment (NAWQA) Program suggest that endosulfan generally has low rates of detection in groundwater. Surface water concentrations are highly variable, but are generally highest in water bodies that drain areas of high agricultural use.

Endosulfan and endosulfan sulfate have been detected in a variety of food items. Typical values are <0.1 ppb; however, maximum values for some food items were nearly 100 ppb. It has also been detected in fish and seafood at varying levels. The general population is primarily exposed to endosulfan through dietary intake. Pesticide applicators and crop pickers may be exposed to higher levels via inhalation, accidental ingestion, and dermal exposure as compared to the general population.

2.2 SUMMARY OF HEALTH EFFECTS

The main target of endosulfan in humans and animals is the nervous system. Exposure to high amounts of endosulfan by any route produces over-stimulation of the central nervous system resulting in hyperactivity, tremors, decreased respiration, dyspnea, salivation, tonic-clonic convulsions, and eventually death. Endosulfan does so by antagonizing gamma-aminobutiric acid (GABA) function, an inhibitory neurotransmitter system, thus allowing stimulary activity to manifest itself unopposed. Other effects such as respiratory, gastrointestinal, cardiovascular, renal, and metabolic effects may be secondary to a prolonged status epilepticus. The latter is defined clinically as seizures lasting for more than 5 minutes, or two or more discrete seizures without recovery of consciousness in between. Refractory status epilepticus was the most common cause of death among 52 patients admitted to an emergency facility. In that report, the amount of endosulfan ingested being >35 g was the independent variable that best predicted patient mortality. Very few studies provided information that allowed estimation of a dose. In one study, a dose of 260 mg endosulfan/kg caused the death of a 43-year-old man. In another study, a dose of approximately 2,571 mg endosulfan/kg was lethal to a 36-year-old man. According to one study, 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. There are two cases of possible permanent neurological impairment following acute exposure to high amounts of endosulfan. Follow-up of additional cases of accidental or intentional exposure to endosulfan is necessary to confirm the results of these two studies.

Endosulfan induces the same type of effects in animals after acute oral doses ≥1.8 mg/kg. Most animals studies have been conducted with technical endosulfan, but a few have examined the effects of the pure α- and β-isomers. Cerebral congestion and edema are often seen in animals that died following acute ingestion of endosulfan. Hyperactivity has also been reported in animals following inhalation and dermal

exposure. Mice generally appear to be more sensitive to the lethal effects of endosulfan than rats. Female rats are more sensitive to the lethal effects of endosulfan than male rats. Tonic contractions of the muscles of the extremities, face, and jaw were reported in dogs in a 12-month study. In general, long-term studies have not reported compound-related morphological alterations in tissues of the nervous system. Repeated exposure of immature rats to doses in the range of 2–6 mg endosulfan/kg/day by gavage has also induced changes in the levels of neurotransmitters in the brain and alterations in neurobehavioral tests. However, repeated exposure of adult rats to doses near 30 mg endosulfan/kg/day via the diet in one study and near 46 mg/kg/day in another study did not significantly affect the results of a functional observational battery (FOB) that included examination of autonomic function, posture and gait, and behavior. In rats, endosulfan was also shown to lower the threshold to seizures caused by a subsequent challenge dose of endosulfan or by electrical stimulation of a certain area of the brain.

Studies in animals, mostly by the oral route, have described a wide range of systemic effects of endosulfan including respiratory, gastrointestinal, hematological, hepatic, renal, endocrine, and metabolic effects; alterations in body weight have also been reported. Many of these effects are secondary to severe neurological effects, particularly in acute-duration studies that used relatively high doses of endosulfan. Acute lethal or near-lethal doses have resulted in congestion in the lungs, liver, kidneys, stomach, and intestines. Intermediate-duration studies have reported serious effects such as myocardial fiber degeneration, and degenerative changes in the liver and kidneys in Wistar rats dosed with 1 mg/kg/day technical endosulfan. The same dose level induced degenerative changes in the endocrine pancreas from New Zealand white rabbits. A higher dose of 2 mg/kg/day induced myocardial fiber edema and pancreas histopathology in Wistar rats. None of these studies provided information on clinical signs. In addition, in all of these studies, endosulfan was administered by gavage and, since only one dose level was tested, no-observed-adverse-effect levels (NOAELs) were not defined. In contrast, a 90-day dietary study in Wistar rats reported that doses up to 37.2 mg/kg/day of technical endosulfan in males and 45.5 mg/kg/day in females did not induce significant compound-related histological alterations in the liver and kidneys; the heart and pancreas were not examined. This suggests that the mode of administration of endosulfan (i.e., diet versus gavage), plays an important role in the toxicity of the chemical, dietary being the more relevant for exposure of the general population. Chronic-duration studies with endosulfan have reported few systemic effects. Increased incidence of glomerulonephrosis and aneurysms of the blood vessels were reported in Wistar rats exposed for 2 years to doses of 3–4 mg/kg/day technical endosulfan; the NOAELs were 0.6–0.7 mg/kg/day and lowest-observed-adverse-effect levels (LOAELs) were 2.9 mg/kg/day for males and 3.8 mg/kg/day for females. Studies in mice exposed to up to 3 mg/kg/day technical endosulfan via the diet reported no toxicity assessed by monitoring clinical signs, hematology

tests, and organ histopathology. A 1-year dietary study in dogs reported abdominal and jaw muscle spasms at the highest dose tested, approximately 2 mg/kg/day technical endosulfan. This effect was likely caused by hyperactivity of the nerve fibers innervating the muscles rather than a direct effect of endosulfan on the muscles. Application of endosulfan onto the skin of animals in doses that induced neurological signs also induced a spectrum of systemic effects similar to that observed following oral exposure to endosulfan. Nose-only exposure of rats to concentrations of aerosolized endosulfan $\geq$3.6 mg/m^3 for 4 hours induced frank neurological effects. Repeated exposure to up to 2 mg/m^3 6 hours/day, 5 days/week for a total of 21 out of 29 days did not result in significant alterations in gross or microscopic appearance of tissues and organ of rats.

Endosulfan was not a skin sensitizer when tested in a group of farm workers. Since no studies have been conducted of populations with prolonged exposure to low levels of endosulfan, it is unknown whether such exposure could alter immunocompetence. Studies of subjects who were acutely exposed to high amounts of endosulfan intentionally or accidentally by the inhalation, oral, or dermal routes have not provided information regarding immunological end points. Intermediate- and chronic-duration studies that conducted microscopic examination of lymphoreticular tissues of rats, mice, and dogs did no show significant alterations. Maximal doses were up to 7.3 mg/kg/day in mice, 48 mg/kg/day in rats, and 1.8 mg/kg/day in dogs. Endosulfan suppressed both cell-mediated and humoral immune responses in male Wistar rats in intermediate-duration studies; the NOAEL and LOAEL values were 0.45 and 0.9 mg/kg/day, respectively. Since these are the only studies that tested immunocompetence, it would be helpful to try to replicate the results. However, the immune system is known to be a sensitive target for organochlorine compounds.

It is unknown whether endosulfan is a reproductive toxicant in humans. The only relevant study located could not demonstrate conclusively that environmental exposure to endosulfan, assessed by measuring endosulfan in adipose tissue, was associated with fertility in men. Endosulfan induced adverse reproductive effects in animals, but results from some studies are difficult to reconcile. For example, doses of 6 mg/kg/day administered to Sprague-Dawley rats on gestation days (Gd) 6–19 did not affect post-implantation loss, but doses of 1 mg/kg/day given to Wistar rats on Gd 6–20 significantly increased post-implantation loss. Differences in strain sensitivity may have played a role. The lowest LOAEL for a reproductive endpoint was 1 mg/kg/day for post-implantation loss in rats and for alterations in sperm parameters in rabbits in a 6-week study. Intermediate-duration gavage studies also reported alterations in sperm parameters in rats dosed with 2.5–5 mg/kg/day endosulfan. No sperm alterations were reported in rats dosed for 8 weeks with 2.9 mg/kg/day endosulfan via the diet. Multi-generation reproductive studies

in rats did not find alterations in fertility or fecundity. This may be due to the fact that rats produce and ejaculate 10 times more sperm than are necessary for normal fertility and litter size. Gavage doses of ≥7.5 mg/kg/day endosulfan for 15–30 days reduced serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in male rats; dietary doses of 2.9 mg/kg/day for 8 weeks did not. Except for a report of testicular necrosis and aspermatogenesis in male rats dosed with 48 mg/kg/day endosulfan via the food, long-term studies with endosulfan have not reported morphological alterations in the reproductive organs of rats, mice, or dogs. The NOAEL in one study was 20 mg/kg/day. Repeated inhalation or dermal exposure of rats to endosulfan also did not induce morphological alterations in the reproductive organs. Endosulfan was neither estrogenic nor anti-estrogenic when administered orally to rats or mice; studies *in vitro* have provided mixed results.

A limited number of studies in humans have provided suggestive evidence of associations between maternal exposure to endosulfan and developmental alterations in the offspring including autism spectrum disorders, alterations in thyroid function, neural tube defects, and delayed sexual maturity in male children. After considering the strengths and limitations of the individual studies, no definite conclusions could be drawn.

Endosulfan induced adverse developmental effects in animals; most studies were conducted in rats. It should be noted that since not all studies provide information regarding maternal effects, it is not totally clear whether the developmental effects occur only in the presence of maternal toxicity. Perinatal exposure of rats to endosulfan induced skeletal variations, reduced offspring weight, and altered sperm parameters in adult male offspring that were not directly exposed, but received gestational and/or lactational exposure to endosulfan. Two of the most recent studies in which Wistar rats were exposed to 1 mg/kg/day endosulfan (only dose level tested) on Gd 6–20 reported significant increases in the incidences of gross, visceral, and skeletal anomalies, and hepatocyte and renal tubule epithelium degeneration in Gd 20 fetuses. The lowest developmental LOAEL was 0.61 mg/kg/day for an 11% reduction in body weight in Sprague-Dawley male rat pups on postnatal day (Pnd) 21 after treatment of the dams by gavage during the entire gestation and lactation periods; the 0.61 mg/kg/day dose was the lowest dose tested. Interestingly, treatment of Wistar rats with a much higher dose of endosulfan of 29.8 mg/kg/day via the diet on Gd 6–21 and during lactation resulted in a reduction of 11 and 4% in male and female pup weight, respectively, on Pnd 21. The apparent difference in sensitivity may be related to the different strains used and to the different mode of administration of the test material (i.e., gavage versus the diet).

Very limited information is available regarding humans exposed to endosulfan and cancer. A case-control study of women exposed to estrogenic substances at work found no association between exposure to endosulfan and other chemicals and breast cancer based on three cases among exposed and seven cases among controls. A small study of children in India presented suggestive evidence of increased incidence of hematological malignancies among children living near areas sprayed with endosulfan. However, the small sample size (n=26) and little control for potential confounders preclude drawing firm conclusions.

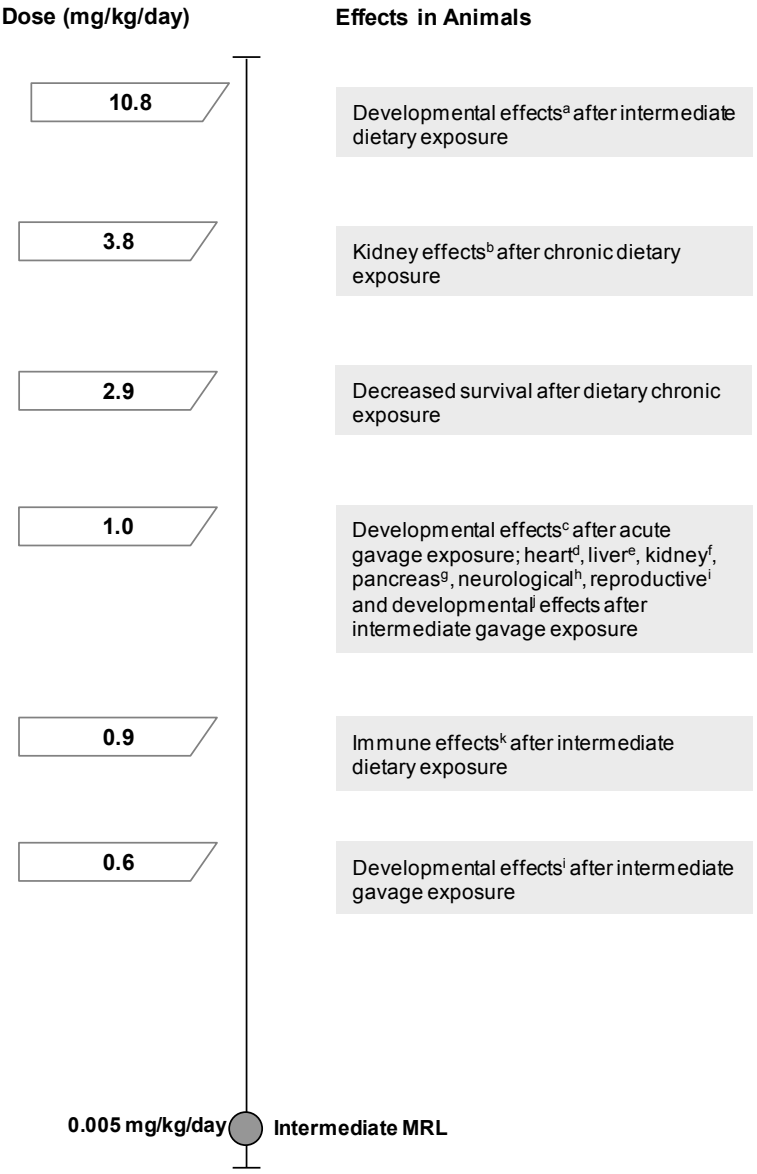
The carcinogenicity of endosulfan has been studied in chronic oral bioassays using rats and mice. While some of these studies have limitations (e.g., poor survival, less-than-lifetime exposures, inadequate reporting of data, use of only one dose level, and use of doses that were possibly less than the maximum tolerated dose) that render them inadequate for drawing definitive conclusions regarding the carcinogenicity of endosulfan, the better quality studies showed 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. 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, but some found evidence of promotion activity. The EPA has not classified endosulfan as to its carcinogenicity.

Heath effects of endosulfan ingestion in laboratory animals and the dose ranges at which these effects occur are shown in Figure 2-1. An estimate of an oral dose posing minimal risk to humans (MRL) is also presented in this figure. An MRL is an estimate of the daily human exposure that is likely to be safe over a certain period of exposure. MRLs are not intended to define clean-up or action levels, but are intended only to serve as a screening tool to help public health professionals decide where to look more closely. Therefore, MRLs are set at levels well below where effects have been observed.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (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

Figure 2-1. Health Effects of Ingesting Endosulfan



[a]Decreased pup's body weight
[b]Glomerulonephrosis
[c]Decreased sperm count in offspring
[d]Myocardial fiber degeneration
[e]Vacuolar degeneration
[f]Tubule cell degeneration
[g]Degenerative changes
[h]Hyperexcitability and brain hemorrhage
[i]Post-implantation loss and uterus alterations
[j]Visceral and skeletal anomalies; liver and kidneys degeneration in fetuses
[k]Decreased immunocompetence
[l]Reduced pup's weight

acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

Inhalation MRLs

No inhalation MRLs were derived for endosulfan due to inadequacies of the database. Information regarding inhalation exposure to endosulfan by humans was inadequate for derivation of inhalation MRLs (Aleksandrowicz 1979; Aschengrau et al. 1998; Ely et al. 1967; Rau et al. 2012; Roberts et al. 2007). 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. Of these reports, only in the cases reported by Aleksandrowics (1979) and Ely et al. (1967) was there evidence of exposure solely to endosulfan. Aschengrau et al. (1998) did not find a significant association between women exposed to estrogenic substances at work (endosulfan was one of them) and breast cancer. Rau et al. (2012) provided suggestive evidence of increased incidence of hematological malignancies among children residing near areas sprayed with endosulfan. The results of Roberts et al. (2007) suggested that maternal exposure to endosulfan during key periods of gestation might be associated with the development of autism spectrum disorders.

The acute-duration (1–14 days) inhalation data available in animals are limited to a single LC_{50} study. In that study, male and female Wistar rats (5/sex/group) were exposed nose-only to various concentrations of aerolized technical endosulfan for 4 hours and observed for 14 days. Trembling and ataxia were observed in rats exposed to the lowest concentrations tested, 12.3 mg/m^3 for males and 3.6 mg/m^3 for females (Hoechst 1983a). Autopsy of the animals that died during the study showed sporadic dark red foci the size of a pinhead in the lungs. Autopsy of animals killed at the end of the study did not reveal

macroscopic abnormalities. This study is considered inadequate for derivation of an acute-duration inhalation MRL for endosulfan since the lowest concentration tested was a serious LOAEL and a NOAEL could not be defined.

Only one intermediate-duration (15–364 days) inhalation study was located in the available literature. In that study, groups of male and female Wistar rats (15/sex/group) were exposed nose-only to concentrations of 0, 0.5, 1, and 2 mg/m^3 aerosolized technical endosulfan 6 hours/day, 5 days/week for a total of 21 exposures over a 29-day period (Hoechst 1984c). Ten rats per sex per group were killed 1 day after the last exposure and the remaining 5 rats/group were killed 29 days later. At termination, the rats were subjected to a complete necropsy and the major organs were weighed. Blood samples were collected for hematology and clinical chemistry tests. A comprehensive number of tissues and organs were processed for microscopic examination. There were no significant alterations in behavior or general health with the exception of one male rat from the high concentration group that was in poor condition from day 12 of the study. There was no mortality during the exposure period or the recovery period. The body weight of the high-concentration male group was lower than the control group from day 20 of the exposure period (<10% difference with controls of day 20). This coincided with a marked decrease in food consumption in that group at that time. While the mean weight of this group remained below controls for the remainder of the study, the rate of growth did not appear to be affected. Results from hematology and clinical chemistry tests showed occasional significant differences between exposed and control rats, but values were still within normal limits for the strain of rat, and in many cases, there was no dose-response relationship. Examination of organs and tissues did not show compound-related gross or microscopic alterations. Because no adverse effects were reported in this study, it is not a suitable basis for an MRL.

No chronic-duration (≥365 days) inhalation MRL was derived for endosulfan due to lack of studies.

Oral MRLs

- An MRL of 0.007 mg/kg/day has been derived for acute-duration (1–14 days) oral exposure to endosulfan based on adverse neurological signs in rabbits.

Acute-duration oral data in humans are available from cases of accidental or intentional ingestion of endosulfan. Some of these cases resulted in death (Bernardelli and Gennari 1987; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Eyer et al. 2004; Lo et al. 1995; Moon and Chun 2009; Parbhu et al. 2009;

Terziev et al. 1974). Although doses were estimated in some of these reports, they cannot be used for MRL derivation because ATSDR does not base MRLs on serious effects such as seizures or lethal doses.

The animal database provides information mainly on lethal doses of endosulfan and neurological effects. Systemic effects such as organ congestion were also reported at doses that induced neurological effects. The lowest LOAEL in an acute-duration oral study was 1 mg/kg/day for a 53% decrease in sperm count in male offspring of Druckrey rats that were dosed by gavage on Gd 12–21 (Sinha et al. 2001); since only one dose level was tested, the true LOAEL may be lower. Moreover, no information was provided in this study regarding clinical signs in the dams during treatment, other than no mortality occurred. A relatively low LOAEL was reported for significant preimplantation loss in mice dosed by gavage with 3 mg/kg/day technical endosulfan on Gd 1–7 (Hiremath and Kaliwall 2002a); the NOAEL was 2 mg/kg/day. The lowest LOAEL for neurological effects was reported in a gestational exposure study in pregnant female New Zealand rabbits that showed hyperactivity and convulsions within 4 days after administration of daily gavage doses of 1.8 mg/kg/day (MacKenzie et al. 1981); the NOAEL was 0.7 mg/kg/day. In a study by Bury (1997), increased incidence of neurological signs was also reported in female Wistar rats within 8 hours after gavage administration of a single dose of 3 mg/kg of endosulfan; the NOAEL was 1.5 mg/kg. Of these studies, the study by Sinha et al. (2001) is not appropriate for MRL derivation since only one dose level was tested and there was no information regarding maternal effects. Hiremath and Kaliwall (2002a) provided only a qualitative description of the results, and there is no indication that statistical methods were used in the study. Therefore, the Bury study (1997) and Mackenzie et al. (1981) study will be considered for potential derivation of an acute-duration oral MRL for endosulfan.

In the Bury study (1997), male and female Wistar rats (10/sex/treated group, 20 controls/sex) were administered a single dose of technical endosulfan (0, 6.25, 12.5, 25, 50, or 100 mg/kg for males; 0, 0.75, 1.5, 3, 6, or 12 mg/kg for females) by gavage in 2% (v/v) mucilage in deionized water. Rats were observed for 15 days, during which time they were administered a functional observational battery (FOB) that assessed multiple parameters and were tested for motor activity. The rats were sacrificed 3 weeks after dosing, and multiple levels of the central and peripheral nervous system were examined microscopically. Neurological signs developed in 10/10 males at ≥25 mg/kg and in 10/10 females at ≥3 mg/kg within 8 hours after dosing. Females dosed with 3 mg/kg endosulfan showed increased incidence of squatting posture, stilted gait, straddled hindlimbs, decreased spontaneous activity, bristle coat, and irregular respiration and panting. The incidences of various signs varied, but all 10 female rats dosed with 3 mg/kg showed stilted gait and squatting posture (100% incidence). No clinical signs were noted in subsequent days. There were no compound-related alterations in body weight or in the FOB and

motor activity tests, or in the pathological evaluations at termination. Based on the increased incidence of clinical signs seen in female rats, LOAEL and NOAEL values of 3 and 1.5 mg/kg, respectively, can be defined in the study.

In the MacKenzie et al. (1981) study, mated female New Zealand White rabbits (20/dose group) were administered technical endosulfan by gavage in corn oil in doses of 0, 0.3, 0.7, or 1.8 mg/kg/day from Gd 6 to 28; dams were sacrificed on Gd 29. Body weight and clinical signs were monitored throughout the study. Reproductive and developmental parameters were evaluated at termination. Since deaths occurred in the high-dose group (not totally clear when), 6 mated females were added to this group for a total of 26 dams. Neurological signs were observed in three high-dose dams within 4 days of the start of treatment (in one female on Gd 6, the day of the first dose, and in two females on Gd 10, after four doses). The signs consisted of noisy and rapid breathing, hyperactivity, and convulsions. No such signs occurred in the other treated groups or in the control group. Although the incidence of neurological effects of 3/26 is not statistically different from 0/20 in the other groups ($p=0.1713$, Fisher Exact Test), it is appropriate to consider the 1.8 mg/kg/day dose level a LOAEL based on the biological significance of the effect. Neurological effects are characteristic of endosulfan and other chlorinated pesticides in humans and animals. Moreover, an additional study in rabbits reported clinical signs including hyperexcitability, dyspnea, hyperpnea, intermittent intervals of tremors and tonic-clonic convulsions, thrashing against the cage walls, depression, and forelimb extension leading to death in 1/9 and 2/9 New Zealand White male rabbits 10–40 minutes following gavage dosing with 1.5 or 3 mg/kg endosulfan, respectively (Hatipoglu et al. 2008). Therefore, the dose level of 1.8 mg/kg/day in the MacKenzie et al. (1981) study is considered an acute LOAEL for neurological signs; the NOAEL is 0.7 mg/kg/day.

Incidence data for neurological signs from the Bury study (1997) and MacKenzie et al. (1981) study were considered for MRL derivation using the benchmark dose (BMD) approach. Inspection of the data from the Bury study (1997) shows that two clinical signs appeared to be the most sensitive, stilted gait and squatting posture, both occurring with a 100% incidence (10/10, all responders) in female rats that exhibited clinical signs at 3 mg/kg. Since neither control rats nor rats dosed with 0.75 or 1.5 mg/kg endosulfan exhibited such signs (0/10, no responders), these data are not considered adequate for BMD analysis (EPA 2000a). Still, the data are adequate to define NOAEL and LOAEL values for clinical signs of 1.5 and 3 mg/kg endosulfan, respectively.

Incidence data for neurological signs in rabbits occurring within 14 days after dosing started in the MacKenzie et al. (1981) study were analyzed using the BMD approach. The incidence data were 0/20,

0/20, 0/20, and 3/26 in the control, 0.3, 0.7, and 1.8 mg/kg/day dose groups, respectively. Models in the EPA Benchmark Dose Software (BMDS version 2.1.1) were fit to the data set to determine potential points of departure (PODs) for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the POD when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) is chosen. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body weight, in the absence of a clear criteria as to what level of change in body/organ weight or body weight gain should be considered adverse, the BMR is defined as a change in weight or weight/gain equal to 1 standard deviation from the control mean (EPA 2000a). Using the criteria for model selection mentioned above, the Gamma model (BMD_{10} 1.76 mg/kg/day; $BMDL_{10}$ 1.23 mg/kg/day) was selected as the best model to fit the incidence of clinical signs in pregnant female rabbits. However, the $BMDL_{10}$ of 1.23 mg/kg/day is not only very close to the BMD_{10} of 1.76 mg/kg/day, a dose that caused serious effects in the study, but it is even closer to a dose of 1.5 mg/kg/day, which caused the same type of serious clinical signs and even death in one of nine rabbits in the Hatipoglu et al. (2008) study, as mentioned above. Taking this into consideration and in the interest of protecting human health, the NOAEL of 0.7 mg/kg/day for clinical signs in the MacKenzie et al. (1981) study is preferred as the POD for derivation of an acute-duration oral MRL for endosulfan. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the NOAEL of 0.7 mg/kg/day results in an acute-duration oral MRL of 0.007 mg/kg/day for endosulfan. A detailed description of the MacKenzie et al. (1981) study is presented in Appendix A.

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

No relevant oral data in humans were located. Although there seems to be a considerable number of intermediate-duration oral studies in animals providing information on systemic effects and also immunological, neurological, reproductive, and developmental effects, many suffer from limitations including inadequate reporting of the results or only one dose level was used. An unequivocal target for endosulfan was not identified in the available studies. The lowest LOAEL for an intermediate-duration oral study was 0.61 mg/kg/day for a significant reduction in body weight in male rat pups (females were not used) on Pnd 21 born to Sprague-Dawley dams exposed to endosulfan by gavage during the entire

period of gestation and lactation (Cabaleiro et al. 2008; Caride et al. 2010). A maternal dose of 6.12 mg/kg/day induced a reduction of approximately 45% in pup body weight on Pnd 21; no NOAEL was identified in these studies. The effect could have been due to poor milk production by the dams or to a direct action of endosulfan/metabolites on the pups via the milk, or both. It is worth noting that treatment of Wistar rats via the diet with a much higher dose of endosulfan, 29.8 mg/kg/day, on Gd 6–21 and during the lactation period resulted in a reduction of 11 and 4% in male and female pup weight, respectively, on Pnd 21, suggesting possible differences in strain sensitivity, but most likely the different mode of administration of the test material, gavage versus diet. A relative low LOAEL of 0.9 mg/kg/day was identified for decreases in humoral and cell-mediated responses in male Wistar rats (females were not tested) administered endosulfan in the diet for up to 22 weeks; the NOAEL was 0.45 mg/kg/day (Banerjee and Hussain 1986). In this study, the humoral immune response was evaluated by measuring serum immunoglobulin concentration and antibody titer against tetanus toxoid; the cell mediated cell response was studied by leucocyte migration inhibition and macrophage migration inhibition tests. Slightly higher LOAELs of 1 mg/kg/day were established in a number of studies for a variety of end points. Singh et al. (2007b) reported increased incidence of myocardial fiber degeneration and degenerative changes in the liver and kidney from female Wistar rats dosed with 1 mg/kg/day technical endosulfan on Gd 6–20. The same group of investigators reported significant increases in the incidences of gross, visceral, and skeletal anomalies, and hepatocyte and renal tubule epithelial degeneration in Gd 20 fetuses from the female Wistar rats mentioned above (Singh et al. 2007a, 2008). The same dose level induced degenerative changes in the endocrine pancreas and brain hemorrhage and edema in New Zealand white rabbits following 6 weeks of dosing (Mor and Ozmen 2010; Ozmen et al. 2010). In all of these studies, endosulfan was administered by gavage and only one dose level was tested; therefore, dose-response relationships could not be constructed. The remainder of the oral intermediate-duration studies tested higher doses of endosulfan. It is important to note that a study in Wistar rats, the same strain of rat used in the single dose level studies mentioned above, reported no significant compound-related alterations in hematology and clinical chemistry tests, body weight, ophthalmology, or gross or microscopic appearance of the liver, kidney, skeletal muscle, or nervous system tissues following administration of doses up to 37.2 and 45.5 mg/kg/day technical endosulfan via the diet to males and females, respectively, for 13 weeks (Sheets et al. 2004). This again indicates that the mode of administration of endosulfan plays a significant role in the manifestation of toxic effects of endosulfan. Of the studies mentioned above, the study by Banerjee and Hussain (1986) is selected for derivation of an intermediate-duration oral MRL for endosulfan. The selection is made on the basis that the study provided enough information to define a NOAEL and LOAEL and used the diet as the vehicle for administering endosulfan. Dosing via the diet is a more relevant route for environmental exposure of humans to endosulfan than gavage. With the

exception of a study by Hoechst (1988c), which reported that doses up to 4.5 mg/kg/day given to Wistar rats 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, the preliminary study by Banerjee and Hussain (1986) is the only one that has examined immunocompetence in response to an infective agent, and would be helpful to try to replicate it. Vos et al. (1982) reported that serum levels of IgM and IgG were not significantly altered in male Wistar rats dosed with 5 mg/kg/day endosulfan for 3 weeks, but resistance to infection was not tested. Data from Banerjee and Hussain (1986) were considered for benchmark modeling analysis. However, only the information regarding serum levels of IgM and IgG, which are presented in a table in the study, could have been subjected to benchmark modeling. Data regarding serum antibody titer to tetanus toxoid as well as leucocyte and macrophage migration inhibition were presented in figures from which only approximate values could be determined. Still, Banerjee and Hussain (1986) indicated in the figures the dose levels at which the responses were significantly different from controls. Therefore, since the lowest dose of 0.45 mg/kg/day (5 ppm in the food) was the NOAEL for serum IgG and IgM levels, antibody titer, and leucocyte and macrophage migration inhibition, the NOAEL/LOAEL approach is preferred for MRL derivation since it includes the three data sets. The intermediate-duration oral MRL for endosulfan is derived by dividing the NOAEL of 0.45 mg/kg/day by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability). This yields an MRL of 0.005 mg/kg/day. A detailed description of the Banerjee and Hussain (1986) study is presented in Appendix A.

The intermediate-duration oral MRL of 0.005 mg/kg/day for endosulfan has also been adopted for the chronic-duration oral MRL based on the information summarized below. Chronic-duration dietary studies have been conducted in rats, mice, and dogs. Studies in Wistar rats were conducted by FMC (1959b) and Hoechst (1989a), the former used 25 rats per sex per group and the latter used 70 rats per sex per group. The results of Hoechst (1989a) were later published as Hack et al. (1995) with emphasis on the neoplastic effects of endosulfan. A 2-year study in NMRI mice was conducted by Hoechst (1988b) and the results were later published as Hack et al. (1995) also with emphasis on the neoplastic effects of endosulfan. A 2-year study in beagle dogs was conducted by FMC (1967) and a 1-year study was conducted by Hoechst (1989c); the former used four dogs per sex per group and the latter used six dogs per sex per group. NCI (1978) conducted long-term studies in Osborne-Mendel rats and B6C3F_1 mice. These studies conducted gross and microscopic examination of organs and tissues in addition to hematology and clinical chemistry tests. All of these studies used comparable doses of technical endosulfan (up to approximately 5 mg/kg/day) except for the NCI (1978) study that used doses

considerably higher in rats (up to 48 and 22 mg/kg/day, in males and females, respectively). The lowest LOAELs in rats were identified in the Hoechst (1989a) study. The most salient findings in that study included reductions in weight gain and increased incidences of marked progressive glomerulonephrosis in male and female rats from the highest-dose groups. These data are presented in Tables 2-1 through 2-4. The incidence of aneurysms in the kidneys of male rats was also increased, but there was no dose-response relationship (10/70, 6/70, 17/70, 10/70, and 19/70 in the control and respective increasing dose groups).

In mice, the highest dose tested in the Hoechst (1988b) study, 2.9 mg/kg/day, caused a significant reduction in survival rate in females (28 versus 45% in controls). No other significant treatment-related effects were reported in chronic-duration studies in mice. No significant adverse effects were reported in the 2-year study in beagle dogs that received doses of endosulfan of up to 1 mg/kg/day via the diet (FMC 1967). In the 1-year study, the dogs were fed a diet containing 0, 3, 10, or 30 ppm endosulfan (0, 0.2, 0.7, or 2 mg/kg/day for males and 0, 0.2, 0.6, or 1.8 mg/kg/day for females) (Hoechst 1989c). Dogs fed a diet with ≥45 ppm endosulfan were sacrificed earlier due to severe neurological effects. In the 30 ppm group, three males and two females experienced violent contractions of the abdominal muscles and upper abdomen and convulsive movements of the chap muscles 2.5–6 hours after feeding. Dogs fed the ≤30 ppm diets did not show significant treatment-related alterations in organs and tissues or in hematology values. Among clinical chemistry parameters, dogs in the ≥10 ppm diets groups showed a significant increase in mean serum alkaline phosphatase activity relative to controls (up to approximately 2-fold) beginning at 1.5 months. In the absence of significant changes in other serum enzymes and lack of treatment-related histological alterations in the liver, the investigators did not consider the changes in alkaline phosphatase activity toxicologically significant.

Of the studies mentioned above, the 2-year study in rats conducted by Hoechst (1989a) is the most appropriate for MRL derivation based on the number of animals used per group (n=70), duration of exposure that covered the entire lifespan of the animals, and identification of valid end points, such as kidney lesions and body weight changes, for which dose-response relationships could be constructed. Data sets for marked progressive glomerulonephrosis and body weight changes in male and female rats reported in the Hoechst (1989a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the four data sets to determine potential points of departure for the MRL. The data set for changes in weight gain in female rats proved not suitable for benchmark modeling even after dropping the two highest doses (out of five dose levels tested). Using the criteria for model selection mentioned earlier (see acute-duration oral MRL), the Log-logistic model

Table 2-1. Incidence of Marked Progressive Glomerulonephrosis in Male Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	70	20
0.1	70	18
0.3	70	22
0.6	70	24
2.9	70	30[a]

[a]p=0.055

Source: Hoechst 1989a

Table 2-2. Incidence of Marked Progressive Glomerulonephrosis in Female Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	70	1
0.1	70	6
0.4	70	6
0.7	70	5
3.8	70	8[a]

[a]p=0.017

Source: Hoechst 1989a

Table 2-3. Data for the Change in Body Weight Gain in Male Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Number of animals tested	Weight gain (g)	Standard deviation
0	70	580	124
0.1	70	570	125
0.3	70	531	131
0.6	70	525	115
2.9	70	479[a]	94

[a]p<0.01

Source: Hoechst 1989a

Table 2-4. Data for the Change in Body Weight Gain in Female Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Number of animals tested	Weight gain (g)	Standard deviation
0	70	398	105
0.1	70	350	107
0.4	70	414	85
0.7	70	363	92
3.8	70	328[a]	100

[a]$p<0.05$

Source: Hoechst 1989a

(BMD_{10} 5.84 mg/kg/day; $BMDL_{10}$ 2.31 mg/kg/day) was selected as the best model to fit the incidence of marked progressive glomerulonephrosis in female rats. The Log-logistic model also provided the best fit for incidence of marked progressive glomerulonephrosis in male rats (BMD_{10} 1.17 mg/kg/day; $BMDL_{10}$ 0.56 mg/kg/day). The Exponential (Model 2) provided the best fit for the decrease in body weight gain in male rats (BMD_{10} 4.60 mg/kg/day; $BMDL_{10}$ 3.41 mg/kg/day). The lower $BMDL_{10}$ of 0.56 mg/kg/day is more health protective and is selected as the point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 0.56 mg/kg/day results in a chronic-duration oral MRL of 0.006 mg/kg/day for endosulfan. Since this MRL is slightly higher than the intermediate-duration oral MRL of 0.005 mg/kg/day derived for endosulfan, the intermediate-duration oral MRL, which is protective of potential effects due to chronic exposure to endosulfan, is adopted also as the chronic-duration oral MRL for endosulfan.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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 3 times as toxic as the β-isomer of endosulfan.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

3.2.1 Inhalation Exposure

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 3.2.3).

3.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to endosulfan. LC_{50} (lethal concentration, 50% kill) values of 12.6 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 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

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

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 in 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 revealed by routine gross and microscopic 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 microscopic examination of the heart and aorta of rats exposed (nose-only) to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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 microscopic 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 technical 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).

Table 3-1 Levels of Significant Exposure to Endosulfan - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	4 hr				12.6 F (LC50)	Hoechst 1983a technical	
2	Rat (Wistar)	4 hr				34.5 M (LC50)	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 3-1 Levels of Significant Exposure to Endosulfan - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
5	Rat (Wistar)	21 d 5 d/wk 6 hr/d	Resp	2			Hoechst 1984c technical	
			Cardio	2				
			Gastro	2				
			Hemato	2				
			Musc/skel	2				
			Hepatic	2				
			Renal	2				
			Endocr	2				
			Dermal	2				
			Ocular	2				
			Bd Wt	2				
			Metab	2				
Immuno/ Lymphoret								
6	Rat (Wistar)	29 d 5 d/wk 6 hr/d		2			Hoechst 1984c technical	
Neurological								
7	Rat (Wistar)	21 d 5 d/wk 6 hr/d		2			Hoechst 1984c technical	

Bd Wt = body weight; Cardio = cardiovascular; d = day; Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological;hr = hour; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

Figure 3-1 Levels of Significant Exposure to Endosulfan - Inhalation

Acute (≤14 days)

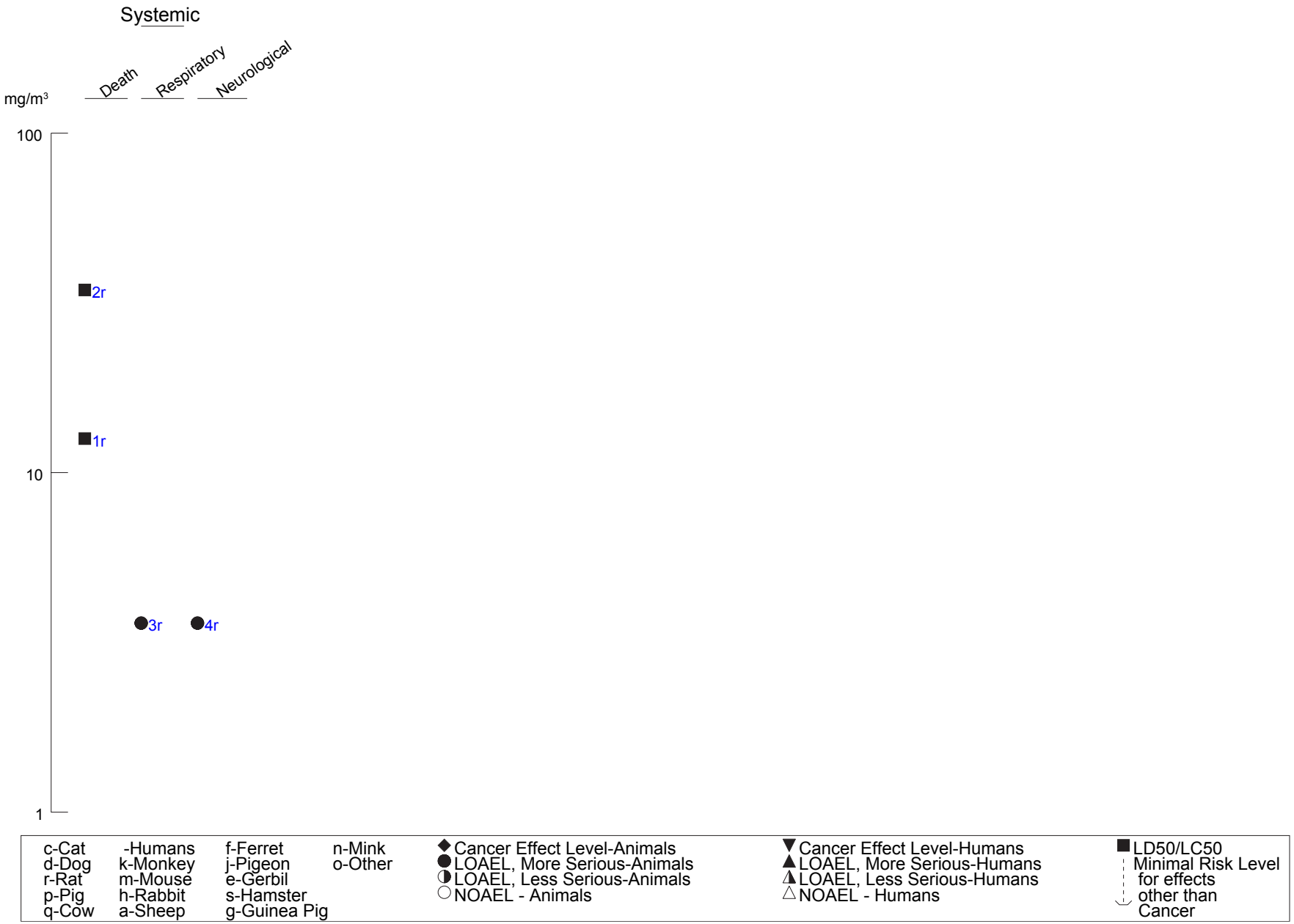
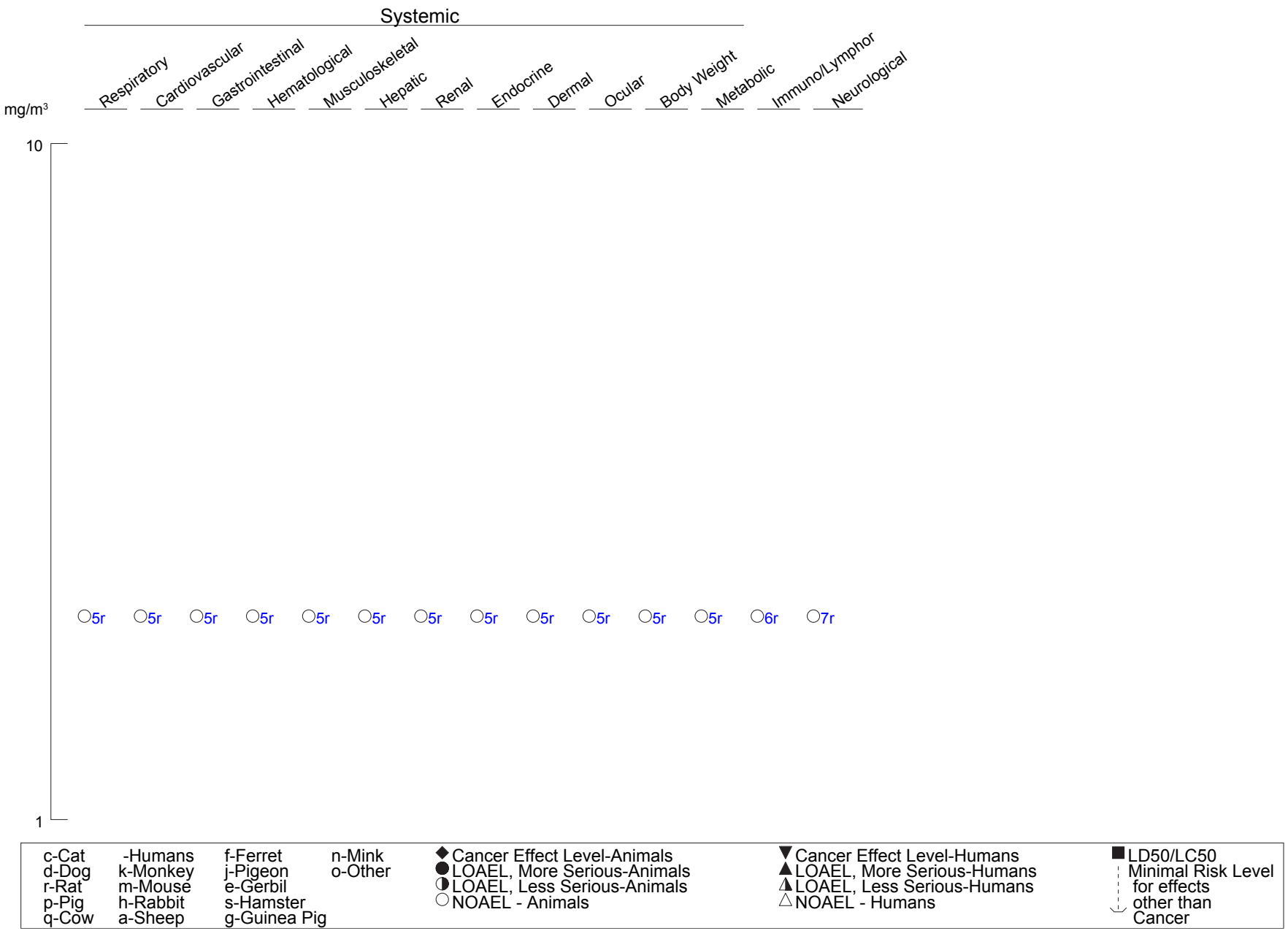


Figure 3-1 Levels of Significant Exposure to Endosulfan - Inhalation *(Continued)*

Intermediate (15-364 days)



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

Routine gross and microscopic 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 technical 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 microscopic examination of skeletal muscle and the diaphragm revealed no treatment-related effects following nose-only inhalation exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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.

Routine gross and microscopic examination of the liver did not reveal any effects of nose-only exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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 microscopic examination of the kidneys and urinary bladder did not reveal any effects of nose-only exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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 microscopic examination of the pituitary gland did not reveal any effects in rats exposed nose-only to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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 microscopic examination of the skin did not reveal any effects of nose-only exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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 microscopic examination of the eyes did not reveal any effects of nose-only exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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.

On day 20 of exposure, body weight gain slightly reduced (<10%) in male, but not female, rats exposed nose-only to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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. The body weight reduction was associated with a marked reduction in food consumption at that time.

Metabolic Effects. No studies were located regarding metabolic effects in humans after inhalation exposure to endosulfan.

Nose-only exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan for 6 hours/day, 5 days/week for a total of 21 out of 29 days had no significant effect on serum electrolytes or glucose levels (Hoechst 1984c).

3.2.1.3 Immunological and Lymphoreticular Effects

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

Routine gross and microscopic examination of the lymph nodes, thymus, and spleen did not reveal any effects of nose-only exposure of rats to concentrations of up to 2 mg/m^3 aerolized technical endosulfan 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.

3.2.1.4 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 (1 L of wine/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 aerosolized technical 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, tremors, tonic-clonic convulsions, and reduced corneal, pupillary, placing, shock, paw-pinch, and cutaneous reflexes were observed in both sexes. Nose-only exposure of male and female rats to concentrations of up to 2 mg/m^3 aerosolized technical endosulfan 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.

3.2.1.5 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 up to 2 mg/m^3 aerosolized technical endosulfan for 6 hours/day, 5 days/week for a total of 21 out of 29 days revealed no adverse effects (Hoechst 1984c).

3.2.1.6 Developmental Effects

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

Roberts et al. (2007) evaluated the hypothesis that maternal residence near agricultural pesticide applications during key periods of gestation could be associated with the development of autism spectrum disorders (ASD) in children. The study population included 269,746 singletons born between 1 January 1996 and 31 December 1998 to mothers residing in 19 counties in California. The final analyses were conducted on 465 cases and 6,975 controls. To exclude associations likely due to multiple testing error, the investigators employed a staged analytical design applying *a priori* criteria to the results of conditional logistic regressions. A total of 249 combinations of compounds, buffer radii, and temporal periods met a pre-established requirement of five exposed cases and controls per cell. Of these, four that described applications of dicofol and endosulfan that occurred during the period immediately before and concurrent with central nervous system embryogenesis met *a priori* criteria and were unlikely to be a result of multiple testing. Multivariate *a posteriori* models comparing children of mothers living within 500 m of field sites with the highest non-zero quartile of organochlorine poundage to those with mothers not living near field sites suggested an odds ratio (OR) for ASD of 6.1 (95% confidence interval [CI] 2.4–15.3). ASD risk increased with the poundage of pesticide applied and decreased with distance from field sites. According to the investigators, strengths of the study included the ability to locate pesticide

applications with relatively high resolution in both space and time, which allowed them to test hypotheses referring to specific temporal periods of vulnerability. The primary limitation was thought to be possible misclassification of exposure. Also, since little information was available regarding the mothers and children other than basic demographic characteristics, the investigators were unable to adjust for confounders potentially important for gestational neurodevelopment, such as the use of prenatal vitamins. Finally, the investigators could not dismiss that women in the "exposed" categories may have been disproportionally employed in agriculture and, therefore, subject to occupational exposures to pesticides beyond drift concentrations.

3.2.1.7 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 among 261 cases and 753 controls, the breast cancer 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. Rau et al. (2012) examined the possible association between levels of endosulfan in the bone marrow from children and acute hematological malignancies. The investigators also assessed whether children with high levels of endosulfan in their marrow resided in areas sprayed with endosulfan. The cohort consisted of 26 children with proven hematological malignancy and 26 age-matched controls with benign hematological disease. The major illness among the cases was acute lymphoblastic leukemia (n=23), whereas immune thrombocytopenic purpura occurred in 50% of controls (n=13). Six out of 26 cases tested positive for endosulfan in the bone marrow compared to 1 out of 26 controls; the concentration of endosulfan in the bone marrow was not provided. All of the children with elevated endosulfan in the bone marrow resided in the areas sprayed with the pesticide. The small sample size and the lack of control for potential confounders make this report of questionable value.

3.2.2 Oral Exposure

3.2.2.1 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 an endosulfan formulation containing 35% active ingredient dispersed in a colorless liquid containing 55% xylene, autopsy revealed no gross anatomical or histological abnormalities attributed to endosulfan (Bernardelli and Gennari 1987). According to the investigators, 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 4 hours after ingestion, she had tonic-clonic convulsions, nausea, vomiting, headache, and dizziness. On admission to the hospital, the concentrations of endosulfan (both isomers) in the gastric contents, blood, and urine were 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 (the endosulfan formulation was unspecified) 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. Eyer et al. (2004) described the case of man who intentionally drank 500 mL of Thiodan® 35 containing 180 g of endosulfan (approximately 2.6 g/kg) who presented with repetitive seizures on admission. The patient did not respond to treatment and died from multiorgan failure on day 10. Twenty-five hours after ingestion, the concentration of endosulfan in serum was approximately 0. 8 mg/L; a terminal half-life in blood of 15.2 hours was estimated for endosulfan. Post-mortem examination conducted 1 day after death showed severe brain edema. Parbhu et al. (2009) reported the case of a 2.5-year-old male who ingested an unknown amount of an 11.6% solution of endosulfan and immediately developed generalized tonic-clonic seizure activity, became unresponsive, and died on day 3. Moon and Chun (2009) reported that 16 out of 52 patients admitted to an emergency facility with acute endosulfan poisoning died. Refractory status epilepticus was the most common cause of death. The amount ingested being >35 g of endosulfan was the independent variable that best predicted patient mortality. Moses and Peter (2010) reported 18.75% mortality among 16 patients admitted to a hospital with documented endosulfan exposure in India.

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} 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). In a 60-day study, 8 of

19 male rats died following gavage dosing with 7.5 mg technical endosulfan/kg/day (Ansari et al. 1984). An LD_{50} value of 76.7 mg/kg technical endosulfan has been calculated from the results of a study in dogs (sex and breed not indicated) (Hoechst 1970). However, technical 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.

In rats, exposed males and females appear to have different sensitivities to the lethal effects of endosulfan exposure. Summary data submitted by Hoechst (1990) from experiments conducted mainly with technical endosulfan 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 endosulfan than male rats. This difference may be related to differences in the toxicokinetics of endosulfan in male and female rats (see also Section 3.4). 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 technical 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.

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 doses were 11 versus 36 mg/kg for α-endosulfan and β-endosulfan, respectively (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). Hoechst (1966a, 1966b) 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 technical endosulfan by gavage in corn oil during gestational days (Gd) 6–14 produced a dose-related increase in maternal deaths in these test groups (Gupta et al. 1978).

In intermediate-duration studies, rats tolerated 6-day/week gavage doses of 20 mg/kg technical endosulfan for 7 weeks (Garg et al.1980), whereas increased mortality was observed in male and female mice at doses of 7.3 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 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). Three out of nine rabbits administered 1.5 mg/kg/day technical endosulfan and five out nine rabbits administered 3 mg/kg/day died in a 30-day gavage study (Hatipoglu et al. 2008). No deaths occurred in rabbits administered 0.75 mg/kg/day. Clinical signs observed in some of the rabbits included hyperexcitability, dyspnea, hyperpnea, tremors and convulsions, depression, forelimb extension, loss of mobility, and eventually death.

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 with technical endosulfan 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 technical endosulfan 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 2.5 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 3-2 and plotted in Figure 3-2. 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.

Table 3-2 Levels of Significant Exposure to Endosulfan - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (albino)	60 d 1 x/d (GO)				7.5 M (6/19 died; 2 on day 3 and 4 on day 14)	Ansari et al. 1984 technical	
2	Rat (Wistar)	once (GO)				24 M (LD50; low protein diet)	Boyd and Dobos 1969 technical	
3	Rat (Long- Evans)	once (GO)				20 M (3 of 14 died following seizure activity)	Gilbert and Mack 1995 technical	
4	Rat (albino)	Gd 6-14 9 d 1 x/d (GO)				10 F (5/32 died)	Gupta et al. 1978 technical	
5	Rat (Wistar)	once (GW)				240 F (LD50)	Hoechst 1975 Beta	
6	Rat (Wistar)	once (GW)				65.7 F (LD50)	Hoechst 1988a Beta	
7	Rat (Wistar)	once (GW)				1740 M (LD50)	Hoechst 1988a Beta	
8	Mouse (albino)	once (GW)				11 F (lethal dose)	Dorough et al. 1978 Alpha	
9	Mouse (albino)	once (GW)				36 F (lethal dose)	Dorough et al. 1978 Beta	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Mouse (albino)	once (GW)				8 F (lethal dose)	Dorough et al. 1978 Alpha	
11	Mouse (albino)	NS (GO)				7.4 M (LD50)	Gupta et al. 1981 technical	
12	Mouse (albino)	once (GW)				14 F (LD50)	Hoechst 1966a Alpha	
13	Mouse (albino)	once				17 F (LD50)	Hoechst 1966b Beta	
14	Mouse (CD-1)	7 d (F)				7.5 M (2 of 10 died)	Wilson and LeBlanc 1998 technical	
15	Dog	once (C)				77 (LD50)	Hoechst 1970 technical	
Systemic								
16	Rat (Wistar)	once (GW)	Bd Wt	100 M 12 F			Bury 1997 technical	
17	Rat (albino)	once (GO)	Metab		40 M (increased blood glucose)		Garg et al. 1980 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Rat (Wistar)	once (GW)	Resp	63 F		70 F (lung congestion)	Hoechst 1988a Beta	
			Gastro			63 F (blood in small intestines; mucus in stomach)		
19	Mouse (albino)	10 d 1 x/d (GO)	Renal			13 M (degenerative changes in kidneys)	Caglar et al. 2003 technical	
20	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)			
Immuno/ Lymphoret								
21	Rat (Wistar)	10 d (GO)		4.5 F			Hoechst 1988c technical	NOAEL is for no alteration in resistance against Trichinella infection.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
22	Rat (Wistar)	once (GW)		12.5 M 1.5 F	25 M (stilted gait) 3 F (stilted gait; straddled hindlimbs)		Bury 1997 technical	
23	Rat (Sprague-Dawley)	Gd 6-19 2 wk 1 x/d (G)		2 F	6 F (flaccidity, hyperactivity)		FMC 1980b technical	
24	Rat (albino)	1 d 1 x/d (GO)			40 M (unspecified neurotoxic signs)		Garg et al. 1980 technical	
25	Rat (Long- Evans)	once (GO)				5 M (seizures)	Gilbert and Mack 1995 technical	
26	Rat (Wistar)	once (GW)				80 F (hyperactivity; convulsions; tremors)	Hoechst 1984e technical	
27	Rat (Wistar)	once (GW)				63 F (clonic spasms)	Hoechst 1988a Beta	
28	Rat (Wistar)	8 d 1 x/d (GO)			6 (changes in transmitter levels in several brain areas)		Lakshmana and Raju 1994 technical	
29	Mouse (albino)	once (GW)				10 F (convulsions)	Hoechst 1966a Alpha	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Mouse (albino)	once (GW)				12.5 F (convulsions)	Hoechst 1966b Beta	
31	Dog Mixed	once (C)		39.5		50 (convulsions, respiratory paralysis)	Hoechst 1970 technical	
32	Rabbit (New Zealand)	10 d 1 x/d (GO)		0.7 F[b]		1.8 F (tachypnea; hyperactivity; convulsions in dams)	MacKenzie et al. 1981 technical	
Reproductive								
33	Rat (Sprague-Dawley)	Gd 6-19 2 wk 1 x/d (G)		6 F			FMC 1980b technical	NOAEL is for post-implantation efficiency, litter size, and sex ratio.
34	Mouse (albino)	Gd 1-7 1 x/d (GO)		2 F		3 F (72% preimplantation loss)	Hiremath and Kaliwal 2002a technical	
Developmental								
35	Rat (Sprague-Dawley)	Gd 6-19 2 wk 1 x/d (G)		2 F	6 F (increased skeletal variations; decreased birth weight and length)		FMC 1980b technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (albino)	Gd 6-14 9 d 1 x/d (GO)				5 F (increased resorptions and skeletal variations)	Gupta et al. 1978 technical	
37	Rat Druckrey	Gd 12-21 1 x/d (GO)				1 M (53% decrease in sperm count; decrease sex organ weights in exposed offspring)	Sinha et al. 2001 technical	
INTERMEDIATE EXPOSURE								
Death								
38	Rat (albino)	60 d 1 x/d (GO)				7.5 M (2/19 died on days 32 and 58)	Ansari et al. 1984 technical	
39	Rat (Long- Evans)	7 wk 3 x/wk (GO)				10 M (4/16 died following 4-5 weeks of dosing)	Gilbert 1992 technical	
40	Rat (Wistar)	30 d (F)				6 F (3 out of 10 died)	Paul et al. 1995 technical	
41	Mouse (CD-1)	13 wk ad lib (F)				7.3 M (10/20 died) 7.5 F (11/20 died)	Hoechst 1984b technical	
42	Rabbit (New Zealand)	30 d 1 x/d (GO)				3 M (5/9 rabbits died)	Hatipoglu et al. 2008 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
43	Rat (Sprague-Dawley)	15-30 d (GO)	Hepatic		10 (liver histopathology)		Choudhary et al. 2003 technical	
			Renal		10 (kidney histopathology)			
44	Rat (albino)	9-18 wk ad lib (F)	Hemato	5 F			Das and Garg 1981 technical	
			Hepatic	5 F				
			Renal	5 F				
			Bd Wt	5 F				
45	Rat (albino)	30 d 1 x/d (GO)	Hemato	1.5 F	5 M (increased RBC and neutrophil count)		Dikshith et al. 1984 technical	
			Hepatic		5 M (increased relative liver weight)			
			Renal	1.5 F				
			Bd Wt	1.5 F				
46	Rat (Wistar)	26 wk ad lib (F)	Hemato	5			FMC 1959b technical	
47	Rat (albino)	7 wk 6 d/wk 1 x/d (GO)	Metab	0.625 M	5 M (decreased blood calcium)		Garg et al. 1980 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
48	Rat (Wistar)	Gd 6-21 Ld 1-21 (F)	Bd Wt	10.8 F	29.8 M (14% reduced body weight on Gd 20)		Gilmore et al. 2006 technical	
49	Rat (albino)	15 d 1 x/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)		
50	Rat (albino)	15 d 1 x/d (GO)	Hepatic	5 F			Gupta and Gupta 1977a technical	
			Endocr	5 F				
			Bd Wt	5 F				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Rat (CrL:COB S CD)	84 d ad lib (F)	Bd Wt	6 F			Hoechst 1984a technical	
52	Rat (Sprague-Dawley)	13 wk ad lib (F)	Hemato		0.8 F (decreased hemoglobin)		Hoechst 1985a technical	
			Hepatic	3.9 M	23.4 M (granular brown pigment; increased liver weight)			
					23.4 F (increased liver weight; centrilobular enlargement, increased serum lipids and cholesterol)			
			Renal	1.9 M	3.9 M (yellow protein in tubule lumen; eosinophilic droplets in cells of proximal convoluted tubules; increased kidney weights)	23.4 M (proteinuria)		
			Dermal	2.3 F	4.6 F (hair loss)			
53	Rat (Sprague-Dawley)	13-26 wk ad lib (F)	Hemato	2.9			Hoechst 1989a; Hack et al. 1995 technical	
54	Rat (Wistar)	6 wk 1 x/d (GO)	Cardio			2 M (myocardial fiber edema)	Kalender et al. 2004a technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Rat (Wistar)	6 wk 1 x/d (GO)	Endocr		2 M (pancreas histopathology)		Kalender et al. 2004b technical	
			Metab		2 M (increased blood glucose)			
56	Rat (Wistar)	30 d (F)	Hepatic		6 M (increased liver AST, ALT and liver and serum AP activities)		Paul et al. 1995 technical	
					3 F (increased serum and liver AST, ALT, and AP activities)			
			Bd Wt	6				
57	Rat (Wistar)	13 wk ad lib (F)	Hemato	45.5 F			Sheets et al 2004 technical	Hepatic and renal NOAELs are for organ histopathology.
			Musc/skel	45.5 F				
			Hepatic	45.5 F				
			Renal	45.5 F				
			Ocular	45.5 F				
			Bd Wt	45.5 F				
			Metab	45.5 F				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
58	Rat (Wistar)	15 d Gd 6-20 1 x/d (GO)	Bd Wt			1 F (29% reduction in final body weight on Gd 20)	Singh et al. 2007a technical	
59	Rat (Wistar)	15 d Gd 6-20 1 x/d (GO)	Cardio			1 F (myocardial fiber degeneration)	Singh et al. 2007b technical	
			Gastro		1 F (increased goblet cell activity)			
			Hepatic			1 F (degenerative changes;vacuolar degeneration)		
			Renal			1 F (proximal convoluted cell tubule degeneration)		
60	Rat (Druckrey)	70 d 5 d/wk (GO)	Bd Wt	10 M			Sinha et al. 1995 technical	
61	Mouse (albino)	30 d 1 x/d (GO)	Bd Wt	4 F			Hiremath and Kaliwal 2003 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
62	Mouse (CD-1)	13 wk ad lib (F)	Resp			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 3-2 Levels of Significant Exposure to Endosulfan - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Dog (Beagle)	146-147 d 1 x/d (F)	Resp	2.9 M			Hoechst 1989c technical	
			Cardio	2.9 M				
			Gastro	2.9 M				
			Hemato	2.9 F				
			Musc/skel	2.9 M				
			Hepatic	2.9 M				
			Renal	2.9 M				
			Endocr	2.9 M				
			Dermal	2.9 M				
			Ocular	2.9 M				
65	Rabbit (New Zealand)	6 wk 1 x/d (GO)	Bd Wt	1 M			Ata et al. 2007 technical	
66	Rabbit (New Zealand)	30 d 1 x/d (GO)	Hemato	3 M			Hatipoglu et al. 2008 technical	
			Bd Wt	1.5 M	3 M (18% reduction in final body weight)			
67	Rabbit (New Zealand)	Gd 6-28 23 d 1 x/d (G)	Resp		1.8 F (noisy and rapid breathing)		MacKenzie et al. 1981 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Rabbit (New Zealand)	6 wk 1 x/d (GO)	Endocr			1 M (degenerative changes in endocrine pancreas)	Ozmen et al. 2010 technical	
			Metab			1 M (36% increase in blood glucose)		
Immuno/ Lymphoret								
69	Rat (Wistar)	8-22 wk ad lib (F)		0.45 M[c]	0.9 M (decreased humoral and cell-mediated response)		Banerjee and Hussain 1986 technical	
70	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	
71	Rat (Wistar)	3 wk ad lib (F)		5 M			Vos et al. 1982 technical	
72	Mouse (CD-1)	13 wk ad lib (F)		2.1 M	7.3 M (decreased neutrophils and relative spleen weight)		Hoechst 1984b technical	
Neurological								
73	Rat (NS)	60 d 1 x/d (GO)		2.5 M		7.5 M (hyperactivity; tremors; convulsions)	Ansari et al. 1984 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
74	Rat (albino)	30 d 1 x/d (GO)				1.5 (hyperexcitation and tremors)	Dikshith et al. 1984 technical	
75	Rat (Long- Evans)	20 d 1 x/d (GO)				5 M (increased seizure activity)	Gilbert 1992 technical	
76	Rat (Wistar)	Gd 6-21 Ld 1-21 (F)		29.8 F			Gilmore et al. 2006 technical	NOAEL is for no significant effect in functional observational battery.
77	Rat (Sprague-Dawley)	13 wk ad lib (F)		2.3	4.6 F (increased brain weight)		Hoechst 1985a technical	
78	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	
79	Rat (Wistar)	90 d 1 x/d (GW)				2 M (inhibition of learning and memory processes)	Paul et al. 1994 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
80	Rat (Wistar)	30 d (F)				3 (impaired learning and memory processes)	Paul et al. 1995 technical	
81	Rat (Wistar)	13 wk ad lib (F)		37.2 M 45.5 F			Sheets et al 2004 technical	NOAELs are for histopathology of central peripheral nervous tissues and neurobehavior.
82	Mouse (CD-1)	13 wk ad lib (F)				7.3 (convulsions)	Hoechst 1984b technical	
83	Dog (Beagle)	146-147 d 1 x/d (F)				2.6 F (extreme sensitivity to noise and optical stimuli; muscle spasms in extremities, face, and jaw; placing and righting reflexes absent)	Hoechst 1989c technical	
84	Rabbit (New Zealand)	30 d 1 x/d (GO)		0.75 M		1.5 M (tremors and convulsions)	Hatipoglu et al. 2008 technical	
85	Rabbit (New Zealand)	6 wk 1 x/d (GO)				1 M (brain hemorrhage and edema; hyperexcitability)	Mor and Ozmen 2010 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
86	Rat (Sprague-Dawley)	44 d Gd 0-21 Ld 0-21 (GO)		0.61 F	6.12 F (11% reduction in litter size)		Cabaleiro et al. 2008 technical	
87	Rat (Sprague-Dawley)	15-30 d 1 x/d (GO)			5 M (35% reduced sperm motility in cauda epididymis)		Choudhary and Joshi 2003 technical	
88	Rat (Sprague-Dawley)	170+ d ad lib (F)		2.5			FMC 1965 technical	3-Generation reproductive study.
89	Rat (Wistar)	Gd 6-21 Ld 1-21 (F)		29.8 F			Gilmore et al. 2006 technical	NOAEL is for mean number of litters.
90	Rat (albino)	15 d 1 x/d (GO)		5 M		10 M (degeneration of seminiferous tubule epithelium)	Gupta and Chandra 1977 technical	
91	Rat (Sprague-Dawley)	11 wk ad lib (F)		8			Hoechst 1982 technical	NOAEL is for mating performance and pregnancy rate.
92	Rat (CrL:COB S CD)	84 d (F)		6 F			Hoechst 1984a technical	2-Generation reproductive study.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
93	Rat Lewis	8 wk ad libitum (F)		2.9 M			Perobelli et al. 2010 technical	NOAEL is for sperm parameters and sex organs histopathology.
94	Rat (Wistar)	15-30 d 1 x/d (GO)	Endocr		7.5 M (reduced testes and plasma testosterone and plasma LH and FSH)		Singh and Pandey 1990 technical	
95	Rat (Wistar)	15 d Gd 6-20 1 x/d (GO)				1 F (increased postimplantation loss; uterus alterations)	Singh et al. 2007b technical	
96	Rat (Druckrey)	70 d 5 d/wk (GO)			2.5 M (22% reduced sperm count; altered spermatogenesis)		Sinha et al. 1995 technical	
97	Rat (Druckrey)	90 d 5 d/wk (GO)				2.5 M (39% reduced sperm and spermatids count and daily sperm production; increased abnormal sperm; altered spermatogenesis)	Sinha et al. 1997 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
98	Mouse (albino)	15 d 1 x/d (GO)		1.5 F	3 F (decreased compensatory ovarian hypertrophy in hemicastrated mice)		Hiremath and Kaliwal 2002b technical	
99	Mouse (albino)	30 d 1 x/d (GO)		4 F			Hiremath and Kaliwal 2003 technical	NOAEL is for lack of estrogenic and antiestrogenic activity.
100	Rabbit (New Zealand)	6 wk 1 x/d (GO)				1 M (decreased sperm volume; increased abnormal sperm morphology and dead sperm)	Ata et al. 2007 technical	
101	Rabbit (New Zealand)	Gd 6-28 23 d 1 x/d (G)		1.8 F			MacKenzie et al. 1981 technical	NOAEL is for number of implants, litter size, and sex ratio.
Developmental								
102	Rat (Sprague-Dawley)	44 d Gd 0-21 Ld 0-21 (GO)			0.61 M (11% reduced pup weight on Pnd 21)	6.12 M (46% reduced pup weight on Pnd 21)	Cabaleiro et al. 2008 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
103	Rat (Sprague-Dawley)	42 d Gd 1-21 Ld 1-21 1 x/d (GO)			0.61 M (11% reduced offspring weight on Gd 21)	6.12 M (44% reduced pup weight on Pnd 21)	Caride et al. 2010 technical	
104	Rat (Wistar)	28 d Gd 15-21 Ld 0-21 1 x/d (GW)			1.5 M (20% reduced daily sperm production in offspring at 65 days of age)		Dalsenter et al. 1999 technical	
105	Rat (Wistar)	63 d Gd 0-21 Ld 1-21 1 x/d (GO)		1.5 M			Dalsenter et al. 2003 technical	NOAEL is for reproductive parameters in offspring exposed during gestation and lactation.
106	Rat (Wistar)	Gd 6-21 Ld 1-21 (F)		3.74 F	10.8 F (11% reduced pup's weight on Pnd 11)		Gilmore et al. 2006 technical	
107	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	
108	Rat (CrL:COB S CD)	84 d (F)		1.3 F	7 F (decreased mean F1b litter weight on Pnd 12)		Hoechst 1984a technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
109	Rat (Wistar)	63 d Gd 1-21 Ld 1-21 1 x/d (GO)		1.5 M			Silva de Assis et al. 2011 technical	NOAEL is for neonatal developmental parameters.
110	Rat (Wistar)	15 d Gd 6-20 1 x/d (GO)				1 F (significant reduction in fetal weight and increased gross, visceral, and skeletal anomalies)	Singh et al. 2007a technical	
111	Rat (Wistar)	15 d Gd 6-20 1 x/d (GO)				1 F (hepatocyte degeneration in fetuses; degeneration of kidney tubular epithelium in fetuses)	Singh et al. 2008 technical	
112	Rabbit (New Zealand)	Gd 6-28 23 d 1 x/d (G)		1.8			MacKenzie et al. 1981 technical	NOAEL is for lack of teratogenicity.
CHRONIC EXPOSURE								
Death								
113	Rat (Wistar)	2 yr ad lib (F)				5 F (decreased survival)	FMC 1959b technical	
114	Mouse (NMRI)	24 mo ad lib (F)				2.9 F (decreased survival)	Hoechst 1988b; Hack et al. 1995 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
115	Rat (Wistar)	2 yr ad lib (F)	Resp	5			FMC 1959b technical	
			Cardio	5				
			Gastro	5				
			Hemato	5				
			Hepatic	1.5	5 M (hydropic hepatic cells)			
			Renal	1.5		5 M (increased kidney weight; renal tubule dilation, degeneration of renal tubule epithelium; albuminous casts; focal interstitial nephritis)		
			Endocr	5				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
116	Rat (Sprague-Dawley)	2 yr ad lib (F)	Resp	3.8 F			Hoechst 1989a; Hack et al. 1995 technical	
			Cardio	0.6 M	2.9 M (aneurysms of blood vessels)			
			Gastro	3.8 F				
			Hemato	3.8 F				
			Musc/skel	3.8 F				
			Hepatic	3.8 F				
			Renal	0.7 F	3.8 F (marked glomerulonephrosis)			
			Endocr	3.8 F				
			Dermal	3.8 F				
			Ocular	3.8 F				
			Bd Wt	0.6 M	2.9 M (17% reduced weight gain)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
117	Rat (Osborne-Mendel)	74-82 wk ad lib (F)	Resp	48 M			NCI 1978 technical	
			Cardio			20 M (calcium deposits in the heart, coronary and mesenteric arteries)		
			Gastro	48 M				
			Musc/skel	48 M				
			Hepatic	48 M				
			Renal			11 F (degeneration of proximal convoluted tubule; degeneration of tubular epithelium; fibrosis and focal mineralization)		
			Endocr		11 M (hyperplasia of parathyroid)			
			Dermal	48 M				
			Bd Wt			20 M (body weight reduced by 23% relative to controls at week 80)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
118	Mouse (NMRI)	24 mo ad lib (F)	Resp	2.9 F			Hoechst 1988b; Hack et al. 1995 technical	NOAELs are for organ histology.
			Cardio	2.9 F				
			Gastro	2.9 F				
			Hemato	2.9 F				
			Musc/skel	2.9 F				
			Hepatic	2.9 F				
			Renal	2.9 F				
			Endocr	2.9 F				
			Dermal	2.9 F				
			Ocular	2.9 F				
			Bd Wt	2.9 F				
119	Mouse (B6C3F1)	78 wk ad lib (F)	Resp	0.9 M			NCI 1978 technical	NOAELs are for organ histology.
			Cardio	0.9 M				
			Gastro	0.9 M				
			Musc/skel	0.9 M				
			Hepatic	0.9 M				
			Renal	0.9 M				
			Dermal	0.9 M				
			Bd Wt	0.9 M				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
120	Dog (Beagle)	2 yr ad lib (F)	Resp	1			FMC 1967 technical	NOAELs are for organ histology.
			Cardio	1				
			Gastro	1				
			Hemato	1				
			Musc/skel	1				
			Hepatic	1				
			Renal	1				
			Endocr	1				
121	Dog (Beagle)	1 yr ad lib (F)	Resp	2 M			Hoechst 1989c technical	
			Cardio	2 M				
			Gastro	2 M				
			Hemato	2 M				
			Musc/skel	2 M				
			Hepatic	2 M				
			Renal	2 M				
			Endocr	2 M				
			Dermal	2 M				
			Ocular	2 M				
			Bd Wt	2 M				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
122	Rat (Sprague-Dawley)	2 yr ad lib (F)		2.9			Hoechst 1989a; Hack et al. 1995 technical	NOAEL is for histology of lymphoreticular tissues.
123	Rat (Osborne-Mendel)	74-82 wk ad lib (F)		48 M			NCI 1978 technical	NOAEL is for histology of lymphreticular organs.
124	Mouse (NMRI)	24 mo ad lib (F)		2.9 F			Hoechst 1988b; Hack et al. 1995 technical	NOAEL is for histology of lymphoreticular tissues.
125	Mouse (B6C3F1)	78 wk ad lib (F)		0.9 M			NCI 1978 technical	NOAEL is for histology of lymphoreticular organs.
126	Dog (Beagle)	2 yr ad lib (F)		1			FMC 1967 technical	NOAEL is for histology of lymphoreticular tissues.
127	Dog (Beagle)	1 yr ad lib (F)		1.8 F			Hoechst 1989c technical	NOAEL is for histology of lymphoreticular tissues.
Neurological								
128	Rat (Sprague-Dawley)	2 yr ad lib (F)		2.9			Hoechst 1989a; Hack et al. 1995 technical	NOAEL is for histology of brain, spinal cord, and sciatic nerve.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
129	Rat (Osborne-Mendel)	74-82 wk ad lib (F)		48 M			NCI 1978 technical	NOAEL is for histology of the brain.
130	Mouse (NMRI)	24 mo ad lib (F)		2.9 F			Hoechst 1988b; Hack et al. 1995 technical	NOAEL is for histology of tissues of the nervous system.
131	Mouse (B6C3F1)	78 wk ad lib (F)		0.9			NCI 1978 technical	NOAEL is for histology the brain.
132	Dog (Beagle)	2 yr ad lib (F)		1			FMC 1967 technical	NOAEL is for histology of tissues of the nervous system.
133	Dog (Beagle)	1 yr ad lib (F)		0.6 F		1.8 F (abdominal and jaw muscle spasms)	Hoechst 1989c technical	
Reproductive								
134	Rat (Sprague-Dawley)	2 yr ad lib (F)		2.9			Hoechst 1989a; Hack et al. 1995 technical	NOAEL is for histology of reproductive organs.
135	Rat (Osborne-Mendel)	74-82 wk ad lib (F)		20 M		48 M (testicular necrosis, aspermatogenesis)	NCI 1978 technical	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
136	Mouse (NMRI)	24 mo ad lib (F)		2.5 M 2.9 F			Hoechst 1988b; Hack et al. 1995 technical	
137	Mouse (B6C3F1)	78 wk ad lib (F)		0.9			NCI 1978 technical	NOAEL is for histology of sex organs.
138	Dog	2 yr ad lib (F)		1			FMC 1967 technical	NOAEL is for reproductive organs histology.
139	Dog (Beagle)	1 yr ad lib (F)		1.8			Hoechst 1989c technical	NOAEL is for histology of reproductive organs.

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

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.007 mg/kg/day for endosulfan; the MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal-to-human extrapolation and 10 for human variability).

c Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.005 mg/kg/day for endosulfan; the MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal-to-human extrapolation and 10 for human variability).

ad lib = ad libitum; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; x = time(s); wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Endosulfan - Oral

Acute (≤14 days)

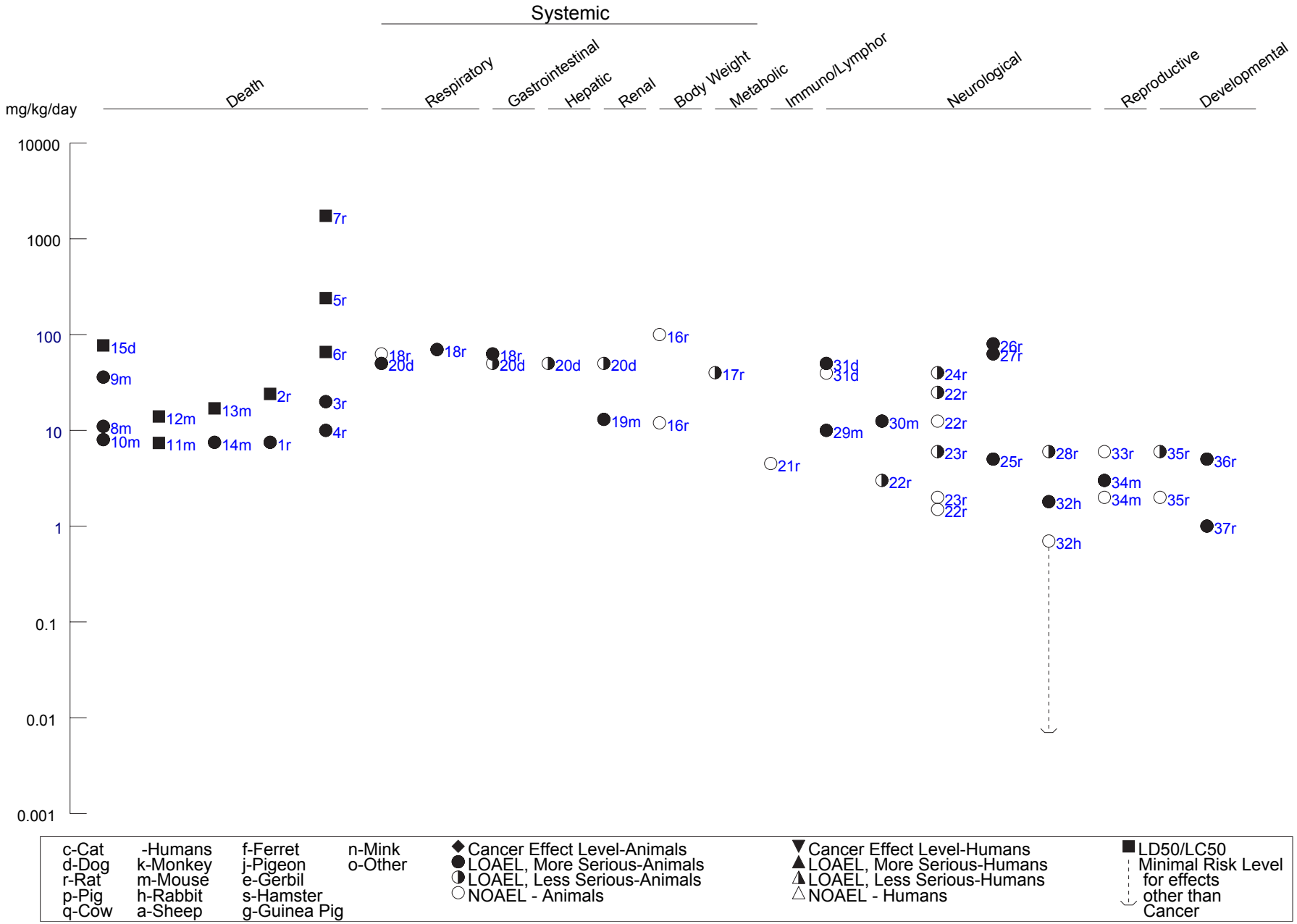


Figure 3-2 Levels of Significant Exposure to Endosulfan - Oral *(Continued)*

Intermediate (15-364 days)

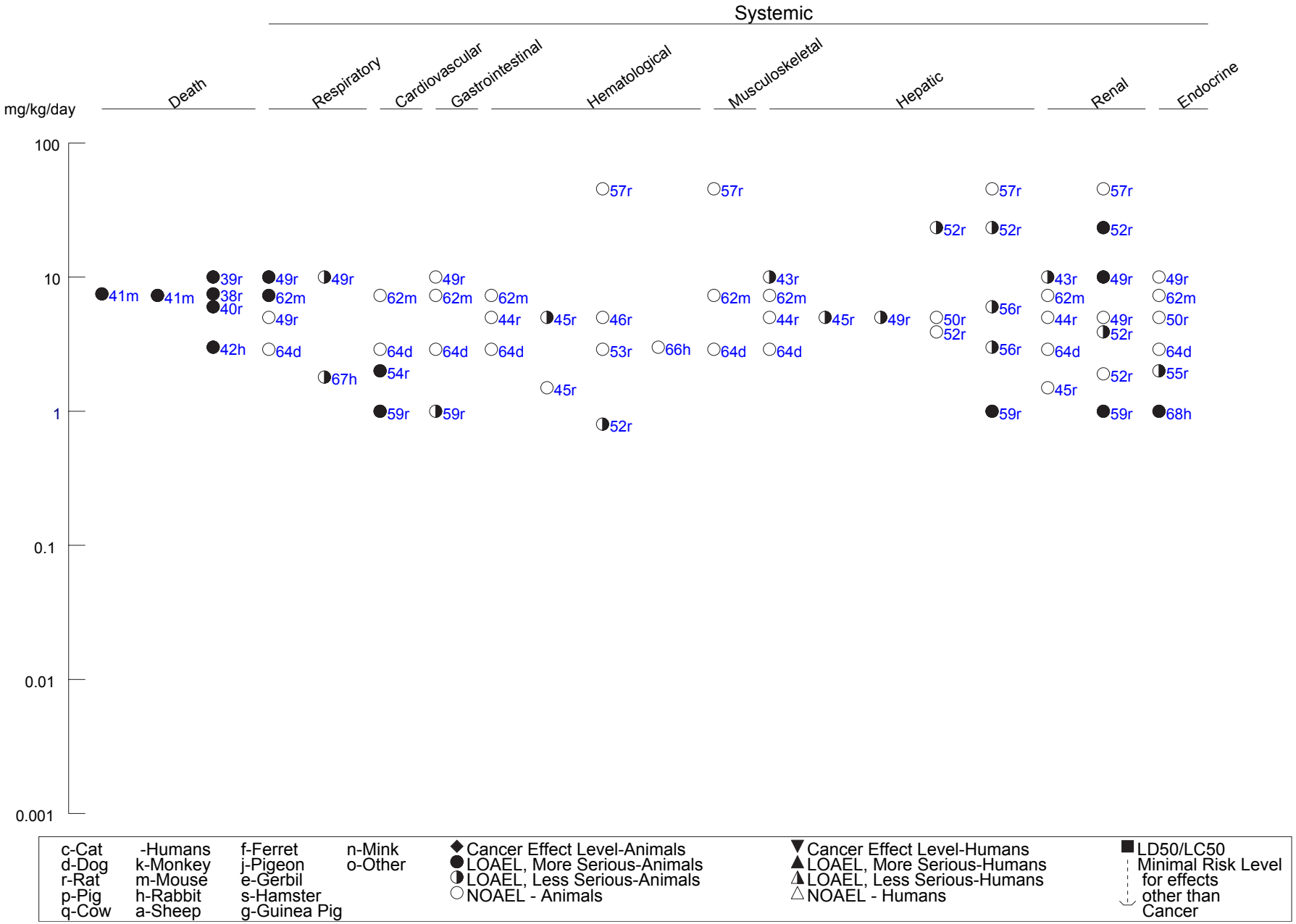
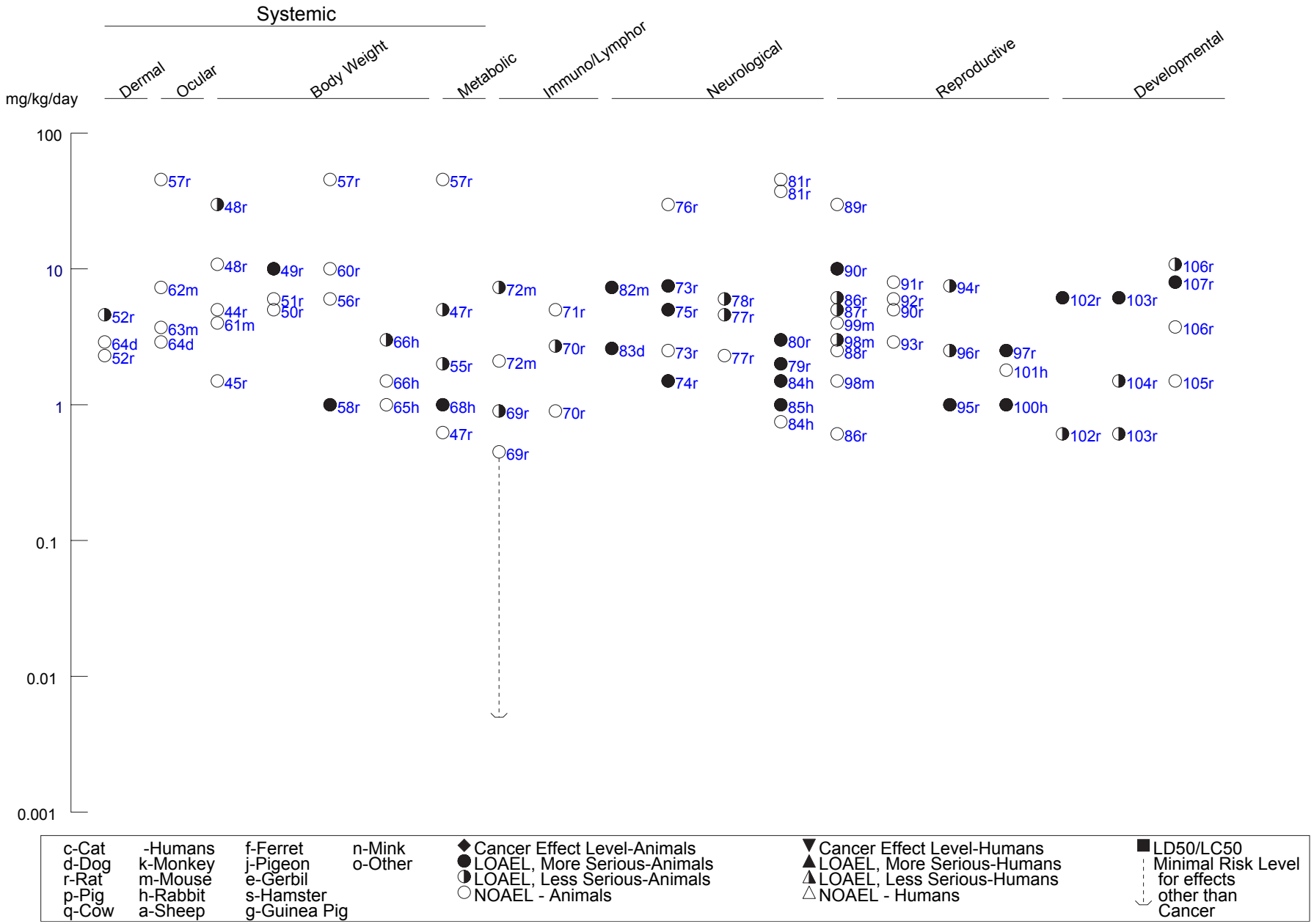


Figure 3-2 Levels of Significant Exposure to Endosulfan - Oral *(Continued)*

Intermediate (15-364 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 Level for effects other than Cancer

Figure 3-2 Levels of Significant Exposure to Endosulfan - Oral *(Continued)*

Intermediate (15-364 days)

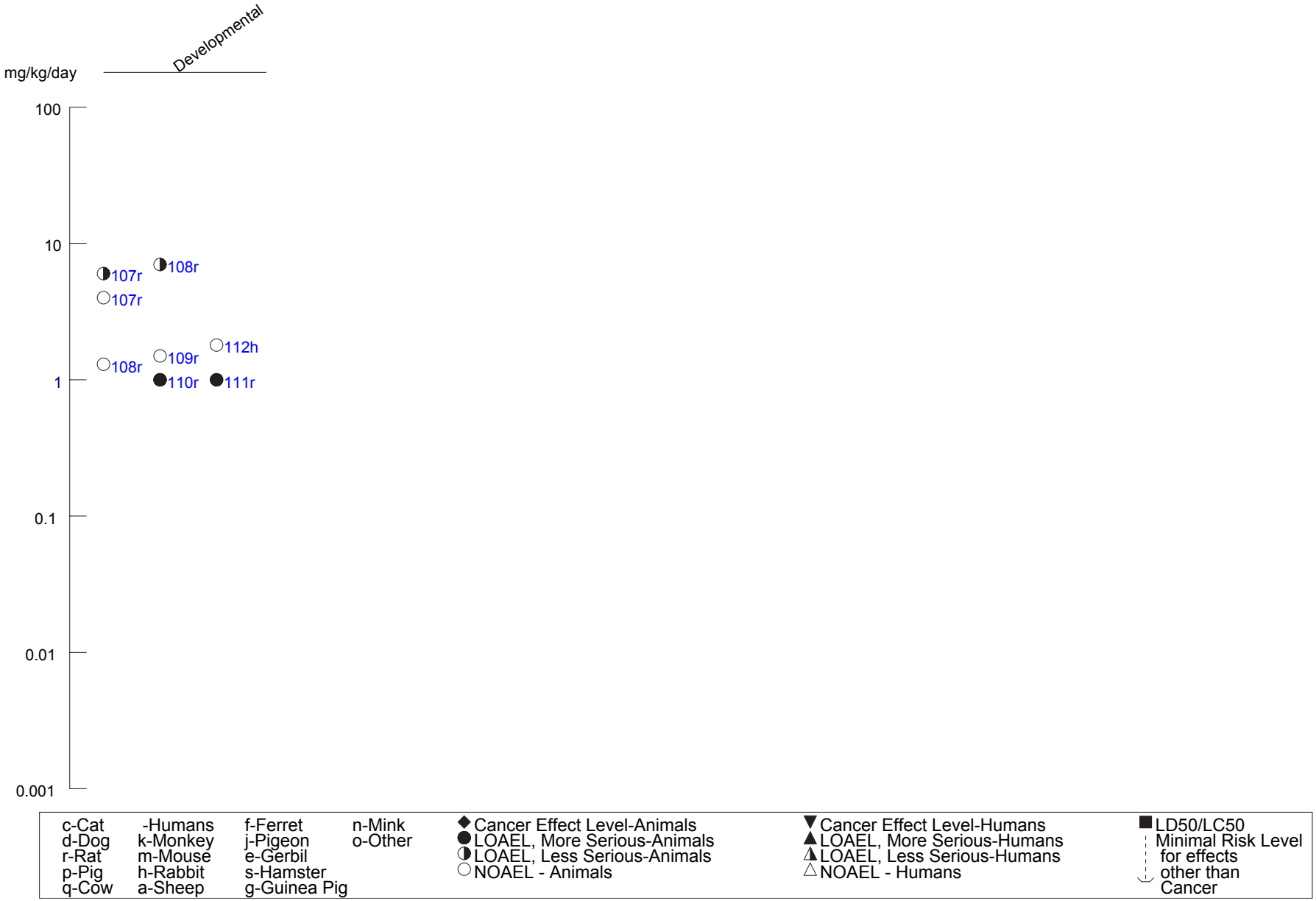
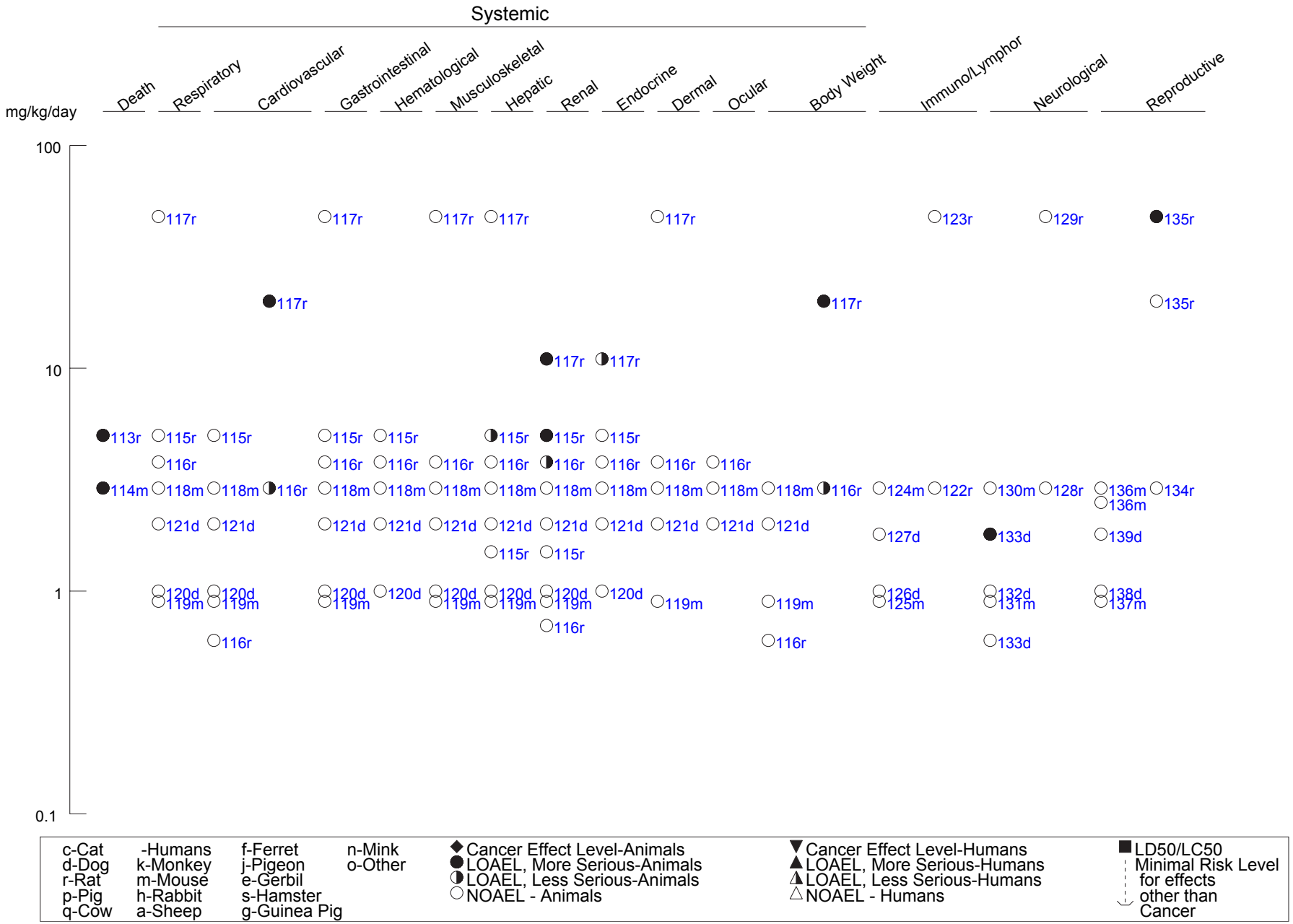


Figure 3-2 Levels of Significant Exposure to Endosulfan - Oral *(Continued)*

Chronic (≥365 days)



3.2.2.2 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, and renal) is observed. It cannot be rule out that some systemic effects observed at dose levels that induce frank neurological effects such as tremors and seizures are secondary to the neurological effects. No long-term targets have been identified in humans largely because no studies of humans chronically exposed to endosulfan have been conducted. However, during longer-term exposure, the kidney appears to be the primary systemic target organs in rats.

The highest NOAEL values and all reliable LOAEL values for systemic effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. 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). It should be noted that these signs and symptoms may also be secondary to endosulfan-induced cardiac failure and/or to aspiration of the solvent. 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 was given activated charcoal to limit gastrointestinal absorption during the first 16 hours following ingestion and his stomach was pumped, 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 not unlikely that some of the observed effects were caused by aspiration, if the patient was lavaged without the airways being controlled (Eddelston et al. 2007). 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 three out of four cases 4 hours after ingesting an unknown amount of endosulfan, and four of these five cases required

mechanical ventilation (Blanco-Coronado et al. 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. Studies in which a limited number of dogs were given single oral doses of technical 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 technical endosulfan in peanut oil by gavage for 15 days (Gupta and Chandra 1977). However, there was high mortality in this dose group (three of eight 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. Intraparenchymal hemorrhages, edema, hyperemia, and degeneration of alveolar pneumocytes were reported in rabbits following administration of ≥1.5 mg/kg/day technical endosulfan by gavage in corn oil for 30 days (Hatipoglu et al. 2008). These dose levels also caused lethality in the rabbits. The NOAEL was 0.75 mg/kg/day.

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, or dogs at sublethal doses of technical endosulfan (FMC 1959b, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989a, 1989c; NCI 1978).

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). Persistent tachycardia and severe hypotension were described in a patient who ingested 35 mL of an organochlorine fluid containing a total of 12.3 g endosulfan (Eyer et al. 2004). Hypotension and abnormalities in the EKG were observed in a study of 52 cases of acute poisoning with endosulfan (Moon and Chun 2009).

Administration of 2 mg/kg/day (only dose level tested) endosulfan by gavage in corn oil to male Wistar rats for 28–42 days induced myocardial fiber edema and congestion and degeneration (Kalender et al. 2004a; Jalili et al. 2007) (Kalender et al. [2004a] used technical endosulfan; the formulation used by Jalili et al. [2007] was not specified). Similar observations were reported in pregnant Wistar rats after administration of 1 mg/kg/day (only dose level tested) technical endosulfan by gavage in olive oil on Gd 6–20 and sacrificed on Gd 20 (Singh et al. 2007b).

In general, longer-term exposure of animals to sublethal concentrations of technical endosulfan has not resulted in gross or microscopic evidence of cardiovascular toxicity (FMC 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989c). However, two rat studies indicated possible toxic effects. 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, which used larger doses of technical endosulfan (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; Eyer et al. 2004; Karatas et al. 2006; Pradhan et al. 1997; Terziev et al. 1974; Yavuz et al. 2007). 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 dose of 63 mg of β-endosulfan/kg by gavage, a dose that 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 given a single oral dose of 30 mg/kg of technical endosulfan exhibited vomiting and stomach irritation (FMC 1958). Following a single oral dose of 50 mg/kg of technical endosulfan, dogs had congestion in the stomach and small intestine (Hoechst 1970). Similarly, rats given single unspecified doses of technical endosulfan in an LD_{50} determination showed irritant gastroenteritis (Boyd et al. 1970). Rabbits treated with a single dose of 15.1 mg/kg of a formulation of endosulfan containing 35% of active ingredient 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. Increased goblet cell activity, blunted villi, and lymphoid depletion were reported in the intestines from female Wistar rats following administration of 1 mg/kg/day (only dose level tested) technical endosulfan on Gd 6–20 and sacrificed on Gd 20 (Singh et al. 2007b).

Longer-term exposure of animals to sublethal doses of technical 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 1959b, 1967; Hack et al. 1995; Hoechst 1984b, 1988b, 1989a, 1989c; NCI 1978). However, convulsive spasms of the abdominal and jaw muscles without vomiting were observed in male and female dogs that consumed 2.0 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 2 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). Moon and Chun (2009) noted thrombocytopenia in 11 (21%) of their patients, but Karatas et al. (2006) reported normal complete blood counts in their study of 23 cases of endosulfan intoxication. No further information was located regarding hematological effects in humans after oral exposure to endosulfan.

Limited information is available regarding hematological effects in animals following acute oral exposure to endosulfan. Female Wistar rats treated with a single gavage dose of ≥22 mg/kg of an unspecified endosulfan formulation had decreased hemoglobin at sacrifice 24 hours after dosing; a group treated with a dose of 33 mg/kg showed decreases in red blood cells, hemoglobin, and packed cell volume (Siddiqui et al. 1987b). It should be noted that the resulting values were still within normal limits. In another study, male New Zealand rabbits administered a single gavage dose of 15.1 mg/kg of an endosulfan formulation with 35% active ingredient also showed a decrease in red blood cells, hemoglobin, and packed cell volume; this dose was lethal to five out of seven rabbits (Ceron et al. 1995). Neither one of these studies has been included in Table 3-2, the Siddiqui et al. (1987b) study because it did not specify the type of endosulfan used and the Ceron et al. (1995) study for using a formulation with 35% active ingredient.

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 technical 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 decreases in hemoglobin, red blood cell count, and mean corpuscular hemoglobin concentration, and an increase in 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, 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 technical endosulfan to cause anemia

(Dikshith et al. 1984; FMC 1959b; Hack et al. 1995; Hoechst 1989a). Also, no significant effects on hematological parameters or on routine gross and histopathological examination of bone marrow and the spleen were observed in mice, dogs, or rabbits during intermediate- and chronic-duration studies with technical endosulfan (FMC 1967; Hatipoglu et al. 2008; Hoechst 1984b, 1988b, 1989c), and in a more recent study in rats (Sheets et al. 2004).

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 also provided doses of 0.025 and 5 mg/kg/day of an unspecified formulation 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. Rhabdomyolysis (destruction of skeletal muscle fibers) was described in 31 out of 52 cases of acute endosulfan poisoning reported by Moon and Chun (2009). 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; Sheets et al. 2004) and chronic-duration (FMC 1967; Hoechst 1988b, 1989a, 1989c; NCI 1978) studies revealed no adverse effects of technical 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). Elevated transaminases were also reported in 4 out of 16 cases of acute endosulfan poisoning described by Moses and Peter (2010). Moon and Chun

(2009) reported that 36.5% of their patients showed hepatic toxicity (ALT activity >100 U/L). The ALT levels started at more than 100 U/L at 1–4 days and reached their highest levels (median 346 U/L, range 123–807 U/L) at 1–8 days after ingestion. The liver function test results returned to normal within 18 days after ingestion in the survival group. In contrast, the patients in the nonsurvival group continued to show ALT levels >100 U/L. In their study of 23 accidental poisoning cases, Karatas et al. (2006) reported that on day 2, three patients still exhibited abnormal liver function in the form of elevated serum AST and ALT. In two of these patients, enzyme levels returned to normal at the end of the 3rd and 10th day, respectively. In the third patient, AST and ALT increased gradually and the patient developed hepatic encephalopathy and was transferred for liver transplant on day 5. 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 technical endosulfan (10 mg/kg, FMC 1958; 50 mg/kg, Hoechst 1970) revealed liver congestion, possibly secondary to endosulfan-induced right heart failure rather than through a direct effect. Similarly, autopsied rats that received unspecified doses of technical 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 an unspecified formulation of endosulfan had increased serum ALT activity, indicating hepatic damage (Siddiqui et al. 1987b). Rabbits that were administered a single gavage dose of 15.1 mg/kg of an endosulfan formulation containing 35% active ingredient, which was lethal to 5 out of 7 rabbits, had significantly increased serum alkaline phosphatase, 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 of 2.5 mg/kg/day technical endosulfan for 7 days (Gupta and Gupta 1977a) and in male rats at doses of 5 mg/kg/day (unspecified formulation) for 2 days (Misra et al. 1980) or 10 mg/kg/day technical endosulfan 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 technical endosulfan for 15 days (Gupta and Gupta 1977a). In male rats, increased liver weight was observed at doses of 5 mg/kg/day after 15 days (Gupta and Chandra 1977) or 30 days (Dikshith et al. 1984). Doses of 3 mg technical endosulfan/kg/day in the food for 30 days significantly increased serum and liver alkaline phosphatase, 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); 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, a dose that was lethal to three out of eight rats (Gupta and Chandra 1977). Also, increased serum alkaline phosphatase was observed in male and female rats in the study by Dikshith et al. (1984). Treatment of Sprague-Dawley rats for 15 days with 10 mg/kg/day (only level tested) technical endosulfan by gavage increased serum ALT (50%), decreased serum alkaline phosphatase, increased bilirubin (3–4-fold), increased urea (66%), and doubled creatinine (Choudhary et al. 2003). Endosulfan induced liver hypertrophy and histopathological changes including dilation of sinusoidal spaces and abnormalities in the nuclei of the hepatocytes. In general, changes after 30 days of treatment were more severe.

Treatment of pregnant Wistar rats with 1 mg.kg/day (only dose tested) technical endosulfan by gavage in oil on Gd 6–20 and sacrificed on Gd 20 revealed degenerative changes in the liver, karyomegaly, engorged sinusoids, vacuolar degeneration, and double nuclei (Singh et al. 2007b). Treatment of rabbits with 1.5 mg/kg/day technical endosulfan by gavage in oil for 30 days increased the weight of the liver 21% (Hatipoglu et al. 2008). Serum activities of alkaline phosphatase and AST were significantly increased in all treated groups (0.75, 1.5, and 3 mg/kg/day), but serum ALT was not. Microscopic examination of the liver showed alteration mainly in the mid- and high-dose groups consisting of hydropic and granular degeneration and fatty changes in hepatocytes. Other lesions included mononuclear inflammatory cell infiltrations in the portal tract, destruction of portal epithelium, and focal parenchymal lymphocytic cell infiltration with degenerative changes. Since only a qualitative description of these findings was provided, these results are not listed in Table 3-2. The results from these studies suggest 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 male rats to doses up to 3.85 mg/kg/day technical endosulfan for 13 weeks via the food had no effect on liver weight (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. More recently, increased liver weight was reported in male and female rats exposed to ≥13.7 and ≥16.6 mg/kg/day technical endosulfan, respectively, for 13 weeks; however, this was attributed to deposition of endosulfan metabolites and to a tissue reaction (Sheets et al. 2004). Moreover, clinical chemistry tests did not provide any evidence of liver pathology. In mice, an increase in liver weight was observed in females exposed via the diet to 4.6 mg/kg/day but not in males at doses of 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) technical endosulfan 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) technical endosulfan 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 following administration of technical endosulfan. Routine gross and microscopic pathology has not revealed adverse hepatic effects in mice exposed to up to 2.5 mg/kg/day (males) or 2.9 mg/kg/day (females) for 2 years (Hack et al. 1995; Hoechst 1988b; NCI 1978), in rats exposed to ≤5 mg/kg/day (females) or 2.9 mg/kg/day (males) for 2 years (Hack et al. 1995; 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). 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). In their study of 52 cases of intoxication, Moon and Chun (2009) reported that 26.9% developed acute kidney injury, which resolved without sequelae in the patients who survived. Acute kidney injury is likely to be mostly due to rhabdomyolisis, which in turn, is due to uncontrolled seizures.

A study in mice dosed by gavage with 13 mg/kg/day technical endosulfan for 10 consecutive days reported that kidneys from treated mice showed prominent mitochondrial degeneration in proximal convoluted tubular cells (Caglar et al. 2003). There were also lipofuscin granules and membraneous structures in some of the cells. Some glomeruli also showed changes such as fusion in pedicels and focal thickening at glomerular basal membrane. Catalase activity in kidney tissue was significantly decreased, while the activities of glucose-6-phosphate dehydrogenase and superoxide dismutase were significantly increased, as were the levels of glutathione and malonaldehyde. The authors suggested that oxidative stress may have played a role in the alterations seen.

In intermediate-duration studies in male rats, congestion and focal degeneration in the epithelial lining of kidney tubules, and glomerulonephritis and glomerulonephrosis were observed in animals treated with doses of 10 mg/kg/day technical endosulfan by gavage for 15–30 days (Choudhary et al. 2003; Gupta and Chandra 1977). No such effects were seen in rats treated with 5 mg/kg/day endosulfan in the Gupta and Chandra (1977) study; only one dose level was used in the Choudhary et al. (2003) study, so a NOAEL was not established in that study. Administration of 1 mg/kg/day technical endosulfan (only dose level tested) by gavage in oil to pregnant rats on Gd 6–20 induced proximal convoluted epithelial cell degeneration, vacuolization, glomerular congestion, and glomerular monocyte infiltration (Singh et al. 2007b). 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 male rats at doses with 6 mg/kg/day technical endosulfan 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 of 3.85 mg/kg/day at the end of 13 weeks of exposure and at doses of 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. Light and electron microscopy of the kidneys of rats that consumed 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). These changes receded considerably during a 30-day recovery period, suggesting that at the doses and the exposure duration tested, endosulfan and/or metabolites accumulate in the kidney without causing detectable toxicity. Results of residue analysis indicated that endosulfan is stored only temporarily in the kidneys. In addition, only endosulfan-sulfate and endosulfan-lactone were detected in any appreciable quantities in the kidneys. Results similar to those of Hoechst (1987) were reported by Sheets et al. (2004), who reported increased kidney weigh in rats dosed via the diet with ≥13.7 mg/kg/day technical endosulfan for 13 weeks; the increase in weight was attributed to the accumulation of an amorphous brown-to-yellow pigment.

Minor changes of questionable biological significance observed in rats administered 5 mg/kg/day of an unspecified endosulfan formulation 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). Doses of approximately 3.8 mg/kg/day for 2 years significantly increased the incidence of marker progressive glomerulonephrosis in female rats (Hack et al. 1995; Hoechst 1989a). It should be noted that in male rats dosed with up to 2.9 mg/kg/day, the increase was less pronounced than in females, but the incidences in all groups, including controls, were considerably higher than in females (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 2.5 mg/kg/day (males) and 2.9 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 (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. Hyperglycemia was reported in a study of six individuals after acute exposure to endosulfan (Blanco-Coronado et al. 1992). A bigger study of 52 subjects with endosulfan intoxication also reported high serum glucose levels on admission (Moon and Chun 2009). However, another study of 23 cases of endosulfan intoxication reported normal glucose in their patients (Karatas et al. 2006).

Administration by gavage of a single oral dose of 5 mg/kg of an unspecified formulation of endosulfan 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 5 days. Both administration protocols caused dilation of the blood vessels of the islets of Langerhans. Kalender et al. (2004b) administered 2 mg/kg/day (only dose tested) technical endosulfan by gavage in corn oil to male Wistar rats for 6 weeks and reported that after 2 weeks of treatment, B cells in islets of Langerhans in the pancreas showed some swollen mitochondria. After 3 or 4 weeks, there was some mitochondrial swelling and dissolution of mitochondrial matrix, and dilation of the endoplasmic reticulum. Some B cells in islet of Langerhans had weak picnotic nucleus at the end of the 5th week, and large and small vacuoles occurred in the cytoplasm. After 6 weeks of treatment, the number of secretory granules decreased and vacuoles produced by granules were increased. A similar study in male New Zealand rabbits administered 1 mg/kg/day (only dose tested) technical endosulfan for 6 weeks reported that endosulfan induced degenerative changes in the pancreas, especially in the B cells (Ozmen et al. 2010). Immunohistochemistry of the pancreas of treated rabbits showed marked reduction in concentration and distribution of insulin, proinsulin, and amylin. It also showed a marked decrease in proinsulin-, insulin-, and amylin-secreting cells and a slight decrease in glucagon-secreting cells. Administration of up to 5 mg technical endosulfan/kg/day by gavage in corn oil 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 technical endosulfan (FMC 1965; Gupta and Chandra, 1977; Hoechst 1984b, 1988b, 1989c). A similar lack of effects was 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 2.9 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.

Effects of endosulfan on sex hormones are summarized in Section 3.2.2.5, Reproductive Effects.

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 technical endosulfan/kg/day in the diet for 147 days revealed no adverse effects (Hoechst 1989c). Female, but not 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/kg/day technical endosulfan caused no significant alterations in the skin (Hoechst 1988b, 1989a, 1989c; NCI 1978). Male rats dosed with approximately 48 mg/kg/day and females with approximately 22 mg/kg/day technical endosulfan in the diet for 78 weeks did not show treatment-related alterations in the skin (NCI 1978).

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 technical 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), 37.2 mg/kg/day (males) and 45.5 mg/kg/day (females) for 13 weeks (Sheets et al. 2004), 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.

Administration by gavage of a single dose of up to 100 mg/kg technical endosulfan to male rats or 12 mg/kg to female rats did not significantly affect body weight during a 3-week observation period following dosing (Bury 1997). Body weight was not significantly affected in rats treated with up to 6 mg technical 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 by gavage with 15.1 mg/kg of a formulation of endosulfan containing only

35% active ingredient 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 with technical endosulfan in which rats were administered 5 mg/kg/day by gavage for 15 days (Gupta and Gupta 1977a), 4 mg/kg/day for 30 days (Hiremath and Kaliwal 2003), 1.5 mg/kg/day by gavage for 30 days (Dikshith et al. 1984), 5 mg/kg/day in the diet for 30 days (Paul et al. 1995), 10 mg/kg by gavage in oil 5 days/week for 90 days (Sinha et al. 1997), or up to 45.5 mg/kg/day for 13 via the diet (Sheets et al. 2004). However, in a study by Gupta and Chandra (1977), rats treated with 10 mg/kg/day of an unspecified formulation of endosulfan by gavage in oil for 15 days gained 30% less weight than controls; this dose also caused lethality. In a study of gestational and lactational exposure of Sprague-Dawley rats, gavage doses of 6.12 mg/kg/day technical endosulfan reduced final body weight on Gd 20 by 14% (Cabaleiro et al. 2008); the NOAEL was 0.61 mg/kg/day. In another study of gestational and lactational exposure, dietary administration of 29.8 mg/kg/day technical endosulfan also reduced Gd body weight by 14%, food efficiency appeared to be reduced at this dose level; the NOAEL for changes in body weight was 10.8 mg/kg/day (Gilmore et al. 2006). In a study of only gestational exposure, gavage doses of 1 mg/kg/day technical endosulfan decreased maternal weight gain by 29% (Singh et al. 2007a). Dosing of rabbits with 1 mg/kg/day (only dose tested) technical endosulfan by gavage in oil for 6 weeks did not significantly affect body weight (Ata et al. 2007), but a dose of 3 mg/kg/day for 30 days induced an 18% reduction in final body weight (Hatipoglu et al. 2008); the NOAEL was 1.5 mg/kg/day in the latter study. A dose of 2 mg technical endosulfan/kg/day by gavage in water for 90 days was 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 not significantly reduced (<10%) in male or female mice treated in the diet with 2.5 or 2.9 mg/kg/day technical endosulfan, respectively, for 24 months (Hack et al. 1995; Hoechst 1988b). Both male and female rats treated with 3–3.5 mg endosulfan/kg/day in the diet for 24 months also exhibited reduction in body weight gain in the range of 17–18% (Hack et al. 1995). The no-effect-level dose was approximately 0.6–0.7 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 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.

Some studies in animals indicate that endosulfan 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 animals, but not younger ones, showed frank neurotoxic effects. None of these studies provided information regarding the composition of the endosulfan formulation used; therefore, they are not presented in Table 3-2. In a study in Wistar rats, dosing males with up to 37.2 mg technical endosulfan/kg/day and females with up to 45.5 mg/kg/day via the diet for 13 weeks did not significantly alter serum levels of phosphorus, potassium, or sodium (Sheets et al. 2004).

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 seven rabbits treated with a single gavage dose of 15.1 mg/kg of a formulation containing only 35% endosulfan, two 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 five 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 were 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.

3.2.2.3 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 technical 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 endosulfan at 4.5 mg/kg/day for 6 weeks and at 0.9 mg/kg/day 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. The intermediate-duration oral MRL was also adopted for the chronic-duration oral MRL for endosulfan.

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 of 4.5 mg/kg/day technical endosulfan 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).

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 technical endosulfan for 2 years at doses of up to 2.9 mg/kg/day (Hoechst 1989a), 2.9 mg/kg/day (Hoechst 1988b), 1 mg/kg/day (FMC 1967), or 48 mg/kg/day (NCI 1978), 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. However, since the Banerjee et al. (1986) study was considered preliminary by the authors, it would be reassuring if the results can be replicated by other laboratories. The highest NOAEL value and all reliable LOAEL values for immunological effects in each species in each duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 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 on three of the cases at an unspecified time after ingestion 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, the patient displayed recurrent convulsions in the first 2 weeks following ingestion. 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 caused by 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 to a 43-year-old man who ingested approximately 100 mL of an unspecified endosulfan formulation (18.8 grams of endosulfan or 260 mg/kg according to the investigators) 1 hour earlier (Boereboom et al. 1998). Since endosulfan appeared to have been already absorbed, as judged by the presence of convulsions, the stomach pumping and activated charcoal may have not had the intended effects. At 4 days after exposure, the man was pronounced brain dead, and autopsy revealed cerebral hernia from massive cerebral edema. Additional accidental and/or intentional cases of acute poisoning with endosulfan resulting in adverse neurological effects have also been reported in other studies (Blanco-Coronado et al. 1992; Lo et al. 1995; Pradhan et al. 1997). 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.

More recently, Eyer et al. (2004) reported two cases of intentional ingestion of endosulfan who presented to the emergency room with persistent seizures. One of the cases, who had consumed 500 mL of a formulation containing 35% active ingredient (180 g of endosulfan according to the investigators), died on day 10 from multiorgan failure. The other case, who responded to treatment, had ingested 35 mL of an organochlorine fluid containing 12.3 g endosulfan. Parbhu et al. (2009) reported that a 2.5-year-old male developed generalized tonic-clonic seizures immediately after ingesting an unknown amount of an 11.6% solution of endosulfan. On day 3, an MRI showed cerebral edema and nuclear medicine flow scan failed to show blood flow to the brain and he was pronounced dead. Kamate and Jain (2011) reported the case of a 2-year-old girl who presented with generalized clonic-status epilepticus to the emergency room after accidentally ingesting endosulfan. Convulsions were controlled by medications and the child gradually regained consciousness after 36 hours of admission. Karatas et al. (2006) reported 23 cases of endosulfan poisoning presenting to an emergency department. On admission, five patients showed seizures and one patient complained of dizziness. The signs and symptoms began 1 hour after ingestion in 12 patients, in the second hour in 9 patients, and in the third hour in 2 patients. Sixteen patients had generalized tonic-

clonic seizures and 3 patients had focal seizures. Most patients were discharged within 2 days after intravenous treatment with diazepam. In a study of 52 cases of acute endosulfan poisoning conducted by Moon and Chun (2009), 48 cases experienced seizures and refractory status epilepticus was the most common cause of death. The median latency to seizure onset after ingestion was 70 minutes and the greatest latency was 210 minutes. Refractory status epilepticus was also the cause of death of a case described by Roberts et al. (2004). Among 16 patients with acute endosulfan poisoning identified by Moses and Peter (2010), neurological toxicity predominated, particularly low sensorium (81%) and generalized seizures (75%), including status epilepticus (33%).

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; FMC 1958; Gilbert and Mack 1995; Hoechst 1970, 1975, 1984e; Kiran and Varma 1988). Convulsions have been observed after a single dose of 5 mg/kg in rats (Gilbert and Mack 1995), and after 4 daily doses of 1.8 mg/kg/day in pregnant rabbits (MacKenzie et al. 1981). At 6 mg/kg/day for 14 days, pregnant rats displayed face rubbing, flaccidity, and hyperactivity (FMC 1980). In a study by Bury (1997), female rats administered a single gavage dose of 3 mg/kg had increased incidences of squatting posture, straddled hindlimbs, decreased spontaneous activity, bristle coat, and irregular respiration and panting. 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).

A study in female Wistar rats tested the effectiveness of phenobarbital (Luminal®) and diazepam (Valium®) in reducing the neurotoxicity and lethality of endosulfan (Hoechst 1984e). The rats were administered a single dose of 80 mg/kg technical endosulfan by gavage and were observed for 14 days. Intraperitoneal administration of the therapeutic agents took place 10–20 minutes after treatment with endosulfan at the stage of hyperactivity, before the occurrence of the convulsive phase. Administration of endosulfan alone to 20 rats resulted in the death of 19 rats within 4 hours. Administration of diazepam in doses ranging from 2 to 60 mg/kg was ineffective in preventing death; 24 out of 25 rats died within the first 24 hours after treatment, with only a slight delaying of mortality. Administration of phenobarbital in doses ranging from 50 to 70 mg/kg resulted in a significant reduction both in mortality and clinical signs of intoxication. At the end of the observation period, 12 out of 30 rats tested (40%) survived. Necropsy of dead rats did not reveal chemical-related abnormalities.

Neurological effects have also been described in some intermediate or chronic ingestion studies of technical endosulfan in experimental animals (FMC 1965, 1967; Hoechst 1984b, 1989a). For example, in female rats given daily gavage doses of 1.5 mg/kg/day 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, dietary administration of 3.74 mg/kg/day technical endosulfan to pregnant rats from Gd 6 to lactation day 21 did not induce signs of hyperexcitability (Gilmore et al. 2006). The difference in the results from these two studies can probably be attributed to the different mode of administration of endosulfan (i.e., gavage versus dietary). In the Gilmore et al. (2006) study, doses ≥10.8 mg/kg/day increased rearing activity, although without a clear dose-response relationship. In addition, doses of up to 29.8 mg/kg/day did not significantly affect the results of a FOB that included examination of autonomic function, posture and gait, and behavior (Gilmore et al. 2006). Sheet et al. (2004) also did not find significant alterations in tests of motor and locomotor activity and in results of a FOB in Wistar rats administered up to 45.5 mg technical endosulfan/kg/day via the diet for 13 weeks. In that study, microscopic examination of the brain at multiple levels and of the spinal cord and peripheral nerves did not show compound-related alterations. Repeated administration of 1.5 mg/kg/day technical endosulfan by gavage to rabbits induced tremors and convulsions and was lethal to three out of nine rabbits, doses of 0.75 mg/kg/day were without effect (Hatipoglu et al. 2008). In another study, gavage administration of 1 mg/kg/day technical endosulfan (only level tested) for 4 weeks also induced hyperexcitability in rabbits (Mor and Ozmen 2010). Gross examination of the rabbit's brain showed marked hyperemia at the meningeal vessels and slight hemorrhages in brains and cerebellum in some rabbits. Light microscopy revealed marked lesions including hemorrhage, marked edema, tissue degeneration, and slight glyosis.

Dogs that ingested feed containing 30 ppm technical endosulfan 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 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. No significant neurological effects were observed in 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 rats, mice or dogs in other intermediate- and chronic-duration studies (FMC 1967; Hoechst 1984b, 1988b, 1989c; NCI 1978).

A series of experiments were conducted in male Long-Evans rats to: assess the generality of an increased and persistent susceptibility to seizures following treatment with technical endosulfan; test the bidirectionality of kindling transfer induced by chemical and electrical means; and 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 have 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 the 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 re-instated 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 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 4, endosulfan sulfate does not appear to be significantly more lipophilic than the parent compound.

In summary, endosulfan induces stimulation of the nervous system in humans as evidenced mainly in acute cases of intoxication. Hyperactivity has also been reported in acute-, intermediate-, and chronic-duration studies in animals. If the animal survives the acute toxic effects, then no long-term neurotoxic effects are evident from behavioral, gross, or microscopic observations. However, some impairment may occur that can be detected only by specialized neurobehavioral testing. Endosulfan can also affect the levels of neurotransmitters in the brain.

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

3.2.2.5 Reproductive Effects

A study was conducted that examined the possible association between levels of some organochlorine pesticides, endosulfan among them, in adipose tissue and infertility in men (Çok et al. 2010). The cohort consisted of 25 infertile men and 21 fertile men. Azoospermic men were chosen among infertile couples who were married for at least 1 year and could not achieve a pregnancy although no contraceptive method was used. The diagnosis of azoospermia was confirmed through two consecutive spermiograms evaluated according to World Health Organization (WHO) criteria. The subjects were asked to complete a questionnaire about their dietary habits, exposure to chemicals in their daily life and at work, home environment, smoking, medical histories, weight, and height. There was no occupational exposure to the

chemicals tested, so exposure was assumed to have been predominantly dietary. While the range of endosulfan in adipose tissue (mg/kg of lipid) from infertile men was much wider than in fertile men, the means did not differ statistically. The small number of subjects examined precludes drawing strong conclusions from this study.

Several studies provide information regarding the effects of endosulfan on reproduction in animals. Exposure of pregnant mice to 3 mg/kg/day technical endosulfan by gavage on Gd 1–7 resulted in a significantly increased percentage of pre-implantation loss; no significant effect was reported with 2 mg/kg/day (Hiremath and Kaliwal 2002a). Similarly, exposure of pregnant rats to 1 mg/kg/day technical endosulfan (only level tested) by gavage on Gd 6–20 resulted in a 4-fold increase in the percentage of post-implantation loss relative to controls (Singh et al. 2007b). Cabaleiro et al. (2008) reported an 11% reduction in litter size in rats exposed by gavage to 6.1 mg/kg/day technical endosulfan on Gd 1–21, but not with 0.61 mg/kg/day. In contrast, administration of a much higher dose of technical endosulfan, 29.8 mg/kg/day, via the diet to pregnant rats on Gd 6–21 resulted in only an 8% reduction in mean litter size (Gilmore et al. 2006). The difference between the results of Cabaleiro et al. (2008) and Gilmore et al. (2006) may be in part due to the exposure duration and mode of administration of the chemical (i.e., gavage versus diet). Administration of estimated doses of up to 9 and 8 mg/kg/day of technical endosulfan to 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). It should be noted that the actual intake of test material was quantified only during the first 2 weeks of exposure. Similarly, administration of 5 mg/kg/day technical endosulfan to male rats and 1.5 mg/kg/day to 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). A two-generation reproduction study in rats detected no effect on the size, mortality, or sex ratio of the litters following consumption of doses of 7 mg/kg/day technical endosulfan 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 histopathological examination of the reproductive organs of male and female rats that ingested doses of technical 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 2.5 mg/kg/day (males) and 2.9 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 1967; Hoechst 1989c).

Raizada et al. (1991) examined the potential estrogenic properties of an unspecified endosulfan formulation in ovariectomized rats. 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. 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 simultaneously endosulfan and estradiol were not significantly different from those seen in rats that received estradiol alone. The study results indicated that endosulfan was neither estrogenic nor anti-estrogenic under the conditions of this assay. Hiremath and Kaliwal (2003) examined the potential estrogenic properties of technical endosulfan in ovariectomized mice. Estrogenic activity was assessed using uterine weight and vaginal cornification as end points. Antiestrogenic activity was assessed by administering technical endosulfan along with 17β-estradiol to a group of mice. Ovariectomized control mice showed a prolonged diestrus. Mice treated with 4 mg/kg endosulfan (only level tested) for 30 days did not show vaginal cornification and showed continuous diestrus without any appearance of estrus, indicating its nonestrogenic activity. In addition, there was no significant change in uterine weight. Mice dosed with endosulfan plus 17β-estradiol showed a significant increase in the duration of estrus and increased uterine weight, indicating that endosulfan did not have antiestrogenic activity under the conditions of the study.

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 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). However, exposure of rats to 2.9 mg/kg/day technical endosulfan (only level tested) in the diet for 8 weeks did not significantly alter the number of mature spermatids in the testes, daily sperm production, number of sperm in the caput/corpus and cauda epididymis, sperm transit time through the epididymis, or sperm morphology (Perobelli et al. 2010).

Altered spermatogenesis was reported in male mice treated by gavage with 3 mg/kg/day of an endosulfan formulation containing 35% active ingredient for 35 days (Khan and Sinha 1996). Gavage doses of 5 mg/kg/day (lowest level tested) of technical endosulfan for 15–30 days reduced sperm motility in the cauda epididymis of rats by 35% (Choudhary and Joshi 2003). Decreased sperm volume and increased abnormal sperm morphology and dead sperm were reported in rabbits dosed by gavage with 1 mg/kg/day technical endosulfan (only level tested) for 6 weeks (Ata et al. 2007). 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 and no information was provided regarding the endosulfan formulation. 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.

A study by Singh and Pandey (1990) indicated a dose-related decrease in testicular testosterone, plasma testosterone, LH, and FSH in groups of male Wistar rats administered technical 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. Decreased serum testosterone was also reported in male rats exposed to 15 mg/kg/day technical endosulfan by gavage for 15–30 days; no significant effects were reported at 10 mg/kg/day (Choudhary and Joshi 2003). In contrast, doses of 2.9 mg/kg/day technical endosulfan provided to male rats via the diet for 8 weeks had no significant effect on serum levels of testosterone, LH, and FSH (Perobelli et al. 2010). 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).

In summary, although the available reproductive studies indicate that endosulfan has no adverse effects on reproductive performance in animals, adverse effects on male reproductive end points have been seen in rats, mice, and rabbits. The lack of effects seen in the studies that examined reproductive performance (specifically fertility rate) in treated males may be due to the fact that, at least rats, produce and ejaculate 10 times more sperm than are necessary for normal fertility and litter size (Amann 1982; Working 1988).

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 3-2 and plotted in Figure 3-2.

3.2.2.6 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. In another study of male newborns from Southern Spain, higher levels of endosulfan sulfate in the placenta (n=220) were associated with lower odds of TSH ≥5 mU/L in cord blood levels (OR=0.36, 95% CI 0.17–0.77, $p<0.008$) (Freire et al. 2011). The investigators suggested that early exposure to endosulfan sulfate could lead to significant alterations in T4 feedback to the hypothalamus, resulting in decreasing TSH levels at birth. A study of 193 Brazilian children younger than 15 years old who lived near a former pesticide factory reported a significant increasing linear trend between serum endosulfan (1 of 19 pesticides analyzed) and total T3 levels (Freire et al. 2012). Serum levels of FT4 were positively and significantly associated with exposure to *p,p'*-DDD, α-endosulfan, and dieldrin; no association was found between pesticide exposure and serum TSH. The study controlled for age, gender, and serum lipid content. It should be noted that no child presented clinical or subclinical hyperthyroidism or hypothyroidism. Saiyed et al. (2003) conducted a study of reproductive development in 117 male schoolchildren of a village in India where endosulfan had been aerially sprayed for more than 20 years. Ninety children with no exposure history served as controls. Exposure pathways probably included a combination of the inhalation, oral, and dermal routes. The children were approximately 13 years old. After controlling for age, the study found significantly lower Tanner scores (development of pubic hair, penis, and testes) and serum testosterone level, and higher LH in the exposed group than in controls. Mean serum levels of total endosulfan were 5–6-fold

higher in the study group than in controls. Based on results from animal studies, the results of Saiyed et al. (2003) seem biologically plausible; however, it is a small study with relatively high nonparticipation rate in the measurement of the Tanner scores (57% of the exposed group and 33% of controls).

Ren et al. (2011) examined the association between placental levels of some organochlorine compounds, endosulfan among them, and risks for neural tube defects in a rural Chinese population with high incidence of neural tube defects. The cohort consisted of 80 cases and 50 controls. The median level of α-endosulfan in placentas from cases was 0.079 ng/g lipid versus 0.054 ng/g in controls (p=0.03). The investigators reported that increased placental levels of α-endosulfan were associated with increased risks of neural tube defects (OR=2.53, 95% CI 1.03–5.99). When potential confounding factors were adjusted for with an unconditional multivariate logistic model, the association remained (OR=3.26, 95% CI 1.10–9.71). Examining the association between placental levels of α-endosulfan and specific subtypes of neural tube defects showed significant associations with anencephaly and spina bifida. After adjusting for maternal occupation, age, education level, parity, folic acid supplementation, passive smoking, and fever or flu during early pregnancy, season of conception, mother's residence, and infant sex only the association with spina bifida remained significant. The simultaneous exposure to multiple organochlorine compounds makes it difficult to determine the specific role of endosulfan.

Developmental effects have been observed in rats following oral administration of technical endosulfan to pregnant dams during gestation. Daily administration of endosulfan at doses of 5 or 10 mg/kg/day by gavage in corn oil 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 of technical endosulfan to pregnant rats by gavage in corn oil 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 technical endosulfan by gavage to pregnant rats during Gd 6–19 (FMC 1980). However, these variations did not increase with dose, and the incidence observed at the highest dose tested (6 mg/kg/day) did not reach statistical significance. 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

could be considered a LOAEL for developmental toxicity in this study; however, the observation of statistically significant changes at lower doses places 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).

More recently, Sinha et al. (2001) reported that exposure of pregnant Druckrey rats to 1 mg/kg/day (lowest dose tested) technical endosulfan by gavage in peanut oil on Gd 12–21 resulted in a 53% reduction in sperm count in cauda epididymis and in reductions in absolute and relative weight of the sexual organs from male offspring examined at 100 days of age. Since the offspring were fostered by untreated dams and were not exposed directly after weaning, the effects were attributed solely to gestational exposure. Two recent studies reported fetal malformations and histological alterations in fetal organs due to gestational exposure to endosulfan. Singh et al. (2007a) reported that administration of 1 mg/kg/day (only dose tested) technical endosulfan by gavage in olive oil to pregnant Wistar rats on Gd 6–20 resulted in a significant decreases in the mean percentage of live fetuses (21%) and mean fetal weight (21%). Also, crown-to-rump length was significantly decreased by 21% in the treated group. Gross, visceral, and skeletal anomalies were significantly increased in the treated group. The most important fetal malformations were internal hydrocephalus, cerebellar hypoplasia, microphthalmia, contracted and notched kidneys, multilobulated liver, dilated renal pelvis, incomplete ossification of skull bones, rib anomalies, and sacral and caudal vertebrae agenesis. Maternal body weight gain during Gd 6–20 was reduced 29% relative to controls. In a later publication, using the same exposure protocol, Singh et al. (2008) conducted microscopic examinations of the liver and kidneys from Gd 20 fetuses. The livers from exposed rats showed vacuolar engorgement, sinusoidal dilation, hepatocyte degeneration, and karyomegaly. The kidneys showed tubular dilation, degeneration of tubular epithelium, necrosis of the tubular epithelium, and interstitial fibroblastic proliferation. No alterations were seen in controls. Since only one dose level was tested, the true LOAEL may be lower than 1 mg/kg/day in these two studies.

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 percentage of live or resorbed fetuses at doses up to 1.8 mg/kg/day technical endosulfan by gavage in corn oil (MacKenzie et al. 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.

In addition to the studies noted above that examined the effect of endosulfan administered only during the period of gestation, several studies have examined the effects of endosulfan on fetal development following administration prior to mating and throughout gestation and lactation. For example, administration of 6 mg/kg/day technical endosulfan via the diet from 2 weeks prior to mating through weaning resulted in a significant decrease in mean litter weight during lactation (Hoechst 1982). Increased pup mortality was observed at 8 mg/kg/day. Maternal toxicity (e.g., decreased body weight and increased relative liver weight) was observed in females at ≥6 mg/kg/day. Dietary doses of 7 mg/kg/day of technical endosulfan for 84 days prior to mating through weaning resulted in an 11% decrease in mean litter weight of rats on Pnd 12 (Hoechst 1984a). Both of these studies are limited in that insufficient information was provided regarding the intake of test material during gestation and lactation. Two recent studies reported significantly reduced (44–46%) male pup weight on Pnd 21 following maternal exposure to 6.12 mg/kg/day technical endosulfan by gavage in sesame oil during gestation and lactation (Cabaleiro et al. 2008; Caride et al. 2010). A lower dose of 0.61 mg/kg/day reduced pup weight by 11% on Pnd 21. In the high-dose group, maternal body weight at the end of gestation was reduced approximately 14% relative to controls. In both studies, birth weight was not significantly affected suggesting that, for this developmental end point, lactational transfer of endosulfan or a metabolite plays a bigger role than transplacental transfer. Cabaleiro et al. (2008) also reported that perinatal exposure to technical endosulfan altered the concentration of aminoacids and neurotransmitters in the prefrontal cortex from offspring on Pnd 15, 30, and 60; however, the toxicological significance of these changes is unknown. In the Caride et al. (2010) study, technical endosulfan was also shown to alter serum levels of prolactin (PL), LH, growth hormone (GH), and thyroid stimulating hormone (TSH) measured in offspring on Pnd 30. In addition, analyses of mRNA in the pituitary showed significantly decreased PL gene expression (high-dose), LH gene expression (both groups), GH gene expression (both groups), and TSH gene expression (both groups). Endosulfan significantly increased nitric oxide synthase 1 and 2 (NOS1, NOS2) gene expression (both groups), but did not significantly affect heme oxygenase-1 (HO-1) gene expression. Nitric oxide is involved in the regulation of pituitary secretion and HO-1 represents a defense mechanism against free radicals. Caride et al. (2010) suggested that nitrosative stress may be implicated in the endocrine toxicity of endosulfan at the pituitary level. Neither Cabaleiro et al. (2008) nor Caride et al. (2010) provided information regarding maternal effects.

Three studies provide information on the sexual maturation of offspring from dams exposed to endosulfan during gestation and lactation. Administration of 1.5 or 3 mg/kg/day technical endosulfan to pregnant Wistar rats by gavage in Tween and distilled water on Gd 15–21 and lactation days 1–21 did not significantly affect number of litters, live births, litter size, birth weight, mortality rate on Pnd 21, or pup weight on Pnd 21 (Dalsenter et al. 1999). Testes descent and preputial separation occurred slightly earlier in exposed rats (about 1 day) and was not considered biologically significant. Examination of sperm parameters showed a decrease in daily sperm production in the low- (20%) and high-dose (39%) groups on day 65 and in the high-dose group (12%) on day 140, and decreases in percent complete spermatogenesis in the low- (16%) and high-dose group (11%) on day 65. Serum testosterone was not affected. The same group of investigators exposed female Wistar rats to 0.5 or 1.5 mg/kg/day endosulfan by gavage in sunflower oil for 21 days before mating and during gestation and lactation (Dalsenter et al. 2003). Treatment with endosulfan did not significantly affect litter size, birth weight, or weight or viability during Pnd 1–21. The age of testes descent and preputial separation was comparable among groups. There was no significant effect of exposure to endosulfan on daily sperm production, sperm number per cauda epididymis, sperm transit, percent abnormal sperm, and serum testosterone levels measured at sacrifice on Pnd 140. In the third study, pregnant Wistar rats were administered doses of 0, 3.74, 10.8, or 29.8 mg/kg/day technical endosulfan via the food on Gd 6–21 and lactation days 1–21 (Gilmore et al. 2006). Offspring were evaluated for clinical signs, body weight, developmental landmarks for sexual maturation, behavioral tests, and ophthalmology. Maternal body weight and weight gain were significantly reduced during gestation, and so was food consumption. Reduced food consumption in the low-dose group was attributed to unpalatability of the diet, but this was less clear for the mid- and high-dose groups. Food efficiency appeared to be reduced in the high-dose group. Mean maternal body weight in the high-dose group on Gd 20 was reduced 14% relative to controls. Exposure to endosulfan did not affect neonatal developmental parameters. Pre- and post-weaning weights were lower in exposed pups than in controls. On Pnd 11, mean pup weight on a litter basis was reduced 8, 11, and 13% in the low-, mid, and high-dose groups, respectively. Preputial separation and vaginal opening were slightly delayed in exposed pups, but the effect on preputial separation was not dose-related, and vaginal opening was within historical controls. The only significant alteration in the results of a FOB was a significant increase in rearing (44% relative to controls) in males from the high-dose group on Pnd 45. Mean total motor activity was not significantly affected and neither was locomotor activity, auditory startle reflex habituation, and results of learning and memory tests. Ophthalmological examination was unremarkable. At termination on Pnd 75, analyses of sperm motility, counts and morphology did not reveal treatment-related alterations. There was a statistically significant decrease in fixed perfused brain weight in high-dose males on Pnd 2, but not in perfused or non-perfused fresh male brain weights on Pnd 75.

Microscopic examination of the brain at various levels, tibial and sciatic nerve, and spinal cord did not show treatment-related effects. Measurement of brain areas showed a 10% decrease in hippocampal gyrus length in high-dose females on Pnd 21. No differences were seen in males. An additional study in which female Wistar rats were exposed prior to and during mating, gestation, and lactation to 0.5 or 1.5 mg/kg/day technical endosulfan by gavage in sunflower oil reported that treatment with endosulfan did not significantly affect maternal weight, but no data were shown (Silva de Assis et al. 2011). Treatment with endosulfan did not affect litter size, birth weight, or neonatal viability, although it reduced mean pup weight by 6% on Pnd 21. Neither body weight nor the weights (absolute or relative) of the pups' liver or kidneys were affected on Pnd 65 or 140. Serum cholinesterase in high-dose pups was reduced 41% on Pnd 65 and was not significantly affected on Pnd 140.

In summary, based on these studies, the evidence for endosulfan-induced adverse developmental effects in animals is inconclusive because fetotoxicity and neonatal effects have occurred at doses that also affected the mothers mainly in the form of reduced maternal weight gain during pregnancy. 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 3-2 and plotted in Figure 3-2.

3.2.2.7 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 technical 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 (1981) 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) technical endosulfan 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 technical 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. Mice of both sexes were then 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 2.5 mg/kg/day in males and 2.9 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, α-endosulfan, and β-endosulfan induced no or few AHF in rats that were not initiated.

3.2.3 Dermal Exposure

3.2.3.1 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 a 4% dust formulation of 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 technical endosulfan (Gupta and Chandra 1975). However, two out of three 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, two of three 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 of Thionex® applied to clipped skin of pregnant rats (number per exposure group was not clearly reported) on gestation day 1 resulted in the 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 to technical endosulfan (Hoechst 1985c, 1985d). Exposure for a total of 21 out of 30 days 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 doses of 27 mg/kg/day (Hoechst 1985c). In contrast, female guinea pigs appeared to be relatively resistant to endosulfan toxicity (Hoechst 1983b). Only 1 of 20 females 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 3.2.2.1).

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

3.2.3.2 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 3-3. 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 technical 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 exposure for 6 hours/day for 5 days to 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 ≥31.25 mg/kg/day (females) and ≥500 mg/kg/day (males) in this study. Congestion of the lungs was also observed at necropsy of rats dying as the result of 30-day, 6-hour/day, 5-day/week exposures to endosulfan at 81 mg/kg/day (males) and 27 mg/kg/day (females) technical endosulfan (Hoechst 1985c). It is probable that these effects are a result of generalized effects on central nervous system activity and attendant sequelae.

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
Rat (CD-1)	once Gd 1					1500 F mg/kg/day	(lethal dose)	El DuPont Denemours & Co. 1973 technical	
Rat (Wistar)	5 d 6 hr/d					31 F mg/kg	(2/3 died)	Hoechst 1989b Beta	
Rat (Wistar)	5 d 6 hr/d					500 M mg/kg	(3/3 died)	Hoechst 1989b Beta	
Rabbit (albino)	1 d					167 F mg/kg	(LD50)	Gupta and Chandra 1975 technical	
Systemic									
Rat (Wistar)	5 d 6 hr/d	Resp		16 F mg/kg/day	(irregular respiration)	31 F mg/kg/day	(lungs filled with blood)	Hoechst 1989b Beta	
		Gastro		16 F mg/kg/day	(diarrhea; mesenteric blood vessels distended	31 F mg/kg/day	(small intestines filled with reddish fluid)		
		Hepatic		31 F mg/kg/day	(dark discoloration of the liver)				
		Dermal	31 mg/kg/day	62 F mg/kg/day	(slight to moderate erythema; slight edema)				

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rabbit (albino)	1 d	Hepatic			100 F Not Specified (congestion; degeneration; necrosis)	Gupta and Chandra 1975 technical	
		Renal			100 F Not Specified (shrunken glomerular tufts; necrosis of tubular epithelial cells)		
		Endocr			100 F Not Specified (swollen adrenal cells with foamy cytoplasm and eccentric nuclei)		
Rabbit	24 hr	Dermal		263 mg/kg (slight erythema)		Industria Prodotti Chimici 1975 technical	
Immuno/ Lymphoret							
Rat (Wistar)	5 d 6 hr/d		500 mg/kg	1000 M mg/kg (spleen reduced in size)		Hoechst 1989b Beta	
Neurological							
Rat (Wistar)	5 d 6 hr/d				16 F mg/kg (decreased activity; convulsions)	Hoechst 1989b Beta	

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE							
Death							
Rat (Wistar)	30 d 5 d/wk 6 hr/d				27 F mg/kg/day (5/6 died)	Hoechst 1985c technical	
Rat (Wistar)	30 d 5 d/wk 6 hr/d				81 M mg/kg/day (3/6 died)	Hoechst 1985c technical	
Rat (Wistar)	30 d 5 d/wk 6 hr/d				48 F mg/kg/day (4/11 died)	Hoechst 1985d technical	
Rat (Wistar)	30 d 5 d/wk 6 hr/d				192 M mg/kg/day (2/11 died)	Hoechst 1985d technical	
Systemic							
Rat (Wistar)	30 d 1 x/d	Hemato		19 M mg/kg (decreased hemoglobin)		Dikshith et al. 1988 technical	
		Hepatic		10 F mg/kg (decreased hepatic GOT and GPT; increased serum AP and LDH)			

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

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

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rat (Wistar)	30 d 5 d/wk 6 hr/d	Resp	9 F mg/kg/day		27 F mg/kg/day (acute lung congestion; dilation of alveolar vessels)	Hoechst 1985c technical	
		Cardio	9 F mg/kg/day		27 F mg/kg/day (blood vessel congestion cardiac ventricles filled with blood)		
		Gastro	27 F mg/kg/day				
		Hemato	27 F mg/kg/day				
		Hepatic	27 F mg/kg/day				
		Renal	27 F mg/kg/day				
		Endocr	27 F mg/kg/day				
		Dermal	27 F mg/kg/day				

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
Rat (Wistar)	30 d 5 d/wk 6 hr/d	Hemato	48 mg/kg/day	192 M mg/kg/day	(elevated serum protein; decreased serum cholinesterase)			Hoechst 1985d technical	
		Hepatic	48 mg/kg/day						
		Renal	48 mg/kg/day						
		Dermal	48 mg/kg/day						
Gn Pig (Pirbright-Whit	3 wk 3 d/wk 6 hr/d	Dermal	587 F mg/kg					Hoechst 1983b technical	
Immuno/ Lymphoret									
Gn Pig (Pirbright-Whit	3 wk 3 d/wk 6 hr/d		587 F mg/kg					Hoechst 1983b technical	
Neurological									
Rat (Wistar)	30 d 5 d/wk 6 hr/d			1 F mg/kg/day	(decreased brain cholinesterase)	81 mg/kg/day	(convulsions; diffuse brain edema)	Hoechst 1985c technical	

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
Rat (Wistar)	30 d 5 d/wk 6 hr/d			12 F mg/kg/day	(piloerection; slight lacrimation)	48 F mg/kg/day	(hypersalivation, tremors convulsions)	Hoechst 1985d technical	

AP = alkaline phosphatase; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; GOT = glutamic-oxalic transaminase; GPT = glutamic-pyruvic transaminase; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; LDH = luteinizing hormone; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); wk = week(s)

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 exposure to 81 mg/kg/day (males) and 27 mg/kg/day (females) technical endosulfan for 6 hours/day, 5 days/week for 30 days (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 reported 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 more severe toxicity.

Diarrhea was observed in rats exposed 6 hours/day for 5 days 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) technical 6 hours/day, 5 days/week for 30 days (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 18.75 mg/kg of an unspecified endosulfan formulation 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 6 hours/day, 5 days/week for 30 days to endosulfan doses of 12–192 mg/kg/day (males) and 3–48 mg/kg/day (females) technical endosulfan (Hoechst 1985d). Similarly negative results were obtained in a comparable 30-day rat study using slightly lower doses of technical endosulfan (Hoechst 1985c). Since Wistar rats were used in the studies by Dikshith et al. (1988) and Hoechst (1985c, 1985d), the different results may be related to the use of different endosulfan formulations: technical grade in the studies by Hoechst (1985c, 1985d) and unknown in the study by Dikshith et al. (1988).

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 technical 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 to doses of technical endosulfan ≥250 mg/kg/day (males) and 31.25 mg/kg/day (females) for 6 hours/day for 5 days 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 technical endosulfan 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 technical endosulfan in males or 48 mg/kg/day in females (Hoechst 1985d). However, dermal application of 18.75 mg/kg/day of an unspecified endosulfan formulation to male rats for 30 days resulted in decreases in hepatic levels of ALT and AST and increases in serum levels of AST, ALT, 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 AST and ALT 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 that received a single dermal application of 100 mg/kg of technical 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, differences in the application vehicle, or different endosulfan formulations. 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 applied a single dermal dose of 100 mg/kg of technical 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 technical endosulfan (males) and 27 mg/kg/day (females) to the skin for 6 hours/day, 5 days/week for 30 days (Hoechst 1985c). However, daily applications of up to 62.5 mg/kg/day (males) or 32 mg/kg/day (females) of an unspecified endosulfan formulation 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 to the skin. 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 250 mg/kg/day in males (Hoechst 1989b). However, daily application of up to 48 mg/kg/day technical endosulfan (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 technical 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).

3.2.3.3 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 that 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 technical endosulfan 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 technical endosulfan 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 β-endosulfan, 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 3-3. 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.

3.2.3.4 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 3.2.1.4 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 (1 L of wine/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. It should be noted that methomyl may have contributed to some of the toxic signs reported. 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). Jindal and Sankhyan (2011) reported the case of a 2-year-old girl who was brought to the emergency room with a history of continuous generalized tonic clonic seizures after her mother applied endosulfan on the head 2 hours prior to the symptoms to

remove head lice. After treating the seizures with diazepam and decontaminating the shaved head with soap and water, the girl was asymptomatic 3 days after the episode. Limitations associated with the occupational 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 technical endosulfan (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 an unspecified endosulfan formulation 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 3-3. 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.

3.2.3.5 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 histopathological examination following exposure of rats to doses of 81 mg/kg/day technical endosulfan (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) of an unspecified endosulfan formulation to the skin of rats for 30 days had no effect on reproductive organ histopathology (Dikshith et al. 1988).

3.2.3.6 Developmental Effects

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

An unspecified number of pregnant rats were applied a single dermal dose of 670 or 1,000 mg/kg Thionex® on clipped skin on gestation day 1, and exencephaly was observed in five and three 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 (1,500 and 2,250 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.

3.2.3.7 Cancer

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

3.3 GENOTOXICITY

Endosulfan has been evaluated for genotoxicity in a variety of *in vivo* and *in vitro* assays. As summarized in Tables 3-4 and 3-5, the results of these assays have been mixed, but the majority of mutagenicity tests reported positive results. Certain studies were unsatisfactory, as indicated below.

Table 3-4. 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
Rat bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei	+	Manjula et al. 2006
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 3-5. Genotoxicity of Endosulfan *In Vitro*

Species (test system)	End point	Results: With activation	Results: 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	Gene mutation	+	–	Antherieu et al. 2007
S. typhimurium TA98, TA97, TA102, TA104, TA100	Gene mutation	+	+	Bajpayee et al. 2006
S. typhimurium TA98, TA100, TA1535, TA1978	Spot test	No data	No data	Dorough et al. 1978
S. typhimurium TA1535/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
Cultured human HepG2 cells	Sister chromatid exchanges	No data	+	Lu et al. 2000
Cultured human lymphocytes	DNA damage, Comet assay	No data	+	Jamil et al. 2004
Cultured human lymphocytes	DNA damage, Comet assay	No data	+	Bajpayee et al. 2006
Cultured human HaCaT cells	DNA strand breaks, Comet assay	No data	+	Antherieu et al. 2007

Table 3-5. Genotoxicity of Endosulfan *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Cultured human HepG2 cells	DNA strand breaks	No data	+	Lu et al. 2000
Cultured human peripheral blood mononuclear cells	DNA damage, oxidative stress	No data	+	Ahmed et al. 2011
Cultured human HepG2 cells	Micronucleus assay	No data	+	Lu et al. 2000
Human liver hepatoblastoma	DNA adducts	+	No data	Dubois et al. 1996
Human lung carcinoma cells	Unscheduled DNA synthesis	No data	–	Hoechst 1988d
Mouse L51784 tK^+/tK^- lymphoma cells	Forward locus mutation	No data	+	McGregor et al. 1988
Fetal rat hepatocytes	DNA adducts	+	No data	Dubois et al. 1996
Chinese hamster ovary cells	DNA damage, Comet assay	No data	+	Bajpayee et al. 2006
Rat hepatocyte culture	Unscheduled DNA synthesis	No data	–	Hoechst 1984d
Sheep peripheral lymphocytes	Micronucleus assay	No data	+	Kovalkovicova et al. 2001

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

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. Both positive (Falck et al. 1999) and negative (Scarpato et al. 1996a, 1996b; Venegas et al. 1998) results were obtained in peripheral lymphocyte micronucleus studies in workers who applied various pesticides, including endosulfan. 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-bromo-deoxyuridine DNA-labeling technique (Falck et al. 1999), but not in an assay utilizing cytochalasin-B to arrest cytokinesis (Scarpato et al. 1996a, 1996b). 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. For these reasons, these studies are not included in Table 3-4.

The induction of genotoxic effects in animals following *in vivo* exposure to endosulfan has been evaluated using the chromosomal aberration test in somatic and germinal cell systems of rats (Dikshith et al. 1978), mice (Kurinnyi et al. 1982; Usha Rani and Reddy 1986), and hamsters (Dzwonkowska and Hubner 1986), the bone marrow micronucleus tests in mice (Usha Rani et al. 1980) and rats (Manjula et al. 2006), and the sex-linked recessive lethal mutation test in *Drosophila* (Velazquez et al. 1984). Endosulfan enhanced chromosomal aberrations in mouse spermatocytes 60 days post-treatment (Usha Rani and Reddy 1986), in mouse bone marrow (Kurinnyi et al. 1982), and in hamster bone marrow (Dzwonkowska and Hubner 1986). It also and induced micronuclei in rat bone marrow following 60 days of treatment (Manjula et al. 2006), but failed to induce chromosomal aberrations in the spermatogonial cells of rats (Dikshith and Datta 1978; Dikshith et al. 1978).

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 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 post-treatment (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 contrast to the 2-day acute mouse study by Usha Rani et al. (1980), a subchronic gavage study in rats administered 3, 6, 9 and 12 mg/kg/day endosulfan for 60 days resulted in increased micronuclei in polychromatic erythrocytes (PCEs) and normachromatic erythrocytes (NCEs) (Manjula et al. 2006). When treated in conjunction with vitamin C, there was a decrease in PCEs and NCEs, which could be attributed to the antimutagenic effect of vitamin C itself. 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 induced micronuclei in rats following oral administration at 3, 6, 9, and 12 mg/kg/day for 60 days (Manjula et al. 2006); however, it did not induce micronuclei in mice fed 21.7 mg/kg/day for 2 days (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).

Endosulfan, its isomers, and metabolites tested positive for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA102 with and without metabolic activation in one study (Bajpayee et al. 2006) and tested positive in strain TA98 without activation in another study (Antherieu et al. 2007). However, in other studies, no mutagenic activity was demonstrated in *S. typhimurium* strains TA97a, TA98, TA100, TA1535, TA1537, or TA1538 without activation (Moriya et al. 1983; Pednekar et al. 1987) or in *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 human 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 HepG2 (human liver hepatoblastoma) cells exposed without activation (Lu et al. 2000). Positive results were also reported in human lymphocyte, HaCaT, and HepG2 cells for DNA damage (strand breaks) in comet assays without metabolic activation (Antherieu et al. 2007; Bajpayee et al. 2006; Jamil et al. 2004). In addition, DNA damage was observed in peripheral blood mononuclear cells (as indicated by the presence of oxidative stress) without activation (Ahmed et al. 2011), and endosulfan was found to induce the formation of DNA adducts in human HepG2 cells, which strongly correlated with high induction of CYP3A gene expression (Dubois et al. 1996). Negative results were reported for mitotic recombination in human lymphocyte cells (L'Vova 1984) and for unscheduled DNA synthesis (UDS) in human lung carcinoma (A 549) cells using liquid scintillation counting (Hoechst 1988d), but the study was inconclusive because no evidence that DNA synthesis was inhibited was presented, and high background levels compromised the sensitivity of the assay.

In mammalian cells, endosulfan produced forward locus gene mutations in mouse lymphoma cells (McGregor et al. 1988) and induced DNA damage in a comet assay in Chinese hamster ovary (CHO) cells in the absence of S9 mix (Bajpayee et al. 2006). Endosulfan also induced the formation of DNA adducts in fetal rat hepatocytes in the presence of S9 mix (Dubois et al. 1996). However, exposure did not induce

UDS in primary rat hepatocytes (Hoechst 1984d) and was negative in a micronucleus assay in sheep peripheral lymphocytes (Kovalkovicova et al. 2001)

In summary, genotoxicity studies of endosulfan have provided evidence that this compound can be mutagenic and clastogenic, and that it can induce effects on cell cycle kinetics in different mammalian species. It induced chromosomal aberrations and gene mutations in mice, hamsters, sheep, and *Drosophila*. 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.

3.4 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. Nearly 80% of the administered oral dose may be absorbed and nearly 20% of 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 main route of excretion of unchanged parent compound and metabolites is in the feces.

3.4.1 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 exposure, thus 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.

3.4.1.1 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 exposure route.

3.4.1.2 Oral Exposure

Although no specific studies were located that quantified the absorption of endosulfan in humans, the onset of seizures approximately 1 hour following ingestion of endosulfan suggests that absorption occurs in the gastrointestinal tract (Karatas et al. 2006; Moon and Chun 2009). 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 five cases of people 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). Yavuz et al. (2007) reported that the blood concentration of endosulfan at autopsy of a man who ate a contaminated homemade pastry was 3.15 mg/L. In a lethal case of a man who ingested 500 mL of Thiodan® 35 containing 180 g endosulfan, the peak concentration in blood was approximately 0.86 mg/L 28 hours after ingestion (Eyer et al. 2004). Another case in the same study had a peak blood concentration of endosulfan of 0.12 mg/L 25 hours after ingesting 35 mL of an organochlorine fluid containing 12.3 g endosulfan; this subject survived (Eyer et al. 2004). α-Endosulfan, 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). Administration of a single gavage dose of 5 mg/kg ^{14}C-endosulfan to male rats resulted in rapid absorption through the gastrointestinal tract, as evidenced by an absorption rate constant of 3.07/hour (Chan et al. 2005). Blood concentration reached a maximum of 0.36 mg endosulfan equivalents/L approximately 2 hours after dosing. The terminal elimination half-life of the radioactivity in blood was 193 hours. These studies indicate that absorption occurs in humans and animals following ingestion of endosulfan.

3.4.1.3 Dermal Exposure

Evidence suggesting that humans absorb endosulfan through the skin was presented in a study by Singh et al. (1992), which 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 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 of dermal absorption was provided in the case of a 2-year-old girl who was brought to the emergency room with a history of continuous generalized clonic tonic seizures for 1 hour after her mother applied endosulfan on her head to remove head lice (Jindal and Sankhyan 2011). Neither the exposure concentration nor the levels of endosulfan in blood were available.

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).

3.4.2 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. No studies were located regarding known or suspected differences between children and adults with respect to endosulfan distribution.

3.4.2.1 Inhalation Exposure

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

3.4.2.2 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 µg/kg, 80 µg/kg, 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 µg/kg, 1,350 µg/kg, and 390 µg/kg in the liver, brain, and kidney, respectively (Boereboom et al. 1998). In three 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 the following respective α- and β-endosulfan 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. 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). In a more recent case reported by Eyer et al. (2004), a man ingested 500 mL of Thiodan® 35 containing 180 g endosulfan and died 10 days later of multiorgan failure. One day after his death, the concentrations of endosulfan (α- plus β-isomers) were 5 µg/g in the bile, 7.5 µg/g in the brain, 26 µg/g in the liver, 0.8 µg/g in the lung, and 110 µg/g in the kidney.

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. A study of Turkish urban primiparous women without occupational exposure reported means of 2 and 28 ng/g (lipid basis) for α- and β-endosulfan, respectively, in breast milk (Çok et al. 2011). A study of Spanish women reported concentrations of endosulfan and metabolites in breast milk ranging from 0.60 to 10.70 ng/mL for endosulfan diol and β-endosulfan, respectively (Cerrillo et al. 2005). Isomers and metabolites of endosulfan were detected in the fat of 30–40% of children from agricultural regions of Spain, demonstrating that endosulfan accumulates in adipose tissue of children after presumably repeated dietary exposure (Olea et al. 1999). The mean concentration of endosulfan and metabolites in the placenta from women from southern Spain ranged from 0.33 to 15.62 ng/g for endosulfan ether and endosulfan lactone,

respectively (Cerrillo et al. 2005). Another study from the same region reported a geometric mean of 4.02 ng/g for total endosulfan in the placenta (Freire et al. 2011). Cerrillo et al. (2005) also reported concentrations in the range of 1.43–13.23 ng/mL for endosulfan and metabolites in blood from umbilical cord. Yet another study of women from the same region reported mean concentrations of 2.44 and 2.83 ng/mL for α- and β-endosulfan, respectively, in cord blood (Mariscal-Arcas et al. 2010).

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 more recent study, administration of a single gavage dose of 5 mg/kg ^{14}C-endosulfan to male rats resulted in the following relative amounts of mg of endosulfan equivalents/L in tissues 8 hours after dosing: gastrointestinal tract (20.28) > liver (5.52) > fat (3.61) > thyroid gland (2.50) > kidneys (1.83) > lung (1.31) > serum (0.75) > heart (0.42) > spleen (0.37) > blood (0.28) > brain (0.27) > testes (0.25) > muscle (0.18) (Chan et al. 2005). After administration of three doses of 5 mg/kg, radioactivity decreased in all tissues 25 hours after administration of the last dose.

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). Respective total endosulfan residues for 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. 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 kidneys, seminal vesicle, and epididymis, with the liver having the least amount. Using gas chromatography-mass spectrometry, Chan and Mohd (2005) measured α-endosulfan, β-endosulfan, endosulfan sulfate, and endosulfan diol in plasma, kidneys, and liver from male rats after 15 daily gavage doses of 5 or 10 mg/kg technical endosulfan and after an additional 15-day period without treatment. None of the four chemicals was detected in plasma samples. After 15 days of dosing, α-endosulfan and β-endosulfan were detected in the kidneys, but not in the liver; neither one was detected in the liver or kidneys after the 15-day recovery period. Traces of endosulfan sulfate were detected in liver, but not in the kidneys, at both sampling times.

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, and 21 posttreatment) after treatment ceased. With the exception of the kidneys, the highest concentrations 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).

3.4.2.3 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) 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 of the α- and β-isomers, respectively, in animals exposed to the lowest doses was as follows: fatty tissue (0.26 and 0.15 ppb) > kidney (0.16 and 0.01 ppb) > blood (0.03 and 0.015 ppb) > liver (0.02 and 0.004 ppb) > brain (0.03 ppb and not detected) in male rats, and fatty tissue (2.4 and 5.8 ppb) > liver (0.50 and 1.2 ppb) > blood (0.56 and 1.2 ppb) > kidney (0.65 and 0.52 ppb) > brain (0.21 ppb and 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).

3.4.2.4 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.

3.4.3 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. Using human liver microsomes, Casabar et al. (2006) showed that the formation of endosulfan

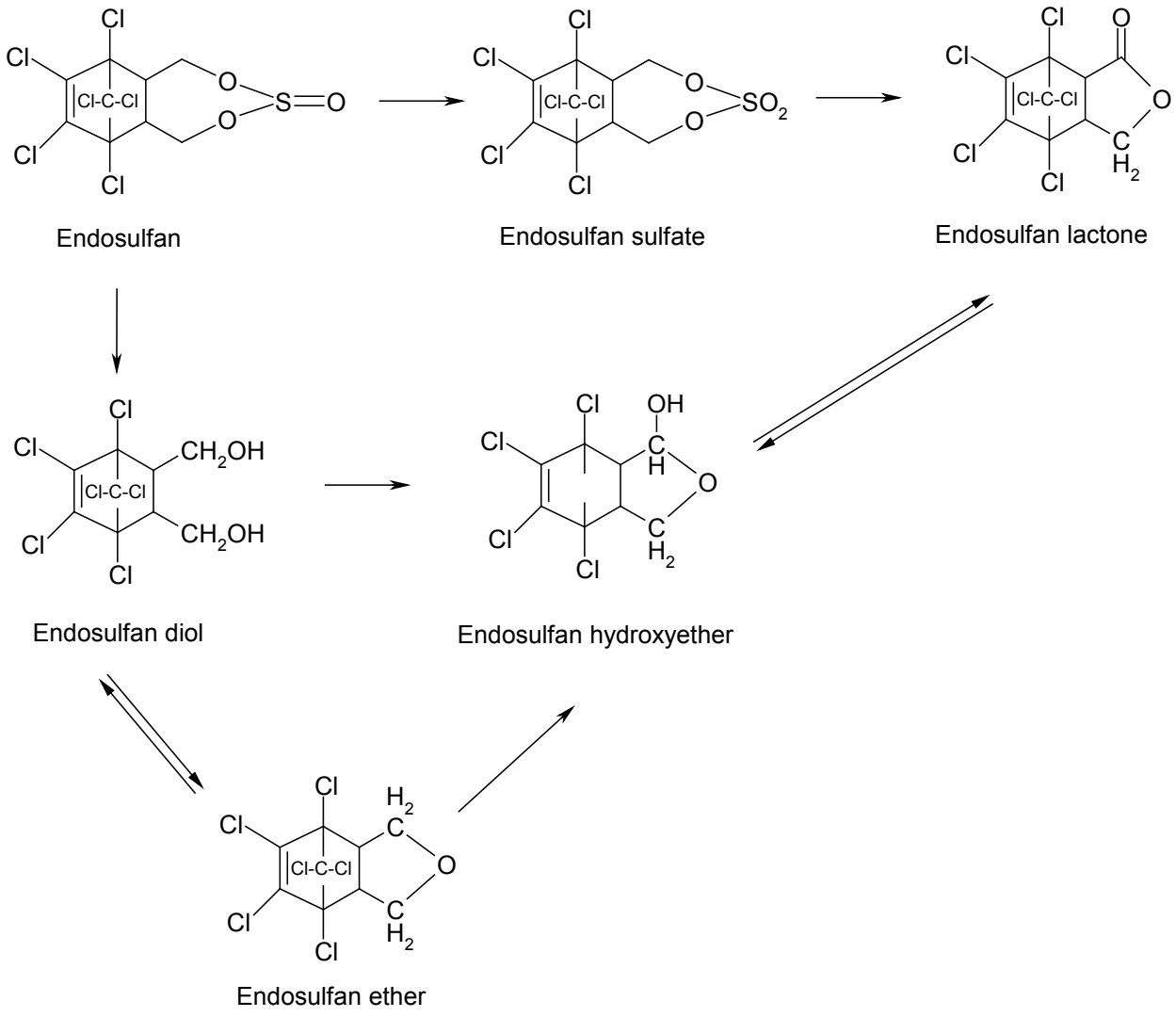
sulfate from α-endosulfan is catalized primarily by cytochromes CYP2B6 and CYP3A4. A similar study by Lee et al. (2006) reported that the stereoselective formation of endosulfan sulfate from α-endosulfan is mediated by CYP2B6, CYP3A4, and CYP3A5, and that from β-endosulfan is mediated by CYP3A4 and CYP3A5. Figure 3-3 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 3.4.4.3) (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).

All of 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

Figure 3-3. Proposed Metabolic Pathway for Endosulfan



Adapted from: Dorough et al. (1978); Gorbach et al. (1968)

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 P450 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.

3.4.4 Elimination and Excretion

Endosulfan and metabolites are eliminated mainly in the feces and urine 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.

3.4.4.1 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.

3.4.4.2 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 (Chan et al. 2005; 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 single oral dose eliminated 19 and 25% of the α- and β-isomer dose, respectively, in the feces and urine in the form of the original compound and its metabolites 24 hours after exposure. After 120 hours, the percentages increased to 88 and 87% of the administered doses, 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 <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-hydroxy-endosulfan ether. Most of the ^{14}C activity in the milk of sheep was due to endosulfan sulfate. In a more recent study, male rats were administered a single gavage dose of 5 mg/kg ^{14}C-endosulfan and urine and feces were collected for 96 hours (Chan et al. 2005). Over the 4-day period, 108.6% of the administered radioactivity was recovered in the excreta, fecal elimination being the major route of excretion with 94.4% of the radioactivity. The cumulative urinary excretion was 12.4%. 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.

3.4.4.3 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, and 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 2 times greater than in the urine (Hoechst 1986).

3.4.4.4 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, species differences, or 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.

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

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

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

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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 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.

The Chan et al. (2006) Model

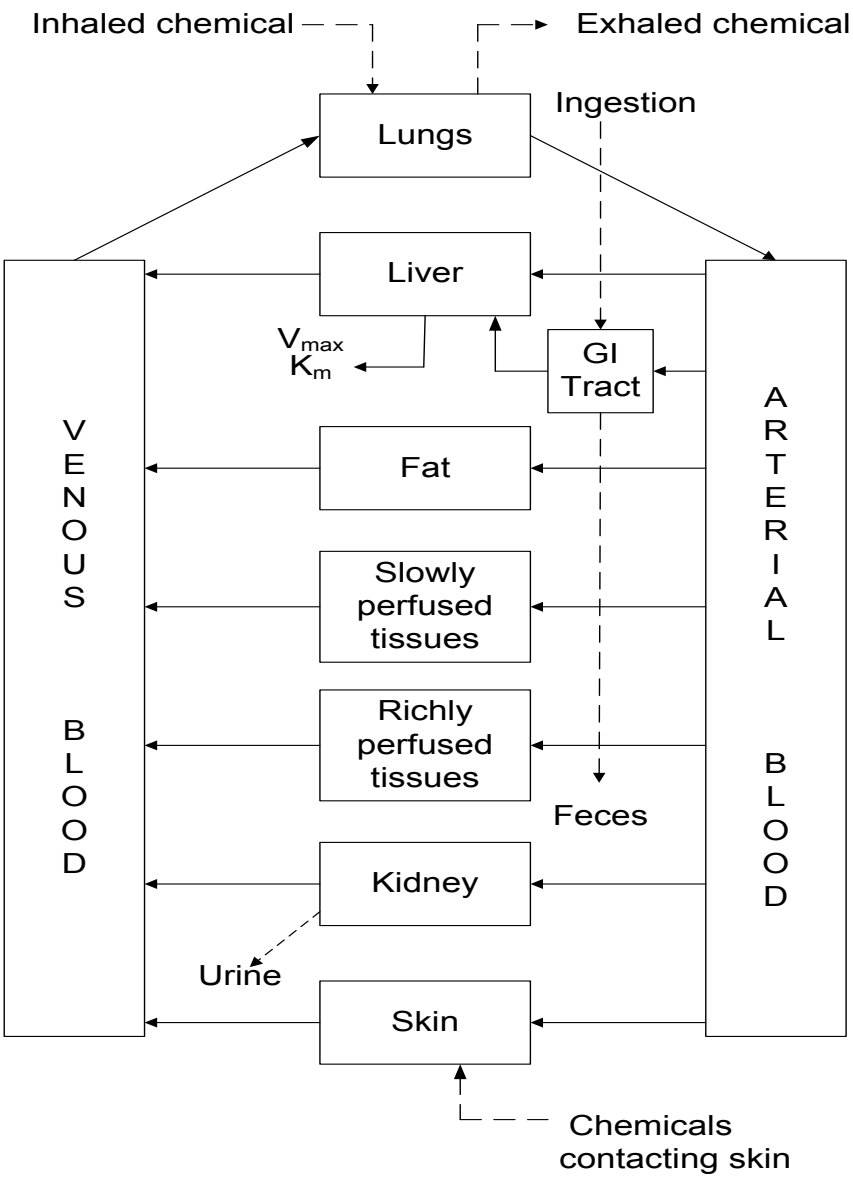
Description of the model. Chan et al. (2006) developed a PBPK model to predict tissue doses of endosulfan in male Sprague-Dawley rats following acute (single or three doses) exposure of the pesticide by gavage. The model comprised nine compartments: gastrointestinal tract, liver, brain, kidneys, fat, testes, well-perfused tissues, poorly-perfused tissues, and the lungs. In the model, the rate of transfer of endosulfan to the tissues was limited by blood flow to the specific tissue, while diffusion was assumed to occur instantaneously in each organ. The model assumed that metabolism occurs only in the liver where the rate of metabolism was described by the Michaelis-Menten equation. Physiological parameters were taken from the literature, whereas partition coefficients and biochemical parameters were determined experimentally and optimized by manual adjustment until the best visual fit of the simulations with experimental data were observed.

Validation of the model. The model was validated by simulating the disposition of ^{14}C-endosulfan in rats following single and repeated gavage doses and comparing the simulated results with the empirical data. Further validation was performed by using experimental data from the literature.

Risk assessment. The rat model developed by Chan et al. (2006) has not been applied to risk assessments.

Target tissues. In general, model simulations for endosulfan concentrations in blood and target tissues (liver, kidneys, brain, and testes) fit reasonably well the shape of the experimental data. However, simulation of total endosulfan disposition from kidneys and liver after repeated oral administration of 5 mg/kg endosulfan resulted in slight overestimation of concentrations at all time points, whereas simulation of total endosulfan disposition from testes resulted in slight underestimation at the last time point.

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



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

Source: adapted from Krishnan and Andersen 1994

Sensitivity analysis. The impacts of the physicochemical and biochemical parameters were examined when each parameter was changed from its original value by 1% at the various time points examined. There was no impact of the partition coefficients for all tissues on the concentrations of endosulfan across all time points examined (1, 2, 4, 8, and 24 hours). Parameters such as absorption rate, and biliary and fecal excretion rates for endosulfan had no impact on the blood and tissue concentrations of endosulfan. However, the sensitivity for maximum metabolic rate and urinary excretion rate were consistently negative across tissue time and external exposure concentration, whereas the sensitivity for Michaelis-Menten constant was consistently positive across all time points and external exposure concentrations.

Species extrapolation. Species extrapolation was not attempted in this model. A human model would be needed for dosimetry extrapolation to humans for MRL derivation.

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

3.5 MECHANISMS OF ACTION

3.5.1 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. Based on results from toxicity studies, the mode of administration of endosulfan (gavage or diet) seems to play a role in the manifestation of the toxicity of endosulfan; effects are manifested at higher dietary dose than gavage doses. 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 it might be associated with a lipid fraction in the blood. 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 (Chan and Mohd 2005; 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; however, the role of metabolism in the toxicity of endosulfan has not been well characterized. Although endosulfan induces microsomal cytochrome P450 in the liver (Casabar et al. 2006; Lee et al. 2006; 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.

3.5.2 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 and metabolic effects, and alterations in the immune system. 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. In addition, it is likely that some of these effects are secondary to the adverse neurological effects. 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. 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 interference with the binding of those neurotransmitters to their receptors, alteration of neurotransmitter levels in brain areas by affecting synthesis, degradation, and/or rates of release and re-uptake.

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 synaptosomes. 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. An *in vitro* study that compared sensitivity of GABA receptors from several vertebrate brain preparations (human, dog, mouse, chicken, quail, and salmon) and two insects to α-endosulfan reported little selectivity for the pesticide (Hainzl et al. 1998). IC_{50} values for the vertebrate preparations ranged between 11 and 33 nM; the IC_{50} values for the two insect sources were 7 and 3 nM. These values also showed that α-endosulfan is considerably more potent with the two insects than with the vertebrate GABA receptors. Further studies from the same group of investigators with human receptor subtypes expressed individually and in combination in insect Sf9 cells showed that the β3 subunit contains the target for α-endosulfan and other subunits differentially modulate the binding to confer compound-dependent specificity and selective toxicity (Ratra et al. 2001).

A study showed that α-endosulfan blocked the chloride uptake induced by GABA in primary cultures of cortical neurons 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, increase 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. α-Endosulfan was also reported to inhibit the glycine receptor in cultured cerebellar granule cell from neonatal mice, but less potently than the GABA receptor (Vale et al. 2003). The strychnine-sensitive glycine receptor also regulates chloride flux inhibitory responses. Currently, the GABA-antagonism mechanism of toxicity is the most widely accepted hypothesis.

Several studies 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 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, gamma-aminobutyric acid [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 intraperitoneal injection of 40 mg/kg of endosulfan. 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.

As summarized in Section 3.4.3 (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 2 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 up to 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.

3.5.3 Animal-to-Human Extrapolations

Almost all of 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; Boereboom et al. 1998; Demeter and Heyndrickx 1978; Eyer et al. 2004; Lo et al. 1995; Moon and Chun 2009; Moses and Peter 2010; Parbhu et al. 2009; 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 and many of the systemic effects observed are

secondary to the neurological effects or to aspiration. 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.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997h). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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 (Soto et al. 1994, 1995; Vanparys et al. 2006). 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 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. Decreased serum testosterone was also reported in male rats exposed to 15 mg/kg/day technical endosulfan by gavage for 15–30 days; no significant effects were reported at 10 mg/kg/day (Choudhary and Joshi 2003). In contrast, doses of 2.9 mg/kg/day technical endosulfan provided to male rats via the diet for 8 weeks had no significant effect on serum levels of testosterone, LH, and FSH (Perobelli et al. 2010).

Raizada et al. (1991) examined the potential estrogenic properties of an unspecified endosulfan formulation in ovariectomized rats. 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. 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 simultaneously endosulfan and estradiol were not significantly different from those seen in rats that received estradiol alone. The study results indicated that endosulfan was neither estrogenic nor anti-estrogenic under the conditions of this assay. Hiremath and Kaliwal (2003) examined the potential estrogenic properties of technical endosulfan in ovariectomized mice. Estrogenic activity was assessed using uterine weight and vaginal cornification as end points. Antiestrogenic activity was assessed by administering technical endosulfan along with 17β-estradiol to a group of mice. Ovariectomized control mice showed a prolonged diestrus. Mice treated with 4 mg/kg endosulfan (only level tested) for 30 days did not show vaginal cornification and showed continuous diestrus without any appearance of estrus, indicating its nonestrogenic activity. In addition, there was no significant change in uterine weight. Mice dosed with endosulfan plus 17β-estradiol showed a significant increase in the duration of estrus and increased uterine weight, indicating that endosulfan did not have antiestrogenic activity under the conditions of the study. 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). More recently, subcutaneous doses of up to 6 mg/kg/day administered to ovariectomized adult rats did not significantly alter uterine weight or the luminal epithelial cell height (Varayoud et al. 2008). However, doses as low as 6 µg/kg/day of endosulfan mimicked the effect of a non-uterotrophic dose of 17β-estradiol in modifying the expression of estrogen-responsive genes such as ERα, progesterone receptor, and complement factor-3, which according to the investigators, could contribute to an increase in implantation failures. In a later publication, the same group of investigators reported that a subcutaneous injection of 0.6 mg/kg/day of endosulfan given to female rat pups from Pnd 1 to 7 altered the expression of estrogen-dependent genes that regulate uterine development and differentiation (Milesi et al. 2012).

Using a pituitary cell line known to respond to estrogens by increasing its secretion of prolactin, Rousseau et al. (2002) reported that endosulfan was able to induce a substantial increase of prolacting expression. The investigators suggested that endosulfan could modulate an estrogen-inducible gene such as prolactin

by acting via second messenger-mediated cellular mechanisms instead of solely competing with estrogens for the nuclear estrogen receptor sites.

α-Endosulfan had 400 times lower *in vitro* binding affinity for a recombinant human progesterone receptor than the natural ligand and 85,000 times lower binding affinity for a recombinant human estrogen receptor (Scippo et al. 2004). The corresponding binding affinities for β-endosulfan for the same human recombinant receptors were 1,760 and 78,000 times lower than the natural ligands. 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). In a recent study, α-endosulfan inhibited the binding of ^{3}H-estradiol to the estrogen receptor in cultured cortical neurons and cerebellar granule cells from mice fetuses and pups; the IC_{50} was 21.7 μM (Briz et al. 2011).

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). Recently Briz et al. (2011) reported that 5 μM α-endosulfan significantly induced MCF-7 cell proliferation, thus defining a lowest-observed-effect concentration (LOEC) half that defined by Soto et al. (1994). Endosulfan significantly increased cell proliferation and ER transactivation gene response in MCF-7 human breast cancer cells at 1 μM; maximum response was obtained at 25 μM (Andersen et al. 2002). In addition, endosulfan potentiated the 17β-estradiol-induced proliferation when it was tested together with a concentration of 17β-estradiol causing a submaximal response. In the same study, endosulfan exhibited

very weak antiandrogenic activity in CHO cells, reducing the response of the synthetic androgen R1881 by 28% (Andersen et al. 2002).

α-Endosulfan 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-hydroxy-estrone (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.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage

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

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

The effects of endosulfan have not been studied in children. 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 (Bernardelli and Gennari 1987; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Demeter and Heyndrickx 1978; Eyer et al. 2004; Lo et al. 1995; Moon and Chun 2009; Moses and Peter 2010; Parbhu et al. 2009; Terziev et al. 1974). Children would likely experience the same health effects seen in adults exposed to endosulfan as evidenced by a

case in which a 2-year-old girl developed seizures after her mother applied an unspecified endosulfan formulation on her head to remove lice (Jindal and Sankhyan 2011). An additional case reported clonic status epilepticus in a 2-year-old girl who accidentally ingested an unspecified endosulfan formulation (Kamate and Jain 2011). These effects of endosulfan in humans 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, which could have been due to an increase in the maximum number of binding sites or to alterations in receptor affinity (Zaidi et al. 1985). The increased binding correlated well with an increase in aggressive behavior and could be reversed by administration of a serotonin blocker; the NOAEL was 0.5 mg/kg/day. Exposure of adults to 3 mg/kg for 30 consecutive days induced significant increased in binding but of a lesser magnitude than in developing rats (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. However, adult rats were not tested with 1 mg/kg/day endosulfan for 30 days, so it is not known whether or not toxicity would be comparable. Neither of these studies provided information regarding the purity of the test substance. Kiran and Varma (1988) administered an unspecified endosulfan formulation 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 3.5.2, 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 to10 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 to 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.

A limited number of studies in humans have provided suggestive evidence of associations between maternal exposure to endosulfan and developmental alterations in the offspring including autism spectrum disorders (Roberts et al. 2007), alterations in thyroid function (Freire et al. 2011, 2012), neural tube defects (Ren et al. 2011), and delayed sexual maturity in male children (Saiyed et al. 2003). After considering the strengths and limitations of the individual studies, no definite conclusions could be drawn. Endosulfan induced adverse developmental effects in animals; most studies were conducted in rats. It should be noted that since not all studies provide information regarding maternal effects, it is not totally clear whether the developmental effects occur only in the presence of maternal toxicity. Perinatal exposure of rats to endosulfan induced skeletal variations (FMC 1980; Gupta et al. 1978), reduced offspring weight (Cabaleiro et al. 2008; Caride et al. 2010; Gilmore et al. 2006; Hoechst 1982, 1984a), and altered sperm parameters in adult male offspring that were not directly exposed, but received gestational and/or lactational exposure to endosulfan (Dalsenter et al. 1999; Sinha et al. 2001). Two of the most recent studies in which Wistar rats were exposed to 1 mg/kg/day endosulfan (only dose level tested) on Gd 6–20 reported significant increases in the incidences of gross, visceral, and skeletal anomalies, and hepatocyte and renal tubule epithelium degeneration in Gd 20 fetuses (Singh et al. 2007a, 2008). The lowest developmental LOAEL was 0.61 mg/kg/day for an 11% reduction in body weight from Sprague-Dawley male rat pups on Pnd 21 after treatment of the dams by gavage during the entire gestation and lactation periods (Cabaleiro et al. 2008; Caride et al. 2010); the 0.61 mg/kg/day dose was the lowest dose tested. Interestingly, treatment of Wistar rats with a much higher dose, 29.8 mg/kg/day endosulfan, via the diet on Gd 6–21 and during lactation resulted in a reduction of 11 and 4% in male and female pup's weight, respectively, on Pnd 21 (Gilmore et al. 2006). The apparent difference in sensitivity may be related to the different strains used and to the different mode of administration of the test material (i.e., gavage versus the diet). Endosulfan was not estrogenic in *in vivo* assays in immature female rats

(Raizada et al. 1991; Wade et al. 1997) or mice (Hiremath and Kaliwal 2003; 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 Section 3.6).

There is no information regarding pharmacokinetics of endosulfan in children or regarding nutritional factors that may influence the absorption of endosulfan. Endosulfan has been detected in the breast milk of women environmentally exposed (Cerrillo et al. 2005; Çok et al. 2011; Lutter et al. 1998), in the placenta (Cerrillo et al. 2005; Freire et al. 2011), and in cord blood (Mariscal-Arcas et al. 2010). The results from these studies indicate that transfer of endosulfan and/or metabolites to the fetus and nursing babies can occur. 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 radioactivity 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 P450 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 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 is 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. 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 at doses that also caused lethality (Dikshith et al. 1978).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to endosulfan are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by endosulfan are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 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 exposure to endosulfan (Chan et al. 2005; 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-Endosulfan 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 women exposed environmentally to endosulfan (Cerrillo et al. 2005; Çok et al. 2011; 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). Endosulfan and metabolites have also been detected in placenta (Cerrillo et al. 2005; Freire et al. 2011) and cord blood (Mariscal-Arcas et al. 2010). No other biomarkers of exposure specific for endosulfan 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.

3.8.2 Biomarkers Used to Characterize Effects Caused by Endosulfan

There are no biomarkers of effect specific for endosulfan in humans. The characteristic effects of acute exposure to high amounts of endosulfan in humans and animals are signs of overactivity of the nervous system such as hyperexcitability, tremors, and convulsions. Although many types of chemicals can induce seizures, non-specific biomarkers of clinical severity after poisoning exist; increased serum creatine kinase activity is a marker of seizure-induced rhabdomyolysis and increased serum lactate is a marker of metabolic acidosis. Other systemic effects observed in these cases are likely to be secondary to neurological effects. There are no studies of humans subjected to long-term exposure to low levels of endosulfan; therefore, no biomarkers for that type of exposure have been identified. The organ most sensitive to longer-term endosulfan exposure of animals appears to be the kidney; however, this effect also is not specific for endosulfan exposure (Hoechst 1989a).

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

3.9 INTERACTIONS WITH OTHER CHEMICALS

There are two reports that involved death in humans after simultaneous exposure to endosulfan and alcohol, but the nature of the interaction is not totally clear and the evidence is weak at best. In one death (Demeter et al. 1977), the blood alcohol concentration in a subject 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 possible that alcohol interfered with the metabolism of endosulfan in the liver and, therefore, delayed endosulfan elimination. On the other hand, the presence of alcohol would probably have been protective since it usually increases the threshold for seizures. A second fatal outcome was reportedly caused by ingestion of alcohol and Posidor (20% endosulfan and 30% dimethoate in xylene) (Demeter et al. 1978). 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. It is possible that some of the effects, such as hyperactivity, tremors, and seizures, may have resulted from the combined contribution of the two pesticides, although through different mechanisms. The investigators did not discuss what the role of alcohol might have been in this case.

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 P450 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.

Endosulfan promoted the hypnotic effects of diazepam by prolonging the duration of the loss of righting reflex (Balasubramamian et al. 1996). The investigators 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; however, little evidence was presented in support their speculation (Balasubramamian et al. 1996). In the same study, endosulfan promoted the convulsant action of picrotoxin by shortening the convulsion latency and increasing convulsion frequency. 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).

3.10 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 6.7, Populations with Potentially High Exposures.

The limited toxicity data available for endosulfan suggest that two subgroups of the population may be more susceptible to endosulfan exposure than the general population. These subgroups include people with kidney or neurological diseases.

The central nervous system is a major target of endosulfan-induced toxicity in both humans and animals (Bernardelli and Gennari 1987; Blanco-Coronado et al. 1992; Boereboom et al. 1998; Boyd and Dobos 1969; Demeter and Heyndrickx 1978; Eyer et al. 2004; Gilbert and Mack 1995; Hoechst 1970, 1975, 1984e; Lo et al. 1995; Moon and Chun 2009; Moses and Peter 2010; Parbhu et al. 2009; 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 1992; Gilbert and Mack 1995).

The observation of marked progressive glomerulonephrosis 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 (Hoechst 1989a).

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 3.7, Children's Susceptibility.

3.11 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. No texts were located that provide information about treatment following specific exposure to endosulfan.

3.11.1 Reducing Peak Absorption Following Exposure

The following has been extracted from HSDB (2012). 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. Contaminated clothing should be removed and the skin and hair should be washed three times. An initial soap washing can be followed by an alcohol washing and another soap washing to remove unabsorbed material. Since leather absorbs pesticides, it is recommended that leather not be worn in the presence of pesticides and all contaminated leather should be discarded. If eye exposure occurs, the exposed eyes should be irrigated with copious amounts of room temperature water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persists, the patient should be seen in a health care facility. After acute high-dose oral exposures, absorption from the gastrointestinal tract may be limited by gastric lavage, generally within 1 hour of ingestion. Gastric lavage can be followed by administration of activated charcoal as a slurry; the usual dose is 25–100 g in adults/adolescents, 25–50 g in children (1–12 years old), and 1 g/kg in infants <1year old. However, there is no evidence of benefit from either charcoal or gastric lavage and clear evidence of harm if the latter is done badly. Gastric lavage may be indicated in patients who are comatose or at risk of convulsing. Oil-based cathartics may facilitate gastrointestinal absorption and, therefore, are not used.

3.11.2 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; HSDB 2012).

3.11.3 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 refractory status epilepticus. It is therefore important to urgently control 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; Eyer et al. 2004; Yavuz et al. 2007); diazepam followed by phenytoin

(Jindal and Sankhyan 2011) have been used to treat tonic-clonic seizures following exposure to high amounts of endosulfan. Lorazepam has also been recommended (HSDB 2012). Phenobarbital or propofol has been suggested if seizures are uncontrollable or recur after diazepam (HSDB 2012). Phenytoin is not recommended for seizures in poisoned patients (Shah and Eddleston 2010). General anesthesia with EEG monitoring should be instigated urgently if diazepam and phenobarbital are not rapidly effective.

Several studies have reported on the amielorating action of antioxidant substances on the effects of endosulfan in animals. The most studied antioxidant appears to be vitamin C. Studies have reported that simultaneous administration of vitamin C and endosulfan reduced alterations induced by endosulfan on sperm parameters in rats and rabbits (Ata et al. 2007; Rao et al. 2005), on genotoxic effects in rats (Manjula et al. 2006), on neurotoxicity in rabbits (Mor and Ozmen 2010), and in parameters of immune response in rats (Pal et al. 2009). Similar mitigating activity has been reported for vitamin E (Jalili et al. 2007; Kalender et al. 2004a; Pal et al. 2009; Zervos et al. 2011), melatonin (Omurtag et al. 2008), and 5-aminosalicylic acid (Jaiswal et al. 2005). There is strong evidence that the mechanism by which these substances ameliorate the effects of endosulfan is by preventing the endosulfan-induced formation of reactive oxygen species and lipid peroxidation (El-Shenawy 2010; Kannan and Jain 2003; Omurtag et al. 2008; Ozdem et al. 2011; Zervos et al. 2011).

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

3.12 ADEQUACY OF THE DATABASE

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

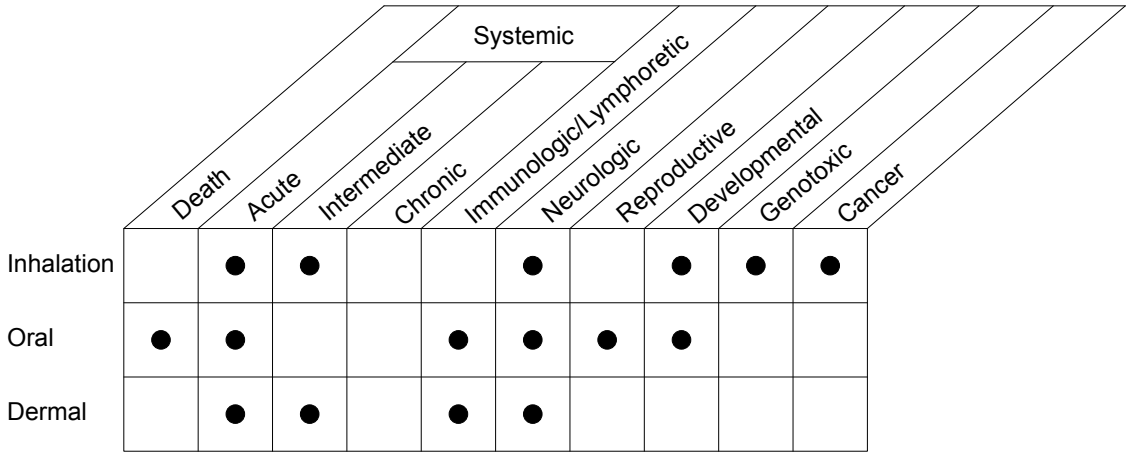
3.12.1 Existing Information on Health Effects of Endosulfan

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to endosulfan are summarized in Figure 3-5. 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* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

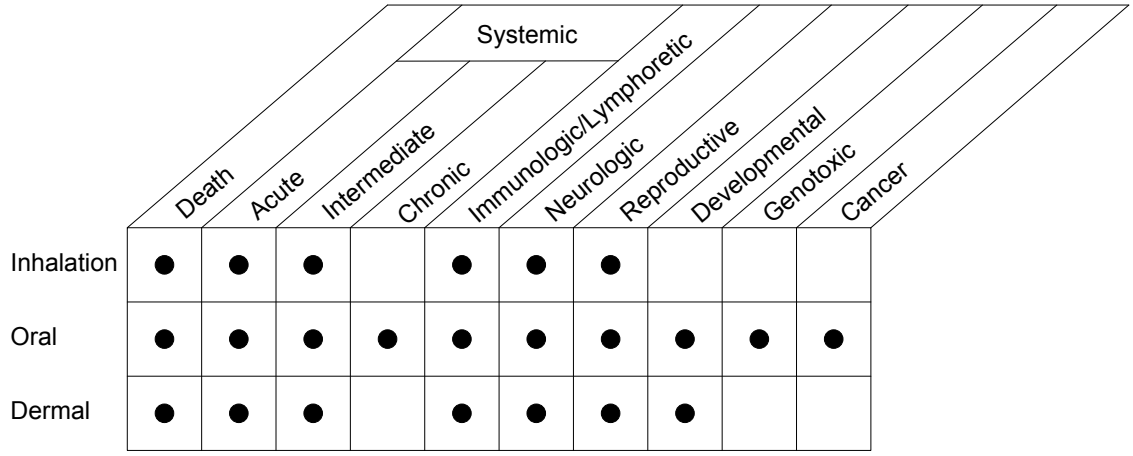
Most of the literature reviewed concerning the health effects of endosulfan in humans described case reports and case series of occupational exposure and accidental or intentional ingestion of endosulfan. The cases of occupational exposure to endosulfan concerned exposures of acute-to-intermediate durations, and the cases of oral exposure were exclusively acute-duration exposure situations. The predominant route of exposure in the occupational case reports/series 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 3-5, 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.

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



Human



Animal

● Existing Studies

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 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 is not a major route of exposure since endosulfan is generally detected at low levels in the ambient atmosphere. 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.

3.12.2 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; Eyer et al. 2004; Jindal and Sankhyan 2011; Karatas et al. 2006; Lo et al. 1995; Moon and Chun 2009; Parbhu et al. 2009; 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; Caglar et al. 2003; Den Tonkelaar and Van Esch 1974; FMC 1958, 1972, 1980; 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; Hiremath and Kaliwal 2002a; Lakshmana and Raju 1994; Lindquist and Dahm 1957; Misra et al. 1980; Nicholson and Cooper 1977; Siddiqui et al. 1987b; Sinha et al. 2001; 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; Eyer et al. 2004; 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; Parbhu et al. 2009; 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; Chugh et al. 1998; Ely et al. 1967; Eyer et al. 2004; FMC 1958, 1959a, 1980; Gilbert and Mack 1995; Gupta and Chandra 1975; Hoechst 1970, 1975, 1983a, 1984e, 1989b; Karatas et al. 2006; MacKenzie et al. 1981; Moon and Chun 2009; Mor and Ozmen 2010; Moses and Peter 2010;

Nicholson and Cooper 1977; Shemesh et al. 1988; Terziev et al. 1974). Adverse systemic effects (respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and metabolic) reported in most cases of acute exposure to high amounts of endosulfan are likely to be secondary to the serious neurological effects (i.e., tremors, seizures) and to aspiration of the pesticide and its solvent (the latter can be highly damaging to the lung). The same occurs in animals (Boyd et al. 1970; Den Tonkelaar and Van Esch 1974; FMC 1958, 1972; Gupta and Chandra 1975; Gupta and Gupta 1977a; Hoechst 1970, 1983a, 1989b; Misra et al. 1980; Siddiqui et al. 1987b; Terziev et al. 1974).

The data in animals are insufficient to derive an acute inhalation MRL because serious effects were observed at the lowest dose tested (Hoechst 1983a). An acute-duration oral MRL was derived for endosulfan based on adverse neurological signs in rabbits administered the compound by gavage (MacKenzie et al. 1981). Additional acute studies do not seem necessary at this time.

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; Choudhary et al. 2003; Dikshith et al. 1984, 1988; Garg et al. 1980; Gilmore et al. 2006; Gupta and Chandra 1977; Gupta and Gupta 1977a; Hatipoglu et al. 2008; Hiremath and Kaliwal 2003; Hoechst 1982, 1983b, 1984a, 1984b, 1984c, 1985a, 1985b, 1985c, 1985d, 1987, 1989c; Kalender et al. 2004a, 2004b; Ozmen et al. 2010; Sheets et al. 2004; Singh et al. 2007a, 2007b; Vos et al. 1982). These studies reported adverse effects on the liver, kidney, reproductive (testes), immune systems and nervous system as well as adverse reproductive and developmental effects. The data in animals were not sufficient to derive an intermediate-duration inhalation MRL, but were sufficient to derive an intermediate-duration oral MRL. An intermediate-duration oral MRL of 0.005 mg/kg/day, based on altered immunocompetence in rats, was derived for endosulfan (Banerjee and Hussain 1986). It is worth mentioning that the results of several studies suggest that at comparable doses, endosulfan seems to be more toxic administered by gavage than through the diet. Studies addressing this issue seem necessary since the diet is the most relevant route of exposure for the general population; therefore, risk assessment values based on gavage studies may not be entirely appropriate.

Chronic-Duration Exposure and Cancer. No information is available on the toxicity of endosulfan to humans following chronic-duration exposure by any route. There are no available data

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 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 kidney. A chronic-duration oral MRL was not derived based on these studies because the potential point of departure from the best study available (Hoechst 1989a) yielded a chronic-duration oral MRL slightly higher than the intermediate-duration oral MRL. For this reason, the intermediate-duration oral MRL was also adopted for the chronic-duration oral MRL for endosulfan. Since no data are available for the inhalation route of exposure, a chronic inhalation MRL could not be derived. 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. Although there are several chronic-duration oral studies with endosulfan in rats, mice, and dogs, there are issues, particularly in the study in dogs conducted by Hoechst (1989c), that would be helpful to clarify. In that study, serum alkaline phosphatase activity was significantly increased relative to controls in males and females dosed with ≥0.6–0.7 mg/kg/day technical endosulfan; the NOAEL was approximately 0.2 mg/kg/day. In the absence of significant alterations in serum transaminases and liver histopathology, the investigators did not consider the changes in alkaline phosphatase activity toxicologically significant.

Very limited information is available regarding exposure to endosulfan and cancer. An occupational study found no association between exposure to endosulfan and breast cancer (Aschengrau et al. 1998). A study of the general population provided suggestive evidence of an association between levels of endosulfan in the bone marrow from children and hematological malignancies (Rau et al. 2012). A very small number of cases in the former study and lack of control of confounders in the latter study preclude drawing definitive conclusions. 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 since skin contact with contaminated soil is an important route of exposure for people living near hazardous waste sites.

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 can be mutagenic, clastogenic, and can induce effects on cell cycle kinetics in two different mammalian species (Ahmed et al. 2011; Antherieu et al. 2007; Bajpayee et al. 2006; Dikshith and Datta 1978; Dikshith et al. 1978; Dorough et al. 1978; Dubois et al. 1996; Dzwonkowska and Hubner 1986; Hoechst 1984d, 1988d; Jamil et al. 2004; Kurinnyi et al. 1982; Lu et al. 2000; L'Vova 1984; Manjula et al. 2006; 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, should populations that have been exposed exclusively to endosulfan be identified, *in vivo* tests of chromosomal aberrations in would provide valuable information on the genotoxic potential of endosulfan in humans.

Reproductive Toxicity. The only relevant information in humans is that from a study that reported no significant association between levels of endosulfan in adipose tissue from men and fertility (Çok et al. 2010). Since the cohort consisted of only 25 infertile men and 21 controls, definitive conclusions could not be drawn from the study.

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 (Ata et al. 2007; Choudhary and Joshi 2003; Sinha et al. 1995, 1997). With the exception the finding of testicular atrophy observed in rats treated with relatively high doses of endosulfan in the diet for up to 82 weeks (NCI 1978), other chronic-duration studies did not report morphological alterations in the reproductive organs of rats, mice, or dogs (Hoechst 1988b, 1989a, 1989c). No information is available on effects on reproductive performance of inhaled or dermally administered endosulfan, but no such studies seem necessary at this time. The fact that studies in rats indicate that endosulfan has no adverse effects on reproductive performance in animals following oral

exposure is not totally unexpected since rats produce and ejaculate 10 times more sperm than are necessary for normal fertility and litter size (Amann 1982; Working 1988).

Developmental Toxicity. A limited number of studies in humans have provided suggestive evidence of associations between maternal exposure to endosulfan and developmental alterations in the offspring including autism spectrum disorders (Roberts et al. 2007), alterations in thyroid function (Freire et al. 2011, 2012), neural tube defects (Ren et al. 2011), and delayed sexual maturity in male children (Saiyed et al. 2003). After considering the strengths and limitations of the individual studies, no definite conclusions could be drawn. A conclusion shared by these studies was that further research is necessary and that the cohorts should be followed up.

No conclusive evidence of developmental toxicity in animals 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, or because the studies provided no information regarding maternal effects (Cabaleiro et al. 2008; Caride et al. 2010; FMC 1980; Gupta et al. 1978; Hoechst 1982; Singh et al. 2007a, 2008). 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. A developmental study in which endosulfan was administered via the diet to rats provided little evidence of developmental toxicity at doses considerably higher than those used in developmental gavage studies (Gilmore et al. 2006). As mentioned before, this issue needs to be addressed with studies of comparative toxicokinetics of gavage and dietary administration of endosulfan. There is no information on postnatal exposures and any associated postnatal developmental effects.

Immunotoxicity. There is virtually no information regarding the effects of endosulfan on the human immune system. However, specially designed studies using rats indicate that both humoral and cellular immune responses can be 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, which has been the case also for other chemicals (Abadin et al. 2007). Since it is the only study that conducted

immunocompetence experiments in rats challenged with a toxin, it would be useful to try to replicate the findings of Banerjee and Hussain (1986). An intermediate-duration oral MRL was derived based on the observation of depressed immune responses (Banerjee and Hussain 1986). 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 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. Very limited information suggests that endosulfan can affect macrophage function (Ayub et al. 2003; Han et al. 2007), but further studies investigating the mechanism of endosulfan-induced immunotoxicity are needed.

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; Bury 1997; Cable and Doherty 1999; Chugh et al. 1998; Ely et al. 1967; Eyer et al. 2004; FMC 1958, 1980; Gilbert and Mack 1995; Gupta and Chandra 1975; Hoechst 1970, 1975, 1983a, 1984e, 1989b; Karatas et al. 2006; Lakshmana and Raju 1994; Lo et al. 1995; MacKenzie et al. 1981; Moon and Chun 2009; Moses and Peter 2010; Nicholson and Cooper 1977; Parbhu et al. 2009; Pradhan et al. 1997; Roberts et al. 2004; 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 exposures; however, chronic effects were observed in dogs (Hoechst 1989c). Two reports of humans acutely exposed to high amounts of endosulfan indicated that persistent cognitive brain damage may result following such exposures (Aleksandrowicz 1979; Shemesh et al. 1988). This could be examined in studies in animals under controlled exposures. Some gavage 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). However, dietary studies that provided considerably higher doses of endosulfan found little or no effects on neurobehavioral tests (Gilmore et al. 2006; Sheets et al. 2004), indicating that the mode of administration of the test material plays a role in the effects observed. As indicated before, this issue should be examined with appropriate toxicokinetic studies. 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 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; Aschengrau et al. 1998; 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; Eyer et al. 2004; Karatas et al. 2006; Lo et al. 1995; Moon and Chun 2009; Moses and Peter 2010; Parbhu et al. 2009; Roberts et al. 2004; Shemesh et al. 1988; Terziev et al. 1974; Yavuz et al. 2007). The predominant routes of exposure in the occupational studies are believed to be inhalation and dermal (workers involved in pesticide manufacture, formulation, and application). There are studies of the general population that examined possible associations between exposure to endosulfan (and additional compounds in some cases) and health outcomes such as cancer (Rau et al. 2012), fertility in men (Çok et al. 2010), and developmental effects (Freire et al. 2011; Garcia-Rodriguez et al. 1996; Ren et al. 2011; Roberts et al. 2007; Saiyed et al. 2003). 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 may be useful, specifically examining the effects of endosulfan on the kidney, since this organ appeared to be a sensitive target in long-term studies in rats (Hoechst 1989a). However, the decision to conduct such a study needs to be balanced by the fact that the risk of exposure will diminish since endosulfan is scheduled to be cancelled for all uses by 2016 (EPA 2002, 2012g). The immune system was a sensitive target for endosulfan in an intermediate-duration study in rats (Banerjee and Hussain 1986). If the results of the Banerjee and Hussain (1986) study can be reproduced, immune parameters of populations with known exposure to endosulfan should also be examined. Exposure to endosulfan by the subjects of epidemiological studies

should be confirmed by analysis of blood and urine for endosulfan isomers and endosulfan sulfate. If endosulfan is found to be associated with adverse effects in any organ or system, then tests of these specific organs or systems may be useful tools to monitor endosulfan exposure in individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Exposure. Endosulfan and metabolites have been detected in the urine from workers exposed to this substance (Arrebola et al. 1999; Cable and Doherty 1999; Vidal et al. 1998). Endosulfan and metabolites have also been detected in the placenta (Cerrillo et al. 2005; Freire et al. 2011), cord blood (Mariscal-Arcas et al. 2010), fat tissue (Olea et al. 1999), and breast milk from the general population (Cerrillo et al. 2005; Çok et al. 2011; Lutter et al. 1998). Endosulfan has also been detected in blood from subjects who accidentally or intentionally ingested high amounts of the pesticide (Blanco-Coronado et al.1992; Boereboom et al. 1998; Eyer et al. 2004; Yavuz et al. 2007). The presence of the parent compound and its metabolites are specific biomarkers for endosulfan exposure. Only in the acute, high-exposure cases there have been attempts to quantitate exposure. Estimating exposure in cases of prolonged low-level exposure, as it may occur for the general population, would require reliable exposure characterization and a better knowledge of endosulfan toxicokinetics in humans.

Effect. There are no biomarkers of effect specific for endosulfan in humans or in animals. The typical effect of exposure to high amounts of endosulfan is overactivity of the nervous system such as hyperexcitability, tremors, and seizures, but exposure to numerous other chemicals results in the same type of effects. There are no studies of populations with prolonged exposure to low levels of endosulfan, so no adverse health effects have been reported.

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; Chan et al. 2005; Chugh et al. 1998; Deema et al. 1966; Demeter and Heyndrickx 1978; Dorough et al. 1978; Ely et al. 1967; Eyer et al. 2004; Gorbach et al. 1968; Gupta and Gupta 1979; Karatas et al. 2006; Moon and Chun 2009; Nath and Dikshith 1979; Nicholson and Cooper 1977; Parbhu et al. 2009; 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. Studies in animals have shown that at comparable doses, endosulfan is more toxic when administered by gavage than via the diet. Of particular interest would be studies that compare the rate of absorption between these two modes of administration.

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). Endosulfan and metabolites have also been detected in placenta (Cerrillo et al. 2005; Freire et al. 2011), cord blood (Mariscal-Arcas et al. 2010), fat tissue (Olea et al. 1999), and breast milk from the general population (Cerrillo et al. 2005; Çok et al. 2011; Lutter et al. 1998). Animal studies describe the distribution of endosulfan following both short-term and long-term oral exposure (Ansari et al. 1984; Braun and Lobb 1976; Chan et al. 2005; Chan and Mohd 2005; 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. Studies that compare the concentration of endosulfan and/or metabolites in blood in gavage and dietary studies could provide an explanation for the seemingly different toxic potency of endosulfan between the two modes of administration. 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 (Boereboom 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 (Chan et al. 2005; 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. A PBPK model was developed for endosulfan that describes toxicokinetics in rats (Chan et al. 2006). The model simulated gavage dosing of rats. It would be useful to incorporate into the model parameters related to dietary administration of endosulfan since studies have shown that endosulfan is considerably less toxic administered in the diet than by gavage. Dietary intake is the most relevant route of exposure to endosulfan by the general population.

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, but toxicokinetics have not been studied (Aleksandrowicz 1979; Ely et al. 1967; Moon and Chun 2009; Moses and Peter 2010; Roberts et al. 2004; 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; FMC 1958; Gilbert and Mack 1995; Gupta and Chandra 1975; Hoechst 1970, 1975, 1983a, 1984e, 1989b; Nicholson and Cooper 1977; Terziev et al. 1974). Other systemic effects observed in humans and in animals are likely to be secondary to the adverse neurological effects. Although no toxicokinetic studies have been performed in humans, 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. As stated in Section 3.11.1, Reducing Peak Absorption Following Exposure, there is information on the procedures that may be used to limit absorption of endosulfan following ingestion (HSDB 2012). Identification of improved procedures to reduce absorption is always valuable. A number of anticonvulsants and sedatives have been used to manage the seizures induced by exposure to high amounts of endosulfan. These include phenytoin, phenobarbital, valproate, propofol, thiopentane, midazolam, diazepam, lorazepam, and clobazam (Moses and Peter 2010). These drugs have been used in different combinations and sequences as the specific situations required. The effectiveness of these drugs varied from case to case and probably depended on the time elapsed between poisoning and initiation of treatment and on the amount of endosulfan taken. Publishing treatments that have proved to be effective in randomized controlled trials in medical journals could help decrease the number of fatalities resulting from endosulfan poisoning, particularly in countries where it is still widely used.

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

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. Cases of children accidentally exposed to high amounts of endosulfan showed the same types of effects observed in adults (Jindal and Sankhyan 2011; Kamate and Jain 2011; Parbhu et al. 2009). However, based on these high-exposure cases in which quantitative exposure information was not available, it is difficult to determine whether children are more susceptible to endosulfan than adults. 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.

A few studies in humans provided suggestive evidence of associations between maternal exposure to endosulfan and developmental alterations in the offspring including autism spectrum disorders (Roberts et al. 2007), alterations in thyroid function (Freire et al. 2011, 2012), neural tube defects (Ren et al. 2011), and delayed sexual maturity in male children (Saiyed et al. 2003). After considering the strengths and limitations of the individual studies, no definite conclusions could be drawn. Studies in animals have reported adverse developmental effects (Cabaleiro et al. 2008; Caride et al. 2010; Gilmore et al. 2006; Singh et al. 2007a, 2008; Sinha et al. 2001), but since not all studies provided information regarding maternal effects, it not totally clear whether developmental effects occur in the absence of maternal toxicity. Perinatal administration of endosulfan to rats by gavage resulted in more severe developmental effects than administration of comparable dose via the diet (Cabaleiro et al. 2008; Gilmore et al. 2006). As indicated earlier, this general issue should be examined with appropriate toxicokinetic studies.

No data were located concerning whether pharmacokinetics of endosulfan in children are different from adults. Endosulfan has been detected in human placenta and cord blood (Cerrillo et al. 2005; Freire et al. 2011; Mariscal-Arcas et al. 2010), so it is reasonable to assume that it can reach the fetus. Although endosulfan has been detected in human milk (Cerrillo et al. 2005; Çok et al. 2011; Lutter et al. 1998), some 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. Cross-foster studies in animals could provide information regarding differential transfer of endosulfan and/or metabolites through the placenta and the mother's milk. 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, to reduce body burden, or to interfere with the endosulfan's mechanism of action.

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

3.12.3 Ongoing Studies

The following ongoing research was identified in the National Institute of Health (NIH) RePORTER (2012) database. Dr. C.S. Watson from the Department of Biochemistry, School of Medicine at the University of Texas Medical Branch in Galveston, Texas, is studying the mechanism by which environmentally relevant chemicals, endosulfan among them, affect through nongenomic pathways the functions initiated by estradiol at the plasma membrane. The research is sponsored by the National Institute of Environmental Health Sciences.

4. CHEMICAL AND PHYSICAL INFORMATION

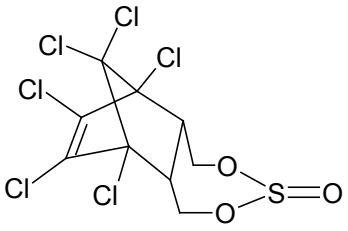
4.1 CHEMICAL IDENTITY

Technical-grade endosulfan contains at least 94% of two pure isomers, α- and β-endosulfan. The α- and β-isomers of endosulfan are present in the ratio of 7:3, respectively (FAO 2011a; Müller et al. 2009). Endosulfan sulfate is a reaction product found in technical endosulfan; it is also found in the environment due to oxidation by biotransformation (Dureja and Mukerjee 1982). The chemical formula, structure, synonyms, and identification numbers for endosulfan, α-endosulfan, β-endosulfan, and endosulfan sulfate are listed in Tables 4-1, 4-2, 4-3, and 4-4, respectively.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of endosulfan, α-endosulfan, β-endosulfan, and endosulfan sulfate are listed in Tables 4-5, 4-6, 4-7, and 4-8, respectively. It should be noted that β-endosulfan is slowly converted to α-endosulfan (Hapeman et al. 1997; Rice et al. 1997).

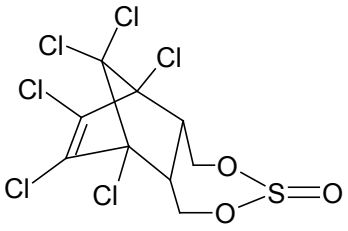
Table 4-1. Chemical Identity of Endosulfan

Characteristic	Information[a]
Chemical name	Endosulfan
Synonym(s)	6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide; Endosulfan technical; 5-Norbornene-2,3-dimethanol-1,4,5,6,7,7-hexachlorocyclic sulfit
Registered trade name(s)	Thiodan; Thionex; Thionate Malix; HOE 2671; FMC 5462; Cyclodan; Thifor; Beosit; Chlorthiepin; Endosulphan[b]
Chemical formula	$C_9H_6Cl_6O_3S$[c]
Chemical structure[e]	
Identification numbers:	
CAS registry	115-29-7[c]
NIOSH RTECS	RB9275000[c]
EPA hazardous waste	P050
OHM/TADS	7216559
DOT/UN/NA/IMDG shipping	2761[c]
HSDB	390
NCI	C00566

[a]All information obtained from HSDB 2012, except where noted.
[b]HSDB 2012; O'Neil et al. 2006
[c]NIOSH 2011

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

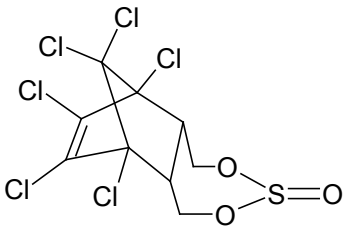
Table 4-2. Chemical Identity of α-Endosulfan

Characteristic	Information
Chemical name	α-Endosulfan[a]
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)-; 5-Norbornene-2,3-dimethanol, 1,4,5,6,7,7-hexachloro-, cyclic sulfite, endo-[b]
Registered trade name(s)	α-Benzoepin; α-Thiodan; β-Thionex[c]
Chemical formula	$C_9H_6Cl_6O_3S$[b]
Chemical structure[e]	
Identification numbers:	
CAS registry	959-98-8[a]
NIOSH RTECS	RB9275100[c]
EPA hazardous waste	No data
OHM/TADS	No data
DOT/UN/NA/IMDG shipping	No data
HSDB	No data
NCI	No data

[a]Tomlin 2003
[b]RTECS 2012; Tomlin 2003
[c]RTECS 2012

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

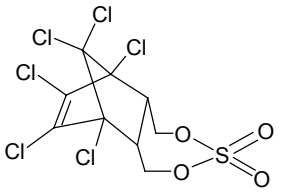
Table 4-3. Chemical Identity of β-Endosulfan

Characteristic	Information
Chemical name	β-Endosulfan[a]
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)-; 5-Norbornene-2,3-dimethanol, 1,4,5,6,7,7-hexachloro-, cyclic sulfite, endo-[b]
Registered trade name(s)	β-Benzoepin; β-Thiodan; α -Thionex[c]
Chemical formula	$C_9H_6Cl_6O_3S$[b]
Chemical structure[e]	
Identification numbers:	
CAS registry	33213-65-9[a]
NIOSH RTECS	RB9875200[c]
EPA hazardous waste	No data
OHM/TADS	No data
DOT/UN/NA/IMDG shipping	No data
HSDB	No data
NCI	No data

[a]Tomlin 2003
[b]RTECS 2012; Tomlin 2003
[c]RTECS 2012

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

Table 4-4. Chemical Identity of Endosulfan Sulfate

Characteristic	Information
Chemical name	Endosulfan sulfate[a]
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; 5-Norbornene-2,3-dimethanol, 1,4,5,6,7,7-hexachloro-, cyclic Sulfate[a,b]
Registered trade name(s)	No data
Chemical formula	$C_9H_6Cl_6O_4S$[a]
Chemical structure[b]	
Identification numbers:	
CAS registry	1031-07-8[a]
NIOSH RTECS	RB9150000[b]
EPA hazardous waste	No data
OHM/TADS	8300205[c]
DOT/UN/NA/IMDG shipping	No data
HSDB	6180[a]
NCI	No data

[a]HSDB 2012
[b]RTECS 2012
[c]OHM/TADS 1989

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

Table 4-5. Physical and Chemical Properties of Endosulfan

Property	Information	Reference
Molecular weight	406.93	O'Neil et al. 2006
Color	Cream to brown; mostly beige	Tomlin 2003
Physical state	Crystalline solid; waxy solid (commercial product)	NIOSH 2011; O'Neil et al. 2006
Melting point:		
Pure	106 °C	O'Neil et al. 2006
Technical	70–100 °C	O'Neil et al. 2006
Boiling point	106 °C	HSDB 2012
Density at 20/4 °C	1.745 g/mL	HSDB 2012
Density for vapor	14	HCDB 1986
Odor:		
α-Endosulfan	Terpene-like; Slight, sulfur dioxide odor	HSDB 2012
Decomposition products	May have a slight odor of sulfur dioxide	HSDB 2012
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25 °C	0.53 mg/L	HSDB 2012
Organic solvents at 20 °C:		
Dichloromethane	200 g/L	Coleman and Dolinger 1982; HSDB 2012; 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}	3.83 (alpha) and 3.62 (beta)	HSDB 2012
Log K_{oc}	4.03 (alpha) and 4.13 (beta)	EPA 2010a
Vapor pressure at 25 ° C	$1x10^{-5}$ mmHg	Coleman and Dolinger 1982; EPA 1982c
Vapor pressure at 25 °C	$1.73×10^{-7}$	HSDB 2012

Table 4-5. Physical and Chemical Properties of Endosulfan

Property	Information	Reference
Vapor pressure at 880 °C	$9x10^{-3}$ mmHg	Maier-Bode 1968; NRCC 1975
Henry's law constant at 20 °C	6.5×10^{-5} atm m^3/mol	HSDB 2012
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data	
Reactivity	Both isomers are slowly hydrolyzed by aqueous acids and alkalis, with the formation of the diol and sulfur dioxide	Tomlin 2003
	α and β isomers are rapidly oxidized by peroxides or permanganate to endosulfan sulfate	HSDB 2012
	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 1995
	Corrosive to iron	O'Neil et al. 2006
	Hydrolyzed rapidly by alkalies	O'Neil et al. 2006
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 4-6. Physical and Chemical Properties of α-Endosulfan

Property	Information	Reference
Molecular weight	406.93	O'Neil et al. 2006
Color:		
Pure	Colorless	HSDB 2012
Technical	Cream to brown, mostly beige	Tomlin 2003
Physical state	Crystalline solid	HSDB 2012
Melting point	108–110 °C	O'Neil et al. 2006
Boiling point	No data	
Density at 20/4 °C Density for vapor	No data	
Odor:	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 22 °C (pH 7.2)	0.15 mg/L	HSDB 2012
Water at 25 °C	0.53 mg/L	HSDB 2012
Organic solvents at 20 °C	No data	
Partition coefficients:		
Log K_{ow}	3.83	HSDB 2012
Log K_{oc}	3.55	HSDB 1999
Vapor pressure at 25 °C	$1x10^{-5}$ mmHg	EPA 1982c
Henry's law constant at 25 °C	$1x10^{-5}$ atm m^3/mol $1.01x10^{-4}$ atm m^3/mol	EPA 1982c 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 °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 4-7. Physical and Chemical Properties of β-Endosulfan

Property	Information	Reference
Molecular weight	406.93	O'Neil et al. 2006
Color	Cream or tan	Tomlin 2003
Physical state	Crystalline solid	Budavari 1996
Melting point	208–210 °C	O'Neil et al. 2006
Boiling point	No data	
Density at 20/4 °C	No data	
Density for vapor		
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 22 °C (pH 7.2)	0.33	HSDB 2012
Water at 25 °C	0.28	HSDB 2012
Organic solvents at 20 °C	Soluble in most organic solvents	O'Neil et al. 2006
Partition coefficients:		
Log K_{ow}	3.62	HSDB 2012
Log K_{oc}	4.1	Verschueren 2001
Vapor pressure at 25 °C	$1x10^{-5}$ mmHg	EPA 1982c
Henry's law constant at 25 °C	$1.91x10^{-5}$ 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 2003
	The β form is slowly converted to the more stable α form at high temperatures	Hapeman et al. 1997; Rice et al. 1997
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 4-8. Physical and Chemical Properties of Endosulfan Sulfate

Property	Information	Reference
Molecular weight	422.95	HSDB 2012
Color	Brown	HSDB 2012
Physical state	Crystalline solid	HSDB 2012
Melting point	181–182 °C 198–201 °C	EPA 1982c; HSDB 2012; White-Stevens 1971
Boiling point	No data	
Density at 20/4 °C Density for vapor	No data	
Odor	Pungent	HSDB 2012
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 22 °C (pH 7.2)	0.22	EPA 1982c; NRCC 1975; OHM/TADS 1989
Water at 25 °C	0.117; 0.22	
Organic solvents at 20 °C	No data	
Partition coefficients:		
Log K_{ow}	3.66	EPA 1979
Log K_{oc}	No data	
Vapor pressure at 25 °C	$1.0X10^{-11}$ mmHg	HSDB 2012
Henry's law constant at 25 °C	$2.61x10^{-5}$ 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 °C	1 ppm=0.058 mg/m^3	Verschueren 1977
mg/m^3 to ppm (v/v) in air at 25 °C	1 mg/m^3=17.29 ppm	Verschueren 1977
Explosive limits	No data	

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

5.1 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 reaction of hexachlorocyclopentadiene and cis-butene-1,4-diol, which forms a bicylic diol, followed by esterification and cyclization with thionyl chloride ($SOCl_2$) (O'Neil et al. 2006). Pure endosulfan is 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 (Müller et al. 2009; FAO 2011a). One degradation or reaction product, endosulfan sulfate, has chemical properties similar to the pure substance and is formed from biotransformation, or oxidation of endosulfan. In the environment, both isomers of endosulfan can be metabolized to endosulfan sulfate by a variety of organisms (EPA 2010a).

As of 2012, there are only four active registrants producing endosulfan products in the United States. These include Makhteshim Chemical Works, Ltd. (Raleigh, North Carolina), Drexel Chemical Company (Memphis, Tennessee), KMG-Bernuth, Inc. (Houston, Texas), and Makhteshim-Agan of North America Inc. (Raleigh, North Carolina). Makhteshim Chemical Works produces technical-grade endosulfan (95%). Drexel Chemical Company produces technical-grade endosulfan (95%), and two emulsifiable concentrates containing 24.6 and 34% endosulfan. KMG-Bernuth produces an emulsifiable concentrate containing 30% endosulfan. Makhteshim-Agan produces two emulsifiable concentrates containing 50 and 33.7% endosulfan (NPIRS 2012). There are several non-U.S. producers of endosulfan (Meister et al. 2011). These producers must register their products with EPA in order to legally import endosulfan products into the United States (EPA 2012a). As a result of a voluntary cancellation and phase-out program, commercial availability of these products in the United States will become completely unavailable by July 31, 2016 (EPA 2012g).

In addition to technical and emulsifiable concentrates available in the United States, the FAO recognizes three other forms of commercial endosulfan that may be available internationally. A dustable powder is a homogeneous mixture of endosulfan and other additives that is fine, free-flowing powder. A wettable powder is a homogeneous mixture that is a fine powder. A miscible oil consists of technical endosulfan, other formulants, and no more than 5% water (FAO 2011a). Like the United States, endosulfan was earmarked for cancellation on a global scale beginning in 2012, after its incorporation into the Stockholm

Convention on Persistent and Organic Pollutants in 2011 (FAO 2011b). Its use in countries adopting this provision is likely to diminish and end completely over the next few years. Continued use of endosulfan products will likely continue in countries that have not adopted this provision.

Few details are available on endosulfan's production volume in the United States. According to the EPA's Reregistration Eligibility Decision (RED) for Endosulfan (EPA 2002), total annual use was estimated at approximately 1.38 million pounds based on survey usage data between 1990 and 1999. The most recent data (2006–2008) indicate total usage in the area of 380,000 pounds annually (EPA 2010a). This is consistent with the general trend of declining use of endosulfan in the United States. These data give a rough estimate of the magnitude of endosulfan production. Since it has been scheduled for cancellation and phase-out, production and usage is expected to decline further.

No information is available in the TRI database on facilities that manufacture or process endosulfan because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 1998c).

5.2 IMPORT/EXPORT

Import and export data for endosulfan were not readily available. EPA regulates and monitors all importing and exporting activities for endosulfan according to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). All importers and exporters of endosulfan products must be registered (EPA 2012a). As of March 2012, there are only four active registrants producing endosulfan products (NPIRS 2012). It is not clear whether these registrants are active importers, exporters, or domestic producers. Although domestic use of endosulfan will end in 2016, FIFRA regulations allow for U.S. producers to export unregistered pesticides (EPA 2012a).

In addition to regulation under FIFRA, endosulfan has been added to the Rotterdam Convention on the Prior Informed Concent (PIC) Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, which the United States is in the process of ratifying (EPA 2012a; FAO 2011b). PIC Convention requirements may require adjustments to the current import and export procedures under FIFRA (EPA 2012a).

5.3 USE

From 2002 to 2012, endosulfan was registered in the United States for restricted (non-residential) use as broad spectrum contact insecticide and acaricide for use on a wide variety of fruits, vegetables, grains, etc. grown for commercial purposes. It is particularly effective against such pests as aphids, fruit worms, beetles, leafhoppers, moth larvae, and whiteflies (EPA 2002, 2010a). The restricted use classification requires that registered products may only be applied by a "certified pesticide applicator" or under the direct supervision of a certified pesticide applicator (EPA 2012b). It is mostly applied as a foliar spray using aircraft or ground equipment, with single application rates ranging from 0.5 to 2.5 pounds of active ingredient per acre (lbs a.i./A) and minimum re-application intervals ranging from 5 to 15 days. Maximum total seasonal or yearly application rates range from 0.5 to 4.0 lbs a.i./A (EPA 2010a).

Beginning July 31, 2012, a voluntary cancellation and phase-out of endosulfan began and is scheduled to end by July 31, 2016. The phase-out will be executed in six phases over this 4-year period. During these phases, use of endosulfan on certain types of crops and products are scheduled to end (EPA 2012a). A detailed schedule of the last use dates for certain crops is included in Table 5-1. The restricted use classification will be maintained throughout the phase-out period.

Historical use trends of endosulfan indicate that its use was declining before the cancellation process was initiated. According to the EPA's RED for Endosulfan (EPA 2002), total annual use was estimated at approximately 1.38 million pounds based on survey usage data between 1990 and 1999 (EPA 2010a). The most prevalent estimated crop uses of endosulfan during this period are summarized in Table 5-2. Approximately 20% of agricultural use consisted of application to cotton crops (USGS 2012a). According to the U.S. Geological Survey (USGS) 2012a pesticide use map for endosulfan, use of endosulfan during the period between 1999 and 2004 was concentrated (≥0.26 lbs per square mile) in the regions of central California, central Washington, southern Idaho, southern Arizona, northeastern Texas, northwestern North Dakota, southeastern Michigan, central Kentucky, northern Tennessee, western New York, southern Pennsylvania, southern New Jersey, eastern North Carolina, southern Georgia, and southern Florida. The most recent data (2006–2008) indicate national usage in the area of 380,000 lbs. a.i. annually (EPA 2010a).

California Department of Pesticide Regulation (CDPR) reported that the state-level use of endosulfan from 2001 to 2010 followed the national trend. In 2001, 153,479 pounds of endosulfan were used over 177,030 acres in the state of California. By 2010, that amount decreased to 35,877 pounds applied to

Table 5-1. Endosulfan Crop Uses and Last Use Dates

Group	Date use ends	Crops being phased out
A	July 31, 2012	Almond, apricot, broccoli, Brussels sprouts, carrots, cauliflower, celery (non-Arizona), citrus (non-bearing), collard greens, dry beans, dry peas, eggplant, filbert, kale, kohlrabi, mustard greens, nectarine (California only), macadamia, plum, prune, poplars grown for pulp and timber, strawberry (annual), sweet potato, tart cherry, turnip, walnut, ornamental trees, shrubs, herbaceous plants Other uses on product labels not listed above or in Group B, C, D, E, or F
B	July 31, 2012	Cabbage, celery (Arizona only), cotton, cucumbers, lettuce, stone fruits not listed in group a, including nectarine (non-California), peaches, sweet cherry, summer melons (cantaloupe, honeydew, watermelon), summer squash, tobacco
C	July 31, 2013	Pear
D	December 31, 2014	All Florida uses of apple, blueberry, peppers, potatoes, pumpkins, sweet corn, tomato, winter squash
E	July 31, 2015	Apple, blueberry, peppers, potatoes, pumpkins, sweet corn, tomato, winter squash
F	July 31, 2016	Livestock ear tags, pineapple, strawberry (perennial/biennial), vegetable crops for seed (alfalfa, broccoli, Brussels sprouts, cabbage, cauliflower, Chinese cabbage, collard greens, kale, kohlrabi, mustard greens, radish, rutabaga, turnip)

Source: EPA 2012g

Table 5-2. 2002 Estimated Annual Agricultural Use of Endosulfan[a]

Crops	Total pounds applied	Percent national use
Cotton	160,060	20.32
Tomatoes	88,607	11.25
Potatoes	87,452	11.10
Apples	62,973	7.99
Tobacco	58,016	7.36
Pears	43,730	5.55
Cucumbers and pickles	34,370	4.36
Lettuce	33,267	4.22
Green beans	28,923	3.67
Squash	28,632	3.63

[a]Represents estimated use over the 5-year period between 1999 and 2004 (refer to USGS 2000).

Source: USGS 2012a

46,513 acres (CDPR 2011). The use data of endosulfan in California from 2001 to 2010 are summarized in Figure 5-1.

Global use of endosulfan is also expected to decline since it has been marked for cancellation after its incorporation into the Stockholm Convention on Persistent and Organic Pollutants in 2011 (FAO 2011b). Its use in countries adopting this provision is likely to diminish and end completely over the next few years. Use of endosulfan products will likely continue in countries that have not adopted this provision.

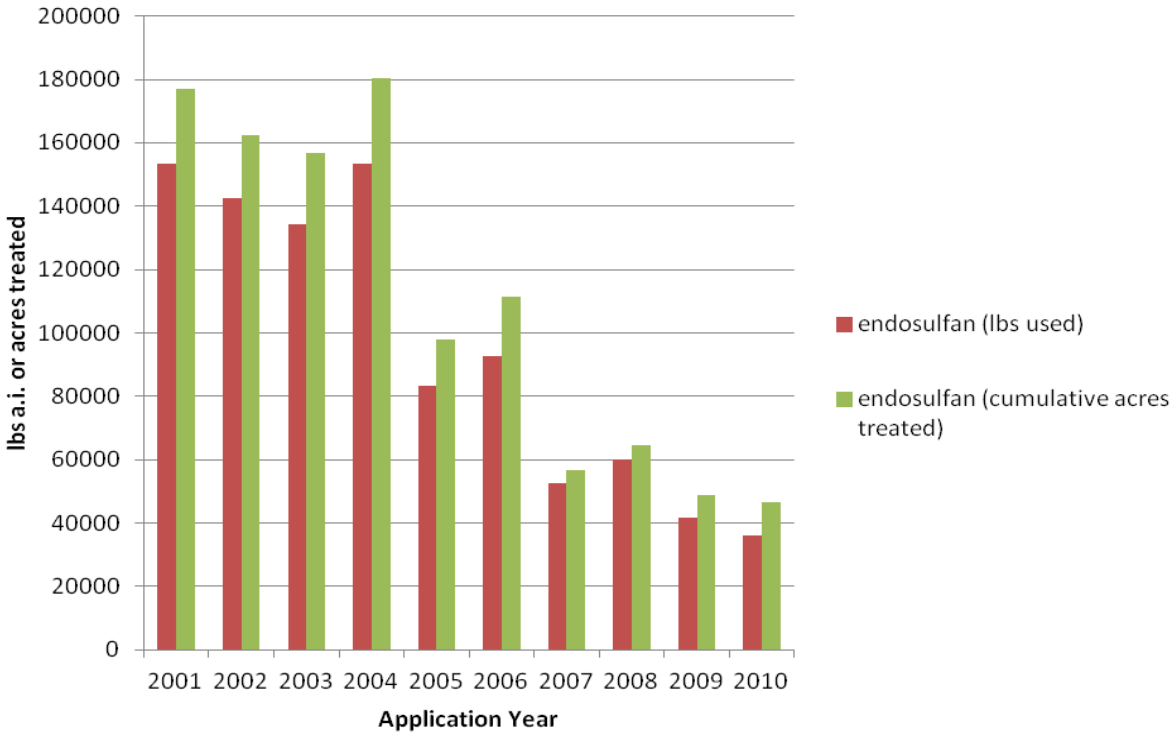
5.4 DISPOSAL

Endosulfan is listed as a hazardous waste under the Resource Conservation and Recovery Act (RCRA), which means that improper disposal of endosulfan products is a violation of federal law (EPA 2001). Disposal of wastes containing endosulfan is controlled by a number of federal regulations (see Chapter 8).

Since endosulfan cannot be used for residential purposes, disposal of this chemical via household hazardous waste programs is not allowed and these programs often prohibit farmers from participating. As a result, many states have enacted Clean Sweep programs, which allow for the safe collection and disposal of pesticide waste from farms, including those that are no longer registered. These programs are often managed by state agencies, but may be funded by various means such as pesticide registration fees, fee-based funds, state funds, EPA grants, participant fees, county funds, in-kind services, and other grants. Several states have permanently funded programs, while others have offered programs for various lengths of time. Most states have held at least one single collection event. Figure 5-2 illustrates which states offer Clean Sweep programs and level of availability (EPA 2001).

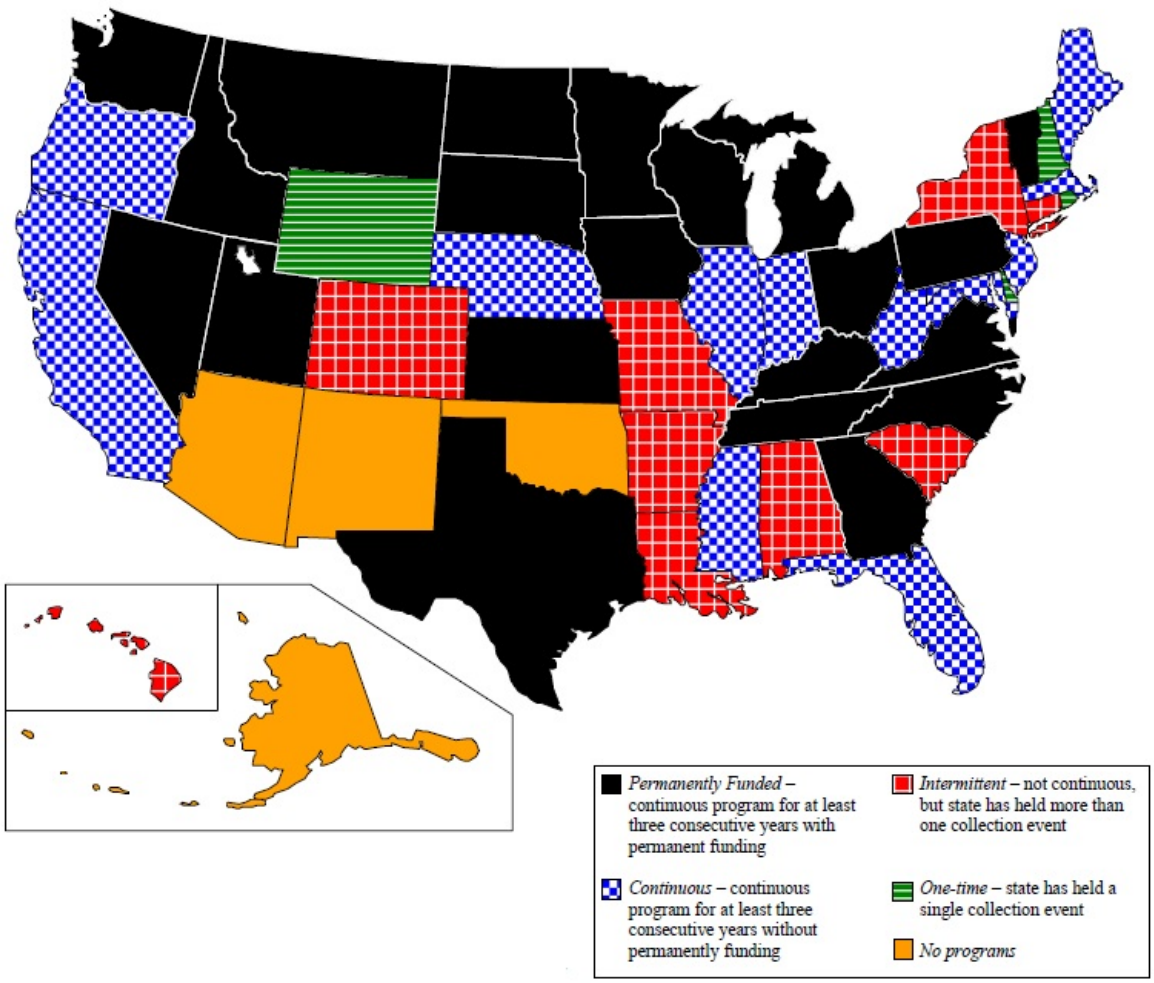
Hazardous wastes, such as endosulfan, are disposed of in high-temperature hazardous waste incinerators or in authorized hazardous waste landfills. In some states, unopened, registered products may be re-used through product exchanges, redistribution tables, and recycling centers (EPA 2001). All registered pesticide products must have storage and disposal instructions included on their label, which must include instructions on how to store, dispose of leftovers, clean an empty container, and dispose of an empty container (EPA 2012c).

Figure 5-1. Endosulfan Use in California



Source: CDPR 2011

Figure 5-2. State Clean Sweep Programs by Category



Source: EPA 2001

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

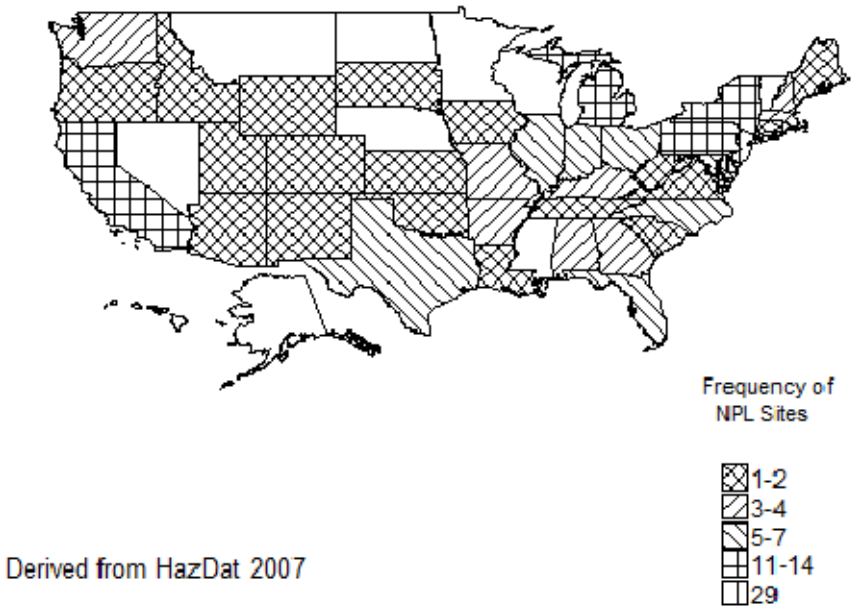
Endosulfan has been identified in at least 176 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for endosulfan is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 174 are located within the United States, 1 is located in Guam, and 1 is located in the Virgin Islands (not shown).

Endosulfan (consisting of 7:3 ratio of α-endosulfan to β-endosulfan) is released to the environment mainly as the result of its use as a restricted-use insecticide. It is not authorized for residential use in the United States. Beginning in July 2012, a voluntary cancellation and phase-out began and is scheduled to be finalized in 2016.

After its release to the environment, endosulfan undergoes a variety of transformation and transport processes. In soil, endosulfan sulfate is the major degradation product from biotic metabolism and is considered to be more persistent than the parent isomers. Neither the α- or β- isomers nor the sulfate are expected to be mobile in soil. Soil erosion, run-off, spray drift, and atmospheric deposition contribute to releases of endosulfan to aquatic ecosystems. In water, hydrolysis to the less toxic endosulfan diol is expected to be the dominant transformation pathway. Volatilization from soil, water, plant surfaces, and transport in dust particles in addition to direct release from spray drift will result in atmospheric levels of endosulfan. Even though monitoring data suggest that most atmospheric endosulfan exists in the vapor-phase rather than the particulate-phase, the relative stability of endosulfan in the atmosphere contributes to its long range transport. Wet deposition of atmospheric endosulfan to remote, high-elevation regions (known as “cold-mountain air trapping”) has been documented in areas of the Sierra Nevada Mountains and the Canadian Rockies. Long-range transport of endosulfan to Arctic regions has been documented and residues have been detected in various Arctic environmental media and biota.

Endosulfan residue concentrations are highest and most prevalent in or nearby regions with intense agricultural activity. Residues have been detected in a variety of media including surface water, sediments, air, aquatic vertebrates, and invertebrates, terrestrial organisms, and in humans. α-Endosulfan, β-endosulfan, and endosulfan sulfate have been detected in a variety of food products during market basket monitoring. Residues are generally higher in fruits and vegetables versus processed foods. As a result, dietary intake is expected to be the major route of exposure to the general adult population and children.

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



The presence of endosulfan residues in placenta, cord blood, and breast milk suggests that pre- and post-natal exposure may occur. However, farm workers are expected to have the highest levels of exposures. Estimated risk levels were high for almost all occupation exposure scenarios associated with pesticide handlers. Exposures associated with post-application scenarios (e.g., cutting, weeding) are also expected to be high.

6.2 RELEASES TO THE ENVIRONMENT

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

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).

6.2.1 Air

There is no information on releases of endosulfan to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

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 aerial spray, ground spray, and airblast. The direct release to the atmosphere is commonly a result of spray drift,

which immediately contaminates the air surrounding the application area. Volatilization and wind suspension occurring from post-application periods can also be a source of endosulfan in air. Atmospheric endosulfan derived from these sources has the potential to contribute to regional and long-range transport (EPA 2010a). Endosulfan was identified in air samples at two current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.2 Water

There is no information on releases of endosulfan to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

Endosulfan is most commonly released to water by atmospheric deposition, spray drift, runoff, and erosion. Direct release to water bodies is restricted and application restrictions require a buffer distance of 300 feet from surface waters for aerial application and 100 feet for ground application. In California, the buffer is 300 feet for both types of applications (EPA 2010a). Endosulfan is not expected to leach through soil to groundwater based on its low water solubility and its tendency to absorb to soil (EPA 2010a; HSDB 2012). Endosulfan was detected in groundwater and surface water at 105 and 27 current or former NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2007).

6.2.3 Soil

There is no information on releases of endosulfan to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

The main routes of release of endosulfan to soils are direct application to crops and atmospheric deposition from spray drift, volatilized material, or from long-range atmospheric transport (EPA 2010a). Endosulfan was detected in soil and sediment at 170 and 37 current or former NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

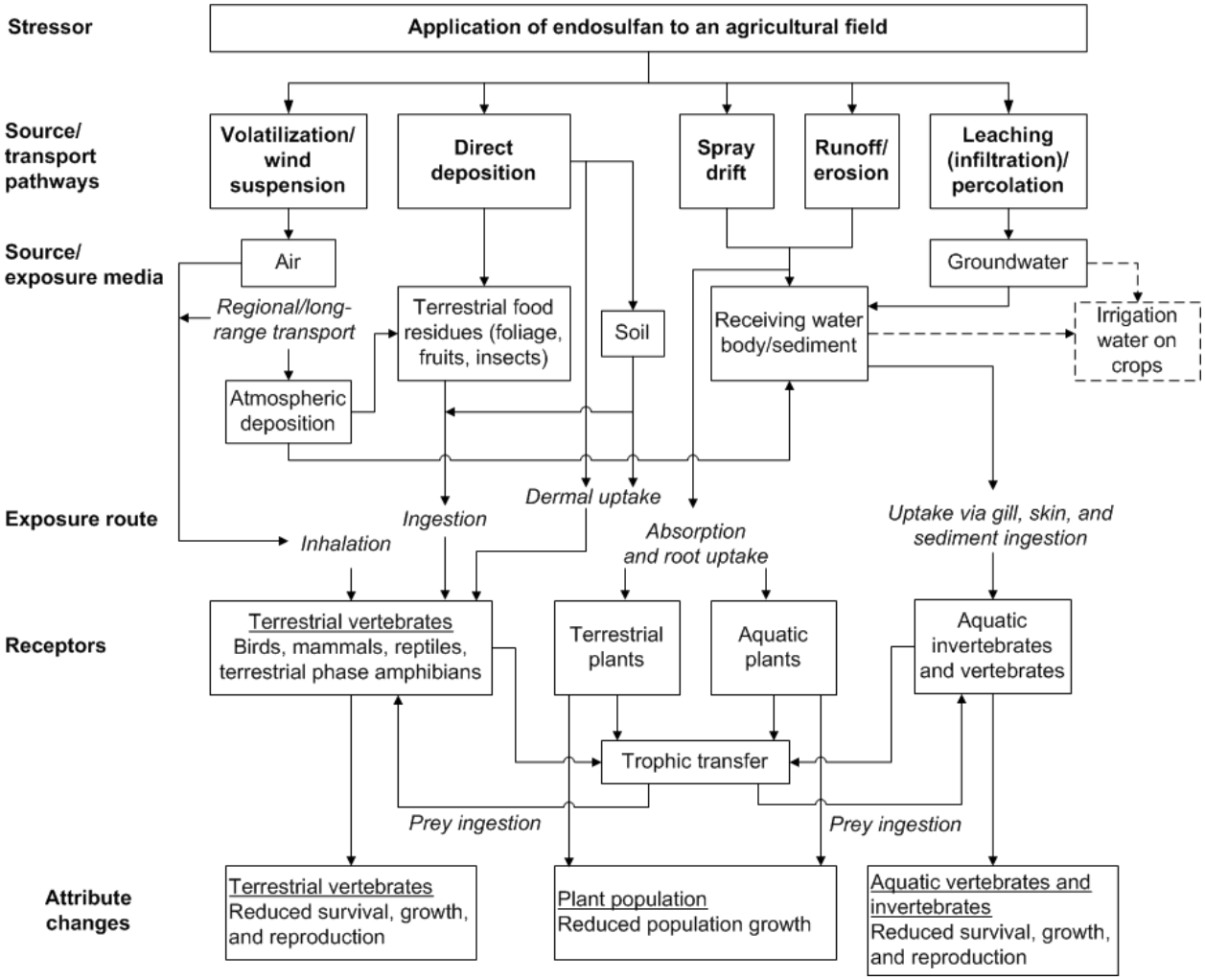
6.3.1 Transport and Partitioning

Endosulfan isomers and endosulfan sulfate are found throughout the environment in various media due to its widespread use, physical properties, and relative persistence. Figure 6-2 contains a conceptual model of how endosulfan moves between environmental compartments starting from field application to potential ecological receptors (EPA 2010a). However, transport and partitioning of endosulfans can be complex and depends greatly on environmental conditions (Weber et al. 2010).

Endosulfan is applied directly to soil through application to crops by either aerial or hand-spray. Measured K_{oc} values (average for four soils) for α- and β-isomers were 10,600 and 13,500 mL/g, respectively, indicating limited mobility in soil (EPA 2010a). Therefore, leaching to groundwater is not expected to be a concern. This is supported by available groundwater monitoring data, which indicate very low rates of detection in extensive groundwater monitoring programs (USGS 2012b). Model field studies also support this conclusion. 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 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). Endosulfan is metabolized in soil to endosulfan sulfate, which is also expected to be immobile based on its estimated K_{oc} of 9,800 (EPA 2010a).

Although it is not applied directly or in the vicinity of water bodies, endosulfan is transported to water via spray drift or atmospheric deposition, or through soil runoff and erosion (EPA 2002, 2010a). Endosulfan has been regularly detected in surface water samples taken from South Florida canals that drain agricultural areas (Harman-Fetcho et al. 2005; Pfeuffer 2011; Scott et al. 2002). Endosulfan transported to water is expected to eventually partition to sediments (EPA 2010a; Weber et al. 2010). However, estimated log air/water partition coefficients for α- and β-endosulfan and endosulfan sulfate ranging from -3.56 to -4.78 indicate that volatilization from water to air is expected to occur, and these chemicals can be considered semi-volatile (EPA 2010a). In a field dissipation study, volatilization was considered to be the dominant route of dissipation for endosulfan and endosulfan sulfate in cotton fields of sub-tropical India. High temperatures and low rainfall were likely influential factors for this behavior (Kathpal et al. 1997). Volatilization of α-endosulfan accounted for 34.5% of total losses from freshly tilled soil during another field study, while volatilization losses of β-endosulfan were much less (14.5%), indicating that

Figure 6-2. Conceptual Model of the Potential Effects of Endosulfan Application on Ecological Receptors



Note: Endosulfan is expected to absorb strongly to soils and is not likely to leach to groundwater.

Source: Adapted from EPA 2010a

the β-isomer is less volatile than the α-isomer (Rice et al. 2002). Volatilization from plant surfaces is also expected to occur, and may be more significant than from soil surfaces. 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). 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 °C, suggesting a beta- to alpha- conversion (Rice et al. 1997). This conversion would also contribute to total volatilization losses of endosulfans from treated fields.

Because of its semi-volatile nature and relative stability in the atmosphere, endosulfan is susceptible to long-range transport in the environment (Weber et al. 2010). These transport and deposition processes can be localized, regional, or long-range. Atmospheric deposition rates of endosulfans (α-, β-, and sulfate) were estimated in the agricultural intensive Choptank River watershed of the Chesapeake Bay region. Total wet deposition (± combined absolute and relative error) for α-endosulfan was estimated at 0.96 ±0.1 kg/year. Estimated depositions for β-endosulfan and endosulfan sulfate were 2.7±0.3 and 0.5±0.06 kg/year, respectively. Deposition processes can be regional in nature. For example, probabilistic source contribution function (PSCF) modeling performed by Hafner and Hites (2003) suggests that atmospheric endosulfans in the Great Lakes Region are generated in the lower Michigan peninsula, and New York State, and to a lesser extent Pennsylvania.

Regional transport of endosulfans to remote, non-agricultural areas has been documented. Endosulfan residues have been detected in air, snow, rain, lichen, surface water, and sediment samples from Yosemite National Park, California. West to east atmospheric movement of these residues from the agricultural San Joaquin Valley is the likely source. Estimated winter and summer deposition rates of endosulfans (α-, β-, and sulfate) were calculated from data collected during the spring and summer of 2009. Winter deposition was estimated at 1.11 $\mu g/m^2$ with 72% of the total deposition occurring during this season. Summer deposition was estimated at 0.44 $\mu g/m^2$ making the total annual deposition 1.55 $\mu g/m^2$. The dominance of winter deposition is due to the fact most of the precipitation in this region occurs as snow (Mast et al. 2012a, 2012b). Long-range transport to remote regions is evident in the numerous studies that have monitored endosulfan in Arctic environmental media (Hageman et al. 2006a; Hung et al. 2005, 2010; Stern et al. 2005; Weber et al. 2010). Like other organochlorine pesticides in Arctic areas, α-endosulfan has been observed to undergo a “spring maximum event”, where air concentration peaks in the spring (April/May) and again in the fall (October/November). This is different from seasonal trends observed in temperate regions where air concentrations peak in the summer months (Hung et al. 2005).

Organochlorine pesticides like endosulfan undergo a phenomenon known as "cold mountain trapping" where cold temperatures (leading to condensation) and high precipitation rates of high-elevation areas in temperate regions cause increased deposition (mostly through snow) (Daly et al. 2005). This phenomenon for endosulfan has been noted in the results of monitoring activities in National Parks in western United States (Hageman et al. 2006a), in Yosemite National Park (Mast et al. 2012a, 2012b), and in National Parks of western Canada (Daly et al. 2007) (see Section 6.4).

Bioaccumulation and biomagnification potential of endosulfan in organisms varies, but generally suggests that it has the potential to bioaccumulate in organisms and biomagnify in the food webs. This potential has been extensively investigated in aquatic organisms. EPA's Ecological Fate and Risk Assessment for Endosulfan (2010a) extensively summarized experimental bioconcentration factors (BCFs) and bioaccumulation factors (BAFs) for aquatic organisms available in the scientific literature. BCF values ranged from 17.1 to 11,583 in fish species (Hansen and Cripe 1991; Jonsson and Toledo 1993; Schimmel et al. 1977; Toledo and Jonsson 1992; Rajendran and Venugopalan 1991). However, values from Hansen and Cripe (1991) and Schimmel et al. (1977) that met quality screening criteria were 1,146 (in sheepshead minnow for α- and β-isomers) and 2,755 (in striped mullet for α- and β-isomers and endosulfan sulfate). Experimental BCF values in aquatic invertebrates (shrimp, mussel, oyster, clam, and crayfish) ranged from 12 to 600 (EPA 2010a; Ernst 1977; Naqvi and Newton 1990; Rajendran and Venugopalan 1991; Roberts 1972; Schimmel et al. 1977). Mesocosm and microcosm bioaccumulation studies reported BAF values similar in range to BCF values ranging from 115 to 1,262 in Bluegill fish, water flea, green algae, oyster, and macrophytes (DeLorenzo et al. 2002; EPA 2010a; Pennington et al. 2004; and unpublished industry studies). BAF is similar to BCF except that BAF takes into account multiple routes of exposure and not just intake from gills. Weber et al. (2010) summarized BAFs based on monitoring data reported for Arctic aquatic fish and mammals. Wet weight BAF values (for α- and β-isomers and endosulfan sulfate) were 1,690 (Arctic char), 7,280 (salmon), and 3,260 (Arctic cod). Lipid weight BAFs (for α- and β-isomers and endosulfan sulfate) were 1.45×10^5 (whole salmon), 3.13×10^5 (whole Arctic cod), 6.76×10^5 (female beluga blubber), 5.65×10^5 (male beluga blubber), 2.21×10^5 (female ringed seal blubber), 2.41×10^5 (male and female ringed seal blubber), and 2.98×10^4–3.52×10^4 (Arctic char muscle). Biomagnification factors (BMFs) were 2.2 for cod to beluga, 1.5 for salmon to beluga, and 0.77 for cod to seals. BMF values represent the ratio of the level of chemical in the predictor versus the concentration in its diet and BMF values greater than 1 indicate a potential to biomagnify up the food web. However, these BMF values may be overestimated since they do not account for metabolism.

Assessing the bioconcentration and biomagnification potential in terrestrial organisms is difficult. Kelly et al. (2007) estimated BMFs for air-breathing organisms ranging from 4.9 to 23 for β-endosulfan. However, this model did account for metabolism. Armitage and Gobas (2007) suggest that application of soil-earthworm-shrew food-chain model illustrates that chemicals with log $K_{oa} \geq 5.25$ and logK_{ow} values ranging from 1.75 to 12 may biomagnify given that they are not rapidly metabolized (half-life ~2.5 days). Estimated logK_{oa} values are 6.41 for both isomers and 8.45 for endosulfan sulfate. A measured log K_{oa} value for both isomers is reported at 8.64 (EPA 2010a). Analyses of two cases of intentional endosulfan poisoning reported terminal half-lives in blood serum of 15.2 hours (from 35% endosulfan formulation) and 8.8 hours (endosulfan content unknown) (Eyer et al. 2004). These half-lives suggest that metabolism of endosulfan may significantly attenuate biomagnification in the terrestrial food chain, based on the Armitage and Gobas model. Although there is a lack of comprehensive, standard biological monitoring data in humans, a variety of endosulfan metabolites (-sulfate, -ether, -lactone, -diol) have been detected in adipose tissue, placenta, cord blood, and breast milk of women at nanoscale concentrations. It is unclear the role of continuous, low-dose exposures and metabolism play in these concentrations (Cerrillo et al. 2005). At the very least, these data indicate that human metabolism of endosulfan occurs and may be complex.

6.3.2 Transformation and Degradation

6.3.2.1 Air

The α- and β-isomers of endosulfan are considered to be stable to direct photolysis in the atmosphere because they do not absorb light at wavelengths >300 nm (EPA 2010a). Photolysis of endosulfan isomers has been observed under laboratory conditions using polar solvents and various surface media, but these results are not likely to be relevant in atmospheric conditions. The α-isomer undergoes isomerization to the β-isomer, which is relatively more stable (Dureja and Mukerjee 1982). Both isomers undergo oxidation to endosulfan sulfate via several processes in the environment. Vapor-phase α- and β-endosulfan are expected to be photooxidized by hydroxyl radicals in the atmosphere. The half-life for this reaction has been estimated at about 2 days, assuming a hydroxyl radical concentration of $5x10^5$molecules per cm^3 and 12-hour days for both isomers. Reaction of α- and β-endosulfan isomers with atmospheric ozone has been estimated to have a half-life of about 320 days, assuming an ozone concentration of $7x10^{11}$ molecules per cm^3. Direct photolysis data for endosulfan sulfate are conflicting. Observations from field studies suggest photolysis may play a role in endosulfan sulfate disappearance. A half-life of about 4 days was estimated for reaction with hydroxyl radicals (EPA 2011a).

6.3.2.2 Water

Endosulfan undergoes hydrolysis to endosulfan diol in surface water and groundwater. The rate of hydrolysis is influenced by pH, and the values reported in the literature vary somewhat. 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 35.4 and 37.5 days, respectively. At pH 5.5, the half-lives were 151 and 187 days, respectively. In the presence of ferric hydroxide, hydrolysis rates increased at pH 7 and 20 °C (Greve and Wit 1971). 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. At pH 5, the half-lives were 54 and 51 days, respectively. At 20 °C 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 hydrolysis half-life of α- and β-endosulfan at pH 5 was >200 days, while the half-life at pH 7 was 11 days for α-endosulfan, 19 days for β-endosulfan, and 184 days for endosulfan sulfate. The major degradation product was endosulfan diol, which is considered to be less toxic than the parent compounds or endosulfan sulfate (EPA 2010a).

Endosulfan degradation in a water-sediment system was analyzed in a European study submitted to the EPA by a registrant. The Ohlau system consisted of water at pH 6.8 and sand sediment at pH 6.1 (0.1% organic carbon) and conducted for 120 days at 20ºC. Despite deficiencies concerning test substance purity and stated redox potential, results were considered acceptable in characterizing endosulfan in an aquatic system featuring an aerobic water column and anaerobic sediment. Data indicated relatively rapid transformation of the endosulfan isomers to the endosulfan diol, presumably by hydrolysis (half-lives ranging from 11 to 16 days). Within a month, the endosulfan parents degraded to about 10% of the nominal amount and the diol reached its maximum formation of 35%. Subsequently, the formation of degradates is dominated by the hydroxyl carboxylic acid (44% after 120 days) and endosulfan sulfate (25% after 120 days). Endosulfan sulfate was presumed to be formed by oxidation in the anaerobic sediment, and did not appear to decline after 50 days (EPA 2010a).

Biotic and abiotic transformations of endosulfan in seawater/sediment microcosms have been reported by Cotham and Bidleman (1989). In biotic tests, half-lives for α- and β-endosulfan 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, the half-life for α-endosulfan was 2–3 days, whereas the half-life for β-endosulfan 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 α- and β-endosulfan, respectively. Endosulfan diol was the main metabolite identified.

6.3.2.3 Sediment and Soil

Biodegradation of endosulfan isomers to endosulfan sulfate is expected to be the dominant fate pathway in soils (EPA 2010a). 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 (20 °C) 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 α- and β-endosulfan, respectively (Miles and Moy 1979). The predominant formation of endosulfan diol in aquatic systems may indicate hydrolytic degradation rather than biodegradation.

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 4 times slower than in culture media; only 50% of the material (initially at 50 ppm) was degraded in 4 weeks (Awasthi et al. 1997). In an aerobic soil metabolism study using five different soils, half-lives of α-endosulfan ranged from 35 to 67 days and half-lives of β-endosulfan ranged from 104 to 265 days with endosulfan sulfate as the major metabolite. Endosulfan sulfate showed no clear signs of degradation. In a two-phase, two-soil anaerobic study, α-endosulfan anaerobic half-lives were 105 and 124 days and β-endosulfan half-lives were 136 and 161 days (EPA 2010a).

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 α- and β-endosulfan were reported to be 60 and 800 days, respectively. In a field study conducted from 1989 to 1990 in northern India, dissipation (which can include multiple fate pathways) 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. The 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 °C at field capacity moisture level (Kathpal et al. 1997). In field dissipation studies submitted to EPA, the half-life of α-endosulfan (encompassing transport and degradation in the soil surface layer) was 46 days in a Georgia tomato field, 70 days in a California cotton field and 6–11 days in a separate California cotton field. The half-life for β-endosulfan was 90 days in a Georgia tomato field, and 103 and 19–63 days in the respective California cotton fields. Endosulfan sulfate was the dominant degradation product (EPA 2010a).

6.3.2.4 Other Media

Numerous studies have demonstrated that endosulfan is oxidized to endosulfan sulfate on plant surfaces and in soils. Initial residues of endosulfan on treated vegetables generally range from 1 to 100 mg/kg. However, residue levels typically decrease to <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).

6.4 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. Concentrations of endosulfan in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 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. The analytical methods available for monitoring endosulfan in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Endosulfan has been included in air monitoring programs and in many air monitoring studies conducted within the last 10 years. Results from these studies establish endosulfan as an air contaminant not only in agricultural areas, but in rural, mountainous, and Arctic regions.

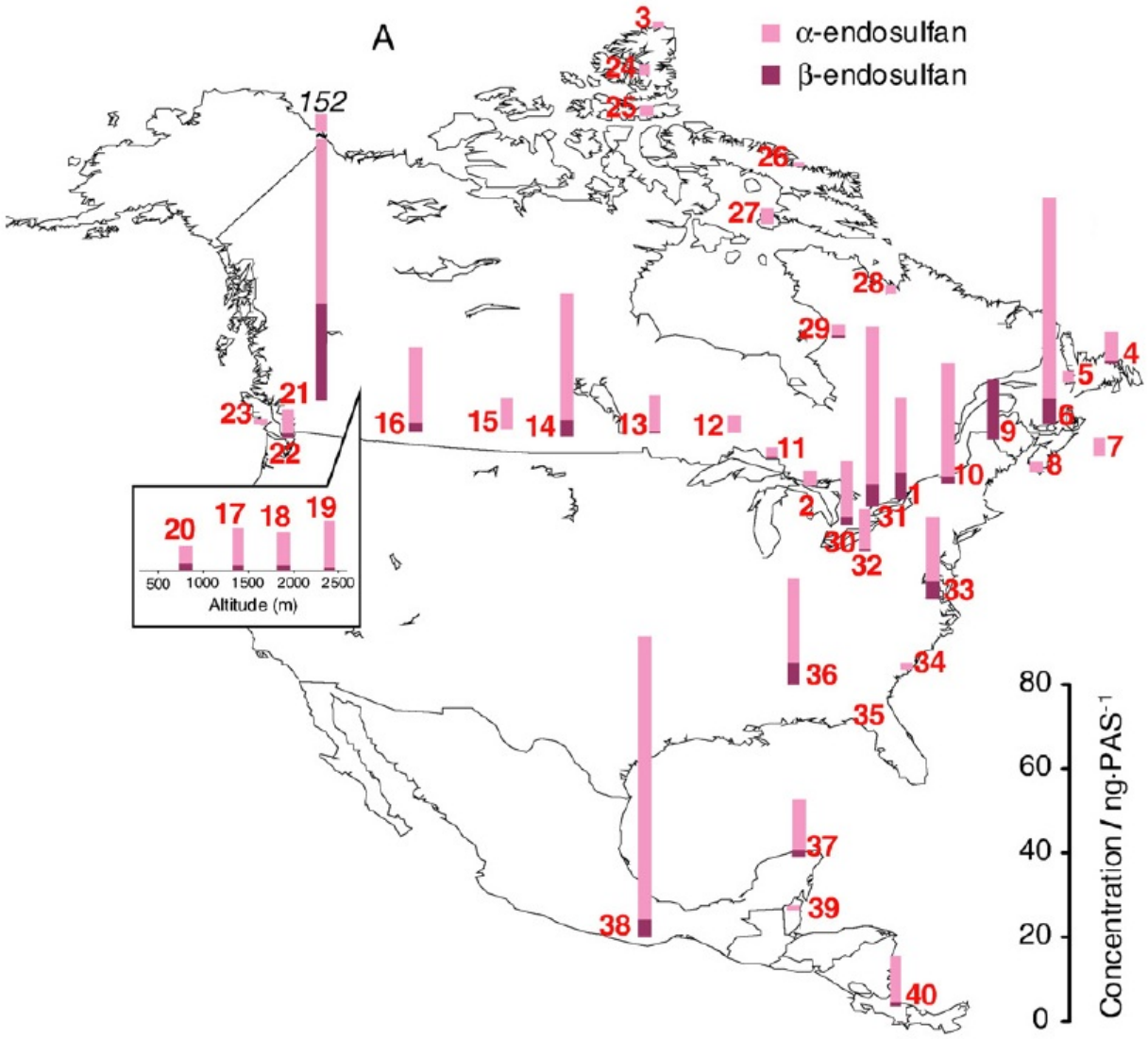
Many studies have established α-endosulfan as one of the most prevalent organochlorine pesticides in the Arctic region (Weber et al. 2010). Results from the Arctic Monitoring and Assessment Program (AMAP) analyses of pesticide concentrations sampled from various sites in the Arctic region at various times between 1993 and 2006, indicate endosulfan undergoes long-range atmospheric transport. Sampling stations were located in Canada, Finland, Iceland, Svalbard/Norway, Russia, United States, and Greenland. Endosulfan was measured in Alert, Canada at average air concentrations ranging from 3.3 pg/m^3 in 1993 to 6.5 pg/m^3 in 2003. Concentrations sampled at Nuuk, Greenland between 2004 and 2005 averaged 4.8 pg/m^3. Similar average concentrations were reported at the Russian Arctic stations. The Yukon region in the Canadian Arctic reported the highest average concentrations of endosulfan at 8.3 pg/m^3 at Tagish in 1994 and Little Fox Lake in 2002–2003 (Hung et al. 2010). Like other organochlorine pesticides, α-endosulfan has been observed to undergo a "spring maximum event" at several Arctic sampling stations, where air concentration peaks in the spring (April/May) and again in the fall (October/November). This is different from seasonal trends observed in temperate regions where air concentrations peak in the summer months (Hung et al. 2005).

Shen et al. (2005) mapped air concentrations of α- and β-endosulfan collected from XAD passive air samplers from 2000 to 2001 located across North America. This map is featured in Figure 6-3.

Endosulfans were detected in outdoor air sampled from three mountainous national park locations in Canada. Passive air samples were taken from sites within Mount Revelstoke National Park in British Columbia, Yoho National Park in British Columbia, and Observation Peak in Banff National Park, Alberta. All three areas lay west of land used for agriculture, but the land in the immediate vicinity of the sampling sites had limited to no agricultural use (Daly et al. 2007).

In 2001, ground level and mid-troposphere (~4,400 m) air samples were collected from the Fraser Valley, British Columbia and analyzed for endosulfan (α- and β-isomers). Ground level samples were taken from rural and urban areas, and mid-troposphere samples were obtained during flight times in aircraft.

Figure 6-3. α- and β-Endosulfan Concentrations Sampled in North America Between 2000 and 2001*



*Collected from XAD passive air samplers

Sources: Shen et al. 2005; Weber et al. 2010

Concentrations of the two isomers in rural areas ranged from ~18 to ~82 pg/m^3, with the exception of a period where concentrations exceeded 250 pg/m^3 for several days. This was attributed to high local use of endosulfan products. Concentrations in urban areas were less variable and ranged from ~4 to ~62 pg/m^3. Endosulfans were consistently below the detection limits in the high altitude samples, and therefore, possible trans-pacific movement of atmospheric endosulfans could not be discussed. The authors suggested that the low detection may be attributed to the low temperatures (0 °C) in the troposphere, which would result in partitioning to particulate matter (Harner et al. 2005).

Total endosulfans (α-, β-, and sulfate) were detected in passive air samplers located within the Global Atmospheric Passive Sampling (GAPS) network, which included polar sites (n=4), background sites (n=16), urban sites (n=6), and rural/agricultural sites (n=12) located worldwide. Sampling took place between December 2004 and March 2005. Endosulfan concentrations were highest compared to other organochlorine pesticides tested. Concentrations were highly variable, ranging from tens to hundreds of pg/m^3, the geometric mean was 58 pg/m^3. The α-isomer was the most abundant in the samples, accounting for ~90% of total endosulfans. Results for β-endosulfan and endosulfan sulfate were often below the detection limit. Concentrations were highest in tropical regions where regional applications and greater soil to air exchanges due to temperature may have occurred (Pozo et al. 2006).

Concentrations of endosulfans (α- and β-isomers and endosulfan sulfate) in air were measured by Hoh and Hites (2004) at four sampling sites located in four states in order to model potential sources. Samples were collected from Sleeping Bear Dunes National Lake Shore in Michigan, Bloomington, Indiana, Rohwer, Arkansas, and Cococrie, Louisiana between 2002 and 2003. The results are presented in Table 6-1. Both Michigan and Indiana sites experienced spikes in endosulfan concentrations during July and August, presumably from local application. Applying the Potential Source Contribution Function (PCSF) model to the results, a large potential source region of endosulfan running from Kentucky, Tennessee, Alabama, and Florida was identified. With the exception of Alabama, these results correlated well with known regional use patterns. Modeling results did not indicate any potential sources west of the sampling sites.

Sun et al. (2006) measured gas phase and particulate phase α- and β-endosulfan in air from seven sampling sites in the Great Lakes region between 1996 and 2003. Samples were taken from sites within the Integrated Atmospheric Deposition Network (IADN), with five of the seven sites located in rural areas. Mean gas phase concentrations from these sites are included in Table 6-2 and mean particulate phase concentrations are included in Table 6-3. Calculated half-lives for gas phase α-endosulfan at these

Table 6-1. Endosulfan (α-, β-, and -sulfate) Concentrations (pg/m^3) in Air Sampled in Michigan, Indiana, Arkansas, and Louisiana

State	Arithmetic mean (± standard error)	Temperature corrected mean (± standard error)[a]	Median	Range	Number
Michigan	142±45	100±18	37	0.56–1,200	42
Indiana	260±70	95±10	79	2.7–2,000	44
Arkansas	100±20	43±4	60	4.7–390	44
Louisiana	100±20	23±6	52	3.6–480	43

[a]Corrected by Clausius-Clapeyron regression

Source: Hoh and Hites 2004

Table 6-2. Average Concentrations of Gas-Phase α- and β-Endosulfan in Air from the Great Lakes Region

	α-Endosulfan		β-Endosulfan	
Site	Average concentration (pg/m^3; ± standard error)	Number of detects	Average concentration (pg/m^3; ± standard error)	Number of detects
Brule River	23±3.8	177	2.1±0.4	113
Eagle Harbor	27±3.6	250	2.2±0.32	153
Sleeping Bear Dunes	86±14	223	8.9±1.3	193
Sturgeon Point	110±11	272	9.5±1.0	213
Chicago	72±9.2	211	6.0±0.75	143
Burnt Island	21±2.8	312	2.6±0.41	276
Point Petre	110±22	385	24±4.3	347

Source: Sun et al. 2006

Table 6-3. Average Concentrations of α- and β-Endosulfan Particulates in Air from the Great Lakes Region

	α-Endosulfan		β-Endosulfan	
Site	Average concentration (pg/m^3; ± standard error)	Number of detects	Average concentration (pg/m^3; ± standard error)	Number of detects
Brule River	3.6±0.24	171	1.1±0.19	120
Eagle Harbor	4.2±0.22	201	1.1±0.16	134
Sleeping Bear Dunes	11±3.6	201	4.0±1.0	169
Sturgeon Point	7.8±0.83	209	3.7±0.47	195
Chicago	5.6±0.31	199	3.3±0.40	161

Source: Sun et al. 2006

locations ranged from 8.2 to 19 years for four of seven sites (results were not statistically significant for other sites). Particulate phase α-endosulfan half-lives ranged from 3.4 to 8.1 years for five of the seven sites (data were not available for the other sites). Calculated half-lives for gas phase β-endosulfan ranged from 3.2 to 9.7 years and particulate phase half-lives ranged from 3.0 to 8.0 years for five of the seven sites (data were not available for the other sites). These half-lives are based on a regression of the temporal trends of the endosulfan levels at these locations and are not to be confused with the estimated atmospheric photooxidation half-lives of α- and β-endosulfan. High outlier concentrations were observed during summer months, and were likely due to agricultural use. Results indicated that endosulfan concentrations (both isomers) increased from the western Great Lakes Region to the eastern region, possibly due to regional use patterns. Particulate α-endosulfan concentrations declined compared to concentrations recorded in previous years. It was not clear whether usage patterns in the region contributed to this declining trend.

α-Endosulfan, β-endosulfan, and endosulfan sulfate were detected in residential indoor air sampled (n=52) as a part of the Arizona Border Study (NHEXAS-AZ), which collected samples from sites in the Yuma, Nogales/Naco, and Douglas areas. These three testing sites had varied geographies and land use. The Yuma area is highly agricultural with a history of pesticide use. The Douglas area is mountainous with a history of mining and smelting. The Nogales/Naco area is a border town with industrial activity prevalent across the border in Mexico. α-Endosulfan averaged 190 ng per 4 standard semipermeable membrane devices (SMPDs), with a range of 10–1,600 ng per 4 SMPD and an 85% detection rate. β-Endosulfan averaged 87 ng per 4 SMPDs, with a range of 3.7–490 ng per 4 SMPD and an 89% detection rate. Endosulfan sulfate averaged 48 ng per 4 SMPDs, with a range of 19–100 ng per 4 SMPD, but a significantly lower detection rate of 5% (Gale et al. 2009).

6.4.2 Water

Endosulfan is monitored extensively in surface water and groundwater through various state, regional, and national programs. Studies analyzing rainwater, snow, and runoff from across the United States have also been published.

The USGS National Water Quality Assessment (NAWQA) program began in 1991 and obtains water quality data from 51 basins nationwide. These basins include approximately 7,300 surface water sites and 9,800 groundwater wells. Consistent with evidence that endosulfan will adsorb to soil, the available NAWQA groundwater samples obtained between 2002 and 2011 revealed an extremely low detection

rate (0.12%) for α-endosulfan and endosulfan sulfate and no detection of β-endosulfan. Only 10 samples collected during this period reported measured or estimated concentrations at levels above detection limits (see Table 6-4). A similarly low rate of detection in surface water and bed sediment was observed for samples obtained between 2006 and 2011. Results from samples containing concentrations above detection limits are summarized in Table 6-5. It is important to note that endosulfan is expected to hydrolyze in aquatic environments to endosulfan diol, which is not analyzed in these samples.

In 2010, EPA published an ecological fate and risk assessment report that summarized the extensive water monitoring data available from NAWQA, EPA's STORET database, California's Department of Pesticide Regulation (CDPR) Surface Water Protection Program Database, and the South Florida Water Management District (SFWMD) DBHydro database, among others. Combining the data from these sources, EPA illustrated regional and national trends of endosulfan presence in U.S. waters over the period of almost 20 years (EPA 2010a).

In south Florida, endosulfan levels in agricultural runoff were analyzed by sampling surface water concentrations in the extensive canals that drain urban and agricultural areas. These canals are managed by the SFWMD. Samples were collected between 1993 and 1997. Average endosulfan concentrations ranged from 9 to 99 ng/L during this period. Using more sensitive analytical methods for samples obtained between 1996 and 1997, endosulfans were detected at a rate of 100% with a peak concentration of 477 ng/L (Scott et al. 2002).

Further analysis of the SFWMD data from 1992 through 2007 by Pfeuffer (2011) revealed several trends concerning endosulfan concentrations in south Florida canals. Surface water concentrations in selected basins for this period are summarized in Table 6-6. Endosulfans were detected in sediment samples taken from South Miami-Dade County (n=142). Endosulfan sulfate had the highest concentration among the three endosulfans in this basin, with an average of 16 µg/kg (25 detections), and a maximum concentration of 120 µg/kg. α-Endosulfan had an average concentration of 6 µg/kg (17 detections) and a maximum of 30 µg/kg. β-Endosulfan had an average concentration of 5 µg/kg (24 detections) and a maximum of 24 µg/kg. Endosulfan has been identified as a chemical of concern in the South Miami-Dade County agricultural area, but the frequency and magnitude of endosulfan detections have decreased since the 1994–1995 growing seasons.

Table 6-4. α-Endosulfan and Endosulfan Sulfate Detected in Groundwater Sampled for the USGS National Water Quality Assessment Between 2002 and 2011[a,b]

State	County	Well depth (ft)	Land use	Well type	Result date	Chemical	Concentration (µg/L)
Alabama	Mobile	68.4	RC	Urban	06/10/2011	α-Endosulfan	0.0066
New Jersey	Monmouth	32	RC	Urban	08/11/2011	α-Endosulfan	0.0165
New Jersey	Camden	32	RC	Urban	07/25/2011	α-Endosulfan	0.01
New Jersey	Camden	37	RC	Urban	07/13/2011	α-Endosulfan	0.0046
New Jersey	Camden	11	RC	Urban	08/18/2011	α-Endosulfan	0.0064
Virginia	Fairfax	120.43	RC	Urban	08/17/2011	α-Endosulfan	0.0074
Alabama	Mobile	68.4	RC	Urban	06/10/2011	Endosulfan sulfate	0.0042
New Jersey	Cumberland	148.5	NA	Other	05/21/2009	Endosulfan sulfate	0.0068[c]
New York	Suffolk	25	RC	Urban	08/23/2006	Endosulfan sulfate	0.0134[c]
New York	Suffolk	254.5	NA	Other	07/24/2007	Endosulfan sulfate	0.0061[c]

[a]Data represent only samples with concentrations above the detection limits tested during this 10-year period. The rate of detection for α-endosulfan and endosulfan sulfate between 2002 and 2011 was extremely low (0.12%); the rate of detection for β-endosulfan was 0%.
[b]Measured from filtered water
[c]Estimated

NA = not available; RC = residential/commercial

Source: USGS 2012b

Table 6-5. α-Endosulfan and Endosulfan Sulfate Detected in Surface Water and Bed Sediment Sampled for the USGS National Water Quality Assessment Between 2006 and 2011[a,b]

State	County	Land use	Result date	Chemical	Value (µg/L)
Arizona	Maricopa	Agricultural	08/24/2009	Endosulfan sulfate	0.0936
Arizona	Maricopa	Agricultural	09/03/2009	Endosulfan sulfate	0.037
Arizona	Maricopa	Agricultural	08/14/2009	α-Endosulfan	0.0107
Arizona	Maricopa	Agricultural	08/24/2009	α-Endosulfan	0.023
Arizona	Maricopa	Agricultural	08/14/2009	Endosulfan sulfate	0.0492
California	Riverside	Mixed	02/25/2011	Endosulfan sulfate	0.011
California	Riverside	Mixed	07/12/2010	Endosulfan sulfate	0.011[c]
California	Riverside	Mixed	06/21/2006	Endosulfan sulfate	0.0122[c]
Colorado	Mesa	Mixed	08/24/2006	Endosulfan sulfate	0.006[c]
Colorado	Weld	Mixed	09/01/2010	Endosulfan sulfate	0.0082
Colorado	Weld	Mixed	08/18/2010	Endosulfan sulfate	0.0099
Colorado	Weld	Mixed	08/01/2006	Endosulfan sulfate	0.007[c]
Connecticut	Hartford	Mixed	07/31/2008	α-Endosulfan	0.0091
Florida	Palm Beach	Cropland	07/06/2006	Endosulfan sulfate	0.011[c]
Florida	Palm Beach	Cropland	05/10/2007	Endosulfan sulfate	0.023[c]
Florida	Palm Beach	Cropland	05/23/2007	Endosulfan sulfate	0.0091[c]
Georgia	Brooks	Mixed	01/23/2008	Endosulfan sulfate	0.008[c]
Georgia	Brooks	Mixed	11/06/2007	Endosulfan sulfate	0.0091[c]
Georgia	Brooks	Mixed	04/22/2008	Endosulfan sulfate	0.0099[c]
Georgia	Brooks	Mixed	03/11/2008	Endosulfan sulfate	0.0103[c]
North Carolina	Greene	Mixed	08/09/2006	Endosulfan sulfate	0.0154[c]
Nevada	Carson City	Mixed	02/09/2010	α-Endosulfan	0.0038[c]
Oregon	Marion	Agricultural	10/11/2005	Endosulfan sulfate	0.0728
Oregon	Marion	Agricultural	12/08/2005	Endosulfan sulfate	0.0162
Oregon	Marion	Agricultural	04/06/2006	Endosulfan sulfate	0.0316
Oregon	Marion	Agricultural	06/14/2006	Endosulfan sulfate	0.0396
Oregon	Marion	Agricultural	08/10/2006	Endosulfan sulfate	0.0563
Oregon	Marion	Agricultural	10/17/2007	Endosulfan sulfate	0.0285
Oregon	Marion	Agricultural	11/07/2007	Endosulfan sulfate	0.024
Oregon	Marion	Agricultural	12/19/2007	Endosulfan sulfate	0.0118[c]
Oregon	Marion	Agricultural	01/09/2008	Endosulfan sulfate	0.0108[c]
Oregon	Marion	Agricultural	02/06/2008	Endosulfan sulfate	0.0088[c]
Oregon	Marion	Agricultural	02/20/2008	Endosulfan sulfate	0.0096[c]
Oregon	Marion	Agricultural	03/05/2008	Endosulfan sulfate	0.012[c]
Oregon	Marion	Agricultural	03/19/2008	Endosulfan sulfate	0.0105[c]
Oregon	Marion	Agricultural	04/09/2008	Endosulfan sulfate	0.0098[c]
Oregon	Marion	Agricultural	05/07/2008	Endosulfan sulfate	0.0126[c]
Oregon	Marion	Agricultural	05/21/2008	Endosulfan sulfate	0.018[c]

Table 6-5. α-Endosulfan and Endosulfan Sulfate Detected in Surface Water and Bed Sediment Sampled for the USGS National Water Quality Assessment Between 2006 and 2011[a,b]

State	County	Land use	Result date	Chemical	Value (µg/L)
Oregon	Marion	Agricultural	06/04/2008	Endosulfan sulfate	0.012[c]
Oregon	Marion	Agricultural	06/18/2008	Endosulfan sulfate	0.0157[c]
Oregon	Marion	Agricultural	07/09/2008	Endosulfan sulfate	0.0232
Oregon	Marion	Agricultural	07/23/2008	Endosulfan sulfate	0.0222
Oregon	Marion	Agricultural	08/20/2008	Endosulfan sulfate	0.0281
Oregon	Marion	Agricultural	09/03/2008	Endosulfan sulfate	0.0196[c]
Oregon	Marion	Agricultural	09/17/2008	Endosulfan sulfate	0.0194[c]
Oregon	Marion	Agricultural	04/23/2008	Endosulfan sulfate	0.0138[c]
Tennessee	Cocke	Mixed	07/29/2010	Endosulfan sulfate	0.0085
Tennessee	Cocke	Mixed	07/22/2010	Endosulfan sulfate	0.0094[c]
Tennessee	Greene	Agricultural	08/21/2008	α-Endosulfan	0.0042[c]
Tennessee	Greene	Agricultural	08/21/2008	Endosulfan sulfate	0.0039[c]
Tennessee	Cocke	Mixed	08/25/2010	Endosulfan sulfate	0.0081
Tennessee	Cocke	Mixed	08/12/2010	Endosulfan sulfate	0.0123
Tennessee	Cocke	Mixed	09/08/2010	Endosulfan sulfate	0.0063[c]
Washington	Yakima	Agricultural	04/19/2010	Endosulfan sulfate	0.0064[c]
Washington	Benton	Mixed	05/19/2008	Endosulfan sulfate	0.0069[c]
Washington	Benton	Mixed	04/16/2008	Endosulfan sulfate	0.0062[c]
Wisconsin	Kewaunee	Not available	09/04/2007	α-Endosulfan	0.3492[c,d]

[a]Data represent only samples with concentrations above the detection limits tested during this 5-year period. The rate of detection for α-endosulfan and endosulfan sulfate between 2006 and 2011 was extremely low (0.55%); the rate of detection for β-endosulfan was 0%.
[b]Measured from filtered water unless otherwise noted.
[c]Estimated
[d]Estimated in bottom sediments (µg/kg)

Source: USGS 2012c

Table 6-6. Endosulfan Concentrations (µg/L) in Surface Water Measured from the South Florida Water Management District (SFWMD)[a]

Basin	Chemical	Number of detections	Average	Maximum	Geometric mean	Median
Citrus (n=373)	α-Endosulfan	3	0.0036	0.0065	0.0031	0.0022
	β-Endosulfan	2	0.0043	0.0052	0.0043	0.0043
	Endosulfan sulfate	2	0.027	0.048	0.026	0.027
South Miami-Dade County (n=311)	α-Endosulfan	63	0.014	0.22	0.011	0.010
	β-Endosulfan	32	0.010	0.078	0.008	0.009
	Endosulfan sulfate	59	0.039	0.45	0.028	0.025
Urban (n=297)	α-Endosulfan	5	0.022	0.076	0.016	0.014
	β-Endosulfan	4	0.026	0.077	0.019	0.026
	Endosulfan sulfate	8	0.029	0.11	0.018	0.017

[a]Samples collected between April 1992 and December 2007.

Source: Pfeuffer 2011

Endosulfans (α- and β-isomers and endosulfan sulfate) were detected in water sampled from 13 sites located in the Biscayne Bay canals of southern Florida (n = 88) obtained between November 2002 and March 2004. These sites were located near ecologically sensitive areas of Everglades National Park and Biscayne National Park. Many of the canals in these areas drain agricultural or mixed agricultural and urban areas. Concentrations of α-endosulfan ranged from 0.21 to 54 ng/L with an 81% detection rate. β-Endosulfan concentrations ranged from 0.20 to 16 ng/L with a 75% rate of detection. Endosulfan sulfate concentrations ranged from 0.22 to 28 ng/L with a 91% rate of detection. Endosulfan concentrations were highest towards the end of the growing season (Harman-Fetcho et al. 2005).

Levels of endosulfans were measured in rain water and air from the Choptank River watershed on the Delmarva Peninsula of the Chesapeake Bay. This watershed is located in an agricultural area and is vulnerable to pesticide runoff and atmospheric deposition. Samples were collected from 8 stations in 2000. In rainwater, α-endosulfan had a 13% rate of detection (n=71), an average concentration of 5.1 ng/L, and a range of 1.3–31 ng/L. β-Endosulfan had a rate of detection of 28%, an average concentration of 7.2 ng/L, and a range of 0.27–81 ng/L. Endosulfan sulfate had a rate of detection of 8.5%, an average concentration of 4.1 ng/L, and a range of 0.98–14 ng/L. Endosulfans were generally only detected in rain from June to early August. Total wet deposition rates were estimated as 0.96±0.1 kg/year for α-endosulfan, 2.7±0.3 kg/year for β-endosulfan, and 0.5±0.06 kg/year for endosulfan sulfate. The authors noted that these estimates are probably low compared to actual rates in areas of high pesticide usage (Kuang et al. 2003).

Snow and rain samples collected from 12 sites within Yosemite National Park, California during the spring and summer of 2008 and 2009 and were analyzed for endosulfan. α-Endosulfan and β-endosulfan were detected in 100% of the snow samples with concentrations ranging from 0.15 to 2.1 ng/L. Endosulfan sulfate was detected in 85% of the samples with concentrations ranging from 0.06 to 1.5 ng/L. They were also among the most frequently detected current-use pesticides in the rainwater samples. Examination of the 2009 rain samples revealed a strong positive correlation between increasing concentrations of endosulfans during the summer months and increasing applications rates in the San Joaquin Valley during the same time. Winter and summer deposition rates were estimated for endosulfans (α- and β-isomers and endosulfan sulfate) and are included in Section 6.3.1, Transport and Partitioning. α-Endosulfan was the only pesticide present above the method quantitation limit in the surface water samples. The authors concluded that estimated water concentrations were sub-parts per trillion and orders of magnitude lower than aquatic benchmarks. Concentrations may be higher during the snowmelt periods of April and May (Mast et al. 2012a, 2012b).

Endosulfan levels in western National Parks were also analyzed by Hageman et al. (2006a, 2006b) as a part of a research project initiated by the U.S. National Parks Service (NPS). Snow pack samples were collected from alpine, sub-Arctic, and Arctic ecosystems from seven National Parks in the spring of 2003. These parks include Sequoia, Rocky, Rainier, Glacier, Denali, Noatak, and Gates of the Arctic. Concentrations of total endosulfans ranged from <0.0040–1.5 ng/L. Calculated deposition rates ranged from <0.19–1,400 ng/m^2. In a follow-up study using data collected from 2003 to 2005, Hageman et al. (2010) estimated the percent concentration due to regional transport for total endosulfans as approximately >90%.

6.4.3 Sediment and Soil

Endosulfans are monitored extensively through national programs such as the USGS NAWQA and National Oceanic and Atmospheric Administration's (NOAA) National Status and Trends (NS&T) Program. The National Sediment Quality Survey (NSQS) includes sediment monitoring data from January 1990 to December 1998. Data from this source has been summarized in EPA's ecological fate and risk assessment report for endosulfan, which was published in 2010. Sediment concentrations of endosulfan reported by NAWQA between 2006 and 2011 showed only one sample above the detection limit in Kewaunee, Wisconsin (see Table 6-5).

The NOAA NS&T Program reported a similarly low rate of detection (5.3%) in sediment samples obtained between 2005 and 2009 (NOAA 2012). Approximately 77 samples reported endosulfan (α- and β-isomers and endosulfan sulfate) above detection limits. These concentrations ranged from 0.08 to 12.59 ng/g dry weight. Details are provided in Table 6-7.

Lake sediment samples were collected from 19 lakes within Yosemite National Park, California during the summer of 2008 and 2009 and analyzed for endosulfan. Endosulfan sulfate was the most dominant endosulfan form detected. Total endosulfan concentrations ranged from 1.0 to 5.7 ng/g dry weight. Concentrations in lichen, lake sediments, and surface water (using SPMDs) displayed a positive correlation between increasing concentrations with rising elevation (Mast et al. 2012a, 2012b).

Endosulfan was detected in sediments obtained from 2 major rivers, 11 creeks or sloughs, 8 irrigation canals, and 2 tailwater ponds located in agricultural areas of California's Central Valley. Samples were

Table 6-7. Sediment Concentrations (ng/g Dry) Obtained by the National Oceanic and Atmospheric Administration (NOAA) National Status and Trends (NS&T) Program Between 2005 and 2009[a]

Study	General location	Latitude	Longitude	Collection date	Chemical	Value
Mussel Watch	Biscayne Bay	25.5333	-80.3232	2/20/2007	Endosulfan sulfate	0.14
Mussel Watch	Commencement Bay	47.2932	-122.433	3/15/2006	β-Endosulfan	0.19
Mussel Watch	Commencement Bay	47.2932	-122.433	3/15/2006	α-Endosulfan	0.62
Mussel Watch	Corpus Christi	27.8522	-97.3598	11/28/2006	Endosulfan sulfate	0.18
Mussel Watch	Eureka	40.8215	-124.171	3/12/2006	Endosulfan sulfate	0.1
Mussel Watch	Everglades	25.9023	-81.5123	2/11/2006	α-Endosulfan	0.34
Mussel Watch	Galveston Bay	29.7045	-94.993	11/17/2006	β-Endosulfan	0.72
Mussel Watch	Galveston Bay	29.7045	-94.993	11/17/2006	Endosulfan sulfate	1.19
Mussel Watch	Green Bay	44.637	-87.8082	9/6/2006	Endosulfan II	0.22
Mussel Watch	Green Bay	44.637	-87.8082	9/6/2006	Endosulfan sulfate	0.43
Kachemak Bay	Homer Harbor	59.6056	-151.426	8/11/2007	Endosulfan sulfate	0.08
Mussel Watch	Hudson River	42.0338	-73.9293	9/24/2009	Endosulfan sulfate	0.83
Mussel Watch	Hudson River	42.0338	-73.9293	9/12/2007	Endosulfan sulfate	1.55
Mussel Watch	Hudson River	41.7089	-73.9406	9/24/2009	Endosulfan sulfate	12.59
Jobos Bay	Jobos Bay-Inner Bay	17.9578	-66.2038	5/28/2008	Endosulfan sulfate	0.15
Jobos Bay	Jobos Bay-Inner Bay	17.9508	-66.2119	5/27/2008	Endosulfan sulfate	0.26
Jobos Bay	Jobos Bay-Inner Bay	17.9508	-66.2119	5/27/2008	β-Endosulfan	0.36
Jobos Bay	Jobos Bay-Inner Bay	17.9391	-66.1852	5/28/2008	β-Endosulfan	2.16
Jobos Bay	Jobos Bay-National Estuarine Research Reserve	17.9268	-66.2408	5/23/2008	β-Endosulfan	0.39
Jobos Bay	Jobos Bay-Outer Bay	17.9537	-66.2892	5/23/2008	α-Endosulfan	0.14
Mussel Watch	Lake Erie	41.9587	-83.233	9/5/2007	α-Endosulfan	0.29
Mussel Watch	Lake Erie	41.6745	-83.2262	9/5/2007	β-Endosulfan	0.33
Mussel Watch	Lake Erie	42.5292	-79.2777	9/17/2009	Endosulfan sulfate	0.72
Mussel Watch	Lake Erie	41.6745	-83.2262	9/10/2009	β-Endosulfan	0.83
Mussel Watch	Lake Erie	42.88	-78.8916	9/20/2009	Endosulfan sulfate	0.94
Mussel Watch	Lake Erie	41.385	-82.5187	9/11/2009	Endosulfan sulfate	1.02
Mussel Watch	Lake Erie	41.6745	-83.2262	9/5/2007	Endosulfan sulfate	1.04
Mussel Watch	Lake Erie	41.6745	-83.2262	9/10/2009	Endosulfan sulfate	1.04
Mussel Watch	Lake Erie	42.5292	-79.2777	9/8/2007	Endosulfan sulfate	1.15
Mussel Watch	Lake Erie	42.1378	-80.0953	9/16/2009	α-Endosulfan	1.17
Mussel Watch	Lake Erie	41.9587	-83.233	9/5/2007	β-Endosulfan	1.26

Table 6-7. Sediment Concentrations (ng/g Dry) Obtained by the National Oceanic and Atmospheric Administration (NOAA) National Status and Trends (NS&T) Program Between 2005 and 2009[a]

Study	General location	Latitude	Longitude	Collection date	Chemical	Value
Mussel Watch	Lake Erie	41.4744	-82.181	9/13/2009	Endosulfan sulfate	1.28
Mussel Watch	Lake Erie	42.88	-78.8916	9/20/2009	β-Endosulfan	1.3
Mussel Watch	Lake Erie	41.7014	-83.4587	9/10/2009	Endosulfan sulfate	1.42
Mussel Watch	Lake Erie	41.6597	-82.825	9/6/2007	Endosulfan sulfate	1.55
Mussel Watch	Lake Erie	41.385	-82.5187	9/11/2009	β-Endosulfan	1.78
Mussel Watch	Lake Erie	41.8933	-83.3248	9/9/2009	Endosulfan sulfate	1.97
Mussel Watch	Lake Erie	41.9112	-80.7877	9/16/2009	Endosulfan sulfate	2.01
Mussel Watch	Lake Erie	41.9247	-80.7183	9/8/2007	Endosulfan sulfate	2.08
Mussel Watch	Lake Erie	41.4994	-81.7188	9/14/2009	Endosulfan sulfate	2.48
Mussel Watch	Lake Erie	41.9247	-80.7183	9/15/2009	Endosulfan sulfate	2.52
Mussel Watch	Lake Erie	41.6597	-82.825	9/12/2009	Endosulfan sulfate	2.53
Mussel Watch	Lake Erie	41.9587	-83.233	9/11/2009	Endosulfan sulfate	2.78
Mussel Watch	Lake Erie	41.9587	-83.233	9/5/2007	Endosulfan sulfate	4.93
Mussel Watch	Lake Michigan	43.2282	-86.3469	9/6/2006	β-Endosulfan	0.19
Mussel Watch	Lake Ontario	44.9799	-74.8916	9/22/2009	Endosulfan sulfate	0.08
Mussel Watch	Lake Ontario	43.3553	-78.6867	9/9/2007	α-Endosulfan	0.17
Mussel Watch	Lake Ontario	44.1442	-76.3247	9/22/2009	α-Endosulfan	0.17
Mussel Watch	Lake Ontario	44.1442	-76.3247	9/11/2007	Endosulfan sulfate	0.25
Mussel Watch	Lake Ontario	43.2578	-77.4953	9/10/2007	Endosulfan sulfate	0.29
Mussel Watch	Lake Ontario	43.4683	-76.5097	9/21/2009	Endosulfan sulfate	0.38
Mussel Watch	Lake Ontario	43.3553	-78.6867	9/9/2007	Endosulfan sulfate	0.47
Mussel Watch	Lake Ontario	44.1442	-76.3247	9/22/2009	Endosulfan sulfate	0.54
Mussel Watch	Lake Ontario	43.2578	-77.4953	9/20/2009	Endosulfan sulfate	0.59
Mussel Watch	Lake Ontario	43.3553	-78.6867	9/19/2009	Endosulfan sulfate	0.67
Mussel Watch	Lake Ontario	43.3387	-78.1878	9/19/2009	Endosulfan sulfate	1.98
Mussel Watch	Lake St. Clair	42.6492	-82.711	9/4/2007	Endosulfan sulfate	0.35
Mussel Watch	Long Beach	33.7232	-118.174	3/7/2006	α-Endosulfan	0.23
Mussel Watch	Marina Del Rey	33.9618	-118.458	3/6/2006	α-Endosulfan	10.85
Mussel Watch	Matagorda Bay	28.6663	-96.2335	12/1/2006	Endosulfan sulfate	0.12
Mussel Watch	Niagara River	43.0468	-78.892	9/18/2009	Endosulfan sulfate	0.28
Mussel Watch	Niagara River	43.0468	-78.892	9/9/2007	Endosulfan sulfate	0.34
Vieques	North Vieques	18.1527	-65.3619	5/28/2007	β-Endosulfan	0.16
Vieques	North Vieques	18.1527	-65.3619	5/28/2007	α-Endosulfan	0.19
Mussel Watch	Pensacola Bay	30.5167	-87.1117	2/1/2006	α-Endosulfan	0.16
Mussel Watch	Puget Sound	47.9727	-122.23	3/17/2006	β-Endosulfan	0.41
Mussel Watch	Puget Sound	47.9727	-122.23	3/17/2006	Endosulfan sulfate	6.25
Mussel Watch	Rappahannock River	37.902	-76.7878	1/6/2007	Endosulfan sulfate	0.08
Mussel Watch	San Diego Bay	32.7247	-117.195	3/5/2006	Endosulfan sulfate	0.11

Table 6-7. Sediment Concentrations (ng/g Dry) Obtained by the National Oceanic and Atmospheric Administration (NOAA) National Status and Trends (NS&T) Program Between 2005 and 2009[a]

Study	General location	Latitude	Longitude	Collection date	Chemical	Value
Mussel Watch	San Diego Bay	32.7247	-117.195	3/5/2006	β-Endosulfan	0.58
Mussel Watch	San Pedro Harbor	33.7067	-118.274	3/7/2006	β-Endosulfan	0.7
Mussel Watch	Sinclair Inlet	47.5852	-122.571	3/15/2006	Endosulfan sulfate	0.23
Mussel Watch	Sinclair Inlet	47.5852	-122.571	3/15/2006	β-Endosulfan	0.39
Vieques	South Southeast Vieques	18.1387	-65.3073	10/24/2007	β-Endosulfan	0.22
Vieques	South Southwest Vieques	18.1055	-65.4413	5/24/2007	β-Endosulfan	0.16
Vieques	South Vieques	18.1057	-65.4391	5/24/2007	β-Endosulfan	0.36
Mussel Watch	Tampa Bay	27.7872	-82.754	2/9/2006	α-Endosulfan	0.39

[a]Data represent only samples with concentrations above detection limits tested during this period. The rate of detection for total endosulfans was 5.3%.

Source: NOAA 2012

obtained during "peak use" periods between July and November 2002, and "winter" samples obtained in March 2003. Peak endosulfan concentrations were limited to ponds adjacent to lettuce fields, but a concentration of 17 ng/g was reported in Del Puerto Creek. The authors noted that endosulfan concentrations were generally below acute toxicity thresholds, but may have contributed to toxicity in a few tailwater ponds and irrigation canals with concentrations greater than several hundred ng/g (Weston et al. 2004).

Residential soil samples collected from 11 homes in Atlanta, Georgia in 2006 did not show β-endosulfan in either yard or foundation samples. The method detection limit for this study was 0.60 ng/g (Riederer et al. 2010).

6.4.4 Other Environmental Media

Endosulfan residues have been detected in a variety of the consumer products, as well as aquatic and terrestrial organisms.

The U.S. Department of Agriculture (USDA) monitors levels of endosulfans and endosulfan sulfate in commodity food items for its Pesticide Data Program. Endosulfan (α- and β-isomers) and endosulfan sulfate were detected in samples collected in 2010 from apples, asparagus, cantaloupe, cilantro, cucumbers, hot peppers, lettuce, mangoes, pears, and sweet bell peppers. The results are summarized in Table 6-8. Cucumbers typically had the highest rates of detection (25.3–38.1%), while asparagus and mangoes had very low detection rates (<1% for all three forms of endosulfan). Endosulfan sulfate residues were detected in 44.5% of cantaloupe sampled with a reported concentrations ranging from 0.005 to 0.064 ppm (USDA 2012). Levels of endosulfan and endosulfan sulfate in domestic foodstuffs were determined as part of FDA's Total Diet Studies series (FDA 2005). The results of this monitoring study are summarized in Table 6-9. The highest mean concentrations were reported for endosulfan sulfate in items such as olive oil (0.01363 ppm), fresh/frozen summer squash (0.02050 ppm), peeled cucumber (0.01099 ppm), and fresh/frozen spinach (0.03654 ppm). Generally, concentrations were higher in fresh/frozen fruits and vegetables versus processed food products. USDA's program analyzes a greater number of samples for each food item compared to FDA's Total Diet Studies. It is important to note that the residue samples in USDA's Pesticide Data Program tended to be higher when compared to results from FDA.

Table 6-8. U.S. Department of Agriculture (USDA) Pesticide Data Program: Distribution of Endosulfan Residues in Fruits and Vegetables (2010)

	α-Endosulfan			β-Endosulfan			Endosulfan sulfate		
Food type	N	Percent detection	Value range (ppm)	N	Percent detection	Value range (ppm)	N	Percent detection	Value range (ppm)
Apple	744	4.3	0.010–0.31	744	8.1	0.010–0.17	744	1.9	0.033–0.087
Asparagus	ND	ND	ND	ND	ND	ND	372	0.3	0.050[a]
Cantaloupe	371	2.4	0.005–0.013	371	0.8	0.005[a]	371	44.5	0.005–0.064
Cilantro	555	1.1	0.010–0.16	325	0.6	0.051–0.19	ND	ND	ND
Cucumber	744	32.8	0.005–0.22	739	25.3	0.007–0.13	734	38.1	0.007–0.16
Hot pepper	186	7.5	0.010–0.083	186	9.1	0.017–0.15	186	15.1	0.005–0.048
Lettuce	743	5.8	0.002–0.051	743	6.2	0.001–0.031	743	6.6	0.004–0.067
Mangoe	372	0.3	0.005[a]	ND	ND	ND	372	0.5	0.005[a]
Pear	743	0.1	0.008[a]	743	2.0	0.008[a]	743	0.3	0.012[a]
Sweet bell pepper	744	11.0	0.004–0.30	744	7.4	0.020–0.38	744	16.9	0.002–0.24

[a]Detected in only one sample.

N = number; ND = not detected

Source: USDA 2012

Table 6-9. Endosulfan Levels in Food Products Sampled for the 2003–2005 Market Basket Survey

	α-Endosulfan				β-Endosulfan				Endosulfan sulfate			
Food type	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)
Apple (red)	8	0.00006	0.0001	0.0002	8	0.00018	0.0002	0.0007	8	0.00018	0.0001	0.0007
Pear, raw	8	0.00001	0.0001	0.0001	8	0.00018	0.0001	0.0004	8	0.00071	0.0003	0.0020
Strawberries, raw/ frozen	8	0.00225	0.0070	0.0110	8	0.00550	0.0100	0.0340	8	0.00293	0.0004	0.0160
Cantaloupe	8	0.00004	0.0003	0.0003	8	0.00015	0.0001	0.0010	8	0.00654	0.0001	0.0230
Raisins	8	0.00003	0.0001	0.0001	8	0.00004	0.0001	0.0002				
Spinach, fresh/ frozen	8	0.00465	0.0001	0.0370	8	0.01080	0.0002	0.0860	8	0.03654	0.0003	0.2850
Collards, fresh/ frozen	8	0.00043	0.0004	0.0030	8	0.00018	0.0001	0.0009	8	0.00091	0.0001	0.0050
Lettuce, iceberg	8	0.00084	0.0003	0.0040	8	0.00046	0.0002	0.0020	8	0.00136	0.0002	0.0050
Broccoli, fresh/ frozen	8	0.00003	0.0002	0.0002	8	0.00003	0.0002	0.0002				
Tomato, raw	8	0.00085	0.0004	0.0030	8	0.00143	0.0004	0.0060	8	0.00103	0.0003	0.0040
Tomato sauce, plain	8	0.00030	0.0001	0.0008	8	0.00049	0.0001	0.0020	8	0.00015	0.0001	0.0007
Green beans, fresh/ frozen	8	0.00146	0.0007	0.0110	8	0.00104	0.0003	0.0080	8	0.00421	0.0007	0.0300
Green beans, canned	8	0.00004	0.0003	0.0003	8	0.00001	0.0001	0.0001	8	0.00004	0.0003	0.0003
Cucumber, peeled	8	0.00171	0.0004	0.0040	8	0.00121	0.0005	0.0020	8	0.01099	0.0009	0.0270
Summer squash, fresh/frozen	8	0.00200	0.0001	0.0060	8	0.00036	0.0001	0.0010	8	0.02050	0.0050	0.0490
Pepper, sweet, green	8	0.00240	0.0002	0.0120	8	0.00556	0.0005	0.0320	8	0.00489	0.0001	0.0280
Squash, winter	8	0.00003	0.0002	0.0002	8	0.00003	0.0002	0.0002	8	0.00499	0.0006	0.0250
Spaghetti w/meat sauce	8	0.00075	0.0002	0.0030	8	0.00085	0.0003	0.0030	8	0.00021	0.0001	0.0005
Dill cucumber pickles	8	0.00315	0.0002	0.0070	8	0.00188	0.0001	0.0050	8	0.00992	0.0004	0.0330
Tomato catsup	8	0.00044	0.0004	0.0010	8	0.00058	0.0001	0.0020	8	0.00024	0.0001	0.0005
Chocolate chip cookies	8	0.00005	0.0002	0.0002	8	0.00003	0.0001	0.0001	8	0.00009	0.0003	0.0004
Candy bar, milk chocolate	8	0.00049	0.0003	0.0020	8	0.00028	0.0001	0.0010	8	0.00145	0.0001	0.0050
BF, macaroni, tomato and beef	8	0.00006	0.0005	0.0005	8	0.00011	0.0009	0.0009	8	0.00011	0.0002	0.0007
BF, applesauce	8	0.00004	0.0001	0.0001	8	0.00010	0.0001	0.0003	8	0.00018	0.0002	0.0005
BF, pears	8	0.00004	0.0001	0.0001	8	0.00009	0.0001	0.0002	8	0.00015	0.0001	0.0003

Table 6-9. Endosulfan Levels in Food Products Sampled for the 2003–2005 Market Basket Survey

	α-Endosulfan				β-Endosulfan				Endosulfan sulfate			
Food type	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)
Yogurt, low-fat, fruit-flavored	8	0.00004	0.0001	0.0002	8	0.00004	0.0001	0.0002	8	0.00003	0.0002	0.0002
Chicken breast, roasted	8	0.00009	0.0007	0.0007	ND	ND	ND	ND				
Brussels sprouts, fresh/frozen	8	0.00001	0.0001	0.0001	8	0.00004	0.0003	0.0003	8	0.00028	0.0002	0.0020
Okra, fresh/frozen	8	0.00062	0.0050	0.0050	8	0.00463	0.0370	0.0370	8	0.00725	0.0580	0.0580
Tuna noodle casserole	8	0.00014	0.0001	0.0008	8	0.00053	0.0001	0.0030	8	0.00039	0.0002	0.0020
Quarter-pound cheeseburger	8	0.00005	0.0002	0.0002	8	0.00005	0.0002	0.0002	8	0.00028	0.0002	0.0020
Taco/tostada with beef and cheese	8	0.00026	0.0003	0.0007	8	0.00026	0.0003	0.0009	8	0.00073	0.0003	0.0020
Pizza, cheese and pepperoni	8	0.00024	0.0002	0.0010	8	0.00050	0.0001	0.0020	8	0.00028	0.0002	0.0009
Black olives	8	0.00006	0.0001	0.0002	ND	ND	ND	ND	8	0.00036	0.0002	0.0009
BF, squash	8	0.00025	0.0020	0.0020	8	0.00004	0.0003	0.0003	8	0.00050	0.0001	0.0030
Breakfast pastry	8	0.00003	0.0002	0.0002	8	0.00005	0.0004	0.0004	8	0.00006	0.0005	0.0005
Macaroni salad	8	0.00004	0.0003	0.0003	8	0.00008	0.0006	0.0006	8	0.00008	0.0001	0.0003
Potato salad	8	0.00016	0.0001	0.0010	8	0.00019	0.0001	0.0010	8	0.00075	0.0002	0.0020
Coleslaw	8	0.00001	0.0001	0.0001	8	0.00003	0.0002	0.0002	8	0.00041	0.0003	0.0020
Lettuce, leaf, raw	8	0.00289	0.0001	0.0050	8	0.00291	0.0001	0.0090	8	0.00607	0.0001	0.0180
Tomato salsa, bottled	8	0.00081	0.0001	0.0030	8	0.00159	0.0003	0.0060	8	0.00079	0.0001	0.0030
Lasagna	8	0.00009	0.0001	0.0003	8	0.00016	0.0002	0.0005	8	0.00010	0.0001	0.0003
Beef with vegetables, Chinese	8	0.00009	0.0003	0.0004	8	0.00008	0.0006	0.0006	8	0.00016	0.0003	0.0007
Chicken with vegetables, Chinese	8	0.00011	0.0001	0.0006	8	0.00005	0.0001	0.0002	8	0.00058	0.0001	0.0030
Chicken filet (broiled) sandwich	8	0.00004	0.0003	0.0003	8	0.00008	0.0002	0.0004	8	0.00016	0.0006	0.0007
Candy, chocolate with nuts	8	0.00005	0.0002	0.0002	8	0.00004	0.0001	0.0002	8	0.00023	0.0002	0.0010
Sweet and sour sauce	8	0.00018	0.0003	0.0006	8	0.00029	0.0004	0.0010	8	0.00008	0.0001	0.0003
Olive oil	8	0.00041	0.0001	0.0010	8	0.00063	0.0002	0.0020	8	0.01363	0.0030	0.0330
BF, plums/prunes with apples/pears	8	0.00001	0.0001	0.0001	8	0.00005	0.0001	0.0003	8	0.00011	0.0001	0.0004
BF, dutch apple betty	8	0.00001	0.0001	0.0001	8	0.00005	0.0002	0.0002	8	0.00008	0.0002	0.0004

Table 6-9. Endosulfan Levels in Food Products Sampled for the 2003–2005 Market Basket Survey

	α-Endosulfan				β-Endosulfan				Endosulfan sulfate			
Food type	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)
BF, chicken with rice	8	0.00001	0.0001	0.0001	8	0.00001	0.0001	0.0001	8	0.00004	0.0003	0.0003
BF, beef and noodles	8	0.00014	0.0001	0.0010	8	0.00026	0.0001	0.0020	8	0.00016	0.0001	0.0010
BF, apples with berries	8	0.00011	0.0001	0.0006	8	0.00021	0.0001	0.0010	8	0.00019	0.0004	0.0006
BF, apples with non-berry fruit	8	0.00010	0.0001	0.0006	8	0.00028	0.0001	0.0010	8	0.00068	0.0002	0.0030
Pork and beans	ND	ND	ND	ND	8	0.00001	0.0001	0.0001	8	0.00001	0.0001	0.0001
Peas	ND	ND	ND	ND	8	0.00004	0.0003	0.0003	8	0.00013	0.0010	0.0010
Peanut butter, smooth	ND	ND	ND	ND	8	0.00003	0.0002	0.0002	8	0.00041	0.0002	0.0009
Peanuts, dry roasted, salted	ND	ND	ND	ND	8	0.00003	0.0002	0.0002	8	0.00036	0.0003	0.0010
Peach, raw/frozen	ND	ND	ND	ND	8	0.00013	0.0010	0.0010	8	0.00009	0.0007	0.0007
Applesauce, bottled	ND	ND	ND	ND	8	0.00005	0.0001	0.0002	8	0.00015	0.0001	0.0005
Cabbage, fresh	ND	ND	ND	ND	8	0.00001	0.0001	0.0001	8	0.00075	0.0020	0.0040
BF, vegetables and beef	ND	ND	ND	ND	8	0.00001	0.0001	0.0001	8	0.00003	0.0002	0.0002
BF, peaches	ND	ND	ND	ND	8	0.00001	0.0001	0.0001	8	0.00003	0.0002	0.0002
Tomato juice, bottled	ND	ND	ND	ND	8	0.00005	0.0001	0.0002	8	0.00001	0.0001	0.0001
Turnip, fresh/frozen	ND	ND	ND	ND	8	0.00019	0.0003	0.0009	8	0.00026	0.0001	0.0009
BF, apricots with mixed fruit	ND	ND	ND	ND	8	0.00001	0.0001	0.0001	8	0.00005	0.0001	0.0003
Cheese, American	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Beef, ground	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00003	0.0002	0.0002
Pork bacon	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Bread, whole wheat	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00003	0.0002	0.0002
Crackers, saltine	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Watermelon	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00005	0.0004	0.0004
Asparagus, fresh/ frozen	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Potato, boiled	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00031	0.0001	0.0006
Potato, baked	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00066	0.0001	0.0020
Potato chips	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00144	0.0005	0.0060
Quarter-pound hamburger	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00011	0.0001	0.0003
Butter	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00095	0.0001	0.0030

Table 6-9. Endosulfan Levels in Food Products Sampled for the 2003–2005 Market Basket Survey

	α-Endosulfan				β-Endosulfan				Endosulfan sulfate			
Food type	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)	N	Level mean (ppm)	Level min (ppm)	Level max (ppm)
BF, vegetables and chicken	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00001	0.0001	0.0001
BF, chicken noodle dinner	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
BF, turkey and rice	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00001	0.0001	0.0001
BF, fruit dessert/ pudding	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0001	0.0002
Cream cheese	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00016	0.0003	0.0007
Pineapple juice, frozen concentrate	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00008	0.0002	0.0004
French fries	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00161	0.0003	0.0070
Eggplant, fresh	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00020	0.0006	0.0010
Fish sandwich	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Clam chowder, New England	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Sour cream	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00004	0.0003	0.0003
Salmon	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00003	0.0002	0.0002
Cranberry juice	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00001	0.0001	0.0001
Potatoes, mashed	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00023	0.0004	0.0005
Carrot, baby, raw	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00013	0.0010	0.0010
Ranch dressing, low-calorie	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00013	0.0010	0.0010
Vegetable oil	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00011	0.0009	0.0009
BF, banana/apple	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00003	0.0001	0.0001
BF, macaroni and cheese	ND	ND	ND	ND	ND	ND	ND	ND	8	0.00005	0.0004	0.0004

BF = baby food; max = maximum; min = minimum; N = number of analyses; ND = not detected; RTF = ready to feed

Source: FDA 2005

Studies of carrot and tomato crops sprayed with endosulfan 2–8 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).

The NOAA's Mussel Watch Program monitors contaminant levels in mussels and oysters in over 280 U.S. coastal sites. In EPA's ecological fate and risk assessment report (EPA 2010a), monitoring levels were summarized from samples analyzed between 1994 and 2009 (see Table 6-10). Endosulfans (α- and β-isomers and endosulfan sulfate) were detected in 64% of samples with an average concentration of 2.0 µg/kg dry weight and a 90th percentile concentration of 4.9 µg/kg dry weight.

Two recent studies monitored endosulfan levels in freshwater fish. In a study monitoring chemical contaminants in bass and carp species in southeastern U.S. rivers, endosulfans were detected at low concentrations (<1.2 ng/g wet weight) and mean concentrations were not calculated due to the large number of samples below the limit of detection. Samples were taken for the Mobile River Basin, Apalachicola-Chattahoochee-Flint River Basin, Savannah River Basin, and Pee Dee River Basin in 2004 (Hinck et al. 2008). Bass, carp, and catfish sampled from the Colorado River basin and tributaries had reported total endosulfan concentrations of <0.02 µg/g, but the largest concentrations (>0.07 µg/g) were found in carp and bass from the Gila River near Arlington, Arizona in August 2003 (Hinck et al. 2007).

USDA's Pesticide Data Program continued its study of pesticide residues in domestic and imported catfish intended for human consumption. The catfish were mostly farm-raised. In 2010, 384 samples were analyzed for residues of α-endosulfan, β-endosulfan, and endosulfan sulfate. α-Endosulfan was only detected at the limit of detection (0.001 ppm) and β-endosulfan was not detected in any samples. Endosulfan sulfate was detected in 30 samples with a rate of detection of 7.8% and at concentrations ranging from the limit of detection (0.001 ppm) to 0.028 ppm (USDA 2012).

Endosulfan was also detected in the muscle of Pacific cod and Pacific halibut collected from coastal waters of Aleutian Islands, Alaska. Sampling areas were grouped according to their level of military activity. In the contemporary military group, the geometric mean concentrations of endosulfan in Pacific cod (n=18) and Pacific halibut (n=26) were 2.5 and 3.3 ng/g wet weight, respectively. In the historical military group, the geometric mean concentration in Pacific cod (n=13) was 5.3 ng/g wet weight and 4.6 ng/g wet weight in Pacific halibut (n=23). The reference group concentrations were 3.2 ng/g wet for

Table 6-10. Concentration of Total Endosulfans (µg/kg Dry Weight) in Bivalves from the National Oceanic and Atmospheric Administration (NOAA) Mussel Watch Database[a]

Statistic	α-Endosulfan	β-Endosulfan	Endosulfan sulfate	Total endosulfans
Number samples	1,429	1,980	1,277	1,980
Number detected	677	841	379	1,258
Percent detected	47%	42%	30%	64%
Minimum	BDL	BDL	BDL	BDL
Average	1.2	0.9	0.5	2.0
50th Percentile	BDL	BDL	BDL	0.39
90th Percentile	2.4	2.5	0.7	4.9
95th Percentile	4.6	4.4	1.5	7.9
99th Percentile	17.8	11.7	5.3	22.1
Maximum	120	37	192	192

[a]Units of µg/kg dry weight (ppb); BDL = below detection limit (~0.2–0.7 ppb). Averages assume 0.0 ppb for concentrations below detection. Data are from 1994–2008.

Source: EPA 2010a

Pacific cod (n=16) and 3.0 ng/g wet weight for Pacific halibut (n=13). Endosulfan was not detected in any of the fish samples of rock greenling (Miles et al. 2009).

China is the world's largest producer and exporter of fishery products. Seafood products including 6 species of shrimp, 2 species of crab, and 14 species of shellfish were collected in June and October 2005 and analyzed for various chemical contaminants. Samples were collected from the Guangdong Province, which borders the South China Sea. α-Endosulfan residues had a frequency rate of 3.8%, arithmetic mean of 0.04 ng/g wet weight and a range of 0.02–1.25 ng/g wet weight. β-Endosulfan residues had a frequency rate of 1.4% and a range of 0.02–0.29 ng/g wet weight. Endosulfan sulfate residues had a frequency rate of 1.4% and a range of 0.01–0.35 ng/g wet weight. Residues were found mostly in shellfish species *Perna uiridis*, *Sinonovacula constricta*, and *Crassostrea gigas* (Guo et al. 2007).

Endosulfans were detected in wine corks produced from the bark of the cork oak tree (*Quercus suber*), which are grown widely in regions of western Mediterranean. Wine corks were collected in spring 1999 from wines produced in Greece, wines produced in Cleveland, Ohio, and from a winery in Bloomington, Indiana (these corks were not used as bottle stoppers). The authors did not specify the origin of the corks used in these wine samples. Total endosulfan levels ranged from 3.8 to 29 ng/g lipid. Concentrations were generally higher in the samples obtained from Bloomington, Indiana. Variation of concentrations was high, and the authors suggested that this was due to differences in pesticide usage where cork oak trees are harvested. The production steps, which include the produce, the cork retailers, and the winery, may also contribute to these variations. Wine to cork exchanges may also have contributed to variations (Strandberg and Hites 2001).

Lichen samples collected from Yosemite National Park, California during the spring and summer of 2008 and 2009 were analyzed for endosulfans (α- and β-isomers and endosulfan sulfate). They were detected in 100% of the samples ranging from 2.0 to 24 ng/g dry weight. These concentrations also showed a positive correlation with increasing elevation, suggesting the occurrence of "cold-mountain trapping" (Mast et al. 2012a, 2012b).

Sparling et al. (2001) claimed that heavy pesticide use in the San Joaquin Valley is contributing to population decline of certain amphibians in the Sierra Mountains, which lies downwind from this agricultural area. Residue levels in Pacific tree frog (*Hyla regilla*) tadpoles and adults were analyzed from samples taken from coastal sites (used as controls), Lassen Volcanic National Park, Lake Tahoe,

Yosemite National Park, and Sequoia National Park. Generally, endosulfan residues were often zero in the coastal sites and in Lassen Volcanic National Park, which are located west and north, respectively, of the San Joaquin Valley. The maximum concentrations (21.9 ppb) occurred in Sequoia or Yosemite National Park. Endosulfans along with DDx compounds also had the highest frequency of detection (~70–80%) throughout the Lake Tahoe, Sequoia, and Yosemite locations. Although endosulfan was not solely implicated, the authors concluded that there was a mixed but increasing occurrence of endosulfan residues along the west to east gradient, which is consistent with the declining amphibian populations in this area.

Endosulfans were detected in blubber of beluga whales (*Delphinapterus leucas*) collected from 15 sites in the Canadian Arctic at various times between 1993 and 2001. Geometric means for endosulfan (isomers not specified) ranged from 9.7 to 76.3 ng/g wet weight from samples taken from males and females of Resolute Bay (1996, 1999), Grise Fjord (2000), Igloolik (1995, 1997), Coral Harbor (2000), and Arviat (1999). Endosulfan sulfate concentrations (geometric means) ranged from 7.0 to 70.6 ng/g wet weight from sites in Chesterfield Inlet (1997, 1999), Sanikiluaq (1994, 2000), Cape Dorset (1999, 2000), Kimmirut (1994, 1996), Iqaluit (1992, 1996), and Pangnirtung (1996, 1997). Endosulfan along with α-hexachlorocyclohexane, comprised the larger proportion of organochlorine residues in the northern Hudson Bay areas. Concentration variations between the sites were statistically significant but concentrations between male and female samples were not (Stern et al. 2005).

Endosulfan was also detected in other higher trophic aquatic organisms. A study analyzed pesticide concentrations in Bonnethead sharks (*Sphyrna tiburo*) in the Florida estuaries of Apalachicola Bay (9 females, 13 males), Tampa Bay (17 females, 15 males), Charlotte Harbor (5 females, 5 males), and Florida Bay (18 females, 13 males). β-Endosulfan and endosulfan sulfate were not detected in liver samples from any of the sampling locations. β-Endosulfan geometric mean concentrations ranged from 12.77 to 15.13 ng/g in muscle and 1.55–6.60 ng/mL in serum. Endosulfan sulfate was only detected in liver samples from Charlotte Bay (geometric mean 1.00±037 ng/g) and serum samples from Florida Bay (geometric mean 1.93±0.93 ng/mL) (Gelsleichter et al. 2005). Skin and blubber samples (post-mortem) from two blue whales (*Balaenoptera musculus*) stranded off the coast of Baja, California were analyzed for chlorinated hydrocarbons. The two whales were juvenile males, both approximately 18 m long (Valdez-Marquez et al. 2004).

6.5 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. A dietary exposure assessment for endosulfan (both isomers and sulfate) was conducted by both the EPA and the CDPR using available monitoring data. Results from the two assessments differed in the data and analytical methods, but both assessments concluded that calculated risks of dietary exposure of endosulfan are below protective benchmarks for all subgroups. The CDPR analysis used residue levels from their own residue monitoring data, as well as data obtained from other sources including consumption data from the USDA Continuing Survey of Food Intakes of Individuals (CFSII), other USDA data, and FDA data. Water residues were not considered in the CDPR dietary exposure assessment since available monitoring data in California did not indicate drinking water or groundwater as a significant source of endosulfan exposure. Results from the CDPR dietary exposure assessment are provided in Table 6-11. The results indicated a chronic dietary exposure (per capita) of 0.19 µg/kg/day and an acute dietary exposure (95th percentile consumption) of 1.85 µg/kg/day for the total U.S. population. Three population subgroups were identified as groups of concern not only from dietary exposure, but also having the highest risk from occupational exposure and/or exposure to the general public. These subgroups were non-nursing infants (<1 year old), children 1–6 years old, and ≥13 year-old nursing females. However, calculated margins of exposure (MOE) were >100 for all subgroups in the CDPR assessment, indicating that these dietary exposures are below levels of concern (Silva and Carr 2010).

The EPA risk dietary exposure assessment used the USDA CFSII data from 1994 to 1996 and 1998 and incorporated drinking water estimated environmental concentrations (EECs) using the DEEM-FCID™ software. Results from the EPA 2007 dietary exposure assessment are provided in Table 6-12. Acute dietary exposure from drinking water for the U.S. population was reported at 0.47 µg/kg/day and chronic exposure was reported at 0.003 µg/kg/day. Acute dietary exposure from food was reported at 0.11 µg/kg/day and chronic exposure was reported at 0.004 µg/kg/day for the U.S. population. Acute dietary exposures (99.9th percentile) from both food and drinking water was reported at 0.48 µg/kg/day and chronic exposure was reported at 0.007 µg/kg/day. EPA evaluated risk by calculating the percent population adjusted dose (%PAD), all of which were below levels of concern. The discrepancies between the exposure and risk results between these two studies can be attributed to the type of data used in the analysis, software used (TAS, Inc. EX™ versus DEEM-FCID™, risk characterization values (MOE versus %PAD), and acute toxicity values used to calculate risk (no-observed-effect level [NOEL] of 0.7 versus 1.5 mg/kg/day) (Silva and Carr 2010).

Table 6-11. California Department of Pesticide Regulation (CDPR) Acute and Chronic Dietary Exposure to Anticipated Endosulfan Residues on Raw Agriculture Commodities (RACs) and the Resulting Dietary Margins of Exposure (MOE)

Population subgroups[a]	Acute exposure (95th percentile)[b,c] CDPR (µg/kg/day)	Chronic exposure[c,d]	Acute MOE[e] CDPR (µg/kg/day)	Subchronic MOE[e]	Chronic MOE[e]
U.S. population	1.85	0.19	378	621	3,001
All Infants <1 year old	3.08	0.22	227	536	2,597
Infant nursing <1 year old	1.90	0.08	367	1,475	7,421
Infant non-nursing, <1 year old	**3.18**	**0.28**	**220**	**421**	**2,039**
Children 1–6 years old	**3.30**	**0.41**	**212**	**288**	**1,407**
Children 7–12 years old	2.09	0.29	336	407	1,943
Female 13–19 years old, not pregnant, not nursing	1.37	0.18	511	656	3,187
Female ≥20 years old, not pregnant, not nursing	1.51	0.14	462	843	4,082
Females 13–50 years old	1.39	0.15	504	787	3,840
Female ≥13 years old, pregnant, not nursing	1.57	0.15	441	787	3,846
Females ≥13 years old nursing	**2.06**	**0.17**	**340**	**694**	**3,448**
Males 13–19 years old	1.37	0.21	513	532	2,668
Males ≥20 years old	1.38	0.15	508	787	3,725
Seniors ≥55 years old	1.65	0.14	425	843	4,132

[a]Bold indicates groups of concern for CDPR dietary risk assessment.
[b]Exposure based on 1989–1992 U.S. Department of Agriculture (USDA) Continuing Survey of Food Intakes of Individuals and residue data from CDPR, Food and Drug Administration, and USDA. Acute and chronic residue files used anticipated residue values for the commodities.
[c]''Acute" users were consumers (95th percentile based on deterministic, point estimates for residues (Exponent DEEM™ software). Chronic was ''per capita" (consumers plus nonconsumers; Exponent DEEM-FCID™).
[d]Adjustments were made for percent of crop treated).
[e]MOE = no-observed-effect level (NOEL) ÷ exposure dose. Acute NOEL = 0.7 mg/kg/day (rabbit developmental toxicity). Subchronic NOEL = 1.18 mg/kg/day (rat reproductive toxicity). Chronic NOEL = 0.57 mg/kg/day (chronic dog study). Chronic dietary exposure data used to calculate subchronic MOE. MOEs based on all U.S. Environmental Protection Agency (EPA) registered RACs. MOEs <100 are of concern.

Source: Silva and Carr 2010

Table 6-12. U.S. Environmental Protection Agency (EPA) Summary of Dietary Exposure and Risk for Endosulfan (2007)

	Acute dietary 99.9th percentile[a]		Chronic dietary	
Population subgroup	Exposure (µg/kg/day)	%aPAD[b]	Exposure (µg/kg/day)	%cPAD[b]
Exposure and risk for drinking water only				
U.S. population	0.47	31	0.003	0.5
All infants <1 year old	1.21	90	0.010	1.7
Children 1–2 years old	0.47	32	0.005	0.8
Children 3–5 years old	0.46	30	0.004	0.7
Children 6–12 years old	0.28	19	0.003	0.5
Youth 13–19 years old	0.31	20	0.002	0.4
Adults 20–49 years old	0.35	23	0.003	0.5
Adults ≥50 years old	0.24	16	0.003	0.5
Females 13–49 years old	0.33	22	0.003	0.5
Exposure and risk for food only				
U.S. population	0.11	7	0.004	0.6
All infants <1 year old	0.14	9	0.004	0.7
Children 1–2 years old	0.24	16	0.013	2.1
Children 3–5 years old	0.18	12	0.009	1.6
Children 6–12 years old	0.13	9	0.003	1.0
Youth 13–19 years old	0.085	6	0.003	0.6
Adults 20–49 years old	0.090	6	0.003	0.4
Adults ≥50 years old	0.10	7	0.003	0.4
Females 13–49 years old	0.090	6	0.003	0.4
Exposure and risk for food and drinking water				
U.S. population	0.48	32	0.007	1.1
All infants <1 year old	1.21	81	0.015	2.4
Children 1–2 years old	0.53	35	0.017	2.9
Children 3–5 years old	0.55	37	0.014	2.3
Children 6–12 years old	0.30	20	0.009	1.5
Youth 13–19 years old	0.32	21	0.006	0.9
Adults 20–49 years old	0.35	24	0.006	0.9
Adults ≥50 years old	0.26	17	0.006	0.9
Females 13–49 years old	0.34	22	0.005	0.9

[a]The EPA uses the 99.9th percentile of exposure from consumption of food alone (EPA 2000b).
[b]The population adjusted dose (PAD) incorporates the oral reference dose (PAD = RfD ÷ Food Quality Protection Act safety factor [FQPA SF]); RfD = no-observed-effect level (NOEL) ÷ (uncertainty factor [UF] = 10 for interspecies variability and 10 for intraspecies variability). Risk (%PAD) = ([exposure ÷ PAD] × 100). A risk estimate <100% of acute (aPAD) or chronic (cPAD) PAD does not exceed EPA's level of concern (EPA 2000b, 2007). Acute oral no-observed-adverse-effect level (NOAEL) = 1.5 mg/kg/day (neurobehavioral toxicity, rat; Bury 1997). Chronic oral NOAEL = 0.6 mg/kg/day (chronic/oncogenicity, rat; Hoechst 1989a). A subchronic %PAD was not calculated by EPA.

Source: Silva and Carr 2010

The CDPR estimated public exposure via non-dietary intake of endosulfan. Under a short-term air, bystander exposure scenario, a time-weighted average (TWA) of 1.63 µg/m^3 at the sampler approximately 6.4 m from the eastern edge of the field was calculated. This value was calculated assuming an application rate of 1.5 lb active ingredient (AI)/acre, or 1.7 kg AI/ha, which is below the maximum application rate for apples. This TWA may be an underestimate when compared to fields that have application rates at the maximum allowed level. Adjusting for the maximum allowable rate, a 24-hour concentration estimate of 2.72 µg/m^3 was calculated. Long- and short-term exposure estimates for child and adult swimmers (incorporating incidental ingestion, dermal, and inhalation exposures) were all low, and the associated risks were below health benchmarks (Beauvais et al. 2010a).

Lee et al. (2002) estimated endosulfan inhalation hazard quotients (HQs) using CDPR data from 1990 to 2000. HQs were defined as daily intake/reference dose and were calculated for acute, chronic, and subchronic exposures for both adults and children (<12 years old). All HQs for endosulfan were <1 for both children and adults, indicating levels that are not a concern. However, HQs were generally higher for children than for adults.

The National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (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.

6.6 EXPOSURES OF CHILDREN

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

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's

behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with the adult general population, the main route of endosulfan exposure for children is through dietary intake. Dietary exposure assessments from the CDPR and EPA-estimated dietary exposure assessments and risks for various child subgroups are provided in Tables 6-11 and 6-12 (Silva and Carr 2010). Calculated risks for all subgroups were below levels of concern, but calculated exposures were generally higher for the child subgroups when compared to the adult sub-groups and the total U.S. population. This is particularly evident in the CDPR results, where calculated exposures (from food only) were 3.18 µg/kg/day for non-nursing infants (<1 year old) and 3.30 µg/kg/day for 1–6-year-old children compared to 1.85 µg/kg/day for the total U.S. population. The EPA dietary exposure assessment results were markedly lower than the CDPR results. The dietary exposure for food only was 0.14 µg/kg/day for all infants (<1 year old) and 0.24 µg/kg/day for children 1–2 years old, compared to 0.11 µg/kg/day for the total U.S. population. The discrepancy between childhood exposures and total population exposures was larger when taking into account intake from both food and drinking water (1.21 µg/kg/day for all infants [<1 year old] and 0.48 µg/kg/day for the U.S. population). Estimated exposures from drinking water were higher for infants and children than from exposures from food intake. It should be noted that the exposure assessments from CDPR and EPA differed in several ways including data sets used, approaches (deterministic vs. probabilistic), populations (users only vs. per capita), and reference points (95^{th} vs. 99^{th} percentiles) (Silva and Carr 2010).

Several studies have been published recently exploring pre-natal and post-natal exposure of endosulfan by analyzing concentrations in breast milk, placenta, and umbilical cord blood. Shen et al. (2007) analyzed α-endosulfan concentrations in placenta and milk from Danish and Finnish mothers (1997–2001). Geometric mean concentrations in Danish and Finnish breast milk samples (n=43 for each group) were 7.41 and 7.3 ng/g lipid, respectively. Geometric mean concentrations in Danish and Finnish placenta samples (n=43 for each group) were 2.28 and 2.52 ng/g lipid, respectively. Placenta concentrations were measured in mothers giving birth to males from southern Spain between 2000 and 2002 (n=220) by Freire et al. (2011). Total endosulfan (sum of α- and β-isomers, endosulfan diol, endosulfan ether, endosulfan sulfate, and endosulfan lactone) geometric mean concentration (n=211) was reported as 4.02 ng/g placenta with a 95% confidence interval of 3.34–4.8 ng/g. The 95^{th} percentile concentration was 27.0 ng/g placenta, and the rate of detection was 95.9%. Cerrillo et al. (2005) also analyzed endosulfan and metabolite levels in mothers and fertile women from Granada and Almeria Provinces in southern

Spain. Concentrations were detected in adipose tissue (fertile women), placenta, umbilical cord blood, and breast milk. Results from this study are summarized in Table 6-13. The authors concluded that endosulfan pre- and postnatal exposure between child and mother is a common event, although contributions from environmental and other dietary sources cannot be ruled out.

In a study investigating correlations between prenatal pesticide exposure and cryptorchidism (a male reproductive birth defect) in babies, Damgaard et al. (2006) compared milk samples from 62 mothers of male infants with cryptorchidism (cases) and 68 mothers of healthy male infants (controls). The joint prospective, longitudinal cohort study occurred in Finland and Denmark from 1997 to 2001. α-Endosulfan was detected in all samples with a median concentration of 6.95 ng/g lipid and range of 1.83–17.84 ng/g lipid. Control concentrations were similar with a 6.66 ng/g lipid median and range of 1.19–22.66 ng/g lipid. The authors stated that although singular exposure to α-endosulfan or any other pesticide examined was not significantly correlated with cryptorchidism, the study suggested that exposure to more than one pesticide at low concentrations represents a risk factor for congenital cryptorchidism.

Fernandez et al. (2007) performed a similar study where various organochlorine pesticide concentrations in placenta samples were compared to occurrences of male genital malformations such as cryptorchidism and hypospadias. Samples were obtained from Granada Province in southern Spain from October 2000 to July 2002. Total endosulfan (sum of α- and β-isomers, endosulfan diol, endosulfan ether, endosulfan sulfate, and endosulfan lactone) arithmetic mean concentration (±standard deviation) was 20.8±25.0 ng/g lipid in the case studies (n=48) and 19.7±29.7 ng/g lipid in the control samples (n=114). Maximum concentrations were 103 ng/g lipid among the case studies and 189.5 ng/g lipid in the controls. The rate of detection for α-endosulfan was 52.4%. As with Damgaard et al. (2006), positive correlations between male genital malformations were not observed for any singular chemical or metabolite. However, the authors noted a 3.5-fold increase in risk for urogenital malformations when the mother reported taking part in agricultural activities. This trend did not appear in the fathers. However, a 2.98-fold increase risk was found when fathers were asked about specific work tasks and chemical exposures. A seasonal trend of births of males with malformations was also observed, with largest occurrences reported in winter. Data from questionnaires were not sufficient enough to correlate this seasonal trend with increased use of organochlorine pesticides during the previous spring.

Table 6-13. Endosulfan and Metabolite Concentrations in Adipose Tissue, Placenta, Umbilical Cord Blood, and Breast Milk of Fertile Women and Mothers from Southern Spain

Chemical	Mean	Standard deviation	Median	Maximum	Percent frequency
In adipose tissue (n=149), ng/g fat[a]					
α-Endosulfan	11.09	86.06	0.50	944.1	26.2
β-Endosulfan	6.63	19.63	2.50	219.7	13.4
Endosulfan ether	1.72	6.58	0.25	61.83	49.6
Endosulfan lactone	0.94	1.38	0.50	9.2	16.1
Endosulfan diol	5.47	28.02	1.25	338.17	26.8
Endosulfan sulfate	16.16	92.52	1.25	882.98	12.8
In placenta (n=200), ng/g placenta or ng/mL homogenate[b]					
α-Endosulfan	3.55	5.8	0.94	28.27	55.5
β-Endosulfan	4.19	16.02	1.00	150.92	49
Endosulfan ether	0.33	0.38	0.20	3.08	50
Endosulfan lactone	15.62	19.23	2.64	74.67	36
Endosulfan diol	12.56	53.25	4.35	527.02	49
Endosulfan sulfate	3.57	5.83	1.61	44.45	67.5
In umbilical cord blood (n=200), ng/mL serum[c]					
α-Endosulfan	3.34	5.70	1.56	60.25	76.5
β-Endosulfan	2.77	1.88	2.00	14.91	62
Endosulfan ether	1.43	1.61	0.81	8.64	42.5
Endosulfan lactone	3.88	7.91	2.07	83.89	60.5
Endosulfan diol	13.23	11.34	9.62	83.32	81
Endosulfan sulfate	2.82	6.09	1.20	36.36	33.5
In breast milk (n=23), ng/mL milk[d]					
α-Endosulfan	0.68	0.35	0.87	1.00	65.2
β-Endosulfan	10.70	8.71	7.29	26.89	43.5
Endosulfan ether	6.08	14.49	0.66	57.58	100
Endosulfan lactone	4.63	1.17	5.00	5.00	91.3
Endosulfan diol	0.60	0.42	0.64	1.00	43.5
Endosulfan sulfate	6.18	4.18	5.00	14.35	26.1

[a]β-Endosulfan was significantly ($p \leq 0.001$) associated with endosulfan lactone. Endosulfan lactone was also associated with endosulfan ether, endosulfan diol, and endosulfan sulfate.
[b]α-Endosulfan was statistically associated with endosulfan lactone ($p \leq 0.001$) and endosulfan sulfate ($p \leq 0.005$); β-endosulfan was significantly associated with endosulfan diol ($p \leq 0.005$). Among the endosulfan metabolites, endosulfan lactone was associated with endosulfan ether ($p \leq 0.005$) and endosulfan sulfate ($p \leq 0.001$).
[c]α-Endosulfan was associated with endosulfan ether, endosulfan lactone, and endosulfan diol ($p \leq 0.001$), while β-endosulfan was associated with endosulfan diol and endosulfan sulfate ($p \leq 0.001$). There was a significant ($p \leq 0.001$) association among endosulfan diol, endosulfan ether, and endosulfan lactone.
[d]α-Endosulfan was significantly associated with endosulfan sulfate ($p \leq 0.05$), while β-endosulfan was associated with endosulfan ether ($p \leq 0.05$) and endosulfan diol ($p \leq 0.01$). There was a statistically significant association between the two commercial products, α-endosulfan and β-endosulfan ($p \leq 0.05$).

Source: Cerrillo et al. 2005

Based on a bystander inhalation exposure scenario calculated by Beauvais et al. (2010a), children may be exposed to as much as 2.72 μg/m^3 of endosulfan (24-hour maximum concentration estimate) if they are within 6.4 m from the edge a field where it is being applied. Endosulfan exposure to children from swimming is expected to be low.

Lee et al. (2002) estimated endosulfan inhalation HQs using CDPR data from 1990 to 2000. HQs were defined as daily intake/reference dose and were calculated for acute, chronic, and subchronic exposures for both adults and children (<12 years old). All HQs for endosulfan were <1 for both children and adults, indicating levels that are not a concern. However, HQs were generally higher for children than for adults.

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 since dietary intake is regarded as the largest source of exposure for endosulfan. 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 are 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.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Farm workers are expected to be exposed to higher amounts of endosulfan compared to the general population. These exposures may occur through direct handling and application or through latent exposure in fields that were previously sprayed (occupational re-entry). Beauvais et al. (2010b) compared the occupational exposure assessments for endosulfan performed by the CDPR and EPA. Dermal, inhalation, and aggregate exposure estimates under selected scenarios are summarized in Table 6-14.

Table 6-14. Dermal, Inhalation, and Aggregate Exposure Estimates by CDPR and EPA for Selected Scenarios (mg/kg/day)[a]

	Short-term[b]			Seasonal[c]			Annual[d]		
Scenario	Dermal	Inhalation	Ag[e]	Dermal	Inhalation	Ag[e]	Dermal	Inhalation	Ag[e]
CDPR									
GB applicator	0.0439	0.001	0.047 (4%)	0.047	0.0005	0.048 (<1%)	0.008	0.00008	0.008 (2%)
HPHW MLA-EC	0.501	0.010	0.513 (<1%)	0.15	0.003	0.153 (<1%)	0.025	0.001	0.026 (<1%)
Aerial flagger	0.371	0.002	0.375 (<1%)	0.057	0.0002	0.057 (<1%)	0.019	0.00005	0.019 (<1%)
LPHW MLA-EC	0.013	0.0001	0.015 (13%)	0.003	0.00002	0.003 (5%)	0.0005	0.000003	0.0005 (25%)
Aerial applicator	0.786	0.004	0.792 (<1%)	0.157	0.001	0.158 (<1%)	0.053	0.0003	0.053 (<1%)
EPA									
GB applicator	0.013	0.00034	0.017 (21%)	NE	NE	NE	NE	NE	NE
HPHW MLA-EC	0.090	0.0026	0.096 (4%)	NE	NE	NE	NE	NE	NE
Aerial flagger	0.066	0.00088	0.070 (5%)	NE	NE	NE	NE	NE	NE
LPHW MLA-EC	0.0083	0.000026	0.0044 (81%)	NE	NE	NE	NE	NE	NE
Aerial applicator	0.033	0.00085	0.037 (9%)	NE	NE	NE	NE	NE	NE

[a]CDPR estimated handler exposures for short-term (defined as acute and up to 1 week), seasonal (intermediate-term intervals, lasting from 1 week to 1 year), and annual durations. EPA defines short-term durations as 1–30 days; thus, short-term exposure estimates by EPA overlap CDPR's short-term and seasonal estimates. Exposures are rounded to three significant figures by CDPR and two by EPA.
[b]Calculated with the following equation: Exposure = [(0.001 µg/mg) x (exposure rate) x (absorption) x (acres treated/day) x (application rate)]/(body weight). EPA assumed a dermal absorption of 45%, and CDPR assumed 47.3%; for inhalation exposure, both assumed 100% absorption. For dermal exposure, EPA assumed a body weight of 60 kg, and CDPR assumed 70 kg; for inhalation exposure, both assumed a body weight of 70 kg.
[c]CDPR calculated seasonal exposure using the same equation as short-term exposure and different exposure rates (average rather than upper bound).
[d]CDPR calculated annual exposure with the following equation: exposure = (seasonal exposure) x (high use months per year)/(12 months per year).
[e]Aggregate = [total worker (occupational exposure: dermal + inhalation)] + dietary exposure. %Diet = [dietary exposure + aggregate exposure] x 100. CDPR calculated short-term dietary exposure = 0.00206 mg/kg/day based on the 95th percentile of user-day exposure for females (≥13 years old), nursing; CDPR calculated seasonal and annual dietary exposure = 0.00017 mg/kg/day (%CT; mean annual consumption for females [≥13 years old]). EPA calculated short-term dietary exposure = 0.003546 mg/kg/day based on the 99.9th percentile of adults ages 20–49 years.

Ag = Aggregate; CDPR = California Department of Pesticide Regulation; EPA = Environmental Protection Agency; GB = groundbloom; HPHW = high-pressure handwand; LPHW = low-pressure handwand; MLA-EC = mixer/loader handling emulsifiable concentrate; NE = not estimated

Source: Beauvais et al. 2010b

Similar to exposure assessments for the general population, CDPR and EPA results differed greatly due to different assumptions regarding exposure. In general, CDPR calculated significantly higher exposures than EPA. The majority of short-term dermal, inhalation, total, and aggregate MOEs were <100, indicating levels of concern. The exceptions were EPA's low-pressure handwand, mixer/loader handling emulsifiable concentrate (LPHW MLA-EC) short-term exposure scenario and CDPR's seasonal and annual LPHW MLA-EC exposure scenario, which had calculated MOEs >100. Exposures from fields previously sprayed were also assessed by CDPR and EPA. Most short-term (2–4 days) and intermediate-term (10–14 days) MOEs for representative re-entry scenarios were <100 from both studies, indicating levels of concern. Representative exposure scenarios included thinning (almonds, peaches), scouting (broccoli, citrus, cotton, lettuce, potatoes), hand harvesting (broccoli, sweet corn, cucumbers, ornamental cut flowers, ornamental plants, strawberries, and tomatoes), and cane turning (grapes) (Beauvais et al. 2010a).

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 300 L 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.

In addition to individuals who are occupationally exposed to endosulfan, 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 NPL hazardous waste sites where endosulfan has been detected in some environmental media (HazDat 2007).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of endosulfan is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 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.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical/chemical properties of endosulfan and endosulfan sulfate are sufficiently well characterized to enable assessment of the environmental fate of the compound (HSDB 2012; NIOSH 2011; O'Neil et al. 2006; Tomlin 2003).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2009, became available in February of 2011. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Although all U.S. producers of endosulfan must be registered under FIFRA, data concerning quantities of endosulfan produced domestically are limited. Annual production can be estimated by analogy to its annual use, for which quantitative data are available. The available use trends over the last two decades indicates use of endosulfan is in decline, based on a reported annual use of 1.38 million pounds between 1990 and 1999 to only 380,000 pounds per year between 2006 and 2008 (EPA 2002, 2010a). As of March 2012, there were only four active registrants of endosulfan in the United States. Over the 4-year phase-out schedule, these registrants will be cancelling their endosulfan products according to a voluntary agreement (EPA 2012g). Despite this cancellation, production data and continued recordkeeping of endosulfan use would be valuable during the years of cancellation and the years following, so as to understand the impact and its effects on exposure to the public and to workers.

Releases and disposal of endosulfan to the environment are well defined based on the regulatory restrictions and the available monitoring data (CDPR 2011; EPA 2001, 2002, 2010a, 2012c, 2012g; NOAA 2012; USGS 2012c).

Environmental Fate. Overall, the environmental fate mechanisms associated with endosulfan are well documented. Endosulfan partitions to air and is subject to long-range transport (EPA 2010a; Hafner and Hites 2003; Hageman et al. 2006a; Hung et al. 2005, 2010; Kathpal et al. 1997; Mast et al. 2012a, 2012b; Rice et al. 2002; Rudel 1997; Stern et al. 2005; Weber et al. 2010). It is immobile in soils (EPA 2010a; Stewart and Cairns 1974). It is transformed in surface waters and soils via hydrolysis (Greve and Wit 1971; HSDB 2012; Kaur et al.1998) and biodegradation (Cotham and Bidleman 1989; HSDB 2012).

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 quantitative 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.

Food Chain Bioaccumulation. Endosulfan is bioconcentrated by aquatic organisms and supporting data are well established (DeLorenzo et al. 2002; EPA 2010a; Ernst 1977; Naqvi and Newton 1990; Pennington et al. 2004; Rajendran and Venugopalan 1991; Roberts 1972; Schimmel et al. 1977; Weber et al. 2010). BMFs from fish to aquatic mammals suggest the potential for biomagnification in aquatic food chains. However, these estimates do not take metabolism into account (Kelly et al. 2007; Weber et al. 2010). Estimating bioconcentration and biomagnification in terrestrial organisms is also difficult due to the lack of biomonitoring data, especially in humans. Recent BMF estimates indicate potential for biomagnification in humans, but understanding of continuous, low-dose metabolism in terrestrial organisms is also lacking (Kelly et al. 2007). Acute poisoning cases suggest that metabolism in humans may be rapid (Eyer et al. 2004). Methods for estimating biomagnification in terrestrial organisms based on octanol/air and octagonal/water partition coefficients require an understanding of its metabolic potential (Armitage and Gobas 2007; EPA 2010a). Further investigations into the bioaccumulation, biomagnification, and metabolism of endosulfan in humans and terrestrial organisms are needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of endosulfan in contaminated media at hazardous waste sites are needed so that the information obtained on levels of endosulfan in the environment can be used in combination with the known body burden of endosulfan to

assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Monitoring data for endosulfan in environmental media are current and extensive. It has been detected in ambient air of temperate and Arctic regions (Daly et al. 2007; Gale et al. 2009; Harner et al. 2005; Hoh and Hites 2004; Hung et al. 2005, 2010; Pozo et al. 2006; Shen et al. 2005; Sun et al. 2006; Weber et al. 2010). Endosulfan is a monitored in groundwater and surface water samples through the USGS NAWQA program, EPA's STORET database, CDPR Surface Water Protection Database, USDA Pesticide Data Program, and SFWMD DB Hydro database, etc. Altogether, these sources contain over 20 years worth of monitoring data for endosulfan in the United States (EPA 2010a). Additional studies have also detected endosulfan in surface water (Harman-Fetcho et al. 2005; Pfeuffer 2011; Scott et al. 2002). Studies have also detected endosulfan in rainwater and snow samples (Hageman et al. 2010; Kuang et al. 2003; Mast et al. 2012a, 2012b). It has been detected in sediment and soil (NAWQA; NOAA NS&T) (Mast et al. 2012a, 2012b; Riederer et al. 2010; Weston et al. 2004). Endosulfan levels in bivalves are monitored as part of the NOAA's Mussel Watch Program and have been summarized by EPA (2010a). The FDA's Total Diet Studies (2005) and USDA's Pesticide Data Program (USDA 2012) detected endosulfan residues in a variety of food products, mostly in fresh and frozen fruits and vegetables. Residues have been detected in fresh and seawater fish and seafood, including catfish caught and raised for human consumption (Guo et al. 2007; Hinck et al. 2007, 2008; Miles et al. 2009; USDA 2012). They have been detected in lichen samples from Yosemite National Park, California (Mast et al. 2012a, 2012b) and wine corks made from cork oak tree (*Q. suber*) (Strandberg and Hites 2001). Endosulfans have been detected in the Pacific tree frog (*H. regilla*) of the Sierra Mountains and California, downwind from the agricultural San Joaquin Valley (Sparling et al. 2001). Endosulfans have been detected in high-trophic aquatic organisms such as beluga whales, blue whales, and Bonnethead sharks (*S. tiburo*) (Gelsleichter et al. 2005; Stern et al. 2005; Valdez-Marquez et al. 2004).

Exposure Levels in Humans. Comprehensive biomonitoring studies for endosulfan are not available. Exposure levels in the general population have been extensively evaluated using available monitoring data. Dietary intake is expected to be the major source of endosulfan exposure to the general public. Dietary exposures were extensively evaluated for various population subgroups by both EPA and CDPR using different data sets and analytical methods. Although the estimated chronic dietary exposures from these studies were significantly different, both values were below protective benchmarks. The major difference between these exposure assessment deals with the incorporation of drinking water into dietary intake. CDPR assumed that drinking water was not a significant source of exposure based on the

monitoring data for California. However, EPA incorporated drinking water into their assessment and their model results estimated drinking water exposure to be the same as food intake (Silva and Carr 2010). Comprehensive biomonitoring studies using samples collected from the U.S. population that can be used to better assess endosulfan exposure in the general population would be valuable. CDPR evaluated short-term, bystander inhalation exposure and estimated long- and short-term exposures for child and adult swimmers (Beauvais et al. 2010a). Lee et al. (2002) estimated inhalation HQs using CDPR data from 1990 to 2000.

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

Exposures of Children. Dietary exposure assessments were conducted by EPA and CDPR, which included estimates for child subgroups. These assessments used monitoring data in food and drinking water rather than biomonitoring data from urine or blood samples. Results from these assessments indicated that childhood exposures were generally higher compared to exposure estimates for the general adult population (Silva and Carr 2010). Several studies measured endosulfan levels in breast milk, placenta, umbilical cord blood, and maternal adipose tissue, and some explored correlations between elevated endosulfan levels and reproductive malformations in male infants (Cerrillo et al. 2005; Damgaard et al. 2006; Fernandez et al. 2007; Freire et al. 2011; Shen et al. 2007). These studies were conducted in Europe and may not be representative of U.S. exposures. Comprehensive biomonitoring studies using samples collected from the U.S. population would be valuable in assessing endosulfan exposure in children. More data would also be helpful to properly assess endosulfan exposure to children who live, play, or attend school near farmlands that are treated with endosulfan. CDPR estimated inhalation exposure levels under a bystander scenario, but this analysis incorporated several assumptions (Beauvais et al. 2010a). The possibility that farming parents' work clothes and shoes may carry endosulfan residues into the home also should be studied.

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

Exposure Registries. Although endosulfan is monitored extensively in food, surface water, groundwater, air, and media, it is not included in comprehensive biomonitoring studies that analyze tissue, blood, or urine. Endosulfan is not included in the CDC's National Health and Nutrition Examination Survey (NHANES), which monitors chemical concentrations in urine and blood collected from the U.S. population. These data would give the best basis for estimating exposures to the general

population, children, and workers. Endosulfan will be gradually phased-out through 2016 and exposures are expected to decrease. As a result, large-scale biomonitoring and environmental monitoring programs will likely be decreased or discontinued. Continuing studies would be valuable in understanding the immediate and long-term impacts on the general population.

6.8.2 Ongoing Studies

No ongoing studies sponsored by NIH or EPA were identified for endosulfan.

7. 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.

7.1 BIOLOGICAL MATERIALS

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 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, brain, and adipose tissue is gas chromatography (GC) equipped with an electron capture detector (ECD) (Cerrillo et al. 2005; Fernandez et al. 2007; Guardino et al. 1996). This is because GC/ECD is relatively inexpensive, is simple to operate, and offers a high sensitivity for halogens (Griffith and Blanke 1974). Fernandez et al. (2007) used a GC/MS isotope dilution method for detection of a variety organochlorine pesticides in human milk samples. Detection limits ranged from 0.1 to 3 ng/mL.

Vidal et al. (1998) discuss a GC-tandem mass spectrometry (GC-MS-MS) method using solid-phase extraction for the analysis of α- and β-endosulfan in urine.

Mariani et al. (1995) have used GC in conjunction with negative ion chemical ionization mass spectrometry to determine α- and β-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 7-1.

7.2 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 (EPA 1992a, 1994b, 1996a, 1996b, 1996c, 1997d, 1997e, 1997f, 2007; FDA 1999a, 1999b, 1999c; Gale et al. 2009; Halsall et al. 1997; Hung et al. 2002; Wania et al. 2003). 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).

The most common methods of sampling and measuring endosulfan in the atmosphere involve high-volume air samplers, where air is forced through a collection device. The collection medium is either glass fiber filters (GFFs) or polyurethane foam plugs (PUFs). The samples are then analyzed with GC/MS. This technique can measure endosulfan levels in air at the picogram level (Halsall et al. 1997; Su et al. 2007). The use of passive air samplers with XAD-2 resin filters is also common for measuring endosulfan concentrations in air. These samples are extracted with dichloromethane and methanol and analyzed with GC/ECD. Wania et al. (2003) reported detection limits of 0.15 pg/μL for α-endosulfan and 0.08 pg/μL for β-endosulfan. Gale et al. (2009) used semipermeable membrane devices (SPMDs) with low-density polyethylene tubing filled with triolein to detect endosulfans in indoor air. The samples were analyzed with GC/MS and GC/ECD and reported mean endosulfan concentrations as ng per SMPD.

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 1994b). At these low concentrations,

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue, placenta	Extraction with hexane and fractionated with HPLC; gravimetric determination of lipid content	GC/ECD/MS	Results reported in ng/g fat, placenta	93.99 (β-endosulfan); 100.03 (endosulfan sulfate)	Cerrillo et al. 2005
Umbilical cord blood	Serum extraction with organic solvents, clean-up using acid treatment with sulfuric acid, elution with HPLC	GC/ECD	Results reported in ng/mL serum	93.99 (β-endosulfan); 100.03 (endosulfan sulfate)	Cerrillo et al. 2005
Human milk	Extraction by shaking with methanol and sodium oxalate; further extraction procedures used organic solvents and clean-up with sulfuric acid treatment, followed by elution with HPLC	GC/ECD	Results reported in ng/mL milk	93.99 (β-endosulfan); 100.03 (endosulfan sulfate)	Cerrillo et al. 2005
Human milk	Heating, shaking for 30 minutes at 37 °C to homogenize, re-freezing, then extraction and clean-up with 2:1 acetone/ hexane	GC/MS (isotope dilution method)	Results reported in ng/g lipid	No data	Damgaard et al. 2006
Placenta	Placenta homogenate dissolved in hexane, elution in glass column then HPLC, drying, dissolution in hexane	GC/ECD	0.1–3 ng/mL (for all organochlorine pesticides)	84–102 (for all organochlorine pesticides)	Fernandez et al. 2007
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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma, brain (alpha and beta)	Brain: homogenization with ethanol, centrifugation, phase separation and evaporation of ethanol and addition of internal standard 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

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

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 1994b).

Methods 508, 508.1, and 525.2 (EPA 1997d, 1997e, 1997f) are applicable to drinking water and groundwater 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 1996c). 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.

Multiresidue methods for fatty and non-fatty foods (fruits, vegetables, seeds, dairy, eggs, meats) published by FDA (FDA 1999a, 1999b, 1999c). 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 7-2.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (vapor and particulate)	High volume air sampler using GFF and PUFs	GC/MS	No data	No data	Halsall et al. 1997; Hung et al. 2002
Air	Passive air sampler with XAD-2 resin filter and extraction with dichloromethane and methanol.	GC/ECD	0.15 pg/µL (α-isomer); 0.08 pg/µL (β-isomer)	No data	Wania et al. 2003
Indoor air	Semipermeable membrane device (SMPD) using low-density polyethylene tubing filled with triolein	GC/MS; GC/ECD	No data	No data	Gale et al. 2009
Drinking water, ground-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, ground-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)	α: 92.6 (17.8% RSD at 0.03 µg/L) β: 87.9 (18.6% RSD at 0.03 µg/L) sulfate: 106 (11.5% RSD at 0.03 µg/L)	EPA 1997e (Method 508.1)
Drinking water	Extraction of sample using LSE; solvent elution using ethyl acetate and methylene chloride; volume reduction	GC/MS	α-endosulfan: 0.11 µg/L; β-endosulfan: 0.074 µg/L; endosulfan sulfate: 0.093 µg/L	α: 121 (6.1% RSD) β: 128 (3.9% RSD) sulfate: 116 (5.4% RSD)	EPA 1997f (Method 525.2)
Waste water	Extraction of sample with methylene chloride; water removal/ volume reduction	GC/MS	5.6 µg/L (endosulfan sulfate)		EPA 2012d (Method 625)
Water; waste water	Extraction of sample (Method 3510, 3520) with direct injection	GC/ECD	0.49 µg/L (α-endosulfan); 6.1 µg/L (β-endosulfan); 2.7 µg/L (endo-sulfan sulfate)	45-153% (α-endo-sulfan); 202% (β-endo-sulfan); 26–144% (endosulfan sulfate)	EPA 1994b (Method 8080A)

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liquid or solid	Extraction of sample with methylene chloride, methylene chloride and acetone or hexane and acetone (depending on solid content); clean-up	GC/ECD	1.3 µg/L (α-endosulfan, groundwater); 0.9 µg/L (β-endosulfan, groundwater); 0.51 µg/L (α-endosulfan, waste water); 0.54 µg/L (β-endosulfan, waste water	52 (α- and β-endosulfan; from sewage sludge); 47 (α-endosulfan, from stillbottoms); 49 (β-endosulfan from stillbottoms)	EPA 1996a (Method 8081A)
Various solid and liquid matrices	Extraction of sample with methylene chloride, hexane-acetone or methylene chloride-acetone (depending on solid content); clean-up	GC/ECD	No data	52–70% (α- and β-endosulfan; from sewage sludge); 41–47% (α-endosulfan, from stillbottoms); 46–49% (β-endosulfan from stillbottoms)	EPA 2007 (Method 8081B)
Various solid and liquid matrices	Extraction of sample with methylene chloride, hexane-acetone or methylene chloride-acetone (depending on solid content)	GC/AED	No data	100 (α-endosulfan); 110 (β-endosulfan II); 114 (endosulfan sulfate)	EPA 2007 (Method 8085)
Water, soil, sediment, waste	Extraction of sample using solvent or SPE	GC/MS	No data	Detection-107 (endosulfan sulfate); 96.3 (α-endosulfan in clay soil); 104 (β-endosulfan in clay soil); 101 (α-endosulfan in topsoil); 105 (β-endosulfan in topsoil)	EPA 1996b (Method 8270)
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	0.014 µg/L (α-endosulfan); 0.004 µg/L (β-endosulfan); 0.066 µg/L (endosulfan sulfate)	97 (α-endosulfan); 93 (β-endosulfan); 89 (endosulfan sulfate)	EPA 1996c (Method 608)

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Municipal and industrial waste water; sludge	Extraction with methylene chloride and acetone, 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	α: 18–158 β: 62–158 sulfate: 31–149	EPA 1992a (Method 1656)
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 1999b (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 1999c (PAM Method 304)
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

AED = atomic emission detector; ECD = electron capture detector; EIA = enzyme-immunoassay; ELCD = electrolytic conductivity detector; GC = gas chromatography; GFF = glass fiber filter; GPC = gel permeation chromatography; HPLC = high-performance liquid chromatography; ITMS = ion trap mass spectrometer; LSE = liquid solid extraction; MS = mass spectrometry; PUF = polyurethane foam; RSD = relative standard deviation; SPE = solid phase extraction; SPME = solid phase micro-extraction

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of endosulfan is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure. GC/ECD and GC/MS are analytical techniques used for measuring endosulfan in cord blood, urine, placenta, and various biological tissues and excreta at low- and sub-ppb levels (Cerrillo et al. 2005; Fernandez et al. 2007; Guardino et al. 1996). 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. 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 3).

Effect. As mentioned in Section 3.8.2, Biomarkers Used to Characterize Effects Caused by Endosulfan, there are no specific biomarkers of effect for endosulfan. The main effect of acute-exposure to high amounts of endosulfan, as occurs in cases of intentional or accidental ingestion or dermal contact with endosulfan, is tremors and seizures. Other systemic effects may be secondary to the seizures. The effects of prolonged exposure to lower levels, as could be the case for exposure of the general population, are not known. If effects under that exposure scenario are eventually defined, then analytical methods with

appropriate sensitivity should be available to determine the levels of endosulfan in blood and body tissues that are associated with those health effects.

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 (EPA 1992a, 1994b, 1996a, 1996b, 1996c, 1997d, 1997e, 1997f, 2007; FDA 1999a, 1999b, 1999c; Gale et al. 2009; Halsall et al. 1997; Hung et al. 2002; Wania et al. 2003). 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 intermediate-duration oral MRL is 0.005 mg/kg/day, which translates to a required limit of detection of 0.175 mg/L, and these methods easily meet that need. GC/ECD or HSD is the method (Method 8080) recommended by EPA (1994b) 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.

7.3.2 Ongoing Studies

No ongoing studies regarding analytical methods sponsored by NIH or EPA were identified for endosulfan.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration oral MRL of 0.007 mg/kg/day for endosulfan based on a NOAEL of 0.7 mg/kg/day for neurological signs in rabbits (MacKenzie et al. 1981). The MRL was derived by dividing the NOAEL of 0.7 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.005 mg/kg/day for endosulfan based on a NOAEL of 0.45 mg/kg/day for immunological effects in rats (Banerjee and Hussain 1986). The MRL was derived by dividing the NOAEL of 0.45 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has adopted the intermediate-duration oral MRL for endosulfan for the chronic-duration oral MRL.

The EPA (IRIS 2012) has derived an oral reference dose (RfD) of 0.006 mg/kg/day for endosulfan based on a NOAEL of 0.6 mg/kg/day for reduced body weight gain in male and female rats and increased incidence of marked progressive glomerulonephrosis and blood vessel aneurysms in male rats in a 2-year feeding study. An uncertainty factor of 100 was used (10 for intraspecies variability and 10 for interspecies extrapolation). No reference concentration (RfC) for chronic inhalation exposures to endosulfan was reported. EPA's Office of Chemical Safety and Pollution Prevention (EPA 2010b) derived a chronic population-adjusted dose (cPAD) of 0.006 mg/kg/day based on the same data from which EPA's RfD was derived.

The EPA, the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP) have not classified endosulfan as to its carcinogenicity (IARC 2012; IRIS 2012; NTP 2011). The American Conference of Governmental Industrial Hygienists (ACGIH) has classified endosulfan as an A4 carcinogen (*not classifiable as a human carcinogen*) (ACGIH 2011).

Endosulfan, endosulfan sulfate, 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 2011i). The statutory source for this designation for endosulfan sulfate, α-, and β-isomers is Section 307 of the Clean Water Act (CWA). In addition to Section 307(a) of the CWA, the designation for endosulfan is based on Section 311(b)(2) of the CWA, and Section 3001 of the Resource Conservation and Recovery Act (RCRA) (EPA 2011i). 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 2011k). If a solid hazardous substance exits in powdered form and has a particle size less than 100 micrometers, then it is subject to the lower number. If the solid does not meet this criterion, then it is subject to the higher number. The threshold reporting quantities for endosulfan are 10 and 10,000 pounds (EPA 2011k). The reportable quantity for endosulfan and its metabolites is 1 pound (EPA 2011k).

Endosulfan is designated as a hazardous substance under Section 311 of the CWA; any discharge of these chemicals over a specified threshold level (10 pounds) into navigable waters is subject to reporting requirements (EPA 2011h).

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 2012). 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 1989). The newly established PEL for endosulfan was set at 0.1 mg/m^3 (OSHA 1989). 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, 2011).

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

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Endosulfan

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2012
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines		WHO 2008
	Endosulfan	No data[a]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2011
	Endosulfan[b,c]	0.1 mg/m^3	
AIHA	ERPGs	No data	AIHA 2011
DOE	PAC-1[d]		DOE 2012
	Endosulfan	0.1 mg/m^3	
	PAC-2[d]		
	Endosulfan	0.8 mg/m^3	
	PAC-3[d]		
	Endosulfan	280 mg/m^3	
EPA	AEGLs	No data	EPA 2011c
	Hazardous air pollutant	No data	EPA 2012e 42 USC 7412
	NAAQS	No data	EPA 2010c
NIOSH	REL (10-hour TWA)		NIOSH 2011
	Endosulfan[e]	0.1 mg/m^3	
	IDLH		
	Endosulfan	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2012 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2011d 40 CFR 116.4
	Endosulfan	Yes	
	Drinking water contaminant candidate list	No data	EPA 1998b 63 FR 10274
	Drinking water standards and health advisories	No data	EPA 2011e
	Master Testing List	No data	EPA 2012f
	National primary drinking water standards	No data	EPA 2009a

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Endosulfan

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	National recommended water quality criteria: freshwater and saltwater		EPA 2009b
	α-Endosulfan and β-endosulfan		
	Freshwater CMC (acute)[f,g]	0.22 µg/L	
	Freshwater CCC (chronic)[f,g]	0.056 µg/L	
	Saltwater CMC (acute)[f,g]	0.034 µg/L	
	Saltwater CCC (chronic)[f,g]	0.0087 µg/L	
	National recommended water quality criteria: human health for the consumption		
	Endosulfan sulfate, α-endosulfan, and β-endosulfan		
	Water plus organism[h]	62 µg/L	
	Organism only[h]	89 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2011h 40 CFR 117.3
	Endosulfan	1 pound	
c. Food			
FDA	EAFUS[i]	No data	FDA 2012
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2011
	Endosulfan	A4[J]	
EPA	Carcinogenicity classification	No data	IRIS 2012
	RfC	No data	
	RfD		
	Endosulfan	0.006 mg/kg/day	
	Identification and listing of hazardous waster		EPA 2011f 40 CFR 261, Appendix VIII
	Endosulfan	P050	
	Inert pesticide ingredients in pesticide products	No data	EPA 2011g
	RCRA waste minimization PBT priority chemical list		EPA 1998a 63 FR 60332
	α-Endosulfan	Yes	
	β-Endosulfan	Yes	
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2011l 40 CFR 264, Appendix IX
	Endosulfan sulfate	Yes	
	α-Endosulfan	Yes	
	β-Endosulfan	Yes	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Endosulfan

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity		EPA 2011i 40 CFR 302.4
	Endosulfan[k]	1 pound	
	Endosulfan sulfate[l]	1 pound	
	α-Endosulfan[l]	1 pound	
	β-Endosulfan[l]	1 pound	
	Effective date of toxic chemical release reporting	No data	EPA 2011j 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity		EPA 2011k 40 CFR 355, Appendix A
	Endosulfan		
	Reportable quantity	1 pound	
	Threshold planning quantity	10/10,000 pounds	
	TSCA chemical lists and reporting periods	No data	EPA 2011m 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2011b 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2011
STATE			
California	Hazardous substance list		Cal/OSHA 2012
	Endosulfan	Yes	
	α-Endosulfan	Yes	
	β-Endosulfan	Yes	
Colorado	Non-criteria reportable pollutant		CDPHE 2011
	Endosulfan	Yes	
Connecticut	Hazard limiting value		Connecticut DEEP 2006
	Endosulfan		
	8-hour HLV	2 μg/m^3	
	30-minute HLV	10 μg/m^3	
Delaware	Chemicals and reportable quantities		Delaware DNREC 2010
	Endosulfan	Yes	
	α-Endosulfan	Yes	
	β-Endosulfan	Yes	
	Endosulfan sulfate	Yes	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Endosulfan

Agency	Description	Information	Reference
STATE *(cont.)*			
Idaho	Toxic air pollutants non-carcinogenic increments		Idaho DEQ 1995
	Endosulfan		
	Occupational exposure level	0.1 mg/m^3	
	Emissions level	0.007 pounds/hour	
	Acceptable ambient concentrations	0.005 mg/m^3	
Maryland	Class II toxic air pollutant requiring emission estimates or ambient impact analysis by existing sources		MDE 2012
	Endosulfan		
	Compliance date	07/01/1990	
Michigan	Exposure limits for air contaminants		MIOSHA 2001
	Endosulfan[e]		
	TWA	0.1 mg/m^3	
New Hampshire	Regulated toxic air pollutants		New Hampshire DES 2012
	Endosulfan, inhalable fraction and vapor		
	Toxicity class	Toxicity Class I	
	24-hour AAL	0.36 µg/m^3	
	Annual AAL	0.24 µg/m^3	
	24-hour *de minimis*	0.0043 pounds/day	
	Annual *de minimis*	1.6 pounds/day	
New York	Limits for air contaminants		New York DOL 2012
	Endosulfan[e]		
	TWA	0.1 mg/m^3	
Tennessee	Limits for air contaminants		Tennessee DOL 2010
	Endosulfan[e]		
	TWA	0.1 mg/m^3	
Vermont	Limits for air contaminants		VOSHA 2005
	Endosulfan[e]		
	TWA	0.1 mg/m^3	
Wisconsin	Reporting levels for air contaminants		Wisconsin DNR 2010
	Endosulfan		
	Reporting level	23.5 pounds/year	

[a]Endosulfan occurs in drinking-water at concentrations well below those at which toxic effects may occur.
[b]Inhalable fraction and vapor is noted because endosulfan exerts sufficient vapor pressure such that it may be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration.
[c]Skin: refers to the potential significant contribution to the overall exposure by the cutaneous route.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Endosulfan

Agency	Description	Information	Reference

[d]PAC-1: mild, transient health effects. PAC-2: irreversible or other serious health effects that could impair the ability to take protective action. PAC-3: life-threatening health effects.
[e]Skin designation
[f]The CMC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed briefly without resulting in an unacceptable effect. The CCC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect. The CMC and CCC are just two of the six parts of an aquatic life criterion; the other four parts are the acute averaging period, chronic averaging period, acute frequency of allowed exceedence, and chronic frequency of allowed exceedence. Because 304(a) aquatic life criteria are national guidance, they are intended to be protective of the vast majority of the aquatic communities in the United States.
[g]This value was derived from data for endosulfan and is most appropriately applied to the sum of α-endosulfan and β-endosulfan.
[h]This criterion has been revised to reflect The EPA's q1* or RfD, as contained in IRIS as of May 17, 2002.
[i]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[j]A4: not classifiable as a human carcinogen
[k]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) and Section 307(a)of the Clean Water Act and Section 3001 of RCRA.
[l]Designated CERCLA hazardous substance pursuant to Section 307(a)of the Clean Water Act.
[m]Acceptable ambient concentrations (AAC) are twenty-four (24) hour averages.

AAL = ambient air limit; ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CCC = criterion continuous concentration; CDPHE = Colorado Department of Public Health and Environment; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = criteria maximum concentration; DEEP = Department of Energy and Environmental Protection; DEQ = Department of Environmental Quality; DES = Department of Environmental Services; DNREC = Department of Natural Resources and Environmental Control; DNR = Department of Natural Resources; DOE = Department of Energy; DOL = Department of Labor; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; HLV = hazard limiting value; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MDE = Maryland Department of the Environment; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PBT = Persistent, Bioaccumulative, and Toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; VDOL = Vermont Department of Labor; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

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

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

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

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

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

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

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

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

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

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

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

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

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

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

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

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

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

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

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

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

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

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

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

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

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endosulfan
CAS Numbers: 115-29-7
Date: October 2012
Profile Status: Final Draft, Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 32
Species: Rabbit

Minimal Risk Level: 0.007 [X] mg/kg/day [ ] ppm

Reference: MacKenzie KM, Felton SM, Dickie SM, et al. 1981. Raltech Study No. 80070. Teratology study with FMC 5462 in rabbits. FMC Corporation. Submitted to U.S. Environmental Protection Agency. MRID504800201.

Experimental design: Groups of mated New Zealand White rabbits (20/ dose group) were administered technical endosulfan by gavage in corn oil in doses of 0, 0.3, 0.7, or 1.8 mg/kg/day from Gd 6 to 28; dams were sacrificed on Gd 29. Body weight was measured on Gd 0 and 6 and at 6-day intervals thereafter. Body weight was also measured on sacrifice day (actual and corrected for gravid uterine weight). Clinical signs were monitored twice daily. At necropsy, the ovaries were removed and examined for gross abnormalities and the number of corpora lutea was recorded. The gravid uterus was weighed and opened after external examination. The following parameters were recorded: number and location of live and dead fetuses, early and late resorptions, empty sites and implantation scars, unusual coloration and variation in amniotic fluid and placenta, and any other abnormalities. Fetuses, were sexed, measured, weighed, examined grossly, and given a thorough visceral examination and then prepared for skeletal examination.

Effect noted in study and corresponding doses: Since deaths occurred in the high-dose group (not totally clear when these deaths occurred), 6 mated females were added to this group for a total of 26 dams. It appears that after the six dams were added to the high-dose group, four dams died before the study termination, three of them possibly due to regurgitation and aspiration of the test material into the trachea and lung and the fourth of unestablished causes. No deaths occurred in the other groups. Neurological signs were observed in three high-dose dams within 4 days of the start of treatment (in one female on Gd 6, the day of the first dose, and in two females on Gd 10, after four doses). The signs consisted of noisy and rapid breathing, hyperactivity and convulsions. No such signs occurred in the other treated groups or in the control group. No rabbits aborted during this study. Treatment with endosulfan did not significantly affect body weight changes between Gd 0 and 29 (corrected or uncorrected). Exposure to endosulfan did not significantly alter pregnancy maintenance, implantation, litter size, sex ratio, mean fetal weight and length, or number and percent of live or resorbed fetuses. There were no dead fetuses in any treatment group or in controls. Exposure to endosulfan also did not result in dose-related increased incidences of gross, soft tissue, or skeletal malformations.

As indicated in Section 2.3, although the incidence of neurological effects of 3/26 reported in the high-dose group within 4 days after dosing started is not statistically different from 0/20 in the other groups ($p=0.1713$, Fisher Exact Test), it is appropriate to consider the 1.8 mg/kg/day dose level a LOAEL based on the biological significance of the effect. Therefore, the dose level of 1.8 mg/kg/day in the MacKenzie et al. (1981) study is considered an acute LOAEL for neurological signs; the NOAEL is 0.7 mg/kg/day.

Incidence data for neurological signs in rabbits occurring within 14 days after dosing started in the MacKenzie et al. (1981) study were analyzed using the BMD approach. The incidence data were 0/20, 0/20, 0/20, and 3/26 in the control, 0.3, 0.7, and 1.8 mg/kg/day dose groups, respectively. Models in the EPA BMDS (version 2.1.1) were fit to the data set to determine potential PODs for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the POD when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) is chosen. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body weight, in the absence of a clear criteria as to what level of change in body/organ weight or body weight gain should be considered adverse, the BMR is defined as a change in weight or weight/gain equal to 1 standard deviation from the control mean (EPA 2000a). Using the criteria for model selection mentioned above, the Gamma model (BMD_{10} 1.76 mg/kg/day; $BMDL_{10}$ 1.23 mg/kg/day) was selected as the best model to fit the incidence of clinical signs in pregnant female rabbits. However, the $BMDL_{10}$ of 1.23 mg/kg/day is not only very close to the BMD_{10} of 1.76 mg/kg/day, a dose that caused serious effects in the study, but it is even closer to a dose of 1.5 mg/kg/day, which caused the same type of serious clinical signs and even death in one of nine rabbits in the Hatipoglu et al. (2008) study. Taking this into consideration and in the interest of protecting human health, the NOAEL of 0.7 mg/kg/day for clinical signs in the MacKenzie et al. (1981) study is preferred as the POD for derivation of an acute-duration oral MRL for endosulfan.

Dose and end point used for MRL derivation: 0.7 mg/kg/day; neurological clinical signs.

[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? Not applicable.

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: Neurological effects are characteristic of endosulfan and other chlorinated pesticides in humans and animals. An additional study in rabbits reported clinical signs including hyperexcitability, dyspnea, hyperpnea, intermittent intervals of tremors and tonic-clonic convulsions, thrashing against the cage walls, depression, and forelimb extension leading to death in 1/9 and 2/9 New Zealand White male rabbits 10–40 minutes following gavage dosing with 1.5 or 3 mg/kg endosulfan, respectively (Hatipoglu et al. 2008).

Agency Contact (Chemical Manager): Jessilynn Taylor

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endosulfan
CAS Numbers: 115-29-7
Date: October 2012
Profile Status: Final Draft, Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 69
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 four 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 was 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.

Effect noted in study and corresponding doses: 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.

Data from Banerjee and Hussain (1986) were considered for benchmark modeling analysis. However, only the information regarding serum levels of IgM and IgG, which are presented in a table, could have been subjected to benchmark modeling. Data regarding serum antibody titer to tetanus toxoid as well as leucocyte and macrophage migration inhibition were presented in figures from which only approximate values could be determined. Still, Banerjee and Hussain (1986) indicated in the figures the dose levels at which the responses were significantly different from controls. Therefore, since the lowest dose of 0.45 mg/kg/day (5 ppm in the food) was the NOAEL for serum IgG and IgM levels, antibody titer, and leucocyte and macrophage migration inhibition, the NOAEL/LOAEL approach is preferred for MRL derivation since it includes the three data sets. The study LOAEL was 0.9 mg/kg/day (10 ppm in the food).

Dose and end point used for MRL derivation: 0.45 mg/kg/day; depressed immune response.

[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, 0.45 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).

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: With the exception of a study by Hoechst (1988c), which reported that doses up to 4.5 mg/kg/day given to Wistar rats 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, the study by Banerjee and Hussain (1986) is the only one that has examined immunocompetence in response to an infective agent, and would be helpful to try to replicate it. Vos et al. (1982) reported that serum levels of IgM and IgG were not significantly altered in male Wistar rats dosed with 5 mg/kg/day endosulfan for 3 weeks, but resistance to infection was not tested.

Agency Contact (Chemical Manager): Jessilynn Taylor

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endosulfan
CAS Numbers: 115-29-7
Date: October 2012
Profile Status: Final Draft, Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 69
Species: Rat

Minimal Risk Level: ATSDR adopts the intermediate-duration oral MRL of 0.005 mg/kg/day for the chronic oral MRL, as explained below.

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.

Chronic-duration dietary studies have been conducted in rats, mice, and dogs. Studies in Wistar rats were conducted by FMC (1959b) and Hoechst (1989a), the former used 25 rats per sex per group and the latter 70 rats per sex per group. The results of Hoechst (1989a) were later published as Hack et al. (1995) with emphasis on the neoplastic effects of endosulfan. A 2-year study in NMRI mice was conducted by Hoechst (1988b) and the results were later published as Hack et al. (1995), also with emphasis on the neoplastic effects of endosulfan. A 2-year study in beagle dogs was conducted by FMC (1967) and a 1-year study was conducted by Hoechst (1989c); the former used four dogs per sex per group and the latter used six dogs per sex per group. NCI (1978) conducted long-term studies in Osborne-Mendel rats and B6C3F1 mice. These studies conducted gross and microscopic examination of organs and tissues in addition to hematology and clinical chemistry tests. All of these studies used comparable doses of technical endosulfan (up to approximately 5 mg/kg/day) except for the NCI (1978) study that used doses considerably higher in rats (up to 48 and 22 mg/kg/day, in males and females, respectively). The lowest LOAELs in rats were identified in the Hoechst (1989a) study. The most salient findings in that study included reductions in weight gain and increased incidences of marked progressive glomerulonephrosis in male and female rats from the highest-dose groups. These data are presented in Tables 1 through 4. The incidence of aneurysms in the kidneys of male rats was also increased, but there was no dose-response relationship (10/70, 6/70, 17/70, 10/70, and 19/70 in the control and respective increasing dose groups).

Table 1. Incidence of Marked Progressive Glomerulonephrosis in Male Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	70	20
0.1	70	18
0.3	70	22
0.6	70	24
2.9	70	30[a]

[a]p=0.055

Source: Hoechst 1989a

Table 2. Incidence of Marked Progressive Glomerulonephrosis in Female Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	70	1
0.1	70	6
0.4	70	6
0.7	70	5
3.8	70	8[a]

[a]p=0.017

Source: Hoechst 1989a

Table 3. Data for the Change in Body Weight Gain in Male Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Number of animals tested	Weight gain (g)	Standard deviation
0	70	580	124
0.1	70	570	125
0.3	70	531	131
0.6	70	525	115
2.9	70	479[a]	94

[a]p<0.01

Source: Hoechst 1989a

Table 4. Data for the Change in Body Weight Gain in Female Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Number of animals tested	Weight gain (g)	Standard deviation
0	70	398	105
0.1	70	350	107
0.4	70	414	85
0.7	70	363	92
3.8	70	328[a]	100

[a]p<0.05

Source: Hoechst 1989a

In mice, the highest dose tested in the Hoechst (1988b) study, 2.9 mg/kg/day, caused a significant reduction in survival rate in females (28 versus 45% in controls). No other significant treatment-related effects were reported in chronic-duration studies in mice. No significant adverse effects were reported in the 2-year study in beagle dogs that received doses of endosulfan of up to 1 mg/kg/day via the diet (FMC 1967). In the 1-year study, the dogs were fed a diet containing 0, 3, 10, or 30 ppm endosulfan (0, 0.2, 0.7,

2 mg/kg/day for males and 0, 0.2, 0.6, 1.8 mg/kg/day for females) (Hoechst 1989c). Dogs fed a diet with ≥45 ppm endosulfan were sacrificed earlier due to severe neurological effects. In the 30 ppm group, three males and two females experienced violent contractions of the abdominal muscles and upper abdomen and convulsive movements of the chap muscles 2.5–6 hours after feeding. Dogs fed the ≤30 ppm diets did not show significant treatment-related alterations in organs and tissues or in hematology values. Among clinical chemistry parameters, dogs in the ≥10 ppm diet groups showed a significant increase in mean serum alkaline phosphatase activity relative to controls (up to approximately 2-fold) beginning at 1.5 months. In the absence of significant changes in other serum enzymes and lack of treatment-related histological alterations in the liver, the investigators did not consider the changes in alkaline phosphatase activity toxicologically significant.

Of the studies mentioned above, the 2-year study in rats conducted by Hoechst (1989a) is the most appropriate for MRL derivation based on the number of animals used per group (n=70), duration of exposure that covered the entire lifespan of the animals, and identification of valid end points, such as kidney lesions and body weight changes, for which dose-response relationships could be constructed. Data sets for marked progressive glomerulonephrosis and body weight changes in male and female rats reported in the Hoechst (1989a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the four data sets to determine potential points of departure for the MRL. The data set for changes in weight gain in female rats proved not suitable for benchmark modeling even after dropping the two highest doses (out of five dose levels tested). Using the criteria for model selection mentioned earlier (see acute-duration oral MRL), the Log-logistic model (BMD_{10} 5.84 mg/kg/day; $BMDL_{10}$ 2.31 mg/kg/day) was selected as the best model to fit the incidence of marked progressive glomerulonephrosis in female rats. The Log-logistic model also provided the best fit for incidence of marked progressive glomerulonephrosis in male rats (BMD_{10} 1.17 mg/kg/day; $BMDL_{10}$ 0.56 mg/kg/day). The Exponential (Model 2) provided the best fit for the decrease in body weight gain in male rats (BMD_{10} 4.60 mg/kg/day; $BMDL_{10}$ 3.41 mg/kg/day). The results of the modeling are shown in Tables A-1, A-2, and A-3.

APPENDIX A

Table A-1. Model Predictions for Increased Incidence of Marked Progressive Glomerulonephrosis in Female Rats Exposed to Endosulfan for 2 Years

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMD	Scaled residuals[b] Dose above BMD	Scaled residuals[b] Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	3	3.87	0.28	-0.09	NA	-1.61	187.00	5.39	3.01
LogLogistic[c,d]	***3***	***3.85***	***0.28***	***-0.17***	***NA***	***-1.55***	***186.84***	***5.84***	***2.31***
LogProbit[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Multistage (1-4 degree)[e]	3	3.85	0.28	-0.16	NA	-1.56	186.86	5.79	2.41
Probit	3	3.87	0.28	-0.10	NA	-1.60	186.98	5.47	2.94

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Slope restricted to ≥1.
[d]Selected model. All models, except for the LogProbit (computation failed) were fit to the data. Gamma and Weibull models were included but are not shown in the table because they defaulted to the Multistage 1 degree model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (LogLogistic Model).
[e]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested)

Table A-2. Model Predictions for Increased Incidence of Marked Progressive Glomerulonephrosis in Male Rats Exposed to Endosulfan for 2 Years

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	3	0.72	0.87	0.50	-0.10	-0.63	441.06	1.47	0.90
LogLogistic[c,d]	***3***	***0.57***	***0.90***	***0.40***	***-0.13***	***-0.58***	***440.91***	***1.17***	***0.56***
LogProbit[c]	3	1.22	0.75	0.73	-0.06	-0.74	441.55	1.93	1.21
Multistage (1-4 degree)[e]	3	0.63	0.89	0.44	-0.12	-0.60	440.96	1.28	0.68
Probit	3	0.71	0.87	0.50	-0.10	-0.63	441.05	1.45	0.88

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Slope restricted to ≥1.
[d]Selected model. All models were fit to the data. Gamma and Weibull models were included but are not shown in the table because they defaulted to the Multistage 1 degree model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold), so the model with the lowest BMDL was selected (LogLogistic model).
[e]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested)

Table A-3. Model Predictions for Decreased Body Weight Gain in Male Rats Exposed to Endosulfan for 2 Years

Model	Test for significant difference *p*-value[a]	Variance *p*-value[b]	Mean *p*-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Linear[d]	<0.0001	0.06	0.09	0.37	NA	-1.43	3701.35	3.99	3.00
Non-constant variance									
Exponential (model 2)[e,f]	***<0.0001***	***0.43***	***0.29***	***0.30***	***NA***	***-1.33***	***3694.57***	***4.60***	***3.41***
Exponential (model 4)[e]	<0.0001	0.43	0.89	NA	NA	NA	3693.08	NA	NA
Exponential (model 5)[e]	<0.0001	0.43	0.89	NA	NA	NA	3693.08	NA	NA
Hill[e]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Linear[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.39
Polynomial (2-degree)[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.39
Polynomial (3-degree)[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.37
Polynomial (4-degree)[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.30
Power[e]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.39

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1
[f]Selected model. Constant variance model did not fit variance data, but non-constant variance model did. With non-constant variance model applied, all models except for the Hill (computation failed) provided adequate fit to means. Although the Exponential 4 and 5 models provided adequate fit to the means, the BMD and BMDL computations failed. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 2 model; the Exponential 3 converged onto the Exponential 2).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation

The lower $BMDL_{10}$ of 0.56 mg/kg/day is more health protective and is selected as the point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 0.56 mg/kg/day results in a chronic-duration oral MRL of 0.006 mg/kg/day for endosulfan. Since this MRL is slightly higher than the intermediate-duration oral MRL of 0.005 mg/kg/day derived for endosulfan, the intermediate-duration oral MRL, which is protective of potential effects due to chronic exposure to endosulfan, is adopted also for the chronic-duration oral MRL for endosulfan.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

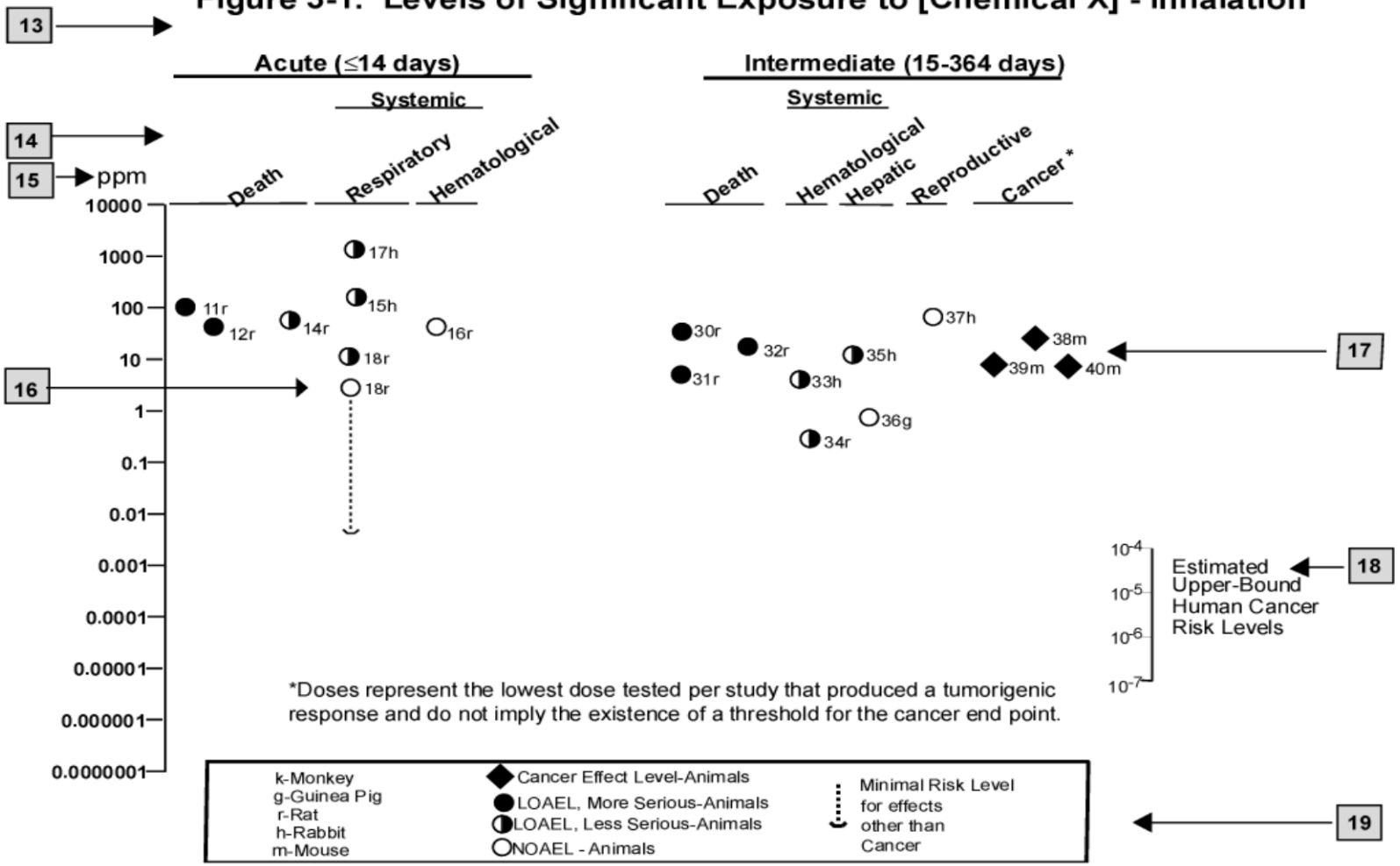
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX