TOXICOLOGICAL PROFILE FOR ENDRIN

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

August 1996

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for endrin was released in May 1989. This edition supersedes any previously released draft or final profile.

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

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

FOREWORD

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

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

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

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audience for the toxicological profiles is health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Super-fund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on April 29,1996 (61 FR 18744). For prior versions of the list of substances, see *Federal Register* notices dated April 17,1987 (52 FR 12866); October 20,1988 (53 FR 41280); October 26,1989 (54 FR 43619); October 17,199O (55 FR 42067); October 17,199l (56 FR 52166); October 28,1992 (57 FR 48801); and February 28,1994 (59 FR 9486). Section 104(I)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Jessilyn Taylor, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Jerry W. Spoo, DVM
Research Triangle Institute, Research Triangle Park, NC

Lorrene Buckley Kedderis, Ph.D., DABT
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1 . Green Border Review. Green Border review assures consistency with ATSDR policy.

2. 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.

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

PEER REVIEW

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

1 . Dr. Gary Booth, Brigham Young University, Provo, Utah;

2 . Dr. Donald Morgan, Private Consultant, Iowa City, Iowa; and

3 . Dr. Martha J. Radike, Department of Environmental Health, University of Cincinnati, Cincinnati, Ohio.

These experts collectively have knowledge of endrin'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(1)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about endrin and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Endrin has been found in at least 120 (8.4%) of the current or former NPL sites. Endrin ketone has been found in at least 37 sites of the current or former sites on the NPL. However, the number of NPL sites evaluated for endrin ketone is not known. As the EPA evaluates more sites, the number of sites at which endrin ketone is found may increase. This information is important because exposure to endrin may cause harmful health effects and because these sites are potential or actual sources of human exposure to endrin.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as endrin, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT IS ENDRIN?

This toxicologic profile focuses on endrin, but because of its close association to both endrin aldehyde and endrin ketone, the profile includes studies with data relevant to human exposure to these compounds when available.

Endrin is a solid, white, almost odorless substance that was used as a pesticide to control insects, rodents, and birds. Endrin has not been produced or sold for general use in the United States since 1986. Little is known about the properties of endrin aldehyde, an impurity and breakdown product of endrin, or endrin ketone, which is a product of endrin when it is exposed to light.

Further information on the properties and uses of endrin, endrin aldehyde, and endrin ketone is in Chapters 3 and 4.

1.2 WHAT HAPPENS TO ENDRIN WHEN IT ENTERS THE ENVIRONMENT?

Endrin does not dissolve very well in water. It has been found in ground water and surface water, but only at very low levels. It is more likely to cling to the bottom sediments of rivers, lakes, and other bodies of water. Endrin is generally not found in the air except when it was applied to fields during agricultural applications.

The persistence of endrin in the environment depends highly on local conditions. Some estimates indicate that endrin can stay in soil for over 10 years. Endrin may also be broken down by exposure to high temperatures (230 (C) or light to form primarily endrin ketone and endrin aldehyde.

It is not known what happens to endrin aldehyde or endrin ketone once they are released to the environment; however, the amount of endrin broken down to endrin aldehyde or endrin ketone is very small (less than 5%). Chapter 5 has information on the presence of endrin, endrin aldehyde, or endrin ketone in the environment.

1.3 HOW MIGHT I BE EXPOSED TO ENDRIN?

Since endrin is no longer produced or used in the United States, you can probably be exposed to it only in areas where it is concentrated, such as a hazardous waste site. You may be exposed to endrin in air, water, or soil if you live near a hazardous waste site. Endrin has been detected at 120 (8.4%) such sites. Children living near hazardous waste sites could be exposed to endrin in contaminated soils, if they eat dirt. Detection of endrin in ground water or drinking water is rare. In the U.S. EPA 1989 National Pesticide in Groundwater Study, in which ground water was collected from areas with significant agricultural land uses as well as urban areas, only two wells were found with detectable levels of endrin. In wells drilled to access ground water near hazardous waste sites, 1.3% of 156 Resource Conservation and Recovery Act (RCRA) sites and 0.9% of 178 Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) or Superfund sites had detectable levels of endrin in the early 1980s. No information about the presence of endrin aldehyde or endrin ketone in the environment was found.

You may also be exposed to endrin by eating foods that contain endrin. Before cancellation of endrin use, reported concentrations of endrin in domestic and imported food samples ranged from 0.05 to 0.50 parts per million (ppm; where 1 ppm = 1 microgram per gram (μg/g) of food). However, no endrin was detected in food samples from a Texas survey and only 0.084% of over 13,000 food samples were found to contain endrin in 1989 after cancellation of endrin use. Endrin was found in less than 1% of all food sampled by the U.S. Food and Drug Administration (FDA) in 1991. Because endrin is no longer used in the United States, residues on imported foods are the main source of potential human exposure in food. The levels of endrin aldehyde or endrin ketone in foods are not known.

Endrin levels can build up (bioaccumulate) in the tissues of organisms that live in water. In the 1986 EPA National Study of Chemical Residues in Fish, concentrations of endrin were found in fish at 11% of 362 sites surveyed (average 1.69 parts per billion [ppb; where 1 ppb = 1 nanogram per gram (ng/g) of food]; maximum 162 ppb). Endrin was also detected in 21 of 31 samples of 2 commercial shrimp species from a Gulf Coast estuary receiving both

industrial discharges, and urban and agricultural runoff. The average concentration was 1,070 and the maximum concentration was 9,470 ppb. Levels of endrin have probably declined, even in such polluted areas, since using endrin was banned.

Endrin has been detected in human breast milk (0.02-6.24 milligrams endrin in each kilogram milk fat [mg/kg]); this may be a route of exposure for nursing infants. However, no studies of endrin in breast milk in United States or Canadian populations have been conducted.

Further information on the ways you may be exposed to endrin is in Chapter 5.

1.4 HOW CAN ENDRIN ENTER AND LEAVE MY BODY?

Endrin and endrin aldehyde can enter your body when you eat foods or drink beverages or breathe air that contain this substance, or when it comes in contact with your skin. When endrin enters your body in any of these ways, it is rapidly changed into other substances. Endrin and its metabolic breakdown products are rapidly removed from the body, usually within a few days, through the urine and feces. There is some evidence that small amounts of endrin may remain in the fatty tissue of your body when you are exposed to high levels. No information is known about how endrin aldehyde or endrin ketone leaves the body.

Further information on endrin uptake and excretion is in Chapter 2.

1.5 HOW CAN ENDRIN AFFECT MY HEALTH?

Exposure to endrin can cause various harmful effects including death and severe central nervous system (brain and spinal cord) injury. Swallowing large amounts of endrin (more than 0.2 mg/kg of body weight) may cause convulsions and kill you in a few minutes or hours.

1. PUBLIC HEALTH STATEMENT

Symptoms that may result from endrin poisoning are headache, dizziness, nervousness, confusion, nausea, vomiting, and convulsions. Some of these symptoms may continue for weeks after exposure to high doses of endrin.

No long-term health effects have been noted in workers, either in factories or during field applications, who have been exposed to endrin by breathing or touching it.

Studies in animals confirm that endrin's main target is the nervous system, probably because the brain and other parts of the nervous system contain much fatty tissue, and endrin tends to stay in those tissues. Birth defects, especially abnormal bone formation, have been seen in some animal studies. While there are no human data on birth defects, evidence in rodents suggests that exposure to high doses of endrin during pregnancy could be a health risk to developing fetuses.

In studies using rats, mice, and dogs, endrin did not produce cancer. However, most of these studies did not accurately evaluate the ability of endrin to cause cancer. No significant excess of cancer has been found in exposed factory workers, although endrin metabolites have been detected in their urine. The EPA has determined that endrin is not classifiable as to its human carcinogenicity because there is not enough information to allow classification. Endrin has also not been classified for carcinogenic effects by the Department of Health and Human Services (DHHS) or the International Agency for Research on Cancer (IARC).

One study in rodents suggests that exposure to endrin aldehyde or endrin ketone may cause liver disease. No other studies were found on how endrin aldehyde or endrin ketone can affect your health.

Further information on the health effects of endrin is in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ENDRIN?

If you are exposed to endrin, the chemical can be detected in your blood, breast milk, or fatty tissue. Tests can measure endrin in the blood or fat of people recently exposed. Endrin is cleared from the blood rapidly, so samples should be taken within l-2 weeks of exposure. Since special analytical equipment is needed (see Chapter 6), these tests are not routinely performed in doctors' offices. Although these tests can be used to confirm that a person has been exposed to endrin, it is not yet possible to use those tests to predict the type or severity of any health effects that might occur. Endrin metabolites have been found in urine (0.001-0.14 micrograms per milliliter [(μ/mL]; where 1 (μ/mL = 1 ppm) and feces of workers exposed to endrin.

Further information on how endrin levels can be measured in exposed persons is in Chapter 6. No information is available on tests for exposure to endrin aldehyde or endrin ketone.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

In order to protect people from potential health effects, the EPA banned the production and use of endrin in the United States in 1986. The EPA's proposed maximum contaminant level (MCL) in drinking water is 0.0002 milligrams per liter (mg/L; I mg/L = 1 ppm). The EPA has also set health advisories which are levels of a chemical in water that are safe. The l-day and 10-day health advisories for endrin are 0.02 mg endrin per liter of water for both children and adults. The longer-term health advisories for children and adults are 0.003 mg/L and 0.01 mg/L, respectively. The lifetime health advisory for children and adults is 0.002 mg/L. The EPA recommends an ambient water quality criteria level of 0.001 mg/L to protect human health.

The National Institute of Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) have established a limit of 0.1 mg endrin per cubic

meter of air (0.1 mg/m^3) averaged over an 8-hour day in an occupational setting for a 40-hour work week. In addition, NIOSH considers that a person could escape within 30 minutes from a concentration of 2,000 mg/m^3 without respiratory protection and without experiencing any escape-impairing or irreversible health effects.

More detailed information on federal and state regulations related to endrin is in Chapter 7. No information can be found on government regulations for endrin aldehyde or endrin ketone.

1.8 WHERE CAN I GET MORE INFORMATION?

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

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

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

2.2.1 Inhalation Exposure

Limited data are available regarding inhalation exposure of humans and animals. Results of these studies are discussed below and presented in Table 2-1 and Figure 2-1.

2.2.1.1 Death

Deaths in humans after occupational exposure to endrin have not been reported, although exposure was high enough to cause tonic-clonic contractions and seizures. One epidemiological study (Ditraglia et al. 1981) showed a significantly increased number of deaths due to nonmalignant respiratory system disease (pneumonia and "other respiratory diseases") in the aldrin/dieldrin/endrin cohort in one manufacturing site. However, the observed increase in deaths due to nonmalignant respiratory disease cannot be clearly attributed to endrin because simultaneous exposure to other chemicals occurred and nonmalignant respiratory disease was not observed at another plant that also manufactured endrin (Ditraglia et al. 1981). In another study, the total observed mortality was 25 in a cohort of 232 aldrin/dieldrin/endrin/telodrin-manufacturing workers versus 38 expected in the general male population (Ribbens 1985). The worker mortality study is limited by small cohort size with resulting low statistical power to detect increased mortality and by the fact that simultaneous exposure also occurred.

A cat exposed twice for one hour to 6,500 mg/m^3 (417 ppm) endrin as a spray of 1.5% aqueous solution died within 24 hours (Ressang et al. 1959). In another inhalation study, 6 species of animals were exposed to endrin vapor at 15 mg/m^3 (0.36 ppm) for 7 hours a day, 5 days a week for up to 130 exposures (Treon et al. 1955). Two of 4 rabbits died after 26 and 90 exposures, and 1 of 3 mice died after 22 exposures. The cat, 2 guinea pigs, 2 hamsters, and 3 rats survived 130 exposures. Diffuse degenerative changes were observed in kidneys, livers, and brains in all animals that died, except in the mouse where effects on the brain were not observed.

The concentrations associated with death in each species are recorded in Table 2-1 and plotted in Figure 2-1. No studies were located regarding lethal effects in humans or animals after inhalation exposure to endrin aldehyde or endrin ketone.

Table 2-1. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Cat (NS)	2x 1 hr				417 (1/1 died)	Ressang et al. 1959 Endrin
	Neurological						
2	Cat (NS)	2x 1 hr				417 (slight degenerative lesions of ganglion cells in the brain)	Ressang et al. 1959 Endrin
	INTERMEDIATE EXPOSURE						
	Death						
3	Mouse (NS)	107 d 5 d/wk 7 hr/d				0.36 (1/3 mice died)	Treon et al. 1955 Endrin
4	Rabbit (NS)	118 d 5 d/wk 7 hr/d				0.36 (2/4 rabbits died)	Treon et al. 1955 Endrin
	Systemic						
5	Mouse (NS)	107 d 5 d/wk 7 hr/d	Hepatic			0.36 (diffuse degenerative changes)	Treon et al. 1955 Endrin
			Renal			0.36 (diffuse degenerative changes)	
6	Rabbit (NS)	118 d 5 d/wk 7 hr/d	Resp			0.36 (granulomatous pneurnonitis)	Treon et al. 1955 Endrin
			Hepatic			0.36 (diffuse degenerative changes)	
			Renal			0.36 (diffuse degenerative changes)	

Table 2-1. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL				Reference
					Less serious (ppm)		Serious (ppm)		
	Neurological								
7	Mouse (NS)	107 d 5 d/wk 7 hr/d		0.36					Treon et al. 1955 Endrin
8	Rabbit (NS)	118d 5 d/wk 7 hr/d					0.36	(diffuse degenerative lesions in brain)	Treon et al. 1955 Endrin

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

d = day(s); hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = times

Figure 2-1. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Inhalation

Acute (≤14 days)

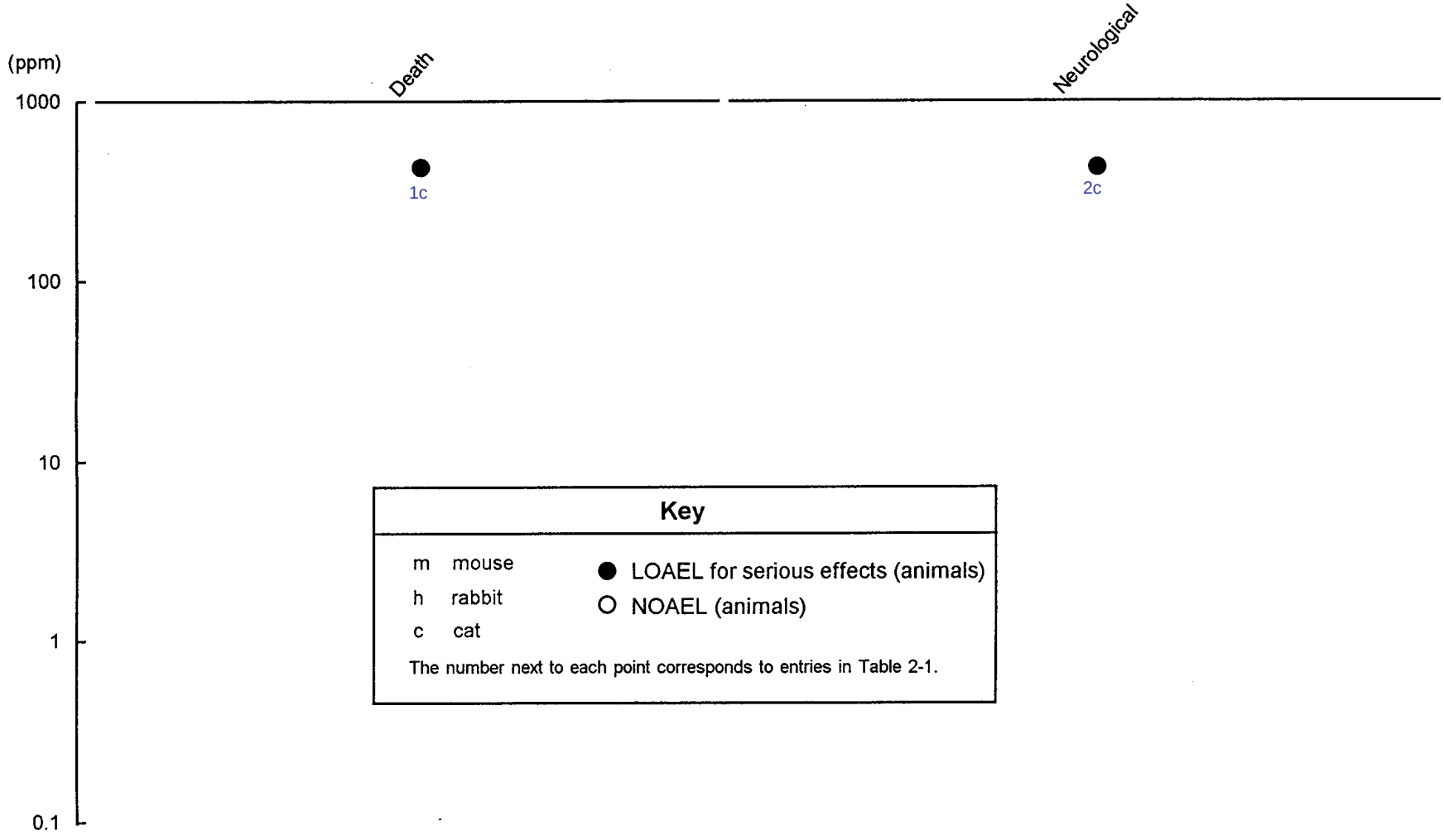
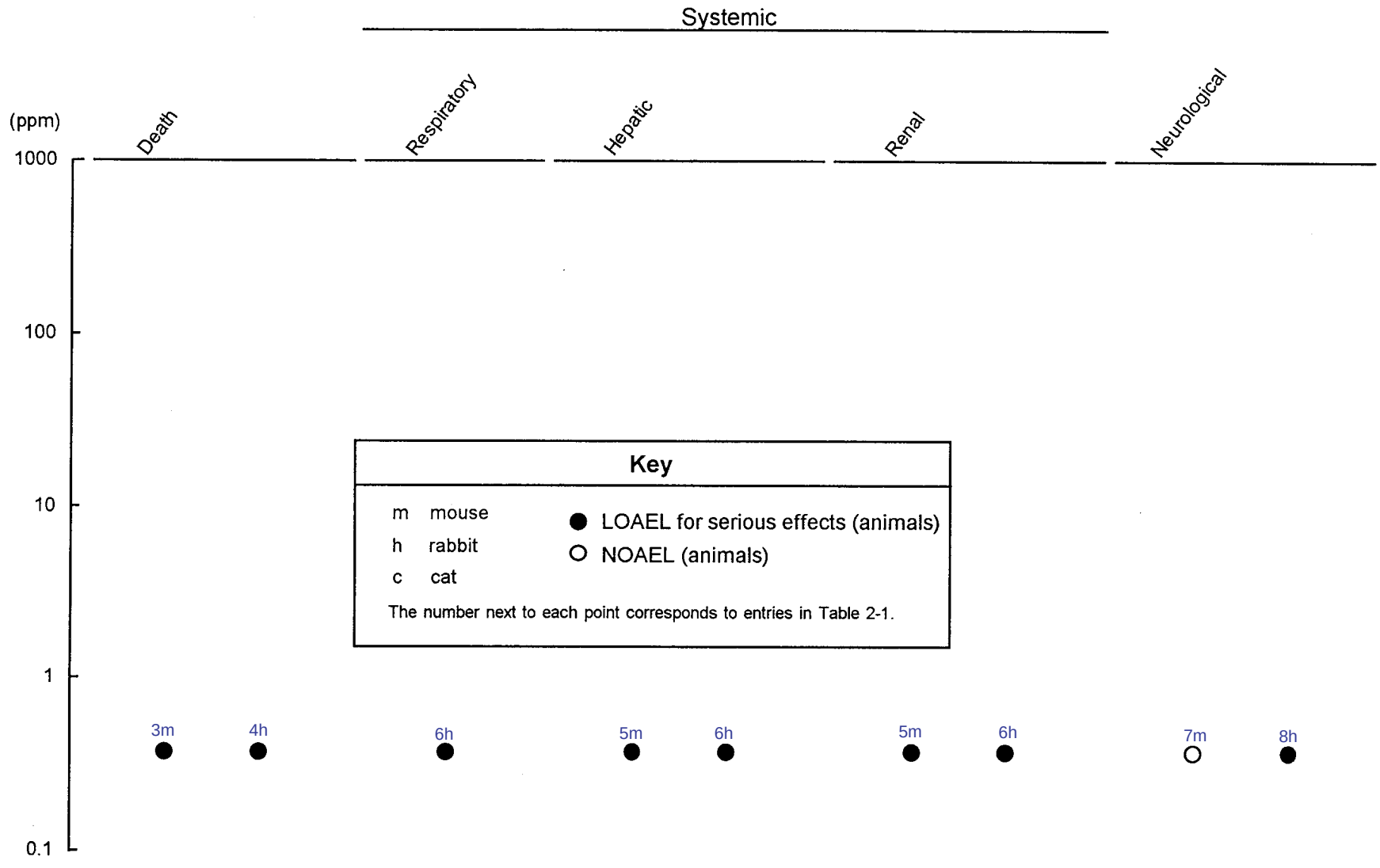


Figure 2-1. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Inhalation (cont.)

Intermediate (15-364 days)



2.2.1.2 Systemic Effects

Studies regarding the systemic effects that have been observed in humans and animals after inhalation exposure to endrin are discussed below. The highest NOAEL and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1. No LSE studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, dermal, ocular, or body weight effects in humans or animals after inhalation exposure to endrin, endrin aldehyde, or endrin ketone.

Respiratory Effects. Respiratory effects were reported in workers involved in the manufacture of aldrin/dieldrin/endrin (Ditraglia et al. 1981). Increased deaths due to nonmalignant respiratory diseases such as pneumonia were observed in workers at one of two plants that manufactured endrin. However, simultaneous exposure to other chemicals occurred, and increased respiratory disease was not observed in the second endrin manufacturing facility.

Two rabbits which survived 118 periods of exposure to 0.36 ppm (15 mg/m^3) of endrin vapors developed a granulomatous pneumonitis (Treon et al. 1955). The pneumonitis was not observed in cats, guinea pigs, hamsters, rats, or mice, but the small number of animals tested limits the usefulness of this study.

No studies were located regarding respiratory effects in humans or animals after inhalation exposure to endrin aldehyde or endrin ketone.

Hepatic Effects. Seven of 592 workers manufacturing aldrin/dieldrin/endrin had abnormal liver function tests, as shown by 3 cases of increased thymol turbidity, increased serum glutamic oxaloacetic transaminase (SCOT) in one worker, and increased serum glutamic pyruvate transaminase (SGPT) in 4 workers (Hoogendam et al. 1965). Exposure to other compounds was not controlled, and test values returned to normal during continued exposure.

Diffuse degenerative changes were observed in the livers of rabbits and mice exposed over 6 months at endrin concentrations of 15 mg/m^3 (0.36 ppm) which caused death (Treon et al. 1955). Details of the liver pathology were not provided.

No studies were located regarding hepatic effects in humans or animals after inhalation exposure to endrin aldehyde or endrin ketone.

Renal Effects. Diffuse degenerative changes were observed in the kidneys of rabbits and mice that died following exposure to 0.36 ppm (15 mg/m^3) of endrin (Treon et al. 1955). No further details of the kidney pathology were provided. No studies were located regarding renal effects in humans after inhalation exposure to endrin, endrin aldehyde, or endrin ketone.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals after inhalation exposure to endrin, endrin aldehyde, or endrin ketone.

2.2.1.4 Neurological Effects

Studies in humans demonstrate that the nervous system is a primary target for endrin toxicity. Convulsions occurred within two hours following occupational exposure to aldrin, dieldrin and endrin (Hoogendam et al. 1962, 1965). After removal from exposure, seizures subsided and complete recovery was achieved in l-3 days. Abnormal electroencephalograms (EEGs) were usually observed in endrin-poisoned workers, and sometimes occurred without any clinical symptoms. Predominately bilateral synchronous theta waves, and synchronous spike and wave complexes were seen (Hoogendam et al. 1962). These are believed to be associated with brain stem injury. Abnormal EEGs generally returned to normal within a period of 0.5-l month after removal of the worker from exposure (Hoogendam et al. 1965).

Inhalation experiments in rabbits and mice showed diffuse degenerative lesions of the brain in rabbits (but not the mouse) that died after exposure to 15 mg/m^3 (0.36 ppm) of endrin for 118 days over a 185-day period (Treon et al. 1955). Seizures were not observed prior to death. Ressang et al. (1959) reported slight degenerative lesions of ganglion cells in the brains of cats exposed to a lethal concentration of endrin via inhalation. No studies were located regarding neurological effects in humans or animals after inhalation exposure to endrin aldehyde or endrin ketone.

No studies were located regarding the following health effects in humans and animals after inhalation exposure to endrin, endrin aldehyde, or endrin ketone:

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Studies of workers in the endrin manufacturing industry have not shown an association between occupational exposure to endrin and any type of human cancer. No excess cancers could be attributed to exposure to endrin in 52 chemical workers in an endrin manufacturing facility after exposures lasting 4-13 years (Versteeg and Jager 1973). Fifteen years later, the same worker cohort showed no evidence of increased cancer rates. The small size of the cohort gives the study a low statistical power (Ribbens 1985).

In a retrospective cohort mortality study of U.S. pesticide manufacturing facilities, standardized mortality ratios (SMR) were calculated for all malignant neoplasms in 2,100 workers in 2 aldrin/dieldrin/endrin plants. The SMRs were lower than expected. For “all malignant neoplasms,” the SMR ranged from 68 to 91, which was well below the expected level (SMR=l00), indicating a possible healthy worker effect (Ditraglia et al. 1981). For one of the plants, there was a limited follow-up and inadequacies were imposed by the loss of 10% of the cohort (Ditraglia et al. 1981). While there was no specific cancer risk at certain manufacturing sites, several occurrences of cancer in the aldrin/dieldrin/endrin plants may be worthy of further study. There were slight excesses of cancer of the esophagus (2 versus 0.85 expected), liver (2 versus 0.89 expected), rectum (3 versus 1.24 expected), and of the lymphatic and hematopoietic systems (6 versus 4.09 expected) in one plant. However, the excesses were not statistically significant, and the elevated SMRs were based on small numbers of observed deaths (l-3 deaths except for lymphatic/hematopoietic cancers which were based on 6 deaths).

No studies were located regarding cancer in animals after inhalation exposure to endrin, endrin aldehyde, or endrin ketone.

2.2.2 Oral Exposure

Ingestion of endrin can cause central nervous system effects as expressed by muscle contractions, hyperexcitability, and in severe cases, convulsions and sometimes death (Curley et al. 1970; Runhaar et al. 1985; Weeks 1967).

Exposure of animals to endrin causes central nervous system effects, particularly convulsions (Deichmann et al. 1970; Quick et al. 1989; Treon et al. 1955). Nonspecific degeneration of the liver, kidney, and brain was observed in animals exposed to lethal doses of endrin (Treon et al. 1955). Endrin can cause abnormal bone formation, hyperactivity, and death in fetuses of dams exposed during gestation (Chernoff et al. 1979a; Gray et al. 1981; Kavlock et al. 1985; Ottolenghi et al. 1974). Most of the carcinogenicity bioassays for endrin were negative (Deichmann et al. 1970). Positive carcinogenic effects of endrin were reported by Reuber (1978); however, Reuber's criteria for classifying tissues as tumorigenic were not consistent with other investigators (EPA 1979f).

No studies were located regarding the health effects of endrin aldehyde or endrin ketone in humans following oral exposure. Limited data from a feeding study in rats suggest that endrin aldehyde and endrin ketone can cause hepatic effects (elevated serum enzymes) (Young and Mehendale 1986).

2.2.2.1 Death

Deaths as the result of acute exposure by ingestion of endrin have been observed in humans in a variety of incidents. In 1967, in Doha, Qatar, and Hofuf in Saudi Arabia, 874 people were hospitalized after an acute exposure to endrin-contaminated flour which resulted in 26 known deaths (Weeks 1967). Deaths occurred within 12 hours of the onset of symptoms of toxicity (convulsions, loss of consciousness, headache, nausea, vomiting); however, recovery of survivors was rapid. Concentrations of endrin in bread eaten by victims ranged from 48 to 1,807 ppm (Curley et al. 1970). The contaminated flour used to make the bread contained 2,153-3,367 ppm endrin.

2. HEALTH EFFECTS

An outbreak of acute human endrin poisoning associated with central nervous system toxicity and 19 deaths in 194 known cases occurred in Pakistan in 1984 (Rowley et al. 1987). The vector for exposure was not identified, but contamination of a food item was the likely cause of poisoning.

Ingestion of 12 g of endrin (dissolved in aromatic hydrocarbons) by a 49-year-old man in a suicide attempt caused convulsions persisting for 4 days; death occurred after 11 days (Runhaar et al. 1985). Death occurred in 11 other cases following ingestion of endrin; the time from administration to death ranged from 1 to 6 hours. In cases where endrin ingestion occurred with milk or alcohol, death occurred more rapidly (within l-2 hours) presumably as the result of enhanced absorption that increased toxicity (Tewari and Sharma 1978).

Endrin is lethal to animals when sufficiently high doses are administered by oral gavage or in the diet. An early study of acute toxicity in animals (Treon et al. 1955) reported that minimum lethal doses in monkeys (l-3 mg/kg) were lower than minimum lethal doses in cats (<5 mg/kg), rats (<5-36 mg/kg), rabbits (5-7 mg/kg), and guinea pigs (lo-36 mg/kg). A single oral dose of 6 mg endrin/kg body weight in a cod liver oil emulsion caused the death of a cat within 24 hours (Ressang et al. 1959). Six-month-old female rats were more sensitive than were 34-week-old rats to lethal effects of endrin; male rats were more sensitive to endrin at 3-4 weeks than 6-month-old rats. The oral LD_{50} (the dose which has been calculated to cause death in 50% of the experimental animal population) was 7.3 and 16.8 mg/kg for 6-month-old and 29-31-day-old female rats, respectively; and 43.4 and 28.8 mg/kg for 6-month-old and 29-31-day-old male rats, respectively (Treon et al. 1955). Female rats, therefore, died at lower doses than male rats, Likewise, the oral LD_{50} in male and female adult Sherman rats was 17.8 and 7.5 mg/kg (Gaines 1960), respectively; and the lowest doses to cause lethality were 10 and 6 mg/kg, respectively (Gaines 1969). Female guinea pigs appeared slightly more susceptible to the lethal effects of orally administered endrin than males; minimum lethal doses were estimated as lo-16 and 24-36 mg/kg endrin (LD_{50} for males was 36 mg/kg and 16 mg/kg for females) (Treon et al. 1955). In subsequent studies, an oral dose of 8 mg/kg caused 100% lethality in female rats (Numan et al. 1990b), and an LD_{50} of 5.6 mg/kg was reported for male rats and 5.3 mg/kg for female rats (Bedford et al. 1975a). Speck and Maaske (1958) found the oral LD_{50} for 6-month-old male Sprague-Dawley rats for endrin to be 40 mg/kg body weight. The oral LD_{50} in female hamsters was 18.6 mg/kg (Chemoff et al. 1979a). Single or repeated doses of endrin to pregnant mice or hamsters during gestation also resulted in maternal or fetal lethality (Chemoff et al. 1979a; Gray et al. 1981; Kavlock et al. 1985).

The acute oral LD_{50} for endrin aldehyde in male mice was reported to be >500 mg/kg, although no experimental details were provided (Phillips et al. 1962). The LD_{50} values and the doses associated with death are recorded in Table 2-2 plotted in Figure 2-2. No studies were located regarding lethal effects in humans or animals following oral exposure to endrin ketone.

Male and female mice administered 0.65 mg/kg (5 ppm) of endrin in feed for 120 days had significant mortality (Good and Ware 1969). Dogs of both sexes administered endrin in feed from 18 days to approximately 19 months had increased mortality at doses of 0.20-0.27 mg/kg/day (5 ppm) or greater, but animals survived at doses of 0.15-0.21 mg/kg/day (4 ppm) (Treon et al. 1955). Pine mice are susceptible to endrin lethality when exposed in the environment (Webb et al. 1973). Two pregnant female rats administered 2 mg/kg/day were found dead on gestation days 13 and 14 (Goldenthal 1978a). Increased mortality was reported for female rats administered 1.25 mg/kg/day (25 ppm) endrin in the diet (Treon et al. 1955).

2.2.2.2 Systemic Effects

Studies regarding the systemic effects that have been observed in humans and animals after oral exposure to endrin are discussed below. The highest NOAEL and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. No studies were located regarding musculoskeletal or ocular effects in humans or animals after oral exposure to endrin, endrin aldehyde, or endrin ketone. No studies were located regarding hepatic, endocrine, ocular, or body weight effects in humans.

Respiratory Effects. Pulmonary edema was observed in a patient after an attempted suicide with endrin and was thought to be due to chemical pneumonitis following aspiration of aromatic hydrocarbons contained in the ingested formulation. The authors state that the hydrocarbons may have been the cause of the pulmonary effects (Runhaar et al. 1985), since hydrocarbon-induced chemical pneumonitis is a well established clinical entity.

Rats treated for 17.6-20.8 months with 0.1 mg/kg/day of endrin exhibited focal hemorrhage and congestion of the lungs (Deichmann et al. 1970). Shortness of breath was reported in rats, but not mice, exposed to endrin for 80 weeks (NCI 1978). Pulmonary hyperplasia and edema were reported in dogs fatally poisoned by diets containing 5 ppm or greater (0.20-0.27 mg/kg/day) of endrin (Treon et

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Human	once (O)				171 M (death 11 days after exposure)	Runhaar et al 1985 Endrin
2	Rat (Carworth Farm E)	once (G) vehicle DMSO				5.6 M (LD_{50})	Bedford et al. 1975a Endrin
						5.3 F (LD_{50})	
3	Rat (Sherman)	once (GO)				17.8 M (LD_{50})	Gaines 1960 Endrin
						7.5 F (LD_{50})	
4	Rat (Sherman)	once (GO)				10 M (LD_{min})	Gaines 1969 Endrin
						6 F (LD_{min})	
5	Rat (CD)	Gd 6-15 (G) vehicle Methocel				2 F (2/25 dead on Gd 13 and 14)	Goldenthal et al. 1978a Endrin
6	Rat (Carworth)	once (GO)				7.3 F (LD_{50})	Treon et al. 1955 Endrin
						43.4 M (LD_{50})	
7	Rat (Carworth)	once (GO)				16.8 F (LD_{50})	Treon el al. 7955 Endrin
						28.8 M (LD_{50})	

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
8	Mouse (CD-1)	Gd 8 (GO)				7 F (3/21 mice died)		Kavlock et al. 1985 Endrin
9	Gn Pig (NS)	once (GO)				16 F (LD_{50})		Treon et al. 1955 Endrin
						36 M (LD_{50})		
10	Hamster (Golden Syrian)	10 d Gd 5-14 (GO)				1.5 F (37% of the dams died)		Chernoff et al. 1979a Endrin
11	Hamster (Golden Syrian)	once (GO)				18.6 F (LD_{50})		Chernoff et al. 1979a Endrin
12	Hamster (Golden Syrian)	10 d Gd 5-14 (GO)				1.5 F (57% of the dams died)		Gray et al. 1981 Endrin
13	Rabbit (NS)	once (GO)				7-10 F (LD_{50})		Treon et al. 1955 Endrin
14	Cat (NS)	once (GO)				3 (death; 100%)		Ressang et al. 1959 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Systemic						
15	Rat (Sprague-Dawley)	1-2 d ad lib (F)	Hepatic		8.2 F (increases in alkaline phosphatase(48%), glutamate oxaloacetate transaminase (82%) glutamate pyruvate transaminase (55%), isocitrate dehydrogenase (65%), cholesterol (27%-35%), and soluble proteins (35%); decreases in free amino acids (34-40%) and glucose (41-51%); vacuolization; fatty infiltration)		Ali and Shakoori 1993 Endrin
			Bd Wt	8.2 F			
16	Rat (Sprague-Dawley)	once (GO)	Hepatic		3 F (11% increase in relative liver weight)		Bagchi et al. 1992b Endrin
			Other		1.5 F (increased excretion of metabolites indicative of lipid peroxidation)		
17	Rat (Sprague-Dawley)	once (GO)	Hepatic		3 F (9% increase in relative liver weight, increase in mitochondrial iron and calcium; decrease in microsomal and nuclear iron; increased microsomal and nuclear calcium)		Bagchi et al. 1992c Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
18	Rat (CD)	9d Gd 6-15 (G) vehicle Methocel	Bd Wt	0.5 F	2 F (decreased maternal weight gain (12% of control) during exposure)		Goldenthal et al. 1978a Endrin
19	Rat (Sprague-Dawley)	once (GO)	Hepatic			4 M (necrosis, fatty degeneration, inflammation, cell regeneration, 1.9-fold increase in lipid peroxidation)	Hassan et al. 1991 Endrin
			Renal			4 F (necrosis of the tubules, hyalin and red cell casts, 3.3-fold increase in lipid peroxidation)	
20	Rat (Sprague-Dawley)	once (GO)	Hepatic		4.5 F (14.5% increase in mitochondria1 lipid peroxidation at 6 hr; 28% increase in microsomal lipid peroxidation at 12 hr)		Hassoun et al. 1993 Endrin
21	Rat (CD)	14 d Gd 7-20 (GO)	Hepatic	0.45 F			Kavlock et al. 1981 Endrin
			Bd Wt	0.15 F		0.3 F (maternal body weight gain decreased by 38%)	
22	Mouse (Swiss Webster)	once (GO)	Hepatic			4 F (necrosis, inflammation; 1.8-fold increase in lipid peroxidation)	Hassan et al. 1991 Endrin
			Renal			4 F (tubular necrosis; 1.7-fold increase in lipid peroxidation)	

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
23	Mouse (CD-1)	11 d Gd 7-17 (GO)	Hepatic		0.5 F (relative liver weight increased 7%)		Kavlock et al. 1981 Endrin
			Bd Wt	0.5 F		1 F (maternal body weight gain decreased 24%)	
24	Gn Pig (NS)	once (GO)	Hepatic			4 F (necrosis, inflammation, and 1.3-fold increase in lipid peroxidation)	Hassan et al. 1991 Endrin
			Renal		4 F (cloudy swelling and narrowing of tubular lumen)		
25	Hamster (Golden Syrian)	10 d Gd 5-14 (GO)	Hepatic	3.5 F			Chernoff et al. 1979a Endrin
			Bd Wt	0.75 F		1.5 F (19 times more weight loss than controls)	
26	Hamster (NS)	once (GO)	Hepatic			4 F (necrosis, inflammation, and 1.3-fold increase in lipid peroxidation)	Hassanet al. 1991 Endrin
			Renal			4 F (tubular necrosis, hyalin and calcium containing casts, lipid peroxidation)	
	Immunological/Lymphoreticular						
27	Rat (Sprague-Dawley)	once (GO)			3 F (increase in relative spleen weight, 31% decrease in relative thymus weight)		Bagchi et al. 1992b Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
28	Rat (Sprague-Dawley)	once (GO)			3 F (11% increase in relative spleen weight, 31% decrease in relative thymus weight)		Bagchi et al. 1992c Endrin
	Neurological						
29	Rat (CD)	<= 14 d (GO)			0.5 F (locomotor activity depressed)	4 F (convulsions)	Kavlock et al. 1981 Endrin
30	Mouse (CD-1)	<11 d (GO)			1.5 F (38-46% decrease in locomotor activity)		Kavlock et al. 1981 Endrin
31	Hamster (Golden Syrian)	Gd 8 (GO)		7.5 F		10 F (1/30 animals displayed convulsions)	Chernoff et al. 1979a Endrin
	Reproductive						
32	Rat (CD)	9d Gd 7-15 (GO)		0.3 F			Gray et al. 1981 Endrin
33	Hamster (Golden Syrian)	Gd 8 (GO)		10 F			Chernoff et al. 1979a Endrin
34	Hamster (Golden Syrian)	10 d Gd 5-14 (GO)		1.5 F			Gray et al. 1981 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Developmental						
35	Rat (CD)	9d Gd 6-15 (G) vehicle Methocel		0.5 F	2 F (decreased fetal body weight and crown-rump length)		Goldenthal et al. 1978a Endrin
36	Rat (CD)	14 d Gd 7-20 (GO)		0.45			Kavlock et al. 1981 Endrin
37	Mouse (CD-1)	11 d Gd 7-17 (GO)		0.5	1 (delayed ossification: 38% increase in supraoccipital score; 84% decrease in number of caudal vertebrae; decreased fetal body weight)		Kavlock et al. 1981 Endrin
38	Mouse (CD-1)	Gd 8 (NS)			7 F (increased incidence of supernumerary ribs)		Kavlock et al. 1985 Endrin
39	Mouse (CD-1)	Gd 9 (GO)				2.5 (significant increase in open eye [2.7%] and cleft palate [2.2%])	Ottolenghi et al. 1974 Endrin
40	Hamster (Golden Syrian)	10 d Gd 5-14 (GO)				1.5 (irregular supraoccipitals, visceral abnormalities; 2-fold increase in fetal mortality; 30% decrease in fetal weight)	Chernoff et al. 1979a Endrin
41	Hamster (Golden Syrian)	Gd 8 (GO)		1.5		5.0 (increased incidence [5/7] of mening O-encephaloceles)	Chernoff et al. 1979a Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
42	Hamster (Golden Syrian)	10 d Gd 4-13 (G)-vehicle Methocel		2.5 F					Goldenthal et al. 1978b Endrin
43	Hamster (Golden Syrian)	Gd 9 (GO)					5	(increased incidence of cleft palate and fused ribs; decreased fetal weight)	Ottolenghi et al. 1974 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference
	INTERMEDIATE EXPOSURE								
	Death								
44	Mouse (CFW Swiss)	120 d (F)					0.65	(deaths in 33 of 101 breeding pairs)	Good and Ware 1969 Endrin
45	Dog (Beagle)	18d-9.9 mo 6 d/wk (F)					0.20 M	(death in 1/1)	Treon et al. 1955 Endrin
	Systemic								
46	Dog (Beagle)	18d-9.9 mo 6 d/wk (F)	Resp	0.15			0.20	(respiratory distress, pulmonary hyperplasia and edema)	Treon et al. 1955 Endrin
			Cardio	0.15			0.20	(diffuse degenerative lesions of the heart)	
			Gastro	0.15	0.20	(regurgitation of food)			
			Hepatic	0.15			0.20	(diffuse degeneration, fatty vacuolization)	
			Renal	0.15			0.20	(tubular degeneration and necrosis of convoluted tubules)	
			Bd Wt	0.12	0.15	("did not grow normally" - no data presented)	0.49	(emaciation)	
	Neurological								
47	Dog (Beagle)	18d-9.9 mo 6 d/wk (F)		0.15[b]			0.20	(convulsions, tremors, diffuse degenerative brain lesions)	Treon et al. 1955 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
48	Rat (Long Evans)	79 d (F)		0.1			Eisenlord et al 1968 Endrin
49	Mouse (CFW Swiss)	120 d (F)				0.65 F (reduced litter size)	Good and Ware 1969 Endrin
	Developmental						
50	Rat (Long Evans)	79 d (F)		0.1			Eisenlord et al. 1968 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	CHRONIC EXPOSURE						
	Death						
51	Rat (Carworth)	2 yr (F)				1.25 F (increased mortality) 2.5 M (increased mortality)	Treon et al. 1955 Endrin
	Systemic						
52	Rat (Osborne Mendel)	17.6 - 20.8 mo (F)	Resp			0.1 (congestion, focal hemorrhage)	Deichmann et al. 1970 Endrin
			Hepatic		0.1 (cloudy swelling of centrilobular cells)		
			Renal		0.1 (cloudy swelling of tubule epithelial cells)		
			Bd Wt	0.56			
53	Rat (Osborne-Mendel)	80 wk (F)	Resp		0.13 (short breath, epistaxis)		NCI 1978 Endrin
			Cardio	0.3			
			Gastro		0.13 (diarrhea)		
			Hepatic	0.3 F			
			Renal		0.13 (discolored urine)		
			Endocr		0.13 (thyroid hyperplasia and pituitary cysts)		
			Dermal		0.13 (dermatitis alopecia)		
			Bd Wt	0.3			

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
54	Rat (Carworth)	2 yr (F)	Hepatic	0.05	0.25 M (18% increased relative liver weight)		Treon et al. 1955 Endrin
				0.25	1.25 (diffuse degeneration of liver)		
			Renal	0.25	1.25 (diffuse degeneration of kidneys)		
			Endocr	0.25	1.25 (diffuse degeneration of adrenals)		
			Bd Wt	0.05 M	1.25 M (14% reduction in weight gain)		
				5F			
55	Mouse (B6C3F1)	80 wk (F)	Resp	0.42			NCI 1978 Endrin
			Cardio	0.42			
			Gastro		0.21 (abdominal distention)		
			Hepatic	0.42			
			Renal	0.42			
			Endocr	0.42			
			Dermal		0.21 (hair loss)		
			Bd Wt	0.42			

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference
56	Dog (Beagle)	2 yr 1 hr/d (F)	Hemato	0.1					Kettering 1969 Endrin
			Hepatic	0.025	0.05	(hepatic cell vacuolation, slightly increased liver weights)			
			Bd Wt	0.1					
57	Dog (Beagle)	64 -156 wk 1 hr/d (F)	Hemato	0.059 F					Kettering 1971 Endrin
			Hepatic	0.059 F					
			Renal	0.059 F					
58	Dog (Beagle)	16.4 - 18.7 mo 6 d/wk (F)	Cardio		0.25	(cardiomegaly)			Treon et al. 1955 Endrin
			Hemato	0.075					
			Renal		0.075	(24% increased relative kidney weight)			
			Bd Wt	0.075					
	Immunological/Lymphoreticular								
59	Dog (Beagle)	16.4 - 18.7 mo 6 d/wk (F)		0.075					Treon et al. 1955 Endrin
	Neurological								
60	Rat (Osborne-Mendel)	17.6 - 20.8 mo (mean) (F)					0.1	(convulsions and tremors)	Deichmann et al. 1970 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
61	Rat (Osborne-Mendel)	80 wk (F)		0.25 M				NCI 1978 Endrin
				0.30 F				
62	Rat (Carworth)	2 yr (F)		1.25			2.5 (convulsions, hypersensitivity)	Treon et al. 1955 Endrin
				0.25			1.25 (diffuse degeneration of brain)	
63	Mouse (B6C3F1)	80 wk (F)			0.21 M (hyperexcitability)			NCI 1978 Endrin
					0.33 F (hyperexcitability)			
64	Dog (Beagle)	2 yr 1 hr/d (F)		0.025[c] F			0.05 F (convulsions)	Kettering 1969 Endrin
				0.05 M			0.1 M (convulsions)	
65	Dog (Beagle)	15-38 mo 1 hr/d (F)					0.059 F (seizures)	Kettering 1971 Endrin
	Reproductive							
66	Dog (Beagle)	64-156 Wk 1 hr/d (F)		0.059 F				Kettenng 1971 Endrin

Table 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continue)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Developmental						
67	Dog (Beagle)	64-156 wk 1 hr/d (F)		0.059 F			Kettering 1971 Endrin

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

[b]Used to derive an intermediate oral minimal risk level (MRL) of 0.002 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive an chronic oral MRL of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DMSO = dimethyl sulfoxide; Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = Guinea pig; (GO) = gavage in oil; Hemato = hematological; hr = hour(s); LD50= lethal dose, 50% kill; LDmin= minimum lethal dose; LOAEL = lowest-observable-adverse-effectlevel; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; (0) = Oral; Resp = respiratory; wk = week(s); yr = year

Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral

Acute (≤14 days)

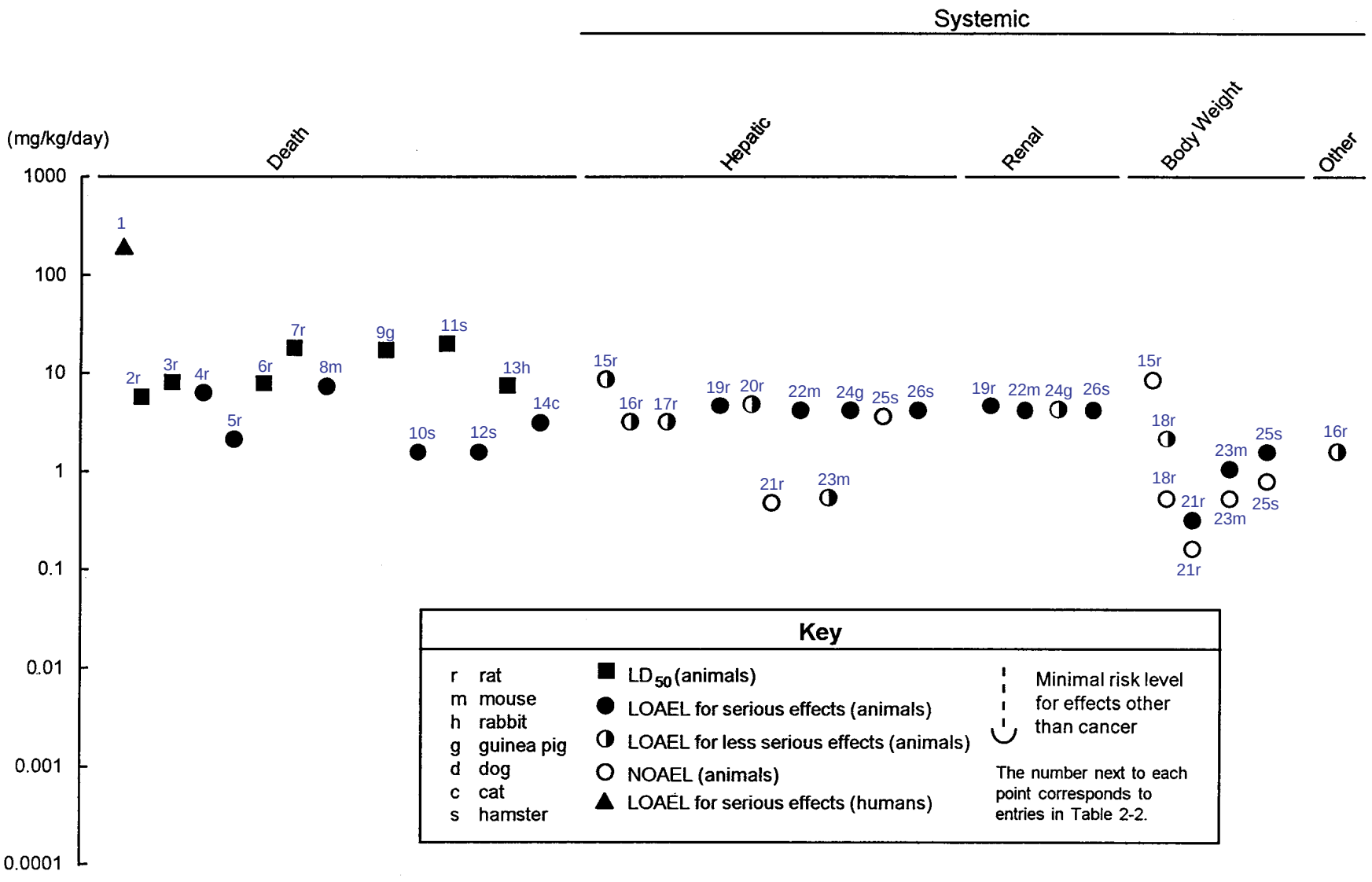


Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continued)

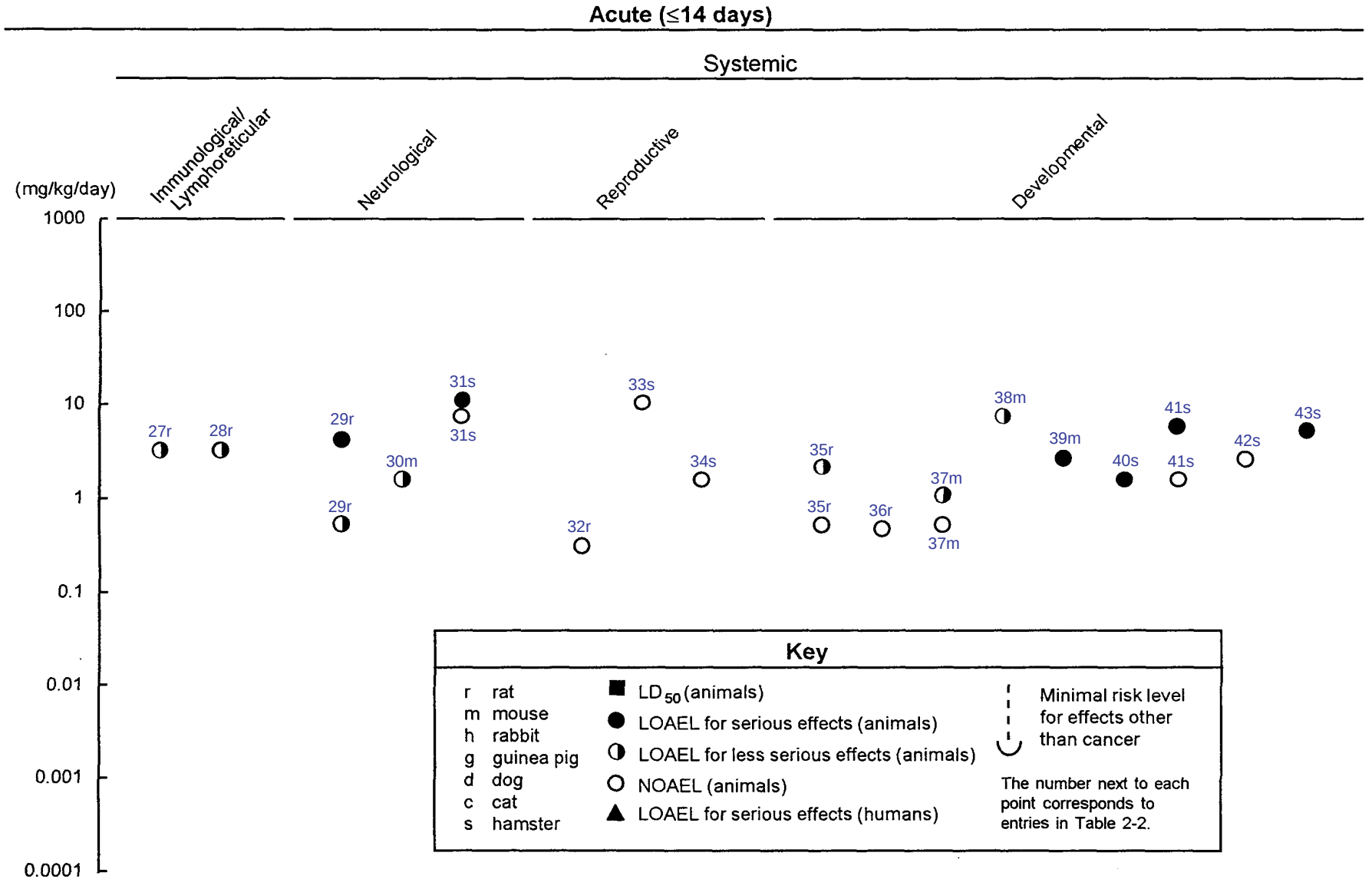


Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continued)

Intermediate (15-364 days)

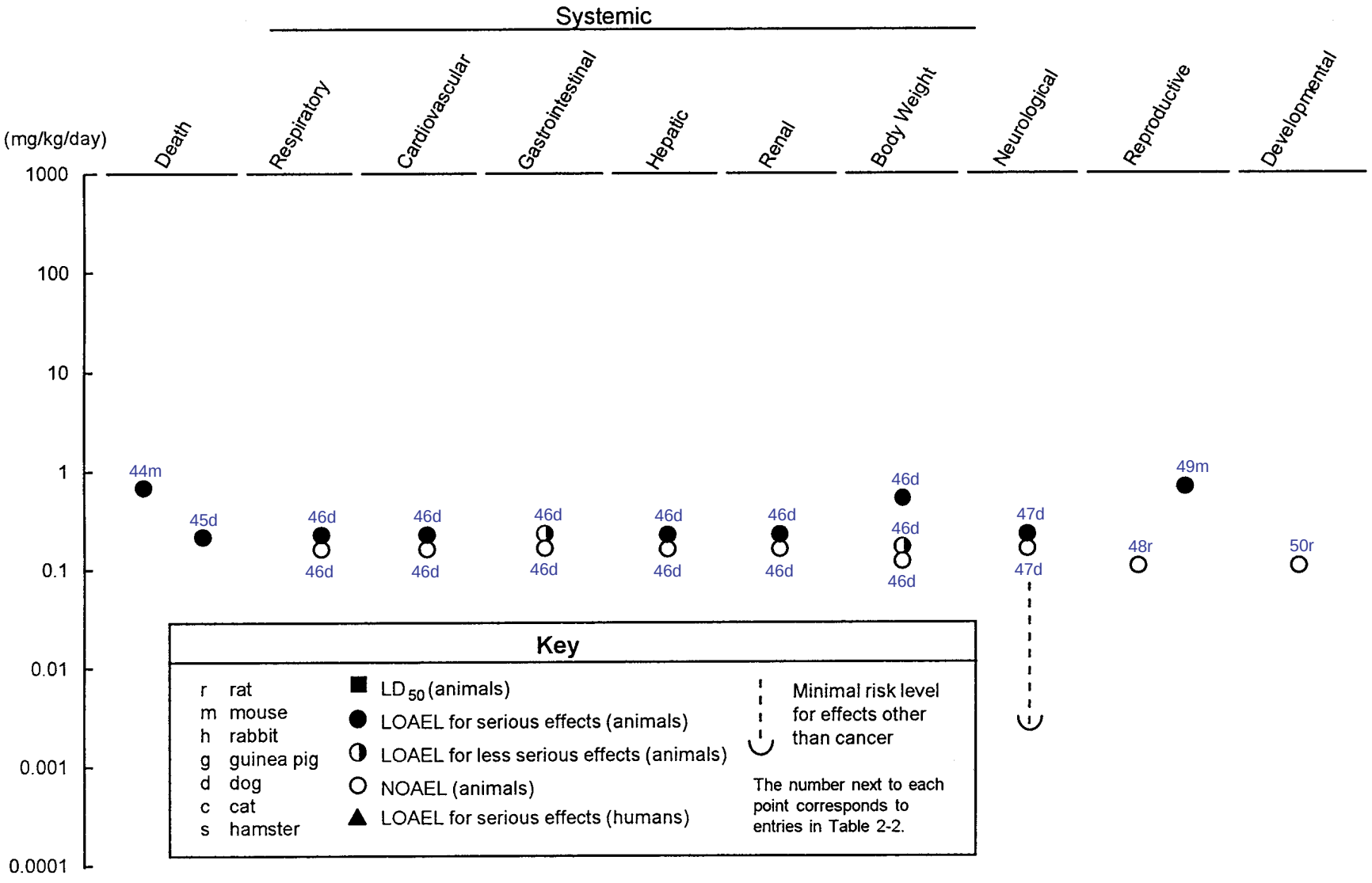
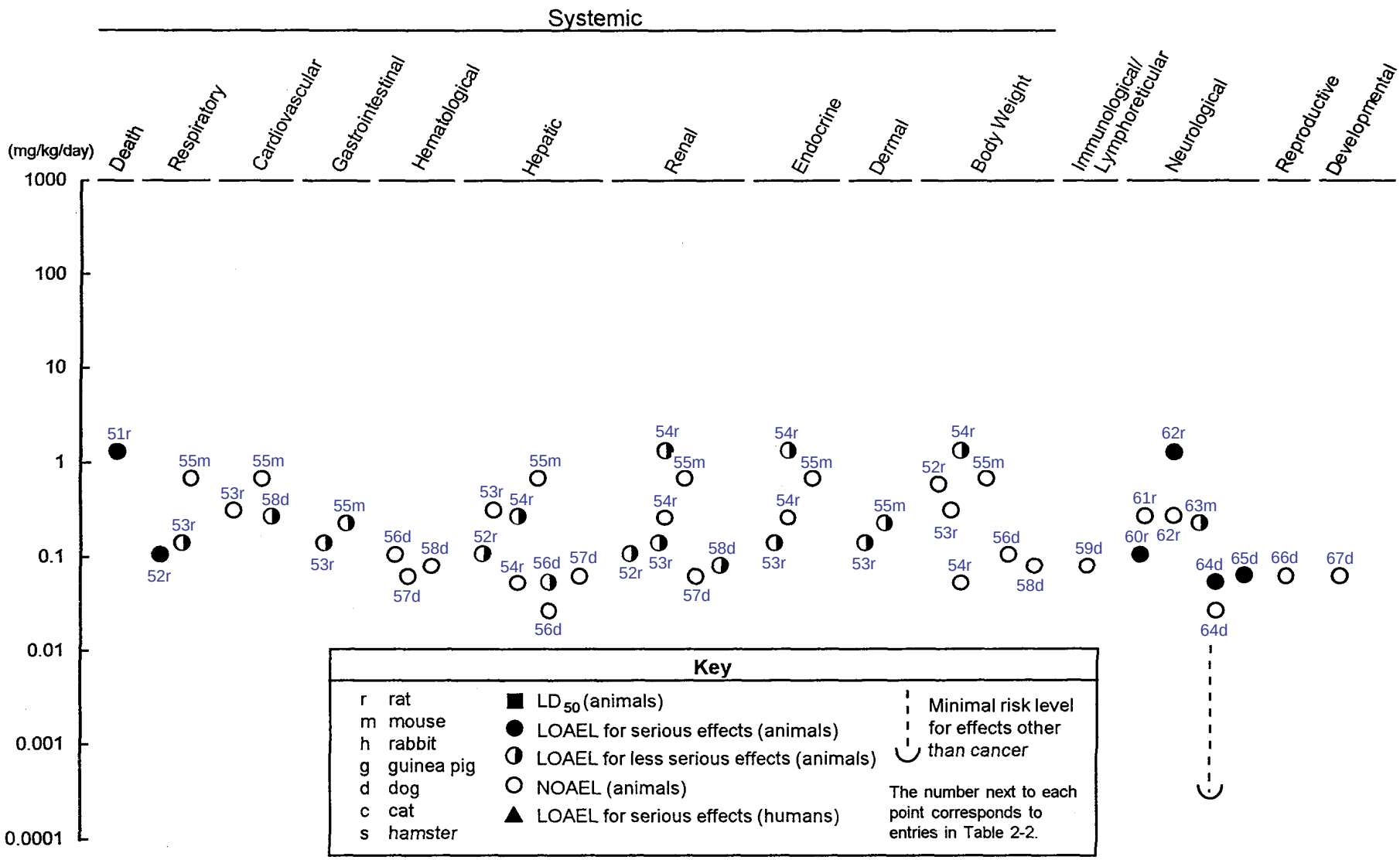


Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continued)

Chronic (≥365 days)



al. 1955). The dogs were observed regurgitating their food and may have aspirated endrincontaminated material. Severe congestion and serofibrinous exudate were observed in the lungs of dogs that died apparently following ingestion of endrin-containing bait (Quick et al. 1989).

No studies were located regarding respiratory effects in humans or animals following oral exposure to endrin aldehyde or endrin ketone.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to endrin, or in humans or animals to endrin aldehyde or endrin ketone. Limited reports of cardiovascular toxicity of orally administered endrin in animals were located. Dogs exposed to 3 ppm endrin in feed (0.12-0.25 mg/kg/day) had significantly enlarged hearts (cardiomegaly), but similar effects were not found at 1 ppm (0.045-0.12 mg/kg/day). Dogs exposed to diets containing 5 ppm endrin (0.20-0.27 mg/kg/day) had diffuse degenerative lesions (Treon et al. 1955). Conclusions cannot be drawn from this study due to the small number of animals used and the lack of details regarding the histopathology performed. No cardiovascular lesions were noted in rats and mice chronically exposed to endrin (NCI 1978).

Gastrointestinal Effects. Nausea and vomiting were reported in people consuming endrincontaminated taquitos (Waller et al. 1992). Rats administered endrin exhibited diarrhea; however, no gastrointestinal lesions were reported for either rats or mice (NCI 1978). Dogs were observed to regurgitate food containing endrin at levels of 5 ppm (0.20-0.27 mg/kg/day) or greater, while endrin concentrations of 4 ppm (0.15-0.21 mg/kg/day) or less were not associated with this effect (Treon et al. 1955).

No gastrointestinal effects from endrin ketone or endrin aldehyde in humans or laboratory animals were located.

Hematological Effects. No hematological effects have been reported in humans exposed to endrin, endrin ketone, or endrin aldehyde. There were no changes in the relative numbers or in the types of formed elements in the peripheral blood of male and female Beagle dogs which were administered endrin in their diet for periods of 16.4-18.7 months (Treon et al. 1955). No hematological changes were observed in Beagles administered 0.0025-0.1 mg/kg/day for 2 years or in Beagles administered 0.003-0.059 mg/kg/day for 64-l 56 weeks (Kettering 1971).

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to endrin, endrin aldehyde, or endrin ketone.

In a study by Ali and Shakoori (1993), female Sprague-Dawley rats were dosed with a diet containing a diluted 20% emulsifiable concentrate of endrin. The average endrin intake was calculated by the authors of the study to be 8.2 mg/kg/day. One group (4 animals) was sacrificed 24 hours after treatment began, and the other at 48 hours after treatment began. At sacrifice, the animals were weighed, and their livers removed and weighed, and a representative hepatic tissue sample collected for histopathological analysis. Endrin treatment did not significantly affect relative liver weights. At 24 hours, endrin exposure caused significant increases of alkaline phosphatase (AP), glutamate oxaloacetate transaminase (GOT), and glutamate pyruvate transaminase (GPT) (48, 82, and 55%, respectively), relative to controls; at 48 hours, AP ($p<0.0$), GOT ($p<0.00$) and GPT ($p<0.01$) were increased 69, 97, and 71%, respectively, relative to controls. Endrin exposure also resulted in a significant increase (65%) in isocitrate dehydrogenase (ICDH; $p<0.05$) at 48 hours. Serum cholesterol increased by 27 and 35% at 24 and 48 hours, respectively ($p<0.05$); free amino acids decreased by 34 and 40% at 24 and 48 hours, respectively ($p<0.00l$); and glucose decreased by 41 and 51% at 24 and 48 hours, respectively ($p<0.01$ and $p<0.001$). Hepatic DNA and RNA content was not significantly affected by endrin exposure. Histologically, significant alterations were noted in the liver at 48 hours. The prominent alterations included hepatic cell hypertrophy, dilation of sinusoidal spaces, zonal disorganization/degeneration, vacuolization, and fatty infiltration.

A time- and dose-related increase in relative liver weight was observed in rats administered 3-6 mg/kg endrin (Bagchi et al. 1992a, 1992b, 1992c); however, no significant changes in absolute or relative liver weight were noted for rats 24 hours after oral administration of 4 mg/kg endrin (Numan et al. 1990a). Maternal liver enlargement (increased relative liver weight) occurred in pregnant mice administered 0.5 mg/kg/day of endrin during gestation (Kavlock et al. 1981). Liver weight was unaffected in pregnant hamsters and rats at doses up to 3.5 or 0.45 mg/kg/day, respectively (Chernoff et al. 1979a; Kavlock et al. 1981). Rats, mice, and guinea pigs administered 4 mg/kg endrin and sacrificed 24 hours later exhibited moderate hepatic necrosis, fatty degeneration (rats), and inflammation; lipofuscin deposits were also observed in hepatocytes and Kupffer cells (Hassan et al. 1991). Similar changes were observed in control and endrin-treated hamsters; however, the severity was increased in the treated animals, and only livers from treated animals had lipofuscin pigment deposits associated with lipid peroxidation (Hassan et al. 1991). Congestion and serofibrinous exudate

were observed in the livers of dogs that died apparently following ingestion of endrin-containing bait (Quick et al. 1989). Minor histologic changes (cloudy swelling of centrilobular cells) were described in rats administered 2 ppm (0.1 mg/kg/day); the mean survival rate was 18.1-20.8 months (Deichman et al. 1970).

Serum enzyme levels were not significantly increased in rats exposed to 5 ppm (0.5 mg/kg/day) of endrin in the diet for 15 days (Young and Mehendale 1986), although alterations in hepatobiliary function, as measured by phenolphthalein glucuronide or bile flow, were reported (males decreased, females increased). During the third month of exposure, livers of rats exposed to 3.5 mg/kg/day of endrin appeared spotty with zones of basophilic cells around the central and portal veins (Speck and Maaske 1958). Diffuse degeneration of the livers of rats fed 25 ppm or more endrin in the diet (≥1.25 mg/kg/day) for intermediate- and chronic-duration was reported by Treon et al. (1955). This effect not only occurred in the rats killed by endrin, but also in survivors. The diffuse degeneration observed in other organs was only seen in animals killed by endrin. Dogs fed lethal concentrations of 5 ppm or more (0.20-0.27 mg/kg/day) of endrin also had degenerative lesions of the liver, and in some cases, fatty vacuolization occurred (number not specified); hepatic changes were not reported at levels of 4 ppm (0.15-0.21 mg/kg/day) or less (Treon et al. 1955). Slight vacuolization of hepatic cells and slightly increased relative liver weights were observed in dogs fed 2 ppm (0.05 mg/kg/day) and 4 ppm (0.1 mg/kg/day) for 2 years (Kettering 1969). No significant increase of nonneoplastic hepatic lesions was observed in rats or mice chronically administered endrin in a bioassay (NCI 1978) and in female Beagles administered endrin doses as high as 0.059 mg/kg/day for 64-156 weeks (Kettering 1971).

Dietary exposure of rats to 10 ppm (0.5 mg/kg/day) endrin aldehyde or 5 ppm (0.25 mg/kg/day) endrin ketone for 15 days resulted in slight elevations ($p<0.05$) in SGPT and SGOT (Young and Mehendale 1986). However, no alterations in liver weight or in hepatobiliary function, as measured by phenolphthalein glucuronide or bile flow, were reported.

Hassoun et al. (1993) examined the effects of various pesticides on lipid peroxidation and DNA single strand breakage in the hepatic cells of female Sprague-Dawley rats. Animals were dosed orally once with endrin at 4.5 mg/kg, lindane at 30 mg/kg, chlordane at 120 mg/kg, or DDT (dichlorodiphenyl trichloroethane) at 40 mg/kg, or vehicle only (corn oil, control). At 6, 12, and 24 hours post-dosing, 4 animals from each group were sacrificed, their livers removed, and prepared for lipid peroxidation

assay. Lipid peroxidation was measured calorimetrically by determining the amount of thiobarbituric acid reactive substances (TBARS) formed. Exposure to endrin resulted in a 14.5% increase in hepatic mitochondrial lipid peroxidation, compared to controls, beginning at 6 hours (6.99 $\pm$ 0.20 versus 6.10 $\pm$ 0.36; $p<0.05$). Statistically significant (28%) increases in hepatic microsomal lipid peroxidation were also noted in endrin-treated animals beginning at 12 hours (4.98 $\pm$ 0.48 versus 3.89 $\pm$ 0.48; $p<0.05$). Lipid peroxidation remained elevated in both subcellular fractions through 24 hours, when the greatest differences were seen. The authors concluded that single doses of endrin are associated with induction of hepatic lipid peroxidation and suggest that reactive oxygen species and free radicals are involved in the pathology of endrin.

Renal Effects. No studies were located regarding renal effects in humans following oral exposure to endrin, or in humans or animals to endrin aldehyde or endrin ketone. Rats and mice administered 4 mg endrin/kg body weight and killed 24 hours later exhibited moderate tubular necrosis and congestion, inflammation, and interstitial edema. Hamsters and guinea pigs (4 mg/kg body weight, killed 24 hours later) exhibited similar changes without inflammation; cloudy swelling of cells and narrowing of tubular lumina were the only changes observed in exposed guinea pigs (Hassan et al. 1991). Severe congestion and serofibrinous exudate were observed in the kidneys of dogs that died following apparent ingestion of endrin-containing bait (Quick et al. 1989). In animal studies, there was diffuse degeneration of the kidneys of dogs and rats administered lethal concentrations of endrin in the diet (Treon et al. 1955). Dogs exposed to 3 ppm endrin in feed (0.12-0.25 mg/kg/day) had enlarged kidneys. No effects were observed at 1 ppm (0.15 mg/kg/day). The renal damage in dogs was severe at a higher dose (5 ppm or 0.20-0.27 mg/kg/day) and was characterized by necrosis of the convoluted tubules (Treon et al. 1955). Cloudy swelling of tubule epithelial cells was also observed in rats chronically exposed to 2 ppm in the diet (0.1 mg/kg/day) (Deichmann et al. 1970). Renal effects were not observed in the NCI (1978) bioassay of mice and rats; however, discolored urine was reported in rats administered >2.5 ppm (>0.13 mg/kg/day).

Endocrine Effects. Thyroid hyperplasia and pituitary cysts were observed in rats, but not mice, in a chronic bioassay study with endrin administered in the feed (NCI 1978). Treon et al. (1955) found diffuse degeneration of the adrenal glands in rats dosed with >1.25 mg/kg/day in their feed for 2 years; however, the adrenal effects were absent at the 0.25 mg/kg/day dose. There has been no evidence of endocrine effects in occupationally exposed human populations.

No endocrine effects have been reported for endrin aldehyde or endrin ketone in humans or in laboratory animals.

Dermal Effects. Chronic administration of endrin in feed resulted in dermatitis in rats and alopecia in both rats and mice (NCI 1978). There has been no evidence of dermal effects in occupationally exposed populations.

No dermal effects have been reported for endrin aldehyde or endrin ketone in humans or in laboratory animals.

Body Weight Effects. Decreased body weight or body weight gain has been observed in numerous species following endrin exposure and was usually associated with administration of high doses (Chemoff et al. 1979a; Goldenthal 1978a; Kavlock et al. 1981; Treon et al. 1955). Effects on body weight were not observed in one acute-duration study (Ali and Shakoori 1993), in chronicduration rodent toxicity studies (Deichmann et al. 1970; NCI 1978), or in chronic-duration studies in dogs at a dietary level of 0.12-0.25 mg/kg/day (3 ppm) (Treon et al. 1955). A significant reduction (14-17%) in weight gain was noted in male rats exposed to 1.25 mg/kg/day of endrin in feed for 2 years, but not in female rats exposed to levels as great as 5 mg/kg/day by the same route and duration (Treon et al. 1955).

No body weight effects have been reported for endrin aldehyde or endrin ketone in humans or in laboratory animals.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to endrin, or in humans and animals after oral exposure to endrin aldehyde or endrin ketone.

Time- and dose-related increases in spleen-to-body weight ratios were observed in rats administered a single oral dose of 1.5-6 mg endrin/kg body weight, while relative thymus weights were decreased (Bagchi et al. 1992b, 1992c). Concurrent control groups, in which animals received the same experimental handling as treated animals, were not included for comparison of organ weights over time. There were no effects on spleen weight of male and female Beagle dogs who were administered

0.025-0.075 mg/kg/day (1-3 ppm) endrin in their diet for periods of 16.4-18.7 months (Treon et al. 1955).

2.2.2.4 Neurological Effects

Poisoning episodes in humans show that the central nervous system is the primary target system of orally administered endrin. Acute human poisonings by endrin-contaminated food caused symptoms of central nervous system toxicity such as jerking of arms and legs, tonic-clonic contractions, convulsions, and sudden collapse and death (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Davies and Lewis 1956; Rowley et al. 1987; Waller et al. 1992; Weeks 1967).

Neurological effects are commonly observed in animals exposed to endrin. Beagle dogs which had apparently ingested endrin-containing bait exhibited tetanic convulsions (Quick et al. 1989). Death occurred within 45 minutes of the onset of convulsions in 5 of 8 dogs (and later for an additional 2 of 8 dogs). Tremors and convulsions were noted in rats administered endrin at 5 mg/kg for 3 days (Mehorta et al. 1989) or following single high doses (Gaines 1960). Decreased activity levels were observed in pregnant mice (1.5 mg/kg/day) and pregnant rats (0.5 mg/kg/day) acutely administered endrin during gestation. Rats administered 4 mg/kg/day suffered convulsions (Kavlock et al. 1981). Convulsions were also observed in one of 30 golden Syrian hamsters administered 10 mg/kg endrin on gestation day 8 (Chemoff et al. 1979a). Hyperirritability to stimuli, tremors, convulsions, and ataxia occurred in 3 species of animals (dog, rat, and rabbit) administered endrin for acute, intermediate, and chronic durations (Treon et al. 1955).

Rats administered 3.5 mg/kg/day of endrin for one week exhibited excitability and convulsions, in addition to irregular EEG recordings. The EEG changes resolved after exposure for two weeks. At three months of exposure, convulsions could be triggered by noise, and after exposure for seven months, convulsions were readily started (Speck and Maaske 1958). Hyperexcitability was observed in male mice administered 3.2 ppm (0.21 mg/kg/day) of endrin in feed for 80 weeks; however, no histologic changes in the brain were found. No clinical signs of neurotoxicity or brain lesions were observed in a similar study with rats (NCI 1978). Deichmann et al. (1970) reported episodes of tremors and clonic convulsions in rats fed endrin in the diet for 17.6-20.8 months at concentrations of 2-12 ppm (0.1-0.6 mg/kg/day). A dog exposed to 5 ppm endrin in the diet (0.20-0.27 mg/kg/day) had convulsions, tremors, and diffuse degenerative lesions of the brain; the animal died after 47 days

of feeding. A dietary level of 4 ppm (0.15-0.21 mg/kg/day) was not associated with these effects (Treon et al. 1955). Based on these findings, an intermediate oral MRL value of 0.002 mg/kg/day was calculated for endrin as described in the footnote of Table 2-2. Beagle dogs administered 2 ppm (0.05 or 0.059 mg/kg/day) or 4 ppm (0.1 mg/kg/day) endrin in the diet showed evidence of, or were observed having, convulsions (Kettering 1969, 1971). Petechial hemorrhages and cerebral edema were observed in the brain of one dog having convulsions at the time of death. Based on these findings, a chronic oral MRL value of 0.0003 mg/kg/day was calculated for endrin as described in the footnote of Table 2-2.

No studies were located regarding neurological effects in humans or animals after oral exposure to endrin aldehyde or endrin ketone.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to endrin, or in humans and animals to endrin aldehyde or endrin ketone.

In a 3-generation reproduction study, inbred weanling rats were administered endrin-containing diets at 0, 0.1, 1, or 2 ppm (0.0, 0.005, 0.05, or 0.1 mg/kg/day, respectively) (Eisenlord et al. 1968). There were no effects on indices of fertility, gestation, viability, or lactation. Interpretation of the study results is confounded by the potential presence of infection in controls and, thus, possibly in all animals in the study.

In a single generation reproduction study, groups of 3 female Beagle dogs were administered 0, 0.1, 0.5, 1, or 2 ppm (0.0, 0.003, 0.014, 0.027, or 0.059 mg/kg/day, respectively) endrin in the feed and mated with endrin-treated males from a concurrent chronic toxicity study (Kettering 1971). Four treated females (1 each at 0.014 and 0.027 mg/kg/day and 2 at 0.059 mg/kg/day) never accepted a male and, despite artificial insemination, did not become pregnant. Exploratory laparotomies and necropsies, and microscopic examination of ovaries and uteri at termination of these dogs revealed no specific changes due to endrin. The failure to conceive in the high-dose groups could suggest an endrin-mediated effect on fertility. It was concluded that dietary levels of endrin up to 2 ppm (0.59 mg/kg/day) had no effect on reproduction. However, the low number of animals, presence of a

Brucella canis infection, and failure of 2 of 3 control dogs to bring any pups to weaning confounds interpretation of the study.

Groups of male and female CFW Swiss mice were given diets containing 5 ppm endrin for 120 days beginning 30 days before mating (Good and Ware 1969). There were deaths among one-third of the treatment pairs. There was a significant reduction in the size of the first litter, as well as all litters combined, but no significant change in the days to produce a litter. Endrin treatment did not have any effect on fertility or fecundity, but was associated with fetal mortality.

In mallard ducks, dietary administration of endrin (0.5 or 3 ppm) had no effects on egg production, fertility, and ability to hatch, or 14-day hatchling survival, although a 9.6% drop in embryo survival was observed at the high dose (Roylance et al. 1985).

Results of developmental toxicity studies (see Section 2.2.2.6) in rodents suggest endrin can adversely affect pregnancy outcomes. There was reduced survival of pups in hamsters exposed to a single dose of 5 mg/kg (38% mortality, 3% in untreated controls) during the eighth gestation day (Ottolenghi et al. 1974).

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects after oral exposure to endrin in humans, or in humans and animals to endrin aldehyde or endrin ketone.

Developmental effects of endrin have been observed in hamsters and in mice. A statistically significant increase in the incidence of fused ribs and cleft palate was observed in fetuses from golden Syrian hamsters treated on gestation day 7, 8, or 9 with 5 mg/kg of endrin (0.5 LD_{50} dose). A significant increase in open eye and webbed foot occurred only in fetuses from mothers treated on day 8 (Ottolenghi et al. 1974). A single dose of endrin administered to hamsters on gestation day 8 produced meningo-encephaloceles at a dose of 5 mg endrin/kg body weight and fused ribs at doses above 5 mg/kg (Chemoff et al. 1979a). Hamsters intubated with 1.5 mg/kg/day of endrin on gestation days 5-14 had pups that remained more active than controls through 125 days of age (Gray et al. 1981). However, the 1.5 mg/kg/day dose killed more than half of the dams. Endrin was not teratogenic in a study in which pregnant hamsters were administered up to 2.5 mg/kg/day on gestation

days 4-13; slightly reduced maternal body weight gain was noted during treatment at 2.5 mg/kg/day (Goldenthal 1978b).

Exposure of mice to 2.5 mg/kg on gestation day 9 resulted in significantly increased incidence of open eyes and cleft palate (Ottolenghi et al. 1974). No dose-related evidence of open eyes and cleft palate was seen in mice intubated with 1.5 mg/kg/day on gestation days 7-17 (Kavlock et al. 1981). Exencephaly (2 fetuses from 1 litter affected) and fused ribs (3 fetuses from 1 litter) were seen in offspring of pregnant mice treated with 7 or 9 mg/kg of endrin on gestation day 8 (Kavlock et al. 1985); controls had 2 fetuses affected (2 litters) with exencephaly.

No developmental effects were observed in rats administered 0.45 mg/kg/day of endrin on gestation days 7-20 (Kavlock et al. 1981). In a similar study with mice, there was a dose-related decrease in fetal body weight. There were no dose-related indications of skeletal or visceral anomalies in the mice, but delays in development were reflected in changes in the number of caudal vertebrae, development of the renal pelvis, and ossification of the supraoccipital bones (Kavlock et al. 1981). Increased incidences of supernumerary ribs were noted in the offspring of CD-1 mice administered a single 7 mg/kg endrin dose during gestation day 8 (Kavlock et al. 1985). Irregularly shaped supraoccipital bones, visceral abnormalities, a 2-fold increase in fetal mortality and a 30% decrease in fetal weight were also noted in golden Syrian hamster pups whose mothers received 1.5 mg/kg/day endrin administered by gavage in corn oil on gestation days 5-14. Gray et al. (1981) reported increased locomotor activity in CD rats exposed perinatally to 0.15 mg/kg/day of endrin; the increased activity disappeared by 90 days of age. Administration of 2 mg/kg/day endrin to pregnant female rats on gestation days 6-15 resulted in maternal death, decreased maternal body weight gains during treatment, and an increase in delayed ossification of stemebrae and skull in fetuses (Goldenthal 1978a).

In a 3-generation reproduction study, weanling rats were administered endrin-containing diets at 0, 0.1, 1, or 2 ppm (0.0, 0.005, 0.05, and 0.1 mg/kg/day, respectively) (Eisenlord et al. 1968). There were no effects on indices of fertility, gestation, viability, or lactation. The number of pups in the F_{3a} litter of the high dose group was significantly increased relative to controls (11.2 versus 9.2; p=0.05), while F_{3a} pup body weight in the low dose group was significantly decreased (87% of control; p=0.05). The 21-day survival of F_{3a} (0.005 mg/kg/day) and F_{3b}, litters (all dose groups) was elevated compared with controls due to unexpectedly high mortality in the control group which was attributed to a putative

viral pneumonitis. Interpretation of the study results is confounded by the potential presence of infection in controls and, thus, possibly in all animals in the study.

In a single generation reproduction study, groups of 3 female Beagle dogs were administered 0, 0.1, 0.5, 1, or 2 ppm (0, 0.003, 0.014, 0.027, and 0.059 mg/kg/day, respectively) endrin in the feed and mated with endrin-treated males from a concurrent chronic toxicity study (Kettering 1971). There were no organ weight or morphologic changes in pups from endrin-treated females. However, the low number of treated animals, presence of a *Brucella canis* infection, and failure of 2 of 3 control dogs to bring any pups to weaning confounds interpretation of the study.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to endrin, or in humans or animals after exposure to endrin aldehyde or endrin ketone.

In single dose oral studies with rats, endrin treatment was associated with an increased incidence (2.4-3.5-fold) in the number of DNA single strand breaks in hepatocytes (Bagchi et al. 1992a, 1993a, 1993c; Hassoun et al. 1993). DNA damage was attributed to oxidative injury caused by endrin. Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

Endrin was found not to be carcinogenic in Osborne-Mendel rats and B6C3F_1 mice under the conditions of a National Cancer Institute bioassay (NCI 1978). This conclusion is consistent with previously reported studies concerning endrin carcinogenicity in rats and mice. All reported studies, however, have study design limitations that make them inadequate for assessing the potential carcinogenicity of endrin in humans.

Osborne-Mendel rats administered 0, 1, 3, or 6 ppm endrin in feed for 10 weeks, and then 0, 2, 6, or 12 ppm endrin for an additional 106 weeks, had incidences of malignancies that were similar to control animals (Deichmann et al. 1970). The authors concluded that endrin was not carcinogenic or

tumorigenic. Not all tissues were examined microscopically, however, limiting the conclusi,ons that can be drawn from this study.

An NCI bioassay (NCI 1978) administered time-weighted average (TWA) doses of 1.6-5 ppm endrin in feed to B6C3F_1 mice and 2.5-6 ppm in feed to Osborne-Mendel rats for 80 weeks. No significantly increased incidence of tumors in treated animals was reported, but the study is limited by the less-than-lifetime dosing regime.

The only positive carcinogenic effects of endrin were reported by Reuber (1978). Osborne-Mendel male and female rats fed 0, 0.1, 1, 5, 10, or 25 ppm endrin in the diet for 104 weeks developed high incidences of sarcoma and carcinomas (male rats at 0.1 ppm and females at 0.1 or 1 ppm). Treated rats of both sexes developed tumors in other sites, including the lungs, lymph nodes, thyroid, and renal cortex. However, Reuber's criteria for classifying tissues as tumorigenic are not consistent with those of other investigators (EPA 1979f).

Using EPA guidelines for classification of carcinogens, EPA has classified endrin in Group D, indicating there is inadequate evidence to assess the potential carcinogenicity of endrin in humans (IRIS 1994). The International Agency for Research on Cancer (IARC) (1974) has not evaluated the carcinogenic potential of endrin.

No studies were located regarding carcinogenic effects in humans or animals after oral exposure to endrin aldehyde or endrin ketone.

2.2.3 Dermal Exposure

Although no dermal studies *per se* were found regarding human exposure to endrin, several occupational exposure studies exist (Ditraglia et al. 1981; Hoogendam et al. 1962, 1965; Ribbens 1985; Versteeg and Jager 1973). Wolfe et al. (1963) has shown that dermal exposure in the agricultural setting is significant. Therefore, the results of the occupational exposure studies, which are summarized in the inhalation exposure section (2.2.1), may be relevant to dermal exposure scenarios and, where appropriate, are briefly noted below.

Limited data are available regarding dermal exposure of animal to. endrin. Results of these studies are discussed below and presented in Table 2-3.

2.2.3.1 Death

No studies were located regarding lethal effects in humans after dermal exposure to endrin or in humans or animals after dermal exposure to endrin aldehyde or endrin ketone.

A minimum lethal dose of 94 mg/kg body weight was reported for rabbits (1 of 3 died) exposed dermally to crystalline 100-mesh endrin powder for 24 hours (Treon et al. 1955). Convulsions were also reported. Similarly, 1 of 3 or 1 of 4 female rabbits exposed to daily doses of endrin ranging from 20 to 42 mg/kg/day died after repeated dermal exposures to abraded or intact skin, and 3 of 3 died following exposure of intact skin to 67-91 mg/kg (Treon et al. 1955). Convulsions, tremors, and facial twitching were the chief signs of intoxication. The dermal LD_{50} for endrin in xylene was similar in male (18 mg/kg; minimum lethal dose 10 mg/kg) and female (15 mg/kg) rats (Gaines 1960, 1969). Topical application of 75 mg/kg to a cat resulted in death 22 days later (Ressang et al. 1959). Topical application of a concentrated solution of endrin to 4 bullocks for tick infestation caused death in one bullock within 6 hours after exposure (Pandey 1978).

2.2.3.2 Systemic Effects

Studies regarding the systemic effects that have been observed in humans and animals after dermal exposure to endrin are discussed below. With regard to potential dermal effects, no reports of irritative effects have appeared in the medical or industrial hygiene literature despite several decades of use by hundreds of workers. No reliable studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, dermal, ocular, or body weight effects in humans or animals after dermal exposure to endrin, endrin aldehyde, or endrin ketone.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to endrin. Rabbits fatally poisoned by an acute dermal endrin dose of 94 mg/kg body weight and higher had centrilobular degeneration of the liver (Treon et al. 1955). Details regarding the histopathology of the lesions were not provided, and only a small number of animals were tested. Rabbits surviving multiple skin applications exhibited severe fatty degeneration of the liver.

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Rat (Sherman)	once				15 F (LD_{50})	Gaines 1960 Endrin
Rat (Sherman)	once				10 M (LD_{min})	Gaines 1969 Endrin
Rabbit (NS)	24 hr				94 F (1/3 rabbits died)	Treon et al. 1955 Endrin
Cat (NS)	once				75 (death; 50%)	Ressang et al.1959 Endrin
Systemic						
Rabbit (NS)	24 hr	Hepatic			94 F (centrilobular liver necrosis)	Treon et al. 1955 Endrin
		Renal			94 F (degenerative changes)	
		Dermal	3600 F			
Neurological						
Rabbit (NS)	24 hr				94 F (convulsions, diffuse brain necrosis)	Treon et al. 1955 Endrin

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL			Reference Chemical Form
				Less Serious (mg/kg)		Serious (mg/kg)	
INTERMEDIATE EXPOSURE							
Death							
Rabbit (NS)	25-45x total, 5 d/wk 2 hr/d					2744 F (1/4 rabbit died)	Treon et al. 1955 Endrin
Rabbit (NS)	19-70 x total, 5 d/wk 2 hr/d					2042 F (1/3 rabbits died)	Treon et al. 1955 Endrin
Systemic							
Rabbit (NS)	19-70 x total, 5 d/wk 2 hr/d	Hepatic				20-42 F (fatty degeneration)	Treon et al. 1955 Endrin
		Renal				20-42 F (degenerative changes)	
		Dermal	67-91 F				
Neurological							
Rabbit (NS)	19-70 x total, 5 d/wk 2 hr/d					20-42 F (convulsions, tremors, twitching of facial muscles, brain necrosis)	Treon et al. 1955 Endrin

d = day(s); F = female; hr = hour(s); LOAEL = lowest-observable-aderse-effect level; M = male; LD_{50} = lethal dose, 50% kill; LD_{min} = minimum lethal dose; NOAEL = no-observable-adverse-effect level; NS = not specified; wk = week(s); x = times

No studies were located regarding hepatic effects in humans or animals after dermal exposure to endrin aldehyde or endrin ketone.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to endrin. Diffuse degenerative changes of the kidney occurred in rabbits exposed dermally to lethal doses of endrin once or for an intermediate duration (Treon et al. 1955). No studies were located regarding renal effects in humans or animals after dermal exposure to endrin aldehyde or endrin ketone.

Dermal Effects. No studies were located regarding the dermal effects in humans after dermal exposure to endrin. No damage to the skin at the site of application was observed in rabbits exposed to a single or repeated dermal application of dry endrin (Treon et al. 1955); however, the rabbits had convulsions.

No studies were located regarding the dermal effects in humans or laboratory animals after dermal exposure to endrin aldehyde or endrin ketone.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals after dermal exposure to endrin, endrin aldehyde, or endrin ketone.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to endrin or in humans or animals to endrin aldehyde or endrin ketone.

Uncontrolled exposure to endrin caused twitching and jerking of muscles, dizziness, mental confusion, and epileptiform seizures occurring within 2 hours following occupational exposure (Hoogendam et al. 1962, 1965). Clinical recovery was apparent within l-3 days, and abnormal EEGs (predominantly bilateral synchronous theta waves and synchronous spike and wave complexes) generally returned to normal within 0.5-l month. Convulsions, tremors, and/or twitching of the facial muscles were the chief signs of intoxication of rabbits and rats exposed dermally to endrin (Gaines 1960; Treon et al.

1955). Diffuse degenerative lesions of the brain were observed in rabbits that died (Treon et al. 1955). Convulsions, salivation, lachrymation, staggering gait, hypothermia, and shallow breathing were also recorded in bullocks treated topically with a concentrated endrin solution (Pandey 1978).

No studies were located regarding the following health effects in human or animals after dermal exposure to endrin, endrin aldehyde, or endrin ketone:

2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Studies of workers in the endrin manufacturing industry have not shown an association between occupational exposure to endrin and any type of human cancer (Ribbens 1985; Versteeg and Jager 1973). In a study of four U.S. industries, two of which manufactured endrin, slight excesses of cancer of the esophagus, rectum, and liver, and cancer of the lymphatic and hematopoietic systems were reported (Ditraglia et al. 1981). Although the excesses were not statistically significant and were based on small numbers of deaths, it may prove useful to follow these workers and reexamine their mortality patterns.

No studies were located regarding carcinogenic effects in animals after dermal exposure to endrin or in humans or animals after exposure to endrin aldehyde or endrin ketone.

2.3 TOXICOKINETICS

To date, very little quantitative data exist regarding the toxicokinetics of endrin and its metabolites. Limited data were found regarding the absorption, distribution, metabolism, and excretion of endrin in humans and animals after inhalation, oral, or dermal exposure, which is especially relevant to

occupational exposure scenarios. Endrin appears to be well absorbed orally, and distribution is primarily to fat and skin. Endrin is excreted in urine and feces, and the major biotransformation product is anti-l 2-hydroxyendrin and the corresponding sulfate, and glucuronide metabolites. No studies were found that described the toxicokinetics of endrin aldehyde or endrin ketone.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Quantitative data describing the rate of absorption of endrin following inhalation exposure were not available. Cases of occupational exposure reported by Hoogendam and coworkers (1965) and laboratory animal studies reported by Treon et al. (1955) indicate that when endrin is inhaled and absorbed it can produce serious adverse biological effects.

2.3.1.2 Oral Exposure

Case studies reported that ingested endrin is absorbed by humans (Coble et al. 1967; Curley et al. 1970; Kintz et al. 1992; Rowley et al. 1987; Runhaar et al. 1985; Weeks 1967). No studies have been located which report the rate or extent of absorption that occurs in orally exposed humans or animals.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of endrin in humans after dermal exposure. Agricultural worker exposure studies demonstrated that dermal exposure (18.7 mg/hour without gloves) was significantly greater than respiratory exposure (0.41 mg/hour) and that workers exposed to endrin received about 0.2-1.5% of a toxic dose per hour of exposure. No adverse effects were reported in the worker cohort (Wolfe et al. 1963).

Dermal exposure of rats and rabbits to endrin resulted in toxicity and death (Gaines 1960; Treon et al. 1955), indicating that percutaneous absorption of endrin occurs. It is likely that occupational poisonings reported by Hoogendam et al. (1962, 1965) also involved dermal absorption, but the extent and relative contribution of dermal exposure cannot be determined. Data describing the rate or extent of dermal absorption were not located.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution of endrin in humans or animals after inhalation exposure.

2.3.2.2 Oral Exposure

Measurable levels of endrin have not been found in adipose tissue of the general population (Stanley 1986; Williams et al. 1984). Measurable tissue concentrations of endrin have been observed in cases of acute poisoning. The time of sample collection is critical as endrin residues in tissues decline rapidly after exposure has ceased.

A patient who consumed endrin-contaminated bread had serum levels of endrin of 0.053 ppm (0.053 mg/L); no endrin was detected in cerebrospinal fluid. The sample was taken 30 minutes after a convulsion (Coble et al. 1967). In another bread poisoning incident, blood from patients hospitalized with acute symptoms contained 0.007-0.032 ppm of endrin. Tissues taken at autopsy (elapsed time not specified) contained endrin at the following concentrations: stomach wall, 0.16 ppm; liver, 0.685 ppm; and kidney, 0.116 ppm (Curley et al. 1970).

In a poisoning incident in Pakistan, patients with convulsions (sampling time not specified) had measurable blood levels of endrin ranging from 0.0003 to 0.254 ppm (Rowley et al. 1987). Tissues of a suicide victim contained the following concentrations of endrin 11 days after ingestion of 12 g of endrin in a formulation product: 0.07 mg/L in blood, 89.5 mg/kg in adipose tissue, 0.87 mg/kg in heart, 0.89 mg/kg in brain, 0.55 mg/kg in kidneys, and 1.32 mg/kg in liver (Runhaar et al. 1985).

Autopsy tissues and other biologic specimens from people fatally poisoned with endrin (by the oral or an unspecified route) were analyzed (Tewari and Sharma 1978). The “fatal period” (presumed to be the time from onset of symptoms until death) for the subjects studied ranged from 1 to 6 hours. As is characteristic of oral administration, highest tissue concentrations were observed in the stomach (1.04-14.5 mg/l00 g), intestine (1.31-66 mg/l00 g), and liver (0.94-20 mg/l00 g), followed by

kidney, spleen, heart, and lung. Blood concentrations were low (0.43-0.85 mg/l00 g) compared to tissue concentrations.

A 21-year-old woman was found dead after apparent ingestion of endrin dissolved in xylene; high concentrations of endrin were detected in the stomach contents (47,351 mg/L), blood (544.9 mg/L), and bile (780.5 mg/L) (Kintz et al. 1992). The large amount of endrin found in the blood was interpreted to reflect the short time between ingestion and death.

Endrin tends to bioaccumulate in fat because of its high lipid solubility. Three days after an acute oral dose of 2.5 mg/kg body weight of radio-labeled endrin, the percentages of the administered dose in male rat organs were 1.2% in liver, 0.6% in kidney, 1.7% in fat, 2.3% in skin, and 12.2% in the carcass. Female rats retained higher concentrations in tissues: 2% of the dose in liver, 0.35% in kidney, 8% in fat, 4% in skin, and 28.2% in carcass (Hutson et al. 1975). Following administration of radio-labeled endrin to lactating cows, the highest tissue concentrations were in the fat (about 8% of the total dose). Residues in liver, muscle, kidneys, and fat primarily contained unchanged endrin (Baldwin et al. 1976). Endrin and 12-ketoendrin were detected in the maternal liver and fetal tissue of rats and hamsters administered endrin during gestation (Chernoff et al. 1979a; Kavlock et al. 1981). Concentrations of endrin in fetal tissue ranged from 2 to 8% of those measured in maternal livers, indicating that endrin can cross the placenta. In a dietary study with mallard ducks, treated females developed higher body fat content and greater accumulation of endrin in the fat than males (Roylance et al. 1985). Endrin was deposited in the eggs of treated females at about the dietary concentration of endrin in their feed (0.5 and 3 ppm).

In Beagle dogs that had died after apparent ingestion of endrin-containing bait, the stomach contents contained 34-5,000 mg/kg endrin (Quick et al. 1989). The highest tissue concentrations were found in the fat (5.4-40 mg/kg), followed by liver (0.82-4.5 mg/kg), and brain (0.34-2.7 mg/kg). Lower concentrations were found in lung and muscle. Following administration of 0.1 mg/kg/day in the feed for 128 days, concentrations of endrin in the blood of Beagle dogs showed no accumulation over time (Richardson et al. 1967). At termination, there was no correlation between the concentration of endrin in blood with that in heart, pancreas, liver, kidney, spleen, and lung, although a trend of high concentrations in fat (250-760 ppb) and high concentrations in blood (1-8 ppb) were noted. Highest tissue concentrations of endrin were generally found in fat, followed by muscle (120-310 ppb), heart (125-170 ppb), pancreas (87-280), liver (77-84 ppb), kidney (38-82 ppb), and lung (17-33 ppb).

Concentrations in the spleen were highly variable (7-2,620 ppb). Results from this study may be somewhat confounded by a potential feeding error, as dieldrin (being fed to a concurrent group) was detected in the blood and tissues of the three endrin-treated dogs.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of endrin in humans or animals after dermal exposure.

2.3.3 Metabolism

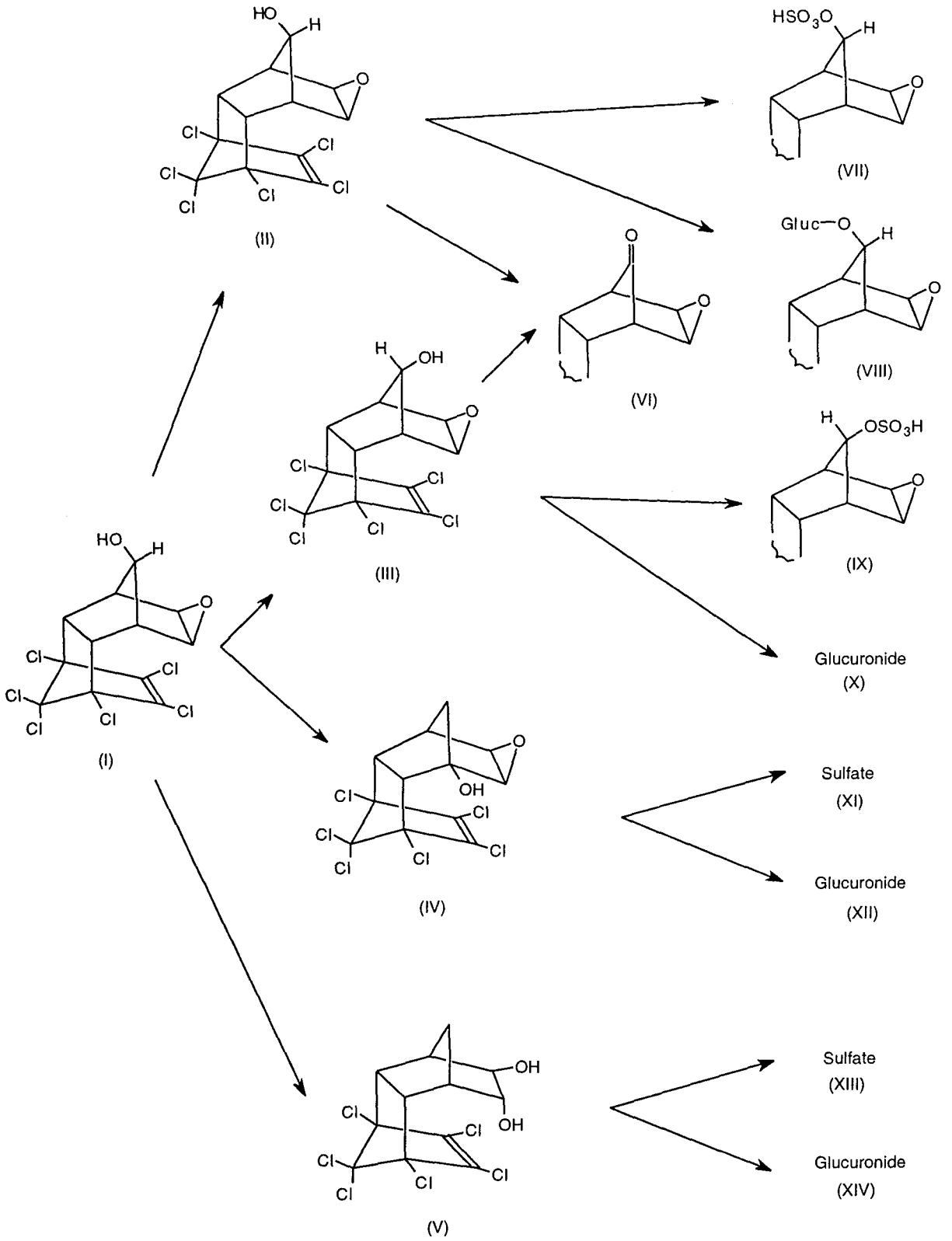
The metabolism of endrin varies among species, regardless of the route of exposure. In all species, oxidation of the methylene bridge in endrin (Compound I in Figure 2-3) to syn-, but mostly anti-12-hydroxyendrin occurs (Compounds II and III), followed by dehydrogenation to 12-ketoendrin (Compound VI). Minor independent pathways involve the hydrolysis of the epoxide to a transdiol (Compound V in Figure 2-3), and hydroxylation of the C-3 position (Compound IV) (Bedford et al. 1975b; Hutson 1981). Hydroxylation at C-3 and C-4 is inhibited by the presence of the bulky hexachlorinated fragment (Hutson 1981).

Hydroxylated metabolites are conjugated as glucuronides and sulfates. The balance of products in this last step and their distribution between urine and feces distinguishes the metabolism between humans, rats, and rabbits (Baldwin and Hutson 1980; Bedford et al. 1975b; Hutson 1981; Hutson et al. 1975), as discussed in Section 2.3.4. Similarly, studies in lactating cows ingesting radio-labeled endrin in the diet for 21 days suggest metabolic pathways similar to those in rats and rabbits with apparent differences between the 3 species attributed more to differences in biliary versus renal excretion (Baldwin et al. 1976).

In workers in pesticide manufacturing plants, anti-12-hydroxyendrin as the glucuronide and 12-ketoendrin were found in both urine and feces (3 of 7 workers) (Baldwin and Hutson 1980).

Anti- and syn-12-hydroxyendrin and 12-ketoendrin are more toxic in the rat than endrin itself. The hydroxyendrins are rapidly converted to the more toxic 12-ketoendrin, and this latter metabolite is most likely the toxic entity of endrin (Bedford et al. 1975a; Hutson et al. 1975).

Figure 2-3. Proposed Metabolic Scheme for Endrin in Mammals



2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Anti-12-hydroxyendrin and 12-ketoendrin were detected in the feces of pesticide manufacturing workers and its glucuronide conjugate and 12-ketoendrin have been detected in the urine (Baldwin and Hutson 1980). In another study, the levels of anti-12-hydroxyendrin increased accompanied by a sharp rise in D-glucaric acid levels in 29 workers after 7 days of exposure (Ottevanger and Van Sittert 1979; Vrij-Standhardt et al. 1979).

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

2.3.4.2 Oral Exposure

Measurements of human serum concentrations of endrin following incidents of acute poisoning indicate rapid decline in concentration after exposure (Coble et al. 1967; Rowley et al. 1987).

The bulk of endrin metabolites excreted by rats are in the bile (Hutson et al. 1975) as glucuronides. Rabbits excrete ^{14}C-endrin in the urine as sulfates (Bedford et al. 1975b). Studies in lactating cows ingesting endrin in the diet for 21 days show that ^{14}C-endrin is readily excreted as unchanged endrin in the milk, accounting for 2.5-4.3% of the total dose (Baldwin et al. 1976). Similarly, endrin has been detected in the milk of lactating women (Alawi et al. 1992; Bordet et al. 1993). Due to its lipophilic nature (partition coefficient [Log_{ow}]: 5.6), endrin was contained in the lipid portion of the milk.

In rats, 55-57% of ^{14}C-endrin was metabolized, mostly as the glucuronide of anti-12-hydroxyendrin, in the bile within 24 hours of dosing with 0.5-2.5 mg/kg (Hutson et al. 1975). Other minor components (<10%) were the glucuronides of 3-hydroxy- and 12-ketoendrin. Male rats eliminated 69% of the radioactive label within 3 days and females eliminated 45%. The major metabolite in female rat urine was 12-hydroxyendrin-O-sulfate. Baldwin et al. (1970) also detected 9-ketoendrin in the urine of rats.

There is a sex difference in rats in production and excretion of 12-ketoendrin, which is observed as a major urinary metabolite in the male rat; the major urinary metabolite in the female rat is the antihydroxyendrin-O-sulfate (Hutson et al. 1975). In studies with isolated perfused livers, ^{14}C-endrin was excreted in the bile of livers from male rats at a rate 2-12 times higher than that for females (Klevay 1971).

In rabbits administered radio-labeled endrin, 50% of the radioactivity was excreted in the urine over a 50-day period (Bedford et al. 1975b). Excretion of the label was 87% complete within 13 days. The major compounds detected in urine were anti-12-hydroxyendrin sulfate and 3-hydroxyendrin sulfate (14%).

A heritable resistance in pine mice to endrin raises the LD_{50} from 3 mg/kg in sensitive voles to 40 mg/kg in resistant animals (Webb et al. 1973). This trait is correlated with the greater excretion of endrin as the anti-12-hydroxy metabolite in the resistant mice. Associations between lethality and concentration of 12-ketoendrin residues has been made for rats (Hutson et al. 1975) rat fetuses (Kavlock et al. 1981), and hamster fetuses (Chemoff et al. 1979a). Toxicity also occurs when endrin itself appears in the tissues.

2.3.4.3 Dermal Exposure

No studies were located concerning excretion of endrin in animals or humans after dermal exposure.

2.4 MECHANISMS OF ACTION

The mechanism by which endrin induces its toxic effects has been the subject of a considerable number of research investigations. Endrin appears to exert its neurotoxic effects at the level of the central nervous system as evidenced by convulsions and seizures in humans and animals, and altered electrophysiologic activity in animals (Speck and Maaske 1958). The 12.5-fold greater toxicity of endrin when administered intracerebrally versus intraperitoneally to male mice supports the brain being the primary target site for endrin (Bloomquist 1992). Endrin decreased the seizure threshold for pentylenetetrazol in mice, although there were no correlations with effects on brain serotonin levels (Miller and Fink 1973). *In vitro* exposure of male rat brain preparations to endrin has been shown to induce noncompetitive inhibition of γ-aminobutyric acid (GABA)-regulated chloride transport (Wafford

et al. 1989) and chloride current in patch clamp studies (Narahashi 1991). Other studies support the correlation between inhibition of GABA-dependent chloride uptake and the acute intracerebral toxicity of endrin (Bloomquist 1992). The results of these studies support the hypothesis that endrin disrupts the GABAergic system, which is an inhibitory neurotransmitter system, thus causing hyperexcitability of the central nervous system.

Mehorta and coworkers (1989) observed that isolated fractions of brain and heart cells from rats orally administered 0.5-10 mg endrin/kg showed significant inhibition of Ca^{+2} pump activity and decreased levels of calmodulin, indicating disruption of membrane Ca^{+2} transport mechanisms; exogenous addition of calmodulin restored Ca^{+2}-ATPase activity. *In vitro* exposure of rat brain synaptosomes and heart sarcoplasmic reticuli decreased total and calmodulin-stimulated calcium ATPase activity with greater inhibition in brain preparations (Mehorta et al. 1989). However, endrin showed no inhibitory effects on the calmodulin-sensitive calcium ATPase activity when incubated with human erythrocyte membranes (Janik and Wolf 1992). *In vitro* exposure of rat brain synaptosomes to endrin had no effect on the activities of adenylate cyclase or 3',5'-cyclic phosphodiesterase, two enzymes associated with synaptic cyclic AMP metabolism (Kodavanti et al. 1988).

Administration of endrin to animals has been associated with hepatic histopathology which includes the presence of lipofuscin pigment (Hassan et al. 1991). One laboratory has studied the ability of endrin to elicit hepatic lipid peroxidation and associated cell injury. Administration of single doses of endrin to rats was associated with increased lipid peroxidation, decreased membrane fluidity, and DNA damage (single strand breaks) in hepatocytes (Bagchi et al. 1992a, 1993c; Hassoun et al. 1993). The authors suggest that membrane alterations and DNA damage may result from the enhanced formation of free radical or reactive oxygen species. Endrin caused dose-related increases in lipid peroxidation in rats resulting in breakdown of polyunsaturated fatty acids as evidenced by the urinary excretion of the lipid metabolites formaldehyde, acetaldehyde, malondialdehyde, and acetone (Bagchi et al. 1992b). Endrin exposure was associated with decreased glutathione concentrations in liver, kidney, heart, spleen, brain, and lungs, and altered glutathione-regulating enzymes in liver and kidney (Numan et al. 1990a, 1990b). Alterations in hepatic calcium and iron homeostasis were associated with acute endrin administration to rats (Bagchi et al. 1992c). Pretreatment with various antioxidants (Vitamin E succinate, ellagic acid) ameliorated endrin-related lethality, histopathologic damage, lipid peroxidation, DNA damage, glutathione depletion, alterations in iron homeostasis, and excretion of lipid metabolites (Bagchi et al. 1992c, 1993c; Hassan et al. 1991; Numan et al. 1990a, 1990b). In studies with dioxin-

responsive and non-responsive strains of mice, there was no clear evidence for involvement of the Ah receptor in endrin-induced lipid peroxidative effects in liver (Bagchi et al. 1993d).

Macrophages from endrin-exposed rats or mice showed an increase in the concentration of nitric oxide (Akubue and Stohs 1992; Bagchi et al. 1993d) and increased chemiluminescence and production of superoxide anion (Bagchi et al. 1993a). Based on these results and those described above for hepatic microsomal and mitochondrial alterations, it appears that multiple sources of reactive oxygen species may be involved in endrin-mediated cell damage.

2.5 RELEVANCE TO PUBLIC HEALTH

The fact that endrin is no longer produced or used in the United States greatly reduces the potential for human exposure. Future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low. The most significant route of exposure is most likely ingestion of imported foods contaminated with endrin; however, there may also be some localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin.

Case reports of endrin toxicity in humans suggest that endrin is well absorbed following ingestion or, as evidenced by accounts in the occupational setting, dermal exposure. Limited data in animals suggest that endrin is also readily absorbed following inhalation exposure as well. Endrin is rapidly metabolized and excreted in the urine and feces. However, low concentrations of endrin may remain in adipose tissue following high exposures.

The central nervous system is the primary target site for endrin toxicity. Convulsions and death have occurred within a few hours of ingestion. Less severe symptoms include headache, convulsions, dizziness, nausea, vomiting, nervousness, and confusion. No long-term health effects have been noted in occupationally exposed workers. Birth defects, especially abnormal bone formation (i.e., fused ribs), have been seen in some laboratory animal studies. In studies using rats, mice, and dogs, endrin did not produce cancer. However, most of these studies were not suitable for accurately evaluating the ability of endrin to cause cancer. There is no evidence that endrin can cause cancer in exposed humans. The EPA has determined that endrin is not classifiable as to its human carcinogenicity (Group D), because the available information is inadequate.

Minimum Risk Levels for Endrin.

Inhalation MRLs

MRLs for inhalation exposure to endrin, endrin aldehyde, and endrin ketone were not derived for any duration category because data are insufficient.

Oral MRLs

- An oral MRL of 0.002 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to endrin.

An intermediate oral MRL was based on a NOAEL of 0.15 mg/kg/day for neurologic effects including convulsions and tremors in dogs administered endrin in the diet for 18 days to 9.9 months (Treon et al. 1955). In that study, a dog exposed to 5 ppm endrin in the diet (0.20-0.27 mg/kg/day) had convulsions, tremors, and diffuse degenerative lesions in the brain; the animal died after 47 days of feeding. A dietary level of 4 ppm (0.15-0.21 mg/kg/day) was not associated with these effects. The central nervous system is the primary target system for endrin as evidenced by reports of neurologic effects including convulsions and tremors in humans and other animal species (Curley et al. 1970; Deichmann et al. 1970; Treon et al. 1955; Waller et al. 1992).

- An oral MRL of 0.0003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to endrin.

The chronic oral MRL was based on a NOAEL of 0.025 mg/kg/day for convulsions in dogs administered endrin in the diet for 2 years (Kettering 1969). Concentrations of 0.05 and 0.1 mg/kg/day were associated with convulsive activity, slight to moderate vacuolization of hepatic cells, and occasional slight increases in liver weights. Other studies have reported hepatotoxicity in animals treated orally with endrin (Hassan et al. 1991; Treon et al. 1955).

Adverse health effects of exposure to endrin are described below. Except for 15-day feeding studies in rats, no information was found regarding health effects associated with oral exposure to endrin

aldehyde or endrin ketone. No information was found regarding the health effects associated with inhalation or dermal exposure to endrin aldehyde or endrin ketone.

Death. Clinical reports in humans and studies in animals demonstrate that death due to central nervous system toxicity is the primary acute lethal effect associated with endrin exposure. A lethal dose of endrin in humans has not been identified, but 0.2-0.25 mg endrin/kg body weight is sufficient to cause convulsions (Davies and Lewis 1956). Liver, kidney, heart, and brain damage were reported following oral and inhalation exposures. Since endrin is no longer used commercially, the general public is not likely to encounter levels sufficient to lead to toxic neurological effects or death. However, endrin may be encountered in hazardous waste sites. Endrin is an acutely toxic pesticide that has caused deaths from the inadvertent ingestion of contaminated foods (Rowley et al. 1987; Tewari and Sharma 1978; Weeks 1967) and from suicides (Runhaar et al. 1985). Excess mortality has not been associated with chronic exposure to endrin (Ditraglia et al. 1981; Ribbens 1985).

Endrin can be lethal to animals following inhalation, oral, and dermal exposure for acute, intermediate, and chronic durations. Fifteen mg/m^3 of endrin in air (0.36 ppm) was lethal to rabbits and mice, but not to a cat, rats, hamsters, or guinea pigs (Treon et al. 1955). The oral LD_{50} of endrin for rats was 7-43 mg/kg, depending on the gender and age of the animal (Treon et al. 1955). A minimum lethal dermal dose of 67-91 mg/kg was reported for rabbits exposed acutely (Treon et al. 1955).

Systemic Effects. Very limited studies were found on the systemic effects of endrin in humans. Liver, kidney, heart, and brain damage occurred in animals, but at relatively high doses or doses causing death. These data suggest that systemic effects involving liver, kidney, and heart may not be a potential area of concern following endrin exposure. No studies were found regarding musculoskeletal or ocular effects of endrin in humans or animals.

Respiratory Effects. Increased deaths due to pneumonia and other nonmalignant respiratory diseases were observed in workers at one of two plants that manufactured endrin (Ditraglia et al. 1981). However, simultaneous exposure to other chemicals occurred, and increased respiratory disease was not observed in the second endrin manufacturing facility. Pulmonary edema was observed in a patient poisoned with endrin, but was thought to be due to chemical pneumonitis from aspiration of aromatic hydrocarbons contained in the formulation (Runhaar et al. 1985). Rats treated for 17.6-20.8 months

with 0.1 mg/kg/day exhibited focal hemorrhage and congestion of the lungs (Deichmann et al. 1970). Other histopathologic effects observed in animals probably occurred secondary to death.

Curdiovascular Effects. Only limited reports of cardiovascular toxicity of endrin were located. Diffuse degenerative lesions of the heart were observed in dogs administered lethal doses of endrin (Treon et al. 1955), and enlarged hearts were observed at sublethal doses. The health significance of these finding is unclear, as the effects were not observed in other animal species.

Gastrointestinal Effects. Nausea, vomiting, diarrhea, and abdominal distention have been reported in people consuming endrin-contaminated foods (Waller et al. 1992); however, no gastrointestinal lesions have been observed in animals (NCI 1978).

Hemutologicul Effects. Hematological effects have not been observed in occupationally exposed worker populations (Hoogendam et al. 1962; Versteeg and Jager 1973). There were no changes in the relative numbers of types of formed elements in the peripheral blood of male and female Beagle dogs administered endrin in their diet for periods of 16.4-18.7 months (Treon et al. 1955).

Heputic Effects. Workers monitored for liver function had increased serum levels of liver enzymes (Hoogendam et al. 1965). Only limited conclusions should be drawn from these results as the levels returned to normal within 1 week to 3 months; concurrent exposure to other chemicals and alcohol was not controlled. Diffuse degenerative hepatic lesions were observed in rabbits and mice exposed to lethal doses of endrin and in surviving animals (Treon et al. 1955). Rats, mice, guinea pigs, and hamsters administered a relatively high dose of endrin exhibited moderate hepatic histopathology (Hassan et al. 1991).

Endrin has been shown to affect microsomal enzyme activity in voles and mice with differing effects (i.e., differing degree and direction of change) depending on species and model substrates (Hartgrove et al. 1977). Maternal liver enlargement occurred in pregnant mice administered endrin (Kavlock et al. 1981). Liver effects of endrin have been observed; however, lesions occurred only at relatively high or lethal doses. While the liver is not the primary target system of endrin toxicity, toxic effects on the liver may occur after large doses (e.g., 4 mg/kg/day in mice, rats, and guinea pigs).

Renal Effects. Lethal doses of endrin caused diffuse degenerative lesions in the kidneys of dogs, mice, rabbits, and rats administered endrin (Treon et al. 1955). Renal histopathologic effects were also observed in rats, mice, and hamsters (Hassan et al. 1991).

Endocrine Effects. Thyroid hyperplasia and pituitary cysts were observed in rats, but not in mice, in a chronic bioassay study with endrin administered in the feed (NCI 1978). There has been no evidence of endocrine effects in occupationally exposed populations.

Dermal Effects. Chronic administration of endrin in feed resulted in dermatitis in rats and alopecia in both rats and mice (NCI 1978). There has been no evidence of dermal effects in occupationally exposed populations.

Body Weight Effects. No specific effects on body weight have been noted in humans. Effects on body weight (decreases) in animals were usually associated with administration of high doses and were not observed in chronic toxicity studies (Chemoff et al. 1979a; Deichmann et al. 1970; Goldenthal 1978a; Kavlock et al. 1981; NCI 1978; Treon et al. 1955).

Immunological and Lymphoreticular Effects. No reports of immunological effects of endrin in exposed humans were found. Very few reports of immunological or lymphoreticular effects due to endrin toxicity have been reported in laboratory animals, and have mainly been limited to either no observed changes in spleen weights in dogs dosed with up to 3 mg/kg/day orally (Treon et al. 1955) tc relative changes in spleen and thymus weight changes in rats dosed with 3 mg/kg/day orally for acute durations (Bagchi et al. 1992b, 1992c). An *in vitro* study of endrin effects on human lymphocyte mitogenic responses to phytohemagglutinin and neutrophil chemotaxis was negative (Lee et al. 1979).

Neurological Effects. The central nervous system is the primary target system of endrin. Acute human poisonings by endrin were characterized by symptoms of central nervous system toxicity such as jerking of arms and legs, twitching facial muscles, tonic and clonic contractions, convulsions and sudden collapse, and death (Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Rowley et al. 1987; Runhaar et al. 1985; Weeks 1967). Changes in EEG patterns were usually observed in poisoned humans (Hoogendam et al. 1962).

Neurological effects occurred in animals exposed to endrin. Behavioral effects (Gray et al. 1981), hyperexcitability, tremors, and convulsions (Deichmann et al. 1970; NCI 1978; Treon et al. 1955) were reported. Irregular EEG recordings were observed in rats (Speck and Maaske 1958). There is some evidence to show that occurrence of convulsions is related to blood-brain barrier permeability changes (Speck and Maaske 1958).

Human and animal evidence suggests there is a health risk for neurological effects only when exposures are high. There remains uncertainty in predicting dose levels for neurobehavioral effects, but 0.2 mg/kg body weight has been proposed as a threshold for convulsions in humans (Hayes 1963).

Reproductive Effects. No reports of reproductive effects in endrin-exposed humans have been located. Early single and 3-generation reproductive studies in dogs and rats, respectively, were inadequate for assessing potential reproductive effects (Eisenlord et al. 1968; Kettering 1971).

Developmental Effects. Developmental effects associated with exposure of humans to endrin have not been reported. Prenatal exposure of animals to concentrations of endrin sufficient to cause maternal toxicity has resulted in a statistically significant increase in the incidence of fused ribs, cleft palate, exencephaly, microencephaloceles, and open eyes in hamsters and mice. Effects were not necessarily reproducible between studies. Adverse developmental effects generally have not been observed in rats (Kavlock et al. 1981) except for temporary increase in locomotor activity of pups (Gray et al. 1981) and delayed ossification at doses which resulted in maternal toxicity (Goldenthal 1978a). Developmental effects were found primarily in one species. It is unknown if these effects would occur in humans.

Genotoxic Effects. No *in vivo* studies of genotoxic effects in humans were located. The results of *in vitro* genotoxicity studies with endrin are summarized in Table 2-4. Endrin was not mutagenic *in vitro* in microbial assays with or without metabolic activation (Ames et al. 1975; Glatt et al. 1983; Moriya et al. 1983; Probst et al. 1981; Zeiger et al. 1987) or in the mouse lymphoma cell assay (McGregor et al. 1991). Exposure of primary rat, mouse, or hamster hepatocytes to endrin did not cause unscheduled DNA synthesis or repair (Maslansky and Williams 1981; Probst et al. 1981; Williams 1980). Sister chromatid exchange frequencies were not significantly elevated in activated and nonactivated human lymphoid cells (Sobti et al. 1983). Chromosomal aberrations observed in

Table 2-4. Genotoxicity of Endrin *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (rat & hamster S-9)	Gene mutation	–	–	Zeiger 1987
Mammalian cells:				
Rat testis	Chromosomal aberration	N/A	N/A	Dikshith and Datta 1973
Mouse lymphoma cell (L5178Y tk+/tk–)	Gene mutation	–	–	McGregor et al. 1991
Fischer 344 rat primary hepatocyte cultures (DNA repair)	DNA damage	–	NA	Maslansky and Williams 1981
Human lymphoid cells	Sister chromatid exchange	–	–	Sobti et al. 1983
CD1 mouse primary hepatocyte cultures (DNA repair)	DNA damage	–	–	Maslansky and Williams 1981
Syrian hamster primary hepatocyte cultures (DNA repair)	DNA damage	–	NA	Maslansky and Williams 1981

– = negative result; DNA = deoxyribonucleic acid; NA = not applicable; the hepatocyte is capable of metabolic activation

testicular cells of rats following injection of endrin are of questionable relevance to human risk assessment due to the route of exposure, which was direct, intratesticular injection (Dikshith and Datta 1973). The ability of endrin to cause an increase in hepatic DNA damage (single strand breaks) is attributed to endrin-induced oxidative damage (Bagchi et al. 1992a, 1993a, 1993c; Hassoun et al. 1993), and is not suggestive of a direct, genotoxic effect of endrin. Data suggest that genotoxicity is not an area of concern in humans.

Cancer. Studies of endrin-exposed workers have not detected significant increases in mortality due to cancer (Ribbens 1985). In two industries manufacturing endrin, small excesses of certain cancers were reported (Ditraglia et al. 1981). However, these findings were not statistically significant, and the studies were limited by concurrent exposure to other chemicals. Endrin was reported to be noncarcinogenic in animal studies (Deichmann et al. 1970; NCI 1978; Treon et al. 1955). Reuber (1978) has reported that endrin is carcinogenic; however, Reuber's criteria for classifying tissues as tumorigenic were not consistent with other investigators (EPA 1979f).

Limitations in existing studies in humans and studies in animals do not allow for a conclusive decision about the potential carcinogenicity of endrin in humans.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to endrin are discussed in Section 2.6.1.

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 endrin are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Endrin

While levels of endrin or endrin metabolites can be measured in tissue and excreta, thereby serving as biomarkers of exposure, the analytical techniques required are somewhat sophisticated and non-routine. Further, measurements of endrin in blood are best suited for detecting recent exposures because endrin is cleared rapidly from blood. The lack of persistence of endrin in human tissues and blood seen in the study of Coble et al. (1967) indicates a brief half-life for endrin on the order of l-2 days. Sera levels of endrin (time to sample not specified) in Pakistani patients who were poisoned with endrin ranged from 0.3 to 254 ppb (0.3-254 (μg/L); survivors had sera levels that ranged from 1.3 to 17.4 ppb (1.3-17.4 (μg /L) (Rowley et al. 1987). An endrin concentration of 0.3 ppb was detected in the cerebrospinal fluid.

Measurements of metabolites of endrin can also be useful in monitoring exposure to endrin. The glucuronide of anti-12-hydroxyendrin and I2-ketoendrin have been detected in feces and urine (Baldwin and Hutson 1980). The anti-12-hydroxyendrin glucuronide marker is the most sensitive and specific urinary marker; however, this is a difficult assay to perform, and its accuracy and precision are limited. D-glucaric acid is a nonspecific marker that may indicate prior exposure to endrin (Hunter et al. 1972; Ottevanger and Van Sittert 1979; Vrij-Standhardt et al. 1979). High levels of D-glucaric acid were detected in workers for up to six weeks, after which levels returned to normal ranges (Ottevanger and Van Sittert 1979).

Organochlorine pesticides have been detected in samples of fat tissues. However, endrin was not found in adipose tissue samples of the general population (Stanley 1986; Williams et al. 1988). In pesticide manufacturing workers, endrin was found in the adipose tissue only after very high exposures. Endrin has been detected in the milk of lactating women (0.02-6.24 mg/kg milk fat) (Alawi et al. 1992; Bordet et al. 1993). In conclusion, the quantitation of endrin exposure, via parent compound or metabolite, remains difficult at best. Further studies characterizing the pharmacokinetics of endrin are needed.

2.6.2 Biomarkers Used to Characterize Effects Caused by Endrin

Changes in the nervous system are the most common effects associated with ingestion of endrin in humans or exposure to its vapors. Various signs and symptoms of exposure include twitching of muscles, dizziness, mental confusion, and epileptiform seizures. Since these effects also occur following exposure to other organochlorine pesticides and other drugs, more specific indicators of endrin exposure are needed to assess adverse health effects which may occur in people living near hazardous waste sites.

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

2.7 INTERACTIONS WITH OTHER CHEMICALS

Very little published information is available about the interaction of endrin with other chemicals. The toxicity of endrin may be influenced by interactions with other chemicals and physical agents. Quails treated with endrin and chlordane had significantly lower endrin residues in brain tissue ($p<0.025$) than birds treated with endrin alone (Ludke 1976). The authors attributed this difference to the presence and accumulative toxic action of one or more of the chlordane components in the nervous system. Dietary endrin pretreatment potentiated CCl_4 hepatotoxicity, producing slight elevation of the serum enzymes SGPT and isocitrate dehydrogenase activities in rats (Young and Mehendale 1986). Changes in various enzymes (e.g., SGOT, SGPT, ATPase, acid and alkaline phosphatase, and glucose-6-phosphatase) appeared earlier in irradiated rats and were more pronounced than in normal rats given endrin alone, except in the case of adenosine triphosphatase (Meena et al. 1978).

Changes in the urinary excretion of D-glucaric acid and decreased serum levels of p,p'DDE (dichlorodiphenyl dichloroethene; a metabolite of DDT) observed in endrin workers were interpreted to signify induction of hepatic enzymes responsible for the metabolism of endogenous and exogenous chemicals (Hunter et al. 1972).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or more enhanced response than most persons exposed to the same level of endrin in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons, we expect the elderly with declining organ function and the youngest of the population with immature and developing organs to be generally more vulnerable to toxic substances than healthy adults. Populations at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Persons with a history of convulsive disorders would be expected to be at increased risk from exposure to endrin. Children may be more sensitive than adults to the acute toxic effects of endrin. In an endrin poisoning episode in Pakistan, children l-9 years old represented about 70% of the cases of convulsions (Rowley et al. 1987). The causative factor responsible for the outbreak was not identified, however, and the age distribution of cases could be explained by age-specific exposure situations. In general, following oral administration, female animals appear to be more susceptible to endrin toxicity than males (Gaines 1960; Treon et al. 1955). The difference may be due to the more rapid excretion of endrin by male versus female rats (Hutson et al. 1975; Klevay 1971; Korte et al. 1970). A sex-related difference in toxicity was not apparent following dermal exposure (Gaines 1960, 1969). No sex-based differences in endtin-related human toxicity have been documented. For example, an equal number of male and female patients were affected in the endrin poisoning episode in Pakistan (Rowley et al. 1987).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to endrin. 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 it. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to endrin may occur by ingestion, inhalation, or by dermal contact. Dermal absorption can be significant. Gastrointestinal absorption is enhanced by dietary fats. While not highly volatile, endrin-laden aerosols or dust particles can be trapped in respiratory mucus and swallowed, leading to gastrointestinal absorption.

As endrin is one of the most toxic cyclodiene organochlorine pesticides, rapid decontamination is suggested to reduce absorption (Clayton and Clayton 1981). Rapid decontamination includes removal of contaminated clothing, washing exposed skin with copious amounts of soap and water, and cleansing the hair and nails thoroughly. It is also suggested that leather clothing, which absorbs pesticides, be discarded (TOMES 1994).

In the event of contamination of the eyes, common treatment includes irrigation with copious amounts of tepid water or physiological saline for at least 15 minutes and, in the event of persistent irritation, pain, swelling, or photophobia, expert ophthalmologic consultation. In the event of acute poisoning, transport to an emergency room is suggested.

Common treatment for inhalation exposure includes removal of the patient to fresh air and observation for respiratory distress. Pulmonary injury may occur from solvents used as carriers for organochlorine pesticides. A hydrocarbon pneumonitis may be produced if aspiration of the liquid solvent occurs. Emergency airway support and 100% supplemental oxygen with assisted ventilation under medical supervision may be necessary.

If ingestion has occurred, gastric lavage is indicated. Emesis (vomiting) should not be induced due to the risk of sudden onset of seizures (Woo 1990) and increased chance of aspiration of stomach contents, which may later lead to aspiration pneumonitis. Administration of activated charcoal and cholestyramine has been used to reduce absorption and enhance elimination by interrupting enterohepatic circulation. Exchange transfusions, peritoneal dialysis, hemodialysis, and hemoperfusion are not likely to be beneficial due to the initial large volume of distribution of organochlorines. Administration of cathartics is ill-advised due to the possibility of increased intestinal absorption of endrin (TOMES 1994).

Following acute exposure to cyclodiene organochlorine pesticides, seizures and respiratory depression may occur (Ellenhorn 1988; Proctor et al. 1988). Benzodiazepines (e.g., diazepam or lorazepam) or other anticonvulsant medications (e.g., phenobarbital) have been commonly used to control seizures (Ford 1993). Organochlorines may sensitize the myocardium to the proarrhythmic effects of adrenergic amines, potentially resulting in initiation of ventricular fibrillation (TOMES 1994).

2.9.2 Reducing Body Burden

Although endrin is a stereoisomer of dieldrin, it does not persist in the body as dieldrin does. The half-life of endrin in humans and animals is 2-6 days (Ert and Sullivan 1992). Thus, endrin is unlikely to accumulate in adipose tissue. There are reports of ingestion of bread contaminated with endrin which caused sudden convulsions in three persons. In one person, the serum level was

0.053 ppm 30 minutes after convulsion and 0.038 ppm after 20 hours. In the other 2 cases, no endrin was detected in the blood at 8.5 or 19 hours after the convulsions occurred (Proctor et al. 1988).

There is no specific antidote and no currently recognized way to enhance elimination. Conventional treatment is entirely supportive. Cholestyramine has been shown to enhance elimination of chlordane and kepone (HSDB 1994), and may enhance elimination after ingestion of endrin. However, its effectiveness in endrin poisoning has not been tested.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The most serious toxicological effect of endrin is central neurotoxicity (Klaasen et al. 1986). Organochlorines interfere with the normal flux of cations across the axon, disrupting central nervous system homeostasis (Finkel 1983; Klaasen et al. 1986). Endrin is one of the most toxic cyclodienes, and seizure activity may develop rapidly after exposure (Proctor et al. 1988). In most cases, recovery is rapid. However, headaches, dizziness, weakness, and anorexia may persist for 2-4 weeks.

Although the exact mechanism causing neurotoxicity is unknown, it is reasonable to suppose that effects on neurotransmitters may be mitigated by pharmacological intervention. Benzodiazepines, which often are used to treat seizures resulting from endrin intoxication, potentiate inhibitory GABA neuronal activity in the central nervous system (Singh and Renzi 1993). Phenytoin has neuronal membrane stabilizing properties and is also frequently used in seizure control.

Strong evidence indicates that endrin increases the activity of hepatic microsomal enzymes (Klaasen et al. 1986). Drugs which are strong inducers of microsomal enzymes may increase the metabolic elimination of endrin.

Ascorbic acid supplementation has been shown to reduce the renal and hepatic toxicity of experimental animals undergoing dieldrin treatment (Bandyopadhyay et al. 1982). The effectiveness of ascorbic acid in humans exposed to endrin is unknown; however, studies in animals suggest that antioxidants can reduce endrin-related oxidative damage (Bagchi et al. 1992c, 1993c; Hassan et al. 1991; Numan et al. 1990a, 1990b).

2.10 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 endrin 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 endrin.

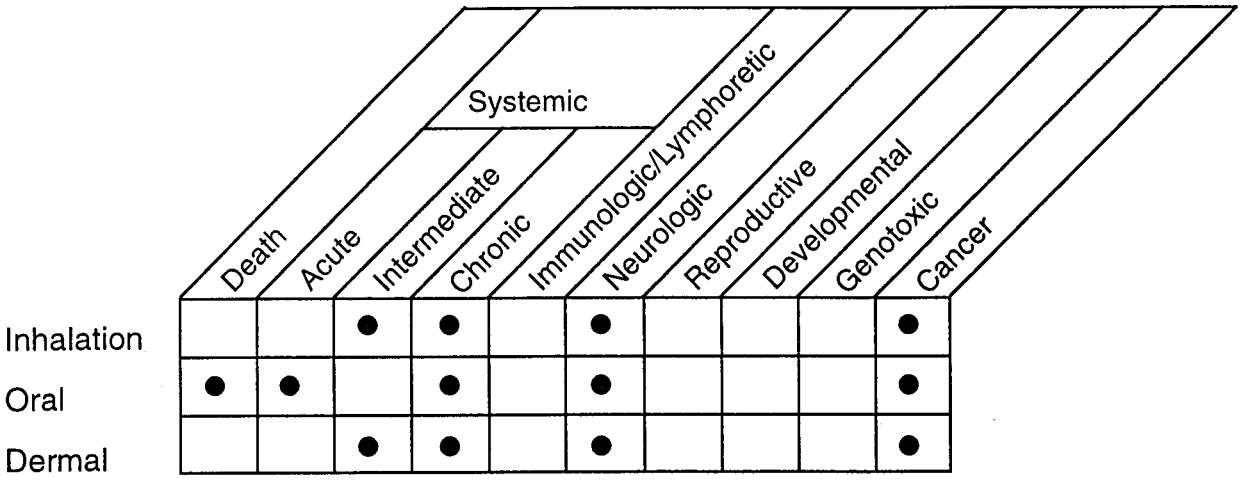
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.10.1 Existing Information on Health Effects of Endrin

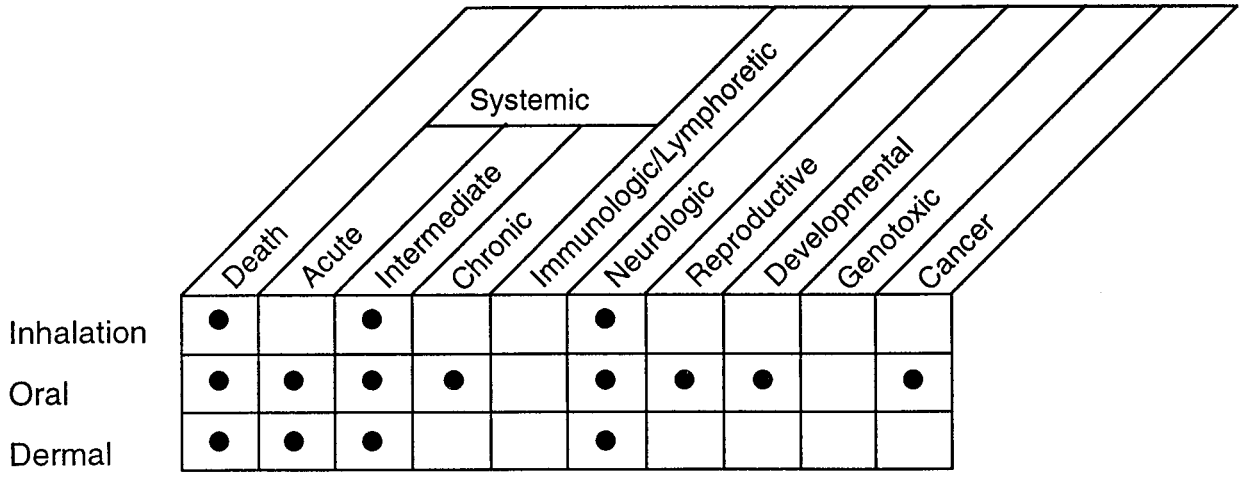
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to endrin are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of endrin. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Only one study (Young and Mehendale 1986) was found on the health effects of endrin aldehyde or endrin ketone in animals following oral exposure.

Figure 2-4. Existing Information of Health Effects of Endrin



Human



Animal

● Existing Studies

2.10.2 Identification of Data Needs

Acute-Duration Exposure. No studies are available on the effects of human exposure to endrin by the inhalation or dermal routes. Acute human poisoning from endrin-contaminated food results in jerking of legs, tonic-clonic contractions, convulsions and sudden collapse, and death (Curley et al. 1970; Rowley et al. 1987; Runhaar et al. 1985; Weeks 1967). Data in animals exposed via inhalation, oral, and dermal routes confirm that endrin can affect the nervous system, causing clinical signs including tremors and convulsions (Chernoff et al. 1979a; Gaines 1960; Kavlock et al. 1981; Treon et al. 1955). Decreases in body weight gain and histopathologic damage to liver and kidneys have been reported in animals following acute oral exposure (Hassan et al. 1991; Treon et al. 1955). Additional studies using other species and a range of dose levels could help determine other potential targets following acute exposure by all three routes, as well as acute threshold levels for effects observed. Data was not found to be sufficient to derive oral or inhalation acute-duration MRLs.

Since information on acute adverse effects of endrin aldehyde or endrin ketone in humans or animals by inhalation, oral, and dermal routes is extremely limited, similar studies are needed to identify potential target tissues.

Intermediate-Duration Exposure. No studies are available on the adverse health effects from intermediate-duration exposure in humans by any route. Studies in animals indicate that exposure to endrin via inhalation can be lethal and causes effects on the nervous and respiratory systems, the liver, the brain, adrenals, and kidneys (Treon et al. 1955). Since systemic effects were observed at levels which caused death, data are not sufficient to derive an intermediate-duration inhalation MRL. Animal studies also demonstrate that oral intermediate-duration exposure can lead to death in several species (rat, mouse, hamster, rabbit, monkeys, cat) (Treon et al. 1955). Endrin was lethal in rabbits following dermal exposure (Treon et al. 1955). No other treatment-related disorders are known. Additional studies for oral and dermal routes using a range of exposure levels would be useful in identifying potential target tissues.

Since no information is available on adverse health effects of endrin aldehyde or endrin ketone following intermediate-duration exposure by the inhalation, oral, and dermal routes in humans or animals, studies using various dose levels and several animal species are needed to identify potential target tissues.

Chronic-Duration Exposure and Cancer. Studies of humans chronically exposed to endrin in the occupational setting indicate target tissues similar to those for acute exposure (Ditraglia et al. 1981; Ribbens 1985; Versteeg and Jager 1973). Quantitative exposure data are lacking in humans, but data in animals are sufficient to derive NOAELs and LOAELs for neurologic, hepatic, renal, and cardiovascular effects in dogs (Kettering 1969; Treon et al. 1955). A chronic MRL was based on a NOAEL for convulsions in dogs administered endrin in the feed (Kettering 1969) and it is anticipated that the chronic MRL should be protective for any exposure of acute or intermediate duration. No studies are available in humans or animals chronically exposed via dermal exposure. Additional studies are needed to determine whether similar effects via oral exposure occur by this route.

Chronic studies of workers exposed to endrin via inhalation have not suggested an association between exposure and the occurrence of any type of cancer (Ditraglia et al. 1981; Ribbens 1985). However, these studies are limited by inadequate exposure data (including concurrent exposure to other chemicals), short follow-up, and small size of study cohort. No studies were located regarding cancer risk in humans via oral or dermal exposure. While no specific cancer risk has been determined, several occurrences of cancer may be worthy of further study. There were slight excesses of cancer of the esophagus, rectum, liver, respiratory system, bladder and urinary system, and of the lymphatic and hematopoietic systems in manufacturing workers exposed to vapors of endrin/aldrin/dieldrin in two plants (Ditraglia et al. 1981). However, as already noted, these findings were not statistically significant, the elevated standard mortality ratios (SMRs) were based on small numbers of observed deaths, and workers were subject to concurrent exposure to chemicals other than endrin.

Oral exposure studies in rats and mice did not show association between exposure to endrin and increased incidence of cancer (Deichmann et al. 1970; NCI 1978; Treon et al. 1955). No chronic studies are available in animals exposed to endrin via inhalation or dermal exposure. In the absence of evidence of a carcinogenic effect in two animal species, additional studies are not warranted at this time.

No studies have been conducted to evaluate adverse health effects in humans or animals following exposure to endrin aldehyde or endrin ketone by the inhalation, oral, or dermal route. Additional human and animal studies via all three of these routes of potential exposure are needed to determine potential carcinogenic risk in people who may be exposed to endrin aldehyde or endrin ketone near hazardous waste sites.

Genotoxicity. No *in vivo* studies were found in humans or animals following inhalation, oral, or dermal exposure to endrin. Microbial assays and one mammalian cell assay have demonstrated that endrin does not have mutagenic potential with or without metabolic activation (Ames et al. 1975; Glatt et al. 1983; McGregor et al. 1991; Moriya et al. 1983; Probst et al. 1981; Zeiger et al. 1987). Similarly, *in vitro* mammalian assays evaluating unscheduled DNA synthesis and sister chromatid exchanges were negative (Maslansky and Williams 1981; Probst et al. 1981; Sobti et al. 1983). Chromosomal aberrations observed in testicular cells of rats following injection of endrin are of questionable relevance to human risk assessment due to the route of exposure, which was direct, intratesticular injection (Dikshith and Datta 1973). Studies demonstrating an increased incidence of DNA single strand breaks suggest that these effects are the consequence of production of reactive oxygen species (Bagchi et al. 1993a, 1993c; Hassoun et al. 1993). The overall weight of evidence based on the existing data suggests that endrin is not mutagenic. Additional studies are not warranted at this time.

No studies have been conducted to evaluate the genotoxicity of endrin aldehyde or endrin ketone in humans or animals by inhalation, oral, or dermal routes of exposure. Studies are needed to determine potential mutagenic risk for people who may be exposed near hazardous waste sites.

Reproductive Toxicity. No information is available on the reproductive effects of endrin in humans after inhalation, oral, or dermal exposure. No studies are available on the reproductive effects of endrin in animals after inhalation or dermal exposure. Acute oral studies in animals and experimentally flawed intermediate-duration studies in rats and dogs suggest endrin can affect reproductive outcomes (Eisenlord et al. 1968; Good and Ware 1969; Kettering 1971). Additional, more definitive intermediate-duration tests evaluating various species and several dose levels via the oral route (and other routes as well) would be useful in assessing the potential reproductive risk in people who may be exposed to low levels of endrin near hazardous waste sites. Further, the demonstrated presence of endrin in milk from lactating mothers emphasizes the need for comprehensive, multigeneration studies in animals.

No studies have been conducted to evaluate the reproductive effects of endrin aldehyde or endrin ketone in humans or animals via the inhalation, oral, and dermal routes of exposure. Additional animal studies and further human case studies are needed to determine the potential reproductive

hazard and to determine threshold levels for effects that may exist via all three of these routes of exposure.

Developmental Toxicity. No information is available regarding the developmental toxicity of endrin in humans by inhalation, oral, or dermal exposure. No inhalation or dermal exposure route studies are available for laboratory animals; however, developmental effects have been demonstrated in laboratory animals exposed via the oral route. Offspring of mice and hamsters exposed to endrin during gestation showed statistically significant increases in the incidence of fused ribs, cleft palate, exencephaly, and microencephaloceles (Chernoff et al. 1979a; Kavlock et al. 1985; Ottolenghi et al. 1974). Additional studies are needed to determine if these effects also occur following inhalation or dermal exposure.

No studies have been conducted on the developmental toxicity of endrin aldehyde or endrin ketone in humans or animals by the inhalation, oral, or dermal route of exposure. Additional studies via the inhalation and dermal routes of exposure evaluating various dosages and in several species would be useful in assessing the potential for endrin aldehyde or endrin ketone to cause developmental effects.

Immunotoxicity. No *in vivo* studies are available in humans or animals regarding the immunotoxicity of endrin after inhalation, oral, or dermal exposure. Results of *in vitro* assays evaluating inhibition of lymphocyte responses and neutrophilic chemotaxis were negative (Lee et al. 1979). Also, immunopathologic changes via inhalation, oral, and dermal routes of exposure were not observed in intermediate-duration studies (Treon et al. 1955). Additional *in vivo* (inhalation, oral, and dermal exposure routes), as well as additional *in vitro* testing involving humoral mediated immunity and nonspecific immunity would certainly be useful in confirming the apparent lack of significant immunotoxic potential.

No studies have been conducted to evaluate the immunotoxicity of endrin aldehyde or endrin ketone in humans or animals by the inhalation, oral, or dermal route of exposure. Additional studies using several dose levels and various animal species would be useful in assessing the immunotoxic potential of endrin aldehyde or endrin ketone in humans following inhalation, oral, or dermal exposure.

Neurotoxicity. Studies in humans indicate that endrin causes changes in the nervous system after inhalation or oral exposure (Curley et al. 1970; Davies and Lewis 1956; Hoogendam et al. 1962, 1965;

Rowley et al. 1987; Runhaar et al. 1985; Waller et al. 1992; Weeks 1967). Clinical symptoms including twitching and jerking of muscles, seizures, dizziness, and mental confusion occurred within 2 hours following occupational exposure. Studies in animals confirm the neurotoxic potential of endrin (Chemoff et al. 1979a; Deichmann et al. 1970; Gaines 1960, 1969; Kavlock et al. 1981; Kettering 1969, 1971; Speck and Maaske 1958; Treon et al. 1955). While existing neurological effects are well characterized following inhalation and oral exposures and, to a lesser extent, dermal exposure, additional exposure data are needed to establish dose-response relationships.

No studies have been conducted to evaluate the neurotoxicity of endrin aldehyde or endrin ketone in humans or animals by an inhalation, oral, or dermal route of exposure. Additional studies using all three of these potential exposure routes are needed to determine if endrin aldehyde and endrin ketone are potential neurotoxicants and to determine threshold levels for effects that may exist.

Epidemiological and Human Dosimetry Studies. There are reports on the adverse effects of endrin in humans (Section 2.2). These reports involve acute exposures in people who ingested endrin-contaminated food (Curley et al. 1970; Davies and Lewis 1956; Waller et al. 1992; Weeks 1967). There are also studies of workers with acute exposures to contaminated air (Hoogendam et al. 1962, 1965). Existing studies identify the nervous system as a major target associated with exposure to endrin. However, reliable quantitative exposure levels that lead to these effects are lacking. Additional quantitative exposure data obtained from individuals occupationally exposed to low levels of endrin would be useful in evaluating potential risk to people living near hazardous waste sites.

Biomarkers of Exposure and Effect.

Exposure. Measurement of endrin and its metabolites can be useful indicators of exposure. Since endrin is cleared from the blood rapidly, such measurements are suitable only for recent exposures. Additional studies are needed to determine the usefulness of metabolites in urine as biomarkers of exposure in humans. A quantitative relationship between the urinary concentration of anti-l2-hydroxyendrin and the dose of endrin should be clarified.

Effect. Changes in the nervous system appear to be the main effect associated with human exposure to endrin. Effects on the nervous system can be monitored in exposed individuals by measuring the incidence of signs and symptoms such as myoclonic jerking, seizures, convulsions, dizziness, and

mental confusion (Carbajal-Rodriguez et al. 1990; Rowley et al. 1987; Runhaar et al. 1985; Waller et al. 1992). Because these effects also occur following exposure to other organochlorine pesticides and drugs, the development of more specific biomarkers of endrin exposure would be useful for studying potential endrin-related adverse health effects.

Absorption, Distribution, Metabolism, and Excretion. There are limited data on the absorption, distribution, metabolism, and excretion of endrin in humans and animals. Limited studies provide qualitative evidence that endrin is absorbed following inhalation, oral, and dermal exposures (Chernoff et al. 1979a; Fleming et al. 1994; Kintz et al. 1992; Teschke et al. 1993; Wolfe et al. 1963), however, no information is available on the rate or extent of absorption that occurs by any of these routes. Additional studies are needed to determine absorption rates following exposure by all routes.

Data are sparse on the distribution of endrin. Limited data in humans indicate that significant amounts of endrin residues are found in adipose tissue of people occupationally exposed, but not in the general population (Baldwin and Hutson 1980; Ottevanger and Van Sittert 1979; Stanley 1986; Teschke et al. 1993; Williams 1986; Williams et al. 1984). Low levels of endrin are found in the liver, kidneys, and brain in people exposed to endrin or endrin-contaminated food (Curley et al. 1970; Runhaar et al. 1985; Tewari and Sharma 1978). The time of sample collection is critical since endrin residues in tissues decline rapidly after exposure has ceased.

No studies were found regarding the metabolism of endrin in humans. However, anti-12-hydroxyendrin and/or the corresponding glucuronide conjugate was found in feces and urine from workers at an endrin manufacturing plant (Baldwin and Hutson 1980). Studies in animals (Bedford et al. 1975a) acutely exposed via the oral route demonstrated that oxidation of the methylene bridge in endrin to syn- and, to a greater extent, anti-12-hydroxyendrin, occur, followed by dehydrogenation to 12-ketoendrin. Minor pathways involving hydrolysis and hydroxylation reactions were also demonstrated (Bedford et al. 1975a).

Data are sparse on the excretion of endrin in humans and animals. The presence of unchanged endrin in the milk fat of lactating cows and humans has been shown (Alawi et al. 1992; Baldwin et al. 1976; Bordet el al. 1993; Kanja et al. 1992; Spicer and Kereu 1993). Existing data indicate that endrin is rapidly transformed in the body after inhalation and oral exposures and is eliminated primarily as metabolites (12-hydroxy endrin, 12-ketoendrin, etc.). The urinary metabolite profile appears to be

species specific. Anti-12-hydroxyendrin and/or its glucuronide conjugate has been found in feces and urine from workers at an endrin manufacturing plant (Baldwin and Hutson 1980). In animals, 12-hydroxyendrin-O-sulfate or 12-ketoendrin were detected in urine of rats after oral exposure (Baldwin et al. 1975; Hutson et al. 1975), while anti-12-hydroxyendrin sulfate and 3-hydroxyendrin sulfate were found in the urine of rabbits (Bedford et al. 1975b). No studies were found regarding excretion of endrin in humans or animals after dermal exposure. Additional studies on the excretion of endrin and its metabolites via the dermal route would be useful since differences in urinary metabolite profiles have been observed following exposure to endrin by other routes (Baldwin et al. 1975; Bedford et al. 1975b; Hutson et al. 1975; Kanja et al. 1992; Spicer and Kereu 1993).

Comparative Toxicokinetics. There are limited data on the kinetics of endrin in humans. Studies in animals suggest that metabolism and urinary metabolite profiles vary among species (Baldwin et al. 1975; Hutson et al. 1975; Kanja et al. 1992; Spicer and Kereu 1993). Additional studies using all three potential routes of human exposure would be useful in understanding differences in species and in determining which animal species is the most appropriate model for human exposure.

Methods for Reducing Toxic Effects. Currently, recommended treatment for endrin toxicity is generally supportive in nature and includes general hygienic procedures for rapid decontamination. Treatment with benzodiazepines and phenytoin may be useful in the treatment of endrin-induced seizures. Further studies using animal models might be helpful in identification of other effective pharmacologic agents to counteract the convulsive effects of endrin.

2.10.3 Ongoing Studies

Two ongoing studies were identified that were related to endrin, endrin aldehyde, or endrin ketone, and are summarized in Table 2-5.

Table 2-5. Ongoing Research for Endrin, Endrin Aldehyde, or Endrin Ketone

Investigator:	Affiliation:	Summary of Research:
Hassoun, EA	Creighton University	Assess abilities of endrin to induce the formation of reactive oxygen species and lipid peroxidation and DNA single strand breaks that result in oxidative stress in fetuses of pregnant mice. The protective effects of some antioxidants will also be assessed using this model.
Roush, RT and Scott, JG	Cornell University	Define the molecular basis for insect resistance to traditional and novel insect control agents, including endrin.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of endrin, endrin aldehyde, and endrin ketone is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of endrin, endrin aldehyde, and endrin ketone is located in Table 3-2.

Table 3-1. Chemical Identity of Endrin, Endrin Aldehyde, and Endrin Ketone

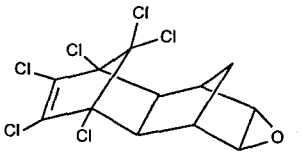
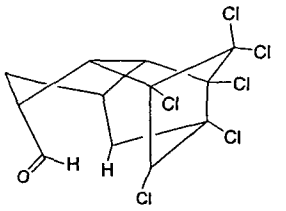
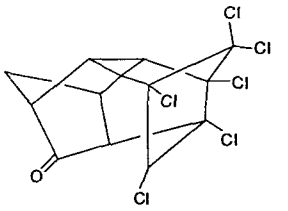
Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone	Reference
Chemical name	2,7:3,6-Dimethanonapth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-	1,2,4-Methenocyclopenta(cd)-pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodeca-hydro-(1α,2β,2aβ,4β,4a β,5β,6aβ,6bβ,7R*)	2,5,7-Metheno-3H-cyclo-penta(a)pentalen-3-one,3b,4,5,6,6a-hexachlorodecahydro-(2α,3aβ,3bβ,4β,5β,6aβ,7α,7aβ,8R*)	EPA 1984a
Synonym(s)	Endrin; 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4A,5,6,7,8,8A- octahydro-endo, endo-1,4:5,8-dimethanonaphthalene, and others	Endrin aldehyde; 1,2,4-methanecyclopenta(c,d) pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachloro-decahydro	Endrin ketone	HSDB 1995
Registered trade name(s)	Mendrin, Hexadrin, Endrex experimental insecticide 269	No data	Delta-keto 153	NLM 1988 Sittig 1980
Chemical formula	$C_{12}H_8Cl_6O$	$C_{12}H_8Cl_6O$	$C_{12}H_8Cl_6O$	EPA 1984a
Chemical structure				EPA 1984a

Table 3-1. Chemical Identity of Endrin, Endrin Aldehyde, and Endrin Ketone (continued)

Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone	Reference
Identification numbers:				
CAS registry	72-20-8	7421-93-4	53494-70-5	EPA 1984a
NIOSH RTECS	IO1575000	PC8580000	PC8600000	RTECS1994
EPA hazardous waste	P051; D012	No data	No data	HSDB 1994
OHM/TADS	7216522	8300215	No data	HSDB 1994
DOT/UN/NA/IMCO ship.	UN 2761; NA 2761; IMO 6.1	UN 2761; IMO 6.1	UN 2811; NA 2761; IMO 6.1	HSDB 1994, 1995
	198	6181	No data	HSDB 1995
HSDB	01565	No data	No data	HSDB 1994
NCI	C00157			

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Dept. 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 3-2. Physical and Chemical Properties of Endrin, Endrin Aldehyde, and Endrin Ketone

Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone	Reference
Molecular weight	380.9	381.9	380.9	EPA 1984a
Color	White Colorless	No data	No data	HSDB 1995; IARC 1974 Worthington and Walker 1983
Physical state	Crystalline solid	Solid	Solid	EPA 1984a; HSDB 1995; IARC 1974
Melting point	235 °C 226–230 °C (decomp.)	145–149 °C, 235 °C (decomp.)	No data	EPA 1981a; HSDB 1995 Worthington and Walker 1983
Boiling point	Decomposes at 245 °C Decomposes above 200 °C	No data	No data	ACGIH 1986 HSDB 1995 IARC 1974
Density at 20 °C	No data	No data	No data	
Specific Gravity	1.7 at 20 °C	No data	No data	EPA 1980a, HSDB 1995
Odor	Mild; odorless	No data	No data	HSDB 1995
Odor threshold:				
Water	0.041 mg/L	No data	No data	Verschueren 1983
Air	1.8×10^{-2} ppm	No data	No data	Fazzalari, 1978
Solubility:				
Water at 25 °C	200 µg/L	50 mg/L, 0.25–0.26 ppm	No data	EPA 1981a
Organic solvents	acetone 17 g/100 mL benzene 13.8 g/100 mL carbon tet. 3.3 g/100 mL hexane 7.1 g/100 mL xylene 18.3 g/100 mL	No data	No data	HSDB 1995 Merck 1989

Table 3-2. Physical and Chemical Properties of Endrin, Endrin Aldehyde, and Endrin Ketone (continued)

Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone	Reference
Partition coefficients:				
Log K_{ow}	5.6, 5.34 (calculated) 5.45 (calculated)	3.146, 4.7, 5.6 (calculated)	4.99 (calculated)	EPA 1981a, HSDB 1995
Log K_{oc}	4.532 (calculated) 5.195 (±0.005)	4.80 (calculated) 3.929–4.653 (calculated)	No data	SRC 1995 HSDB 1995, Kenaga 1980 de Bruijn et al. 1989
Vapor pressure at 25 °C	2.0×10^{-7} mm Hg	2.0×10^{-7} mm Hg	No data	EPA 1981a HSDB 1995 Worthington and Walker 1983
Henry's law constant	4.0×10^{-7} atm-m^3/mol (calculated) 5.41×10^{-7} atm-m^3/mol (calculated)	2×10^{-9} atm-m^3/mol 2.9×10^{-9} atm-m^3/mol 3.67×10^{-8} atm-m^3/mol (calculated)	2.02×10^{-8} atm-m^3/mol (calculated)	EPA 1981a,HSDB 1995 Thomas 1982 SRC 1994a
Autoignition temperature	No data	No data	No data	
Flashpoint	Non-flammable	Non-flammable	No data	HSDB 1995
Flammability limits	No data	No data	No data	
Explosive limits	No data	No data	No data	
Conversion factors	1 ppm = 15.6 mg/m^3 1 mg/m^3 = 0.06 ppm	1 ppm = 15.6 mg/m^3 1 mg/m^3 = 0.06 ppm	1 ppm = 15.6 mg/m^3 1 mg/m^3 = 0.06 ppm	

ACGIH = American Conference of Governmental and Industrial Hygienists; HSDB = Hazardous Substance Data Bank; SRC = Syracuse Research Corporation

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

4.1 PRODUCTION

Endrin is a stereoisomer of dieldrin produced by the reaction of vinyl chloride and hexachloro-cyclopentadiene to yield a product which is then dehydrochlorinated and condensed with cyclopentadiene to produce isodrin. This intermediate is then epoxidized with peracetic or perbenzoic acid to yield endrin. An alternative production method involves condensation of hexachloro-cyclopentadiene with acetylene to yield the intermediate for condensation with cyclopentadiene (EPA 1985e; IARC 1974).

Endrin is no longer manufactured in the United States. Velsicol Chemical Company, Memphis, Tennessee, was the producer of endrin until the final voluntary cancellation of registration with the Office of Pesticide Programs in 1991 (Bishop 1984, 1985, 1986; EPA 1983e; USDA 1995). It is estimated that 2.345 million kg (5.1-9.9 million pounds) of endrin were sold in the United States in 1962, while less than 450,000 kg (990,000 pounds) were produced in 1971 (IARC 1974). More recent estimates of domestic production of endrin could not be found (HSDB 1995). As with many toxic chemicals, information on production or use of pesticides is often proprietary, and quantitative estimates of production of endrin are virtually impossible to obtain (Bason and Colbom 1992). Chemical manufacturers in the United States however, can legally produce pesticides for export that are currently banned or not registered for use in the United States (FASE 1996). No information on the production of endrin was available from the Toxic Release Inventory (TRI) because endrin is not one of the chemicals that facilities are required to report (EPA 1995a).

Endrin aldehyde and endrin ketone were never commercial products, but occurred as impurities of endrin or as degradation products (EPA 1985e; IARC 1974; SRI 1987). While commercial preparations of solid endrin were typically 95-98% pure, the following chemicals (in addition to endrin aldehyde and endrin ketone) have been found as trace impurities: aldrin, dieldrin, isodrin, heptachloronorbornadiene, and heptachloronorborene (HSDB 1995). The active ingredient would often be mixed with one or more organic solvents for application in a liquid form. Carriers included xylene, hexane, and cyclohexane (HSDB 1995; Zabik et al. 1971).

4.2 IMPORT/EXPORT

Data on historic imports and exports of endrin are sparse. The most recent data that could be located indicate that about 21,000 kg (46,000 pounds) of endrin were imported into the United States in 1972 (IARC 1974). No information on export volumes of endrin was located. Recently, however, the Foundation for Advancements in Science and Education reported that almost 75% of the 750,000 tons of pesticides the United States exported from 1992 to 1994 lacked chemical-specific information (FASE 1996). Many of the exported pesticides were organochlorine pesticides which had been banned for use in the United States.

4.3 USE

Endrin was first used as an insecticide, rodenticide, and avicide beginning in 1951 to control cutworms, voles, grasshoppers, borers, and other pests on cotton, sugarcane, tobacco, apple orchards, and grain (EPA 1979e; HSDB 1995). It was also used as an insecticide agent on bird perches (EPA 1985f). Unlike aldrin/dieldrin, with which it has many chemical similarities, endrin apparently was never used extensively for termite-proofing or other applications in urban areas (Blus et al. 1989; HSDB 1995). Endrin's toxicity to nontarget populations of raptors and migratory birds was a major reason for its cancellation as a pesticide agent (Blus et al. 1989). (EPA 1979f; USDA 1995). Except for use as a toxicant on bird perches, which was canceled in 1991, all other uses of endrin in the United States were voluntarily canceled by the manufacturer in 1986 (Bishop 1984, 1985, 1986; EPA 1983e; USDA 1995). It has been estimated that 6,250 kg (13,780 pounds) of endrin were used annually in the United States prior to 1983 (Gianessi 1986). Since endrin may still be used as a pesticide agent in foreign countries, residues on imported food items are still of some concern (FDA 1990, 1991, 1992; Hundley et al. 1988) (see Section 5.4.4). Both the EPA and FDA revoked all food tolerances for endrin in 1993 (USDA 1995).

4.4 DISPOSAL

Because endrin and endrin aldehyde are listed as hazardous substances, disposal of wastes containing these compounds is controlled by a number of federal regulations (see Chapter 7). Land disposal restrictions apply to wastes containing endrin or endrin aldehyde (EPA 1986d, 1987b). Chemical treatment (reductive dechlorination) or incineration are possible disposal methods (HSDB 1995; IRPTC

1985). Past disposal methods included land disposal (EPA 1987c; Sittig 1980). In general, disposal methods for endrin residues or endrin-containing wastes are similar to those for wastes containing aldrin/dieldrin (HSDB 1995). No information was found in the available literature on regulations or methods for the disposal of endrin ketone.

No information was found in the available literature on the amounts of endrin, endrin aldehyde, or endrin ketone disposed of in the United States by any method.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Endrin was introduced in the United States in 1951 as an avicide, rodenticide and insecticide. Its principal use to control the cotton bollworm and tobacco budworm peaked in the early 1970s. In 1979, the EPA canceled some uses of endrin and indicated its intent to cancel all uses of endrin (EPA 1979f; USDA 1995). By 1986, all uses were voluntarily canceled (Bishop 1984, 1985, 1986; EPA 1993e; USDA 1995), except for its use as a toxicant on bird perches, which was canceled in 1991 (USDA 1995). Endrin also was a contaminant in dieldrin (Verschueren 1983); however, all uses of this pesticide have been canceled since the mid-1980s (EPA 1992b). Consequently, there are no longer any significant releases of endrin to the environment in the United States.

Endrin tends to persist in the environment mainly in forms sorbed to sediments and soil particles. A conservative estimate of its half-disappearance time in sandy loam soils is approximately 14 years (41% of endrin applied still remained in the soil after 14 years) (Nash and Woolson 1967). Therefore, the exposure risks from endrin to the general population of the United States are likely to steadily decrease over time.

Migration of endrin into groundwater would not generally be expected from normal agricultural application. However, endrin has been detected in some groundwater, suggesting that leaching may be possible in some soils under certain conditions (Cohen 1986; EPA 1989; HazDat 1996). Biodegradation does not appear to be a significant fate process for endrin in soils (Nash and Woolson 1967). Hydrolysis in moist soils is also not expected to be significant (EPA 19798). In combination, losses from volatilization, photodegradation (Burton and Pollard 1974; EPA 1985e; Knoevenagel and Himmelreich 1976; Zabik et al. 1971), and heat transformation (primarily to endrin ketone, with minor amounts of endrin aldehyde) (EPA 19798; Phillips et al. 1962) account for the rapid decrease in endrin residues on soil surfaces exposed to bright sunlight.

In spite of its low vapor pressure, endrin has been found to volatilize significantly (20-30%) from soils within days after application (Nash 1983). In air, endrin will be primarily absorbed to particulates which may be re-entrained to soil or surface water via wet or dry deposition. Laboratory studies have indicated that a predominant mechanism for the transformation and degradation of endrin

in air under field conditions is via photochemical reactions and rearrangements to yield primarily endrin ketone, with minor amounts of endrin aldehyde (Burton and Pollard 1974; EPA 1985e; Zabik et al. 1971). Endrin may also be transformed by heat in the atmosphere, yielding primarily the pentacylic ketone and endrin aldehyde (EPA 1979g; Phillips et al. 1962). Endrin may also react with photochemically generated hydroxyl radicals in air, with a predicted half-life ranging from 1.45 hours (Howard 1991) to 1.8 days (SRC 1995a).

Endrin may be transported from soil to surface water via runoff from rain or irrigation. When released to water, endrin strongly adsorbs to sediment (Kenaga 1980) and bioconcentrates significantly in aquatic organisms (ASTER 1995; EPA 1980a; Metcalf et al. 1973). Endrin appears to be biomagnified only slightly through various levels of the food chain (Metcalf et al. 1973). It is likely that endrin released to surface water will undergo photoisomerization to endrin ketone, with minor amounts of endrin aldehyde also being formed (Burton and Pollard 1974; Zabik et al. 1971). Endrin may be biodegraded in water, but most laboratory studies indicate that this will not be a significant fate process (Eichelberger and Lichtenberg 1971; Sharom et al. 1980b; Tabak et al. 1981). In addition, neither hydrolysis nor volatilization is a significant fate process for endrin in water. The estimated half-life for endrin in water is more than 4 years (EPA 1979g; Howard 1991). Degradation of endrin in soils under field conditions is not a significant fate process with a half-disappearance time of the order of 14 years (Nash and Woolson 1967).

No studies on the environmental fate of endrin aldehyde or endrin ketone could be found in the available literature. Limited information on the physical and/or chemical properties of endrin aldehyde indicates that it is highly insoluble in water (EPA 1981a), highly immobile in soil, and will not volatilize significantly from water or soil. Any endrin aldehyde in air should exist predominantly in the adsorbed phase (Eisenreich et al. 1981). Atmospheric endrin aldehyde will be transported to soil and surface water via wet and dry deposition of associated particles. Endrin aldehyde may react with photochemically generated hydroxyl radicals in the atmosphere, with an estimated half-life of 3.6 hours (SRC 1995a). In water, adsorption to sediments and bioconcentration are likely to be significant transport processes. Neither hydrolysis nor oxidation (via peroxy radicals or singlet oxygen) of endrin aldehyde is expected to be significant in aquatic systems (EPA 1979g, 1981a). The estimated half-life for endrin aldehyde is more than four years (EPA 1979g). By analogy to aquatic systems, neither hydrolysis nor oxidation is expected to be a significant transformation process for

endrin aldehyde in soil. No information could be found on the biodegradation of endrin aldehyde in aquatic systems, sediment, or soil.

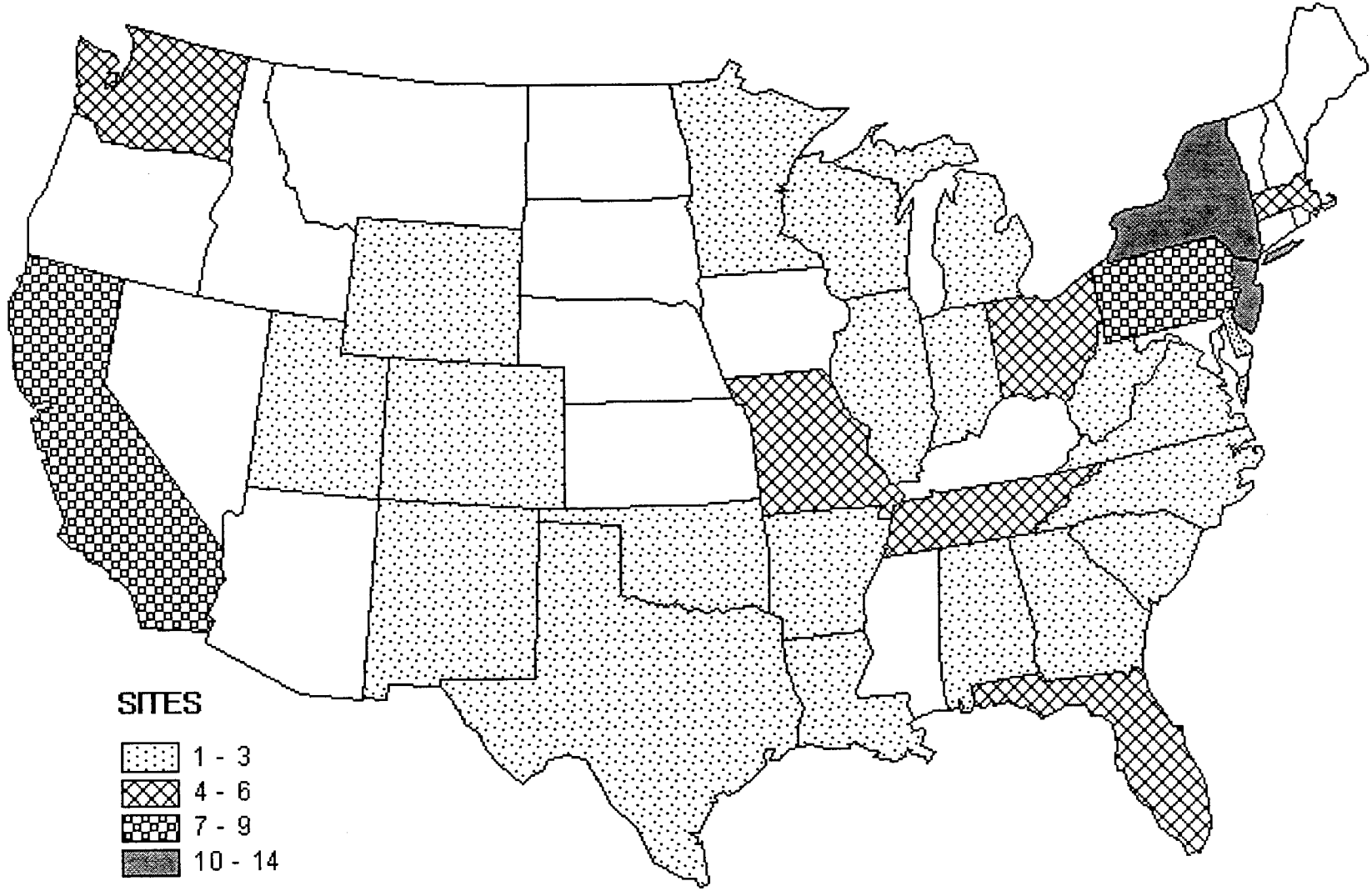
Endrin ketone may react with photochemically generated hydroxyl radicals in the atmosphere, with an estimated half-life of 1.5 days (SRC 1995a). Available estimated physical/chemical properties of endrin ketone indicate that this compound will not volatilize from water; however, significant bioconcentration in aquatic organisms may occur. In soils and sediments, endrin ketone is predicted to be virtually immobile; however, detection of endrin ketone in groundwater and leachate samples at some hazardous waste sites suggests limited mobility of endrin ketone in certain soils (HazDat 1996). No other information could be found in the available literature on the environmental fate of endrin ketone in water, sediment, or soil.

Information on current levels of endrin in the environment is limited; however, the available data indicate that concentrations in all environmental media are generally negligible or below levels of concern. The FDA has concluded that endrin is no longer present in the environment to the extent that it may be contaminating food or feed at levels of regulatory concern (USDA 1995). No information could be found in the available literature on levels of endrin aldehyde or endrin ketone in the environment.

The main sources for potential human exposure to endrin are residues on imported food items, unused stocks, unregistered use, inappropriate disposal, and hazardous waste sites; however, there is no current evidence of significant exposures from any of these sources. Furthermore, it should be noted that in environmental media, especially in contaminated soils and sediments, the amount of endrin chemically identified by analysis is not necessarily the amount that is toxicologically available.

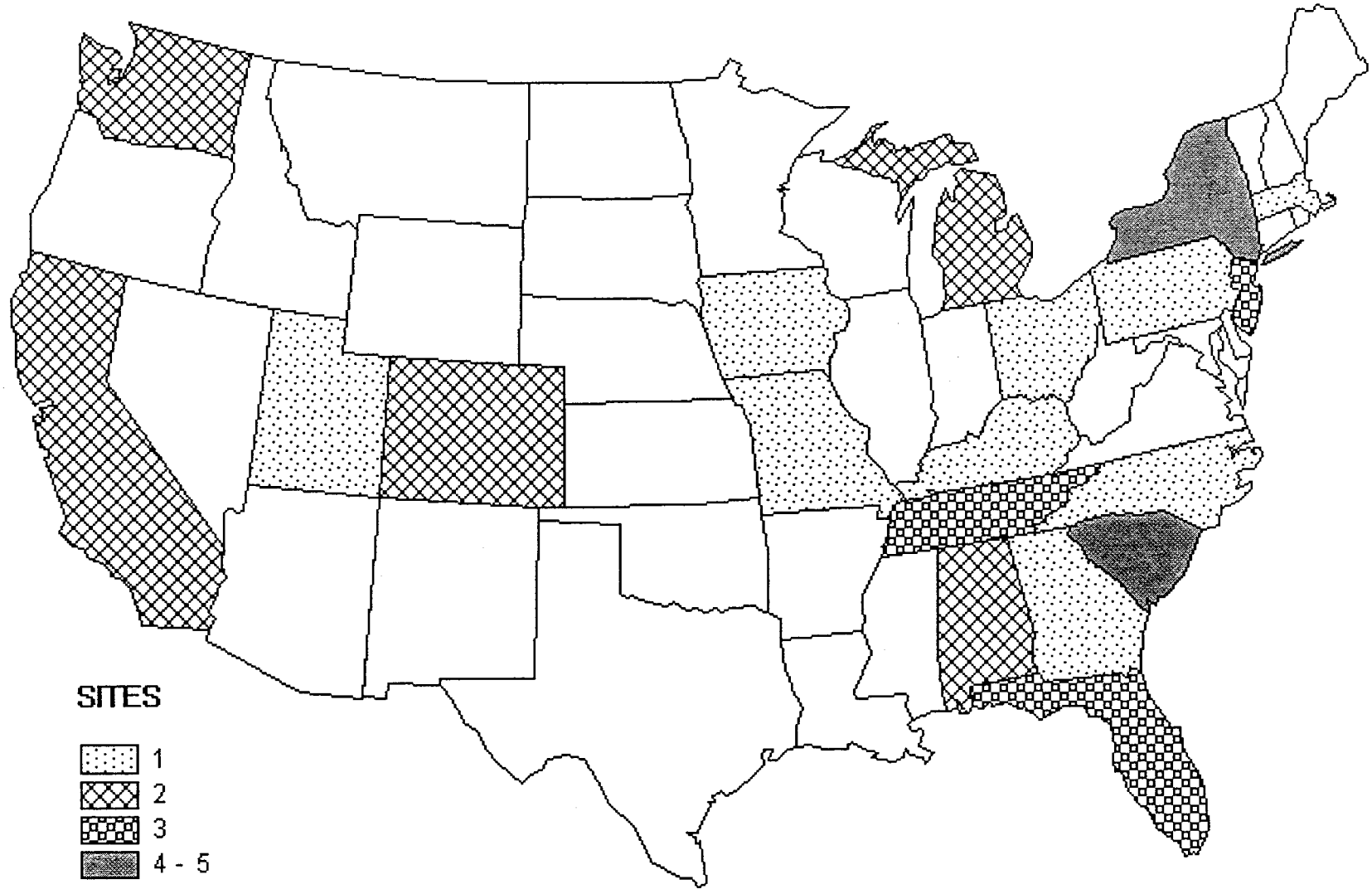
Endrin has been identified in at least 102 of the 1,430 current and former hazardous waste sites that have been proposed for inclusion in the NPL (HazDat 1996), although the total number of sites evaluated for endrin is not known. The frequency of these sites can be seen in Figure 5-1. Of these sites, 102 are located in the United States. Endrin ketone has been identified in at least 37 of the 1,430 current and former hazardous waste sites that have been proposed for inclusion in the NPL (HazDat 1996). However, the number of sites evaluated for endrin ketone is not known. The frequency of these sites can be seen in Figure 5-2. Of these sites, 37 are located in the United States.

Figure 5-1. Frequency of Sites with Endrin Contamination



Derived from HazDat 1996

Figure 5-2. Frequency of Sites with Endrin Ketone Contamination



Derived from HazDat 1996

Endrin aldehyde has not been identified in any of the 1,430 current and former hazardous waste sites that have been proposed for inclusion in the EPA National Priorities List (NPL) (HazDat 1996); however, the number of sites evaluated for endrin aldehyde is not known.

5.2 RELEASES TO THE ENVIRONMENT

No information is available in the Toxic Release Inventory (TRI) database on the amounts of endrin, endrin aldehyde, or endrin ketone released to the environment from facilities, that manufacture or process these compound because these chemicals are not included under SARA, Title III and, therefore, are not required to be reported (EPA 1995a).

Because virtually all uses of endrin in the United States were voluntarily canceled by 1986 (Bishop 1984, 1985, 1986; EPA 1993e; USDA 1995) (see Section 4.3), releases to the environment of endrin, or of endrin aldehyde and endrin ketone which occur as impurities or degradation products of endrin, have decreased dramatically over the last decade.

5.2.1 Air

In the past, emissions from endrin production and processing facilities and agricultural applications were primary sources of releases of endrin to the atmosphere. During the period when endrin was extensively used in agriculture, 33% of the applied endrin was found to volatilize within 11 days, after which time further evaporation ceased (Nash 1983).

There is also a potential for atmospheric release of endrin, endrin aldehyde, and endrin ketone from hazardous waste sites. Endrin has been detected in air samples collected at 4 of the 102 NPL sites where endrin has been detected in some environmental medium (HazDat 1996). No information was found on detections of endrin aldehyde or endrin ketone in air at any NPL hazardous waste site (HazDat 1996)

5.2.2 Water

In the past, endrin could have been released to surface water from manufacturing and processing facilities. No information on direct discharges or loadings of endrin into surface water was found. Based on amounts measured in rainfall at various stations in Canada, loading estimates for endrin and

a number of other organochlorine pesticides have been attempted for portions of the Great Lakes basin (Strachan 1988). The sources for such loadings to receiving waters are not clear, but would likely involve in-place contaminants related to endrin's past uses as a pesticide agent. Current studies in Oklahoma indicate that in some areas of the United States endrin is still being released to surface water from farmland soils that have been treated with endrin in the past (Petty et al. 1995).

There is also a potential for release of endrin, endrin aldehyde, and endrin ketone to water from hazardous waste sites. Endrin has been detected in surface water samples collected at 10 of the 102 NPL sites, in groundwater samples collected at 37 of the 102 NPL sites, and in leachate samples collected at 2 of the 102 NPL sites where endrin has been detected in some environmental medium (HazDat 1996). Endrin ketone has been detected in surface water samples collected at 5 of the 37 NPL sites, in groundwater samples collected at 16 of the 37 NPL sites, and in leachate samples collected at 2 of the 37 NPL sites where endrin ketone has been detected in some environmental medium (HazDat 1996). No information was found on detections of endrin aldehyde in surface water, groundwater, or leachates at any NPL hazardous waste site (HazDat 1996)

5.2.3 Soil

Past use of endrin as an agricultural pesticide has been the principal source of its release to soils or aquatic sediments. There is also a potential for release of endrin, endrin aldehyde, and endrin ketone to soils and sediments from hazardous waste sites. Endrin has been detected in soil samples collected at 44 of the 102 NPL sites, and in sediment samples collected at 19 of the 102 NPL sites where endrin has been detected in some environmental medium (HazDat 1996). Endrin ketone has been detected in soil samples collected at 23 of the 37 NPL sites, and in sediment samples collected at 5 of the 37 NPL sites where endrin ketone has been detected in some environmental medium (HazDat 1996). No information was found on detections of endrin aldehyde in soils or sediments at any NPL hazardous waste site (HazDat 1996).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Endrin is extremely persistent when released to the soil. It adsorbs strongly to soil particles and tends to be immobile, based on an estimated K_{oc} of 34,000 (Kenaga 1980; Swann et al. 1983). Endrin on

soil may be transported to surface water via runoff from rain or irrigation. Since endrin in solid form is hydrophobic and sorbs strongly to soil particles, migration into groundwater would not generally be expected from normal agricultural application. In laboratory studies, endrin was found to be almost completely adsorbed to samples of sandy loam and organic soil (Sharom et al. 1980a). In sandy soil only 13.6% of the endrin was leached from the soil after 10 successive 200 mL water rinses. In organic soil, only 1.5% of the endrin was leached from the soil after 10 successive 200 mL water rinses. The mobility factors calculated for the sandy soil and organic soil were 0.52 and 0.040, respectively. Only dieldrin, leptophos, and p,p'-DDT were less mobile in the 2 soil types than endrin.

However, endrin has been detected in some leachates and groundwaters from NPL hazardous waste sites (see Section 5.2.2) and in various other groundwaters, suggesting that leaching may be possible in some soils under certain conditions (Cohen 1986; EPA 1989; HazDat 1996). Furthermore, because endrin formulations in solvent carriers such as xylene or hexane were also commonly used, endrin could move into groundwater from spills of such formulations. Similarly, migration to groundwater might also occur at waste sites where endrin residues become mixed with organic solvents (Jaquess et al. 1989).

Despite endrin's low vapor pressure of 2.0×10^{-7} mm Hg (EPA 1981a), initial volatilization of 20-30% after agricultural application to soil has been reported to be rapid (Nash 1983). Within 11 days, however, further volatilization was no longer detected (Nash 1983). Unlike some other chlorinated pesticides, endrin volatilization was not enhanced after a rainfall. Small amounts of endrin in soil may also be transported to the air by dust particles.

The presence of significant concentrations of endrin transformation products (including endrin ketone, endrin aldehyde, and endrin alcohol) in a variety of plants grown in soil treated with endrin for periods as long as 16 years prior to planting (Beall et al. 1972; Nash and Harris 1973) indicates that there may be significant uptake of endrin and/or its transformation products by plants from endrin-treated soil.

Because of its high log K_{oc} and log K_{ow} values (4.53 and 5.34-5.6, respectively; see Table 3-2), when released to water, endrin strongly adsorbs to sediment (Kenaga 1980; Swann et al. 1983) and bioconcentrates significantly in aquatic organisms (ASTER 1995; EPA 1980a; Metcalf et al. 1973). Typical bioconcentration factors (BCFs) for freshwater and marine organisms range from 80 to 49,000

(Table 5-l). Biomagnification of endrin with increasing trophic level is not expected to be significant (Leblanc 1995). Metcalf et al. (1973) reported a ratio of biomagnification through the aquatic food 7chain to bioconcentration by direct uptake from water to be 2 for endrin compared to 2.50 for DDT. These authors used a model laboratory aquatic ecosystem containing algae (*Oedogonium cardiacurn*), snails *(Physa sp.),* water fleas *(Daphnia magna),* mosquito larvae (*Culex pipens quinquefasciatus),* and mosquito fish *(Gambusia afinis).*

Based on its very small calculated Henry's law constant of $4.0x10^{-7}$-$5.4xl0^{-7}$ atm-m^3/mol (see Table 3-2) and its strong adsorption to sediment particles, endrin would be expected to partition very little from water into air (Thomas 1990). The half-life for volatilization of endrin from a model river 1 meter deep, flowing 1 meter per second, with a wind speed of 3 meters per second, was estimated to be 9.6 days; whereas, a half-life of greater than 4 years has been estimated for volatilization of endrin from a model pond (Howard 1991). Adsorption of endrin to sediment may reduce the rate of volatilization from water.

In air, endrin is expected to be associated primarily with particulate matter, based on its low vapor pressure and high K_{oc} (Kenaga 1980). However, small amounts of endrin in the atmosphere may exist in the vapor phase (Eisenreich et al. 1981). Because of its low solubility (200 (µg /L, see Table 3-2) endrin would not be expected to be removed significantly from the atmosphere by wet deposition. Particle-adsorbed endrin will be removed from the atmosphere by both wet and dry deposition. In recent studies in the Great Lakes area, endrin was found in 5% of 450 wet deposition (rain/snow) samples collected between 1986-1991, at volume weighted mean concentrations ranging from 0.02 to 0.98 ng/L (ppt) (Chan et al. 1994).

No studies on the environmental transport and partitioning of endrin aldehyde could be found in the available literature. Values of the estimated log K_{ow} for endrin aldehyde vary widely, ranging from 3.1 to 5.6 (see Table 3-2). Based on the lowest estimated log K_{ow}, the K_{oc} value for endrin aldehyde can be estimated to be approximately 1,000 (Lyman 1990), indicating a low mobility in soil (Swann et al. 1983). Using the higher estimated values of log K_{ow} (4.7-5.6), the K_{oc} value for endrin aldehyde can be estimated to range from 8,500 to 380,000 (Lyman 1990), indicating that this compound will be virtually immobile in most soils (Swann et al. 1983). Because of its low vapor pressure of

Table 5-1. Bioconcentration Data for Endrin

Species common name scientific name	Exposure type	Duration (days)	BCF[a]	Reference
Freshwater				
Algae *Microcystis aeruginosa*	–	7	200	Vance and Drummond 1969 (cited in EPA 1980a)
Algae *Anabaena cylindrica*	–	7	222	Vance and Drummond 1969 (cited in EPA 1980a)
Algae *Scenedesmus quadricauda*	–	7	156	Vance and Drummond 1969 (cited in EPA 1980a)
Algae *Oedogonium sp.*	–	7	140	Vance and Drummond 1969 (cited in EPA 1980a)
Water flea *Daphnia magna*	S	1	2,600	Metcalf et al. 1973
Mosquito *Culex pipiens quinquefasciata*	S	1	2,100	Metcalf et al. 1973
Stonefly *Pteronarcys dorsata*	F	28	1,000	Anderson and Defoe 1980
Pouch snail *Physa sp.*	S	33	49,000	Metcalf et al. 1973
Mussels *Mixed species*	–	21	3,000	Jarvinen and Tyo 1978
Channel catfish *Ictalurus punctatus*	–	41–55	2,000	Argyle et al. 1973 (cited in EPA 1980a)
Flagfish *Jordanella floridae*	–	65	15,000	Hermanutz 1978
Flagfish *J. floridae*	F	15	7,000	Hermanutz et al. 1985
Fathead minnow *Pimephales promelas*	F	47	10,000	Mount and Putnicki 1966 (cited in EPA 1980a)
Fathead minnow *P. promelas*	–	56–300	7,000	Jarvinen and Tyo 1978
Fathead minnow *P. promelas*	F	2–304	80[b]	Veith and Kosian 1983
Black bullhead *Ictalurus melas*	F	4	3,700	Anderson and Defoe 1980
Black bullhead *I. melas*	F	7	6,200	Anderson and Defoe 1980

Table 5-1. Bioconcentration Data for Endrin (continued)

Species common name scientific name	Exposure type	Duration (days)	BCF[a]	Reference
Saltwater				
Grass shrimp *Palaemonetes pugio*	F	145	1,600	Tyler-Schroeder 1979
American oyster *Crassostrea virginica*	F	2	1,670	Mason and Rowe 1976
American oyster *C. virginica*	F	7	2,780	Mason and Rowe 1976
Sheepshead minnow (embryo-juveniles) *Cyprinodon variegatus*	–	33	4,800	Schimmel et al. 1975 (cited in EPA 1980a)
Sheepshead minnow *C. variegatus*	–	141–161	6,400	Hansen et al. 1977
Spot *Leiostomos xanthurus*	–	5–8 mos	1,450	Lowe 1966 (cited in EPA 1980a)

[a]BCF listed is the highest bioconcentration factor (BCF) value reported in the cited reference
[b]Calculated quantitative structure-activity relationship (QSAR) value

F = flow-through exposure system; mos = months; S = static system

$2.0x10^{-7}$ mm Hg and Henry's Law constant ranging from $2x10^{-9}$-$3.7xl0^{-8}$ atm-m^3/mol (see Table 3-2), endrin aldehyde would not be expected to volatilize significantly from soil or water (Eisenreich et al. 1981; Thomas 1990). Any endrin aldehyde in air should exist predominantly in the adsorbed phase (Eisenreich et al. 1981). Atmospheric endrin aldehyde will be transported to soil and surface water via wet and dry deposition of associated particles. In water, adsorption to sediments and bioconcentration are likely to be significant partitioning processes. Based on the lowest estimated value of 3.1 for log K_{ow} (see Table 3-2), the BCF value for endrin aldehyde can be estimated to be only 86 (Veith et al. 1979), indicating little tendency to bioconcentrate in aquatic organisms. Using the higher estimates of 4.7-5.6 for log K_{ow} (see Table 3-2), BCF values for endrin aldehyde are estimated to range from to 2,000 to 11,000 (Veith et al. 1979), indicating a much higher tendency for bioconcentration.

No studies on the environmental transport or partitioning of endrin ketone could be found in the available literature, and only limited information was found on estimated values of physical and chemical properties. The very low estimated value of $2.02x10^{-8}$ atm-m^3/mole for Henry's Law constant for endrin ketone (see Table 3-2) indicates that this compound will not volatilize from water. Based on the estimated log K_{ow} of 4.99 (see Table 3-2), the BCF value for endrin ketone can be estimated to be 3,500 (Veith et al. 1979), indicating that endrin ketone may be removed from water via bioconcentration in aquatic organisms. Also based on an estimated log K_{ow} of 4.99, the K_{oc} value for endrin ketone can be estimated to range from 5,500 to 90,000 (Lyman 1990), indicating that this compound will be virtually immobile in soil and sediments (Swann et al. 1983). However, detection of endrin ketone in groundwater and leachate samples at some NPL sites suggests some limited mobility of endrin ketone in certain soils (HazDat 1996).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Field studies on the transformation of endrin in the atmosphere were not located in the available literature. Photochemical isomerization of endrin, primarily to the pentacyclic ketone commonly called delta ketoendrin or endrin ketone, was observed after exposure of thin layers of solid endrin on glass to sunlight (Burton and Pollard 1974). Minor amounts of endrin aldehyde were also formed in this reaction. Results of seasonal studies indicated that this isomerization would proceed with a half-life

(first-order kinetics) of 5-9 days in intense summer sunlight, with complete conversion to the pentacyclic ketone in 15-19 days. Knoevenagel and Himmelreich (1976) reported that photodegradation of solid endrin in the laboratory proceeded with a half-life (first-order kinetics) of 20-40 hours. In laboratory studies conducted by Zabik et al. (1971) on endrin formulations in hexane and cyclohexane (similar to those commonly used for pesticide applications), endrin was found to undergo photolytic dechlorination when exposed to ultraviolet radiation, yielding a pentachlorinated half-cage ketone as the major product. This degradation product was also detected in environmental samples. Endrin may also be transformed by heat in the atmosphere, yielding primarily the pentacylic ketone and endrin aldehyde (EPA 19798; Phillips et al. 1962). Endrin may also react with photochemically generated hydroxyl radicals in air, with a predicted half-life (first-order kinetics) ranging from 1.45 hours (Howard 1991) to 1.8 days (SRC 1995a). No information could be found on the products of this reaction. The reaction of endrin with ozone in air is not significant. The predicted first-order rate constant for this reaction is $3.6x10^{-20}$ cm^3/molecule-sec, corresponding to a half-life of 320 days (SRC 1995a).

Endrin aldehyde may react with photochemically generated hydroxyl radicals in the atmosphere, with an estimated overall first-order rate constant of $106x10^{-12}$ cm^3/molecule-see, which corresponds to a half-life of 3.6 hours, assuming a 24-hour concentration of hydroxyl radicals of $0.5x10^6$ molecules/cm^3 (SRC 1995a). Endrin ketone may react with photochemically generated hydroxyl radicals in the atmosphere, with an estimated overall first-order rate constant of $10.8x10^{-12}$ cm^3/molecule-set, which corresponds to a half-life of 1.5 days, assuming a 24-hour concentration of hydroxyl radicals of $0.5x10^6$ molecules/cm^3 (SRC 1995a). No other information could be found in the available literature on the transformation and degradation of endrin aldehyde or endrin ketone in air.

5.3.2.2 Water

Laboratory studies of the fate of endrin in water samples suggest a significant degree of stability, although there is evidence of varying degrees of biodegradation in some systems. Endrin was among the more stable of 12 insecticides incubated in water collected from the drainage canal of a vegetable-growing site near Toronto, with about 80% of endrin remaining in the natural water after incubation for 16 weeks (Sharom et al. 1980b). There was little indication of chemical degradation of endrin in these studies. Studies in which sealed water samples from the Little Miami River were exposed to

sunlight and artificial fluorescent light showed no measurable degradation of endrin over an 8-week period (Eichelberger and Lichtenberg 1971). However, microorganisms in fish pond water and algae from a fish pond were able to metabolize endrin (Patil 1972). In the case of the algae, the metabolite was 12-ketoendrin. The rate of metabolism was 35% for the water sample and 24% for the algal culture in one month. Using the static culture procedure, Tabak et al. (1981) found no biodegradation of endrin in domestic waste water samples.

Based on laboratory experiments on solid endrin (Burton and Pollard 1974) and on endrin in organic solvents (Zabik et al. 1971), it is likely that endrin released to surface water will undergo photoisomerization to endrin ketone, with minor amounts of endrin aldehyde also being formed. Under real world conditions, endrin released to surface waters would not be expected to biodegrade or hydrolyze to any significant extent (Eichelberger and Lichtenberg 1971; EPA 19798). Endrin is very resistant to hydrolysis, with an estimated half-life (first-order kinetics) of more than 4 years (EPA 19798). The predominant removal of endrin from water by photodegradation and sorption to suspended particulates or sediments (see Section 5.3.1) is consistent with the observed low incidence of detected endrin in ambient surface waters based on analyses of EPA National Urban Runoff Program (Cole et al. 1984) and STORET (Staples et al. 1985) data as described in Section 5.4.2.

Little information could be found in the available literature on the transformation and degradation of endrin aldehyde in water. Neither hydrolysis nor oxidation (via peroxy radicals or singlet oxygen) are expected to be significant in aquatic systems (EPA 1981a). By analogy to endrin, the hydrolysis halflife (first-order kinetics) of endrin aldehyde in water is probably greater than four years (EPA 1979g). No information could be found on the biodegradation of endrin aldehyde in aquatic systems.

No information could be found in the available literature on the transformation and degradation of endrin ketone in water.

5.3.2.3 Sediment and Soil

Biodegradation does not appear to be a significant degradation process for endrin in soils. The actual measurement of biodegradation of endrin under field conditions on well drained agricultural soil indicate a biodegradation half-disappearance time of approximately 14 years (Nash and Woolson

1967), suggesting that endrin is resistant to biodegradation in soils under natural conditions. In this study, 41% of the initial endrin applied to an agricultural field was present in the soil after 14 years,

Laboratory studies indicate that endrin can be biodegraded in various soils under various conditions; however, caution should be exercised in extrapolating laboratory results to field conditions. Twenty different isolates of soil organisms belonging to several different species (5 identified, 4 unidentified) were found to biodegrade endrin in the laboratory under aerobic conditions (Patil et al. 1970). The study revealed endrin as one of the more easily biodegradable insecticides, while lindane, for example, was not degraded by any of the 20 isolates. In contrast, Bartha et al. (1967) found no biodegradation of endrin, but they used rather insensitive analytical techniques compensated for by high endrin concentrations (0.25 ppm) that would not occur in normal agricultural practice. Nitrification was enhanced by endrin in this experiment. Endrin was also biodegraded to four unidentified metabolites in laboratory microcosms using flooded rice soils (Gowda and Sethunathan 1976). The most rapid degradation was seen in the saline acid sulfate soil, pokkali, followed by alluvial and laterite soils, where endrin concentrations dropped l0-20-fold in 55 days. Sandy soils were least active and reduced endrin concentration only by about 40% in 55 days. The addition of organic matter, such as rice straw, approximately doubled the rate of biodegradation. Half-disappearance times of endrin in soils ranged from less than 20 days under optimal conditions to about 80 days under less favorable conditions. A degradation half-life (first-order kinetics) of 26-32 weeks was reported for endrin (initial concentration approximately 1.6-2.0 ppm) in a clay soil under controlled, aerobic environmental conditions (30 (C; soil water content 10-33%), with slower degradation observed in soils with the lowest moisture content (Ghadiri et al. 1995). First-order rate equations best described the degradation. Virtually complete anaerobic biodegradation of endrin in laboratory microcosms within 4 days has been reported; however, the researchers caution that under natural conditions redox environments in many soils will not be suitable for anaerobic degradation, and that endrin residues sorbed to soil particles would often be rendered unavailable to bacteria (Maule et al. 1987).

In combination, losses from volatilization, photodegradation (Burton and Pollard 1974; EPA 1985e; Knoevenagel and Himmelreich 1976; Zabik et al. 1971), and heat transformation (primarily to endrin ketone, with minor amounts of endrin aldehyde) (EPA 1979g; Phillips et al. 1962) are likely to account for a rapid decrease in endrin residues on soil or plant surfaces exposed to bright sunlight. Studies have also been conducted indicating significant concentrations of endrin transformation

products (including endrin ketone, endrin aldehyde, and endrin alcohol) in plants grown in endrintreated soil (Beall et al. 1972; Nash and Harris 1973).

Little information could be found in the available literature on the transformation and degradation of endrin aldehyde in sediment and soil. By analogy to aquatic systems, neither hydrolysis nor oxidation (via peroxy radicals or singlet oxygen) would be expected to be significant transformation processes. No information could be found on the biodegradation of endrin aldehyde in sediment or soil.

No information could be found in the available literature on the transformation and degradation of endrin ketone in sediment and soil.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to endrin depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Endrin's sensitivity to thermal degradation, however, may sometimes make it difficult to interpret analytical work conducted in the 1960s and 1970s because temperatures used in many types of gas chromatography analytical procedures for organochlorine pesticides at that time have been shown to isomerize endrin into a variety of ketones, aldehydes, alcohols, and other unidentified products (Phillips et al. 1962). In reviewing data on levels monitored or estimated in the environment, it should also be noted that the amount of the chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

Endrin is relatively nonvolatile with a vapor pressure of 2.0×10^{-7} mm Hg (EPA 1981a; Worthing and Walker 1983). Despite its low volatility, initial loss of agriculturally applied endrin through volatilization was found to be comparable to more volatile pesticides (Nash 1983). No recent data on atmospheric concentrations of endrin could be found in the available literature. Endrin was detected in air samples collected at 4 of the 102 NPL sites where endrin has been detected in some environmental medium; however, concentrations were not available (HazDat 1996).

Limited information was found on atmospheric concentrations of endrin between 1970 and the mid-1980s, prior to cancellation of virtually all uses (Bishop 1984, 1985, 1986; EPA 1993e; USDA 1995) (see Section 4.3). The data were insufficient to identify any trends. The mean and maximum airborne concentrations of endrin in the United States in 1970-71 were reported to be 0.2 ng/m^3 and 19.2 ng/m^3, respectively (Lee 1977). For that same time period, mean airborne concentrations at suburban sites near Jackson, Mississippi, and Columbia, South Carolina, were reported to be 0.1 ng/m^3 and 0.2 ng/m^3, respectively (Bidleman 1981; Kutz et al. 1976). Endrin was not detected at Boston, Massachusetts, suburban sites (Bidleman 1981). A survey of airborne contaminants in the Great Lakes area in 1981 did not detect endrin (Eisenreich et al. 1981).

Atmospheric concentrations of endrin in the vicinity of manufacturing facilities were higher than those found in non-source areas of the United States. Eight hundred meters from 2 formulation plants in Arkansas and 275 meters from one formulation plant in Tennessee, mean airborne concentrations of endrin were reported to be 3.3 ng/m^3 and 3.5 ng/m^3, respectively, during 1970-72 (Lewis and Lee 1976). Endrin was also detected in air in industrial or source-dominated regions of the Mississippi Delta in 1972-74, and in Tennessee in 1971 (EPA 1985e).

Endrin may also be found in atmospheric precipitation. In an analysis of pesticides in rainfall from four stations in Canada in 1984, detectable concentrations of endrin were found at each site (Strachan 1988). There was a noticeable pattern of decline in detections within the summer season (May-August). In more recent studies in the Great Lakes area, endrin was found in 5% of 450 wet deposition (rain/snow) samples collected between 1986 and 1991, at volume weighted mean concentrations ranging from 0.02 to 0.98 ng/L (ppt) (Chan et al. 1994).

No information was found in the available literature on concentrations of endrin aldehyde or endrin ketone in ambient outdoor air or in indoor air. In addition, no information was available on occupational exposures to these chemicals.

5.4.2 Water

Very little recent information on concentrations of endrin in water could be found in the available literature. Unlike DDT, chlordane, aldrinidieldrin, and a variety of other chlorinated pesticides, endrin was never used extensively in urban areas. This is reflected in the results from EPA's Nationwide

Urban Runoff Program, which showed no detections in 86 high-flow water samples from 51 urbanized watersheds from 19 cities (Cole et al. 1984). Analysis of EPA STORET monitoring information from ambient surface water showed a significant percentage of detections for endrin (32% of 8,789 samples), but most were near the detection limits, with a national median concentration of 0.001 ppb (Staples et al. 1985). A similar analysis of STORET data for endrin aldehyde showed that this compound was not found in 770 samples of ambient surface water. More recently, endrin was not detected (detection limit 49 ng/L [0.045 ppb]) in surface water from the Yakima River Basin, Washington (Foster et al. 1993). However, in 1991-92, endrin was detected in first flush (first 20 minutes) stormwater runoff samples at 4 of 6 sites in Louisville, Kentucky, at levels that exceeded U.S. Federal criteria (0.003 (µg /L, [ppb]) (Marsh 1993). Maximum, minimum, and mean concentrations at the 4 sites ranged from 0.03 to 0.05, 0.02 to 0.04, and 0.03 to 0.04 (ppb), respectively. Endrin was not detected (detection limit not specified) in 3-hour composite samples of stormwater runoff from any of the 6 sites. Endrin has been detected in surface water samples collected at 10 of the 102 NPL sites where it was detected in some environmental media (HazDat 1996).

Recent studies using semipermeable membrane devices to determine bioavailable (dissolved) organochlorine pesticide residues in streams receiving irrigation rainwater from agricultural activity in the Luger Altus Watershed in southwestern Oklahoma indicate that endrin may still be present in this aquatic ecosystem several years after discontinuation of its use (Petty et al. 1995). Calculated concentrations of bioavailable endrin at 6 sampling sites ranged from not detected (detection limit not specified) to 110 (µg /L (ppb). Concentrations were higher in spring than in summer. There is an uncertainty in these estimates because they were derived from the dialysate data using models and preliminary data on uptake kinetics.

Endrin is rarely detected in drinking water and any trace amounts of endrin that might be encountered in raw drinking water supplies will likely be removed in the treatment systems used by most communities. In 1966 and 1967, when the use of endrin was not restricted, endrin was detected in 5 of 67 raw water samples from the Mississippi and Missouri Rivers (Schafer et al. 1969). At a later time when endrin use was substantially restricted, an Iowa study of 33 community water supplies using surface water found no detectable concentrations of endrin in the distribution systems (Wnuk et al. 1987). In an extensive water quality monitoring program conducted by the California Department of Health Services, endrin was detected (detection limit not specified) in only 2 of 5,109 public drinking water sources sampled from 1984 to 1992, at mean and maximum concentrations of 0.06 and

0.10 ppb, respectively (Storm 1994). Concentrations did not exceed the Maximum Concentration Level (MCL) of 0.2 ppb. In another recent study, endrin was not detected (detection limit not specified) in 32 samples each of raw water and highly treated reclaimed waste water undergoing evaluation as a possible supplement to raw water sources in San Diego, California (De Peyster et al. 1993).

Detections of endrin in groundwater are also rare except from wells near hazardous waste sites. The EPA Pesticides in Groundwater Data Base (EPA 1989) contains groundwater data collected with good quality assurance/quality control (QA/QC) provisions from areas with significant agricultural land uses as well as from urban areas. Analysis of these data indicated there were only two wells with detectable levels of endrin within the entire United States. A detection occurred in a well in California (concentration not reported) where point source problems or spills were deemed the likely sources. Endrin contamination found in an Illinois well at an average concentration of 0.02 ppb was considered likely to have resulted from ordinary agricultural uses. In a groundwater contamination study of California's 58 counties, in which over 50 pesticides were evaluated from both point and nonpoint sources, endrin was detected in only one sample (Cohen 1986). In a more recent study, endrin was detected at 0.9% of 178 CERCLA sites and 1.3% of 156 RCRA sites sampled; however, endrin concentrations were not reported (Plumb 1987). Endrin was also found in groundwater samples collected at 37 of the 102 NPL and in leachate samples collected at 2 of the 102 NPL sites where endrin has been detected in some environmental media; however, concentrations were not reported (HazDat 1996).

No information was found in the available literature on levels of endrin aldehyde or endrin ketone in surface or groundwater. Endrin ketone has been detected in surface water samples collected at 5 of the 37 NPL sites, in groundwater samples collected at 16 of the 37 NPL sites, and in leachate samples collected at 2 of the 37 NPL sites where endrin ketone has been detected in some environmental medium; however, concentrations were not reported (HazDat 1996).

5.4.3 Sediment and Soil

Very little recent information on levels of endrin in soils was found in the available literature. From the available data it appears that, in general, endrin was found infrequently and at relatively low levels in both urban and cropland soils in the United States. Endrin was detected in only 10 of

1,483 cropland soil samples in 1972 at concentrations up to 2.13 ppm (detection limit of 0.01 ppm) (Carey et al. 1979). These studies were part of the National Soils Monitoring Program carried out by EPA and the USDA under the National Pesticide Monitoring Program, which covered a total of 1,533 sampling sites in 37 states. Endrin detections were documented in the following states: Alabama, Arkansas, Georgia, Illinois, Louisiana, Nebraska, New York, North Carolina, and South Dakota, as well as at sites from one or more of the mid-Atlantic states of Delaware, Maryland, and New Jersey. Endrin was also detected at a level of 0.017 ppm at a single site in California in a study that targeted rice-growing cropland soils in Arkansas, California, Louisiana, Mississippi, and Texas (Carey et al. 1980). Endrin was not detected in urban soils from 13 of 14 U.S. cities included in a 1970 study of pesticide residues in urban soils (25-30 soil sampling sites were used for each of the urban areas) (Carey et al. 1976). The only detection was at a single site near Memphis, Tennessee, where the Velsicol Chemical Company (which produced endrin at that time) is located. The reported concentration for this site was 0.07 ppm; the mean concentration for all 28 Memphis sites was <0.01 ppm.

Relatively little literature was identified concerning the analysis of endrin in aquatic sediments. The available data indicate that, historically, sediment concentrations of endrin have been very low. In a recent study of sediment contaminants in Casco Bay, Maine, endrin was found at concentrations near or below the method detection limit (<0.25 ppb) (Kennicutt et al. 1994). In the National Surface Water Monitoring Program conducted from 1976 to 1980, endrin was detected in 1.3% of the sediment samples analyzed (detection limit not reported) with a maximum concentration of 2.9 ppb (Carey and Kutz 1985). An analysis of EPA STORET data indicated endrin was detected in 24% of the 1,802 sediment records listing endrin as a parameter code. The median endrin concentration for all records was 0.001 ppb (Staples et al. 1985). A similar analysis of STORET data indicated that endrin aldehyde was not found in any of 251 samples of sediment (Staples et al. 1985). In a study by Ford and Hill (1991) to evaluate organochlorine pesticide residues in sediments and aquatic animals in the vicinity of the Yazoo National Wildlife Refuge in the Mississippi Delta, a region that has experienced very high usage of pesticide agents, detectable levels of endrin were not found in sediments (detection limit 0.01 ppm [l0 ppb]). Similarly, endrin was not detected in sediment or pore water samples (detection limits 0.49 and 0.01 ppm [490 and 10 ppb], respectively) from 18 mosquito control impoundments in St. Lucie County, Florida, where organochlorine pesticides had been heavily used through the early 1960s (Parkinson et al. 1993).

There is a potential for endrin to be present in soils and sediments at hazardous waste sites. Endrin has been detected in soil samples collected at 44 of the 102 NPL sites and in sediment samples collected at 19 of the 102 NPL sites where endrin has been detected in some environmental medium; however, concentrations were not reported (HazDat 1996). Endrin was not detected (detection limit 0.01 ppm [l0 ppb] wet weight), however, in soils derived from dredged materials at 9 confined disposal facilities bordering the Great Lakes (Beyer and Stafford 1993).

No information was found in the available literature on levels of endrin aldehyde in soil or endrin ketone in sediment or soil. Endrin ketone has been detected in soil samples collected at 23 of the 37 NPL sites and in sediment samples collected at 5 of the 37 NPL sites where endrin ketone has been detected in some environmental medium; however, concentrations were not reported (HazDat 1996).

5.4.4 Other Environmental Media

Endrin has been found in many foods, but current levels appear to be very low and not of concern for human health. The FDA has concluded that endrin is no longer present in the environment to the extent that it may be contaminating food or feed at levels of regulatory concern (USDA 1995). An FDA survey of pesticide residues in samples of domestic and imported food and feed commodities from Fiscal Year (FY) 1982 to 1986 lists endrin levels for specific food items up to 0.50 ppm (500 ppb) (Hundley et al. 1988). This study was conducted by surveillance sampling with follow-up compliance sampling for sources of foodstuffs where the concentrations in surveillance samples violated EPA tolerance levels. In surveillance sampling, endrin was detected in 0.05% (3 of 6,391 samples) and 1.5% (183 of 12,044 samples) of domestic and imported foods, respectively. The incidence of violative surveillance samples (endrin residues $\geq$0.05 ppm [50 ppb]) was higher for imported foods (0.1%; 12 violations) than for food items from domestic sources (0.02%; 1 violation). In follow-up compliance monitoring of 1,239 samples of imported foods, endrin was found in 11 samples (0.9%); 2 of these samples (0.2%) were violative. In imported foods, endrin was detected in mung beans, cucumbers, pickling cucumbers, cantaloupe, acorn squash, cabocha squash, Italian squash, summer squash, and yellow squash (Hundley et al. 1988). No follow-up compliance monitoring of domestic samples for endrin residues was performed.

In a more recent study of pesticide residues in food conducted in 10 states between 1988 and 1989, endrin was not detected in any of the 13,980 samples analyzed in 1988. In 1989, the detection

frequencies for endrin and endrin ketone were 0.084% and 0.007%, respectively, for the 13,085 samples analyzed (Minyard and Roberts 1991). In a Canadian study, reported concentrations of endrin in composite samples of fresh root vegetables, fruit, leafy and other above-ground vegetables, and cows' milk ranged from 0.27 to 0.37 ppb; endrin was not detected in composite samples of fresh meat and eggs (detection limit 0.01 ppb) (Davies 1988). Endrin was detected each year in regulatory monitoring of domestic and imported foods conducted by the FDA from 1989 to 1994 as part of its Pesticide Residue Monitoring Program (FDA 1990, 1991, 1992, 1993, 1994, 1995). Concentrations were not reported; however, <1% of the surveillance samples had any pesticide residue levels that were above established tolerances. Endrin was also detected in the FDA Total Diet Studies in 1987, 1988, 1989, and 1991, but not in 1990 (FDA 1988, 1989, 1990, 1991, 1992). Reports of 1992-94 FDA Total Diet Studies did not indicate whether endrin was detected in those years (FDA 1993, 1994, 1995). In the years in which endrin was detected in the FDA Total Diet Studies, it was not among the most frequently detected pesticides. Concentrations of endrin found in the FDA Total Diet studies were not reported. However, in an overall summary for the 5-year period 1986-91, average dietary intakes of endrin for 8 age/sex groups (6-l l-month-old infants, 2-year-old children, 14-16-year-old males and females, 25-30-year-old males and females, and 60-65-year-old males and females) were all estimated to be <0.000l (μg /kg body weight per day, less than 0.03% of the EPA RfD of 0.3 (μg /kg body weight per day (FDA 1993). A food basket survey patterned after the FDA approach that was conducted in San Antonio, Texas did not find detectable concentrations of endrin (detection limit 0.050 ppm [50 ppb]) in 6,970 produce items (Schattenberg and Hsu 1992).

Overall, in 234 ready-to-eat foods tested 37 times each as part of the FDA Total Diet Studies from 1982 to 1991, endrin was found only 26 times at an average concentration of 0.0027 (μg /g (2.7 ppb) in 9 different foods: broccoli, cantaloupe, collards, cucumbers, onion rings, dill pickles, pumpkin pie, summer squash, and winter squash (KAN-DO Office and Pesticides Team 1995). Concentrations ranged from 0.0011 (μg /g (1 .l ppb) (broccoli) to 0.0041 μg/g (4.1 ppb) (summer squash). In a summary of 1985-91 FDA pesticide residue findings, endrin was not reported in more than 10,000 surveillance samples of domestic and imported foods that may be eaten by infants or children, or in more than 4,000 analyses of Total Diet Study foods eaten by infants and children (Yess et al. 1993).

Other studies further indicate that the occurrence of endrin in the US. food supply is very low. In a 1990-91 FDA survey of pesticide residues in milk representing most of the U.S. supply consumed in

metropolitan areas, endrin was detected at trace levels (0.0005-0.001 ppm [0.5-l.0 ppb]) in only 2 of 806 composite samples (one sample each from Atlanta, Georgia and Dover, Delaware) (Trotter and Dickerson 1993). In another statistically based FDA study in 1992-93, endrin was not found as a violative residue in any of 710 domestic or 949 imported pear samples (Roy et al. 1995). Endrin was not reported among the pesticides detected in a 1994 FDA survey of pesticide levels in 160 samples of catfish, crayfish, shrimp, trout, salmon, oysters, and various other species from important aquaculture areas of the United States (FDA 1995). Comparable results were found in similar studies conducted by the FDA in 1990-93 (FDA 1995).

Because of the persistence of endrin in the environment and its potential to bioconcentrate significantly in aquatic organisms, there has been continued concern over the levels of endrin in fish and shellfish. This concern, however, appears to be limited primarily to specific sites where endrin was used heavily in agriculture or was discharged by industrial plants. In 1963, at the height of agricultural endrin use, endrin levels in catfish poisoned by endrin exceeded 4 ppm (4,000 ppb) during a fish kill (Mount and Putnicki 1966). Endrin was detected in 2 species of commercial *Penaeus* shrimp collected at 21 of 31 stations in the Calcasieu River Estuary in Louisiana, a Gulf Coast estuary receiving both industrial discharges, and urban and agricultural runoff (Murray and Beck 1990). The maximum, mean, and median concentrations of endrin reported were 9.47, 1.07, and 0.25 ppm (9,470, 1,070, and 250 ppb), respectively. Several more recent national studies, however, indicate that contaminated fish or shellfish currently are not a likely source of potentially high human exposure to endrin. In the National Contaminant Biomonitoring Program, maximum endrin concentrations in whole fish from around the United States for the periods 1976-77, 1978-79, 1980-81, and 1984 were 0.40, 0.11, 0.30, and 0.22 ppm (400, 110, 300, and 220 ppb), respectively. Corresponding geometric mean concentrations were $\leq$0.01 ppm (10 ppb) (Schmitt et al. 1985, 1990). The percentage of stations where detectable endrin residues were present also showed a relatively steady decline from 47.2% in 1976-77 to 28% in 1984. The maximum concentration of 0.22 ppm (220 ppb) in 1984 was recorded near Memphis in the vicinity of the Velsicol Chemical Company. In portions of the Mississippi Delta within or bordering the Yazoo National Wildlife Refuge, endrin was found at the 0.01 ppm (10 ppb) detection limit in whole-body tissue samples from such rough fish as carp, smallmouth buffalo, bowfin, and spotted gar collected in 1988 (Ford and Hill 1991). In the 1986 National Study of Chemical Residues in Fish conducted by the EPA, endrin was detected in fish tissue samples at 11% of the 362 sites surveyed. The maximum, mean, and median concentrations of endrin reported were

0.162 ppm, 0.002 ppm, and not detected (<0.0025 ppm) (162, 2, and <2.5 ppb), respectively (EPA 1992b).

Endrin concentrations also have been monitored in several studies in the Great Lakes region. Endrin was detected in 8 fish species from 3 Great Lakes-influenced rivers in Michigan at average concentrations ranging from not detected (detection limit not specified) to 8.03 ppb wet weight (Giesy et al. 1994). Average concentrations exceeded 1.5 ppb for samples from only 2 of 23 species/site combinations and were less than 0.5 ppb for samples from 17 of 23 species/site combinations. Endrin was detected (detection limit 0.02 ppm [20 ppb] wet weight) in 5 of 10 samples of lake trout (mean concentration 0.03±0.01 ppm [30±10 ppb]) collected in Lake Michigan in 1982 (Miller 1993). It was not detected in 10 samples of lake trout collected in Lake Superior or in 18 samples of chinook salmon collected in Lake Michigan. Endrin was not detected (detection limit 2 ng/g [ppb] wet weight) in 16 skinless fillets of both rainbow trout *(Oncorhyncus mykiss*) and black bullheads *(Ameiurus melas)* cultivated for 6 and 3.5 months, respectively, in Lake Ontario waters (Buttner et al. 1995). Endrin also was not detected (detection limit not specified) in samples of whole Zebra mussels *(Dreissena polymorpha)* from populations infesting two power generating stations in Lake Erie (Doherty et al. 1993).

Endrin has been detected in several marine fish species in regional or state monitoring studies. From 1990 to 1993, endrin was found in 40 of 47 whole or fillet samples of red drum *(Sciaenops ocellutus)* at 2 of 4 sites along the South Carolina coast, at mean concentrations of 5.61±8.94 and 0.65±3.67 ppb wet weight (Mathews 1994). In this same study, endrin was found in 33 of 74 flounder *(Pamlichthys lethostigma)* samples, and in 19 of 58 seatrout *(Cynoscion nebulosus)* samples at only one coastal site, at mean concentrations of 0.14±0.81 and 2.68±11.13 ppb, respectively. Endrin was detected in all of 10 liver tissue samples from cod *(Gadus morhua)* in the Northwest Atlantic at a mean concentration of 9 ppb (range, 5-19 ppb), but not in muscle or ovary samples (Hellou et al. 1993).

There may be a potential for contamination of fish and wildlife in the vicinity of hazardous waste sites. Endrin was detected in fish samples collected at 4 of the 102 NPL sites and in game animal samples collected at one of the 102 NPL sites where endrin has been detected in some environmental medium; however, levels of contamination were not reported (HazDat 1996).

Endrin was not detected (detection limit 0.005 ppm, wet weight) in liver samples of 118 mink from declining populations in coastal plain regions of Georgia, North Carolina, and South Carolina (Osowski et al. 1995). These results were not significantly different from levels found in nondeclining control populations (n= 46, median concentration 0.012 ppm, maximum concentration 0.49 ppm) from the Piedmont areas of these states. Endrin also was not detected (detection limit 0.01 ppm wet weight) in earthworms from 9 confined disposal facilities bordering the Great Lakes (Beyer and Stafford 1993).

No information was found on concentrations of endrin aldehyde or endrin ketone in other environmental media.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Endrin is no longer registered for use in the United States. Consequently, the current potential for exposure of the general population to endrin appears to be very limited and will likely continue to diminish even more over time. Members of the general population may be exposed to very low levels of endrin through ingestion of contaminated foodstuffs, particularly those that are imported from areas where endrin is still being used. However, the FDA has concluded that endrin is no longer present in the environment to the extent that it may be contaminating food or feed at levels of regulatory concern (USDA 1995). Several studies indicate that human exposures are far below the levels of concern for human health. Based on results of FDA Total Diet Studies conducted from 1978 to 1982, estimated average dietary intakes were <0.001 (µg /kg (ppb) body weight/day for infants and toddlers for all 5 years (Gartrell et al. 1986). However, actual intakes must have been lower than these estimates because the reported average dietary intakes were based on the mean concentration of the positive samples only. A report summarizing the FDA Total Diet Studies from April 1982 to April 1984, indicated an estimated daily intake for 6-l l-month-old infants of 0.0003 (µg /kg (ppb)body weight/day for that period, with estimated daily intakes for 14-16-year-old males and 60-65-year-old females essentially zero (Gunderson 1988). Endrin intakes, in (µg /kg (ppb) body weight/day, estimated from the Total Diet Study analyses, were <0.000l, <0.000l, and 0.0001 in FY 1989 for 6-l l-month-old infants, 14-16-year-old males, and 60-65-year-old females, respectively (FDA 1990), and <0.000l in FY 1991 for all age categories (FDA 1992). Estimated endrin intakes were not reported for FY 1990 (FDA 1991). In an overall summary of FDA Total Diet Studies for the 5-year period 1986-91, average dietary intakes of endrin for 8 age/sex groups (6-l l-month-old infants, 2-year-old children,

14-16-year-old males and females, 25-30-year-old males and females, and 60-65year-old males and females) were all estimated to be <0.0001 μg/kg (ppb) body weight per day, less than 0.03% of the EPA oral RfD of 0.3 (μg /kg (ppb) body weight per day (FDA 1993). In Canada, where endrin was registered for use from 1954 to 1990, a dietary intake study estimated the adult annual intake of endrin at approximately 32 (g (0.001 (μg /kg [ppb] body weight/day) (Davies 1988).

Although endrin bioaccumulates significantly in aquatic organisms (ASTER 1995; EPA 1980a; Metcalf et al. 1973), recent studies indicate that in the United States endrin levels in fish and shellfish are not of concern for human health (EPA 1992a; Ford and Hill 1991; Murray and Beck 1990; Schmitt et al. 1985, 1990). Dietary exposures to endrin from domestic fish were estimated from 1984 to 1988 FDA surveillance data to be $1.7x10m^{-5}$ (μg /kg (ppb) body weight/day (Ahmed et al. 1993). At present, there are no fish consumption advisories for endrin in effect in the United States (EPA 1995b).

The most recent National Human Adipose Tissue Survey did not detect endrin in adipose tissues from the general U.S. population (Stanley 1986). Endrin also was not detected in adipose breast tissue from breast cancer patients (n=5) or controls (n=5) in the United States (Djordjevic et al. 1994). A 1984 study based on autopsied adipose tissue from 141 cadavers from six Canadian Great Lakes municipalities showed no detectable concentrations of endrin (detection limit 2.4 ppb) (Williams et al. 1988). In a 1990-91 survey, only very low levels of endrin (average concentration 3.27 ng/g (ppb); range 0.23-8.56 ng/g [ppb] lipid) were found in adipose tissue samples from 3 of 41 residents of British Columbia, Canada, where endrin was registered for use from 1954 to 1990 (Teshke et al. 1993).

Endrin has been detected in the milk of lactating women living outside the United States; however, no data from the United States could be located. Data from other countries indicate that there is some correlation between the levels of endrin used in or transported to an area and concentrations found in breast milk. Endrin was not detected in breast milk samples from a remote area of Papua, New Guinea (Spicer and Kereu 1993). In a recent investigation of Inuit exposure to organochlorine pesticides through the aquatic food chain in arctic Quebec, endrin was detected in only 1 of 107 breast milk samples from Inuit women, at a concentration of <8 ng/g (ppb) in milk fat, and in none of 50 samples from southern Quebec Caucasian women (Dewailly et al. 1993). In France, where endrin has not been used for over 20 years, endrin was detected in 8 of 20 human milk samples collected 20-90 days after parturition. Concentrations ranged from 0.02 to 0.84 ppm (20-840 ppb) in milk fat,

with a mean concentration of 0.06 ppm (60 ppb) (Bordet et al. 1993). Higher levels of endrin were found in human milk in a study conducted in Jordan, where endrin has been widely used over the past 40 years (Alawi et al. 1992). In this study, endrin was detected in samples from 3 of 15 donors at concentrations ranging from 0.26 to 6.24 ppm (260-6,240 ppb) in milk fat. The median and maximum daily intakes of endrin for breast-fed infants were estimated to be 1.55 and 12.70 mg/kg (ppm) (1,550 and 12,700 ppb) body weight, respectively. The relevance of these findings to the U.S. population is unclear.

Although all uses of endrin in the United States were canceled by 1991 (Bishop 1984, 1985, 1986; EPA 1993e; USDA 1995), occupational exposures to endrin, endrin aldehyde, and endrin ketone may occur among workers involved in the handling and treatment of materials at hazardous waste sites, and among agricultural workers at sites formerly treated with endrin. No information was found in the available literature on current occupational exposures. In the past, exposures of agricultural workers were significant. Seasonal agricultural workers dusting potatoes with 1% endrin dust were calculated to be exposed to a dermal dose of 2.0 mg/kg (ppm) body weight/day and an inhalation dose of 0.04 mg/kg (ppm) body weight/day at a time when agricultural use of endrin was near its peak (Wolfe et al. 1963).

Occupational exposure to endrin was not evaluated during the National Occupational Exposure Survey (NOES) conducted from 1981 to 1983 or its predecessor, the National Occupational Hazard Survey (NOHS) conducted from 1972 to 1974. The surveys conducted by NIOSH were designed to provide data necessary to describe potential exposure agents and profile health and safety programs in United States workplaces. According to OSHA (1974), the g-hour TWA permissible exposure level (PEL) for endrin is 0.1 mg/m^3. NIOSH (1992) advises that the recommended exposure limit for occupational exposure to endrin not exceed 0.1 mg/m^3 for a 10-hour TWA workday. In addition, the American Conference of Government Industrial Hygienists (ACGIH) recommended threshold limit value (TLV-TWA) for occupational exposure is 0.1 mg/m^3 (ACGIH 1988).

No information could be found in the available literature on general population or occupational exposures to endrin aldehyde or endrin ketone.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Endrin has not been registered for use in the United States since voluntary cancellation of its final use as a toxicant on bird perches in 1991 (USDA 1995). All other uses of endrin were voluntarily canceled by 1986 (Bishop 1984, 1985, 1986; EPA 1993e; USDA 1995). Therefore, there are currently no population groups exposed to high levels of endrin associated with its application as a pesticide agent. Populations exposed to higher than background concentrations of endrin, endrin aldehyde, or endrin ketone include those living near hazardous waste sites where these compounds are present. Skin contact with or ingestion of endrin-contaminated soil may be an important source of exposure for children living near such hazardous waste sites. In addition, groundwater may be a source of exposure to endrin for adults and children if they consume drinking water from contaminated wells.

5.7 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 endrin is available. Where adequate information is not available, ATSDR, in conjunction with the 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 endrin.

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

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of endrin have been sufficiently documented to permit estimation of its environmental fate (ACGIH 1986; EPA 1981a, 1984a; HSDB 1995; Verschueren 1983). More complete information on the physical and chemical properties of endrin aldehyde and endrin ketone would be useful.

Production, Import/Export, Use, Release, and Disposal. Endrin is no longer registered for use and is not likely to be imported into the United States (Bishop 1984, 1985, 1986; EPA 1993e; HSDB 1995; USDA 1995). Consequently, the risk of human exposure to endrin (and to endrin aldehyde and endrin ketone, which occur as impurities or transformation products of endrin) from these activities is expected to be minimal. However, recent information suggests that several organochlorine pesticides that have been banned from use or have been voluntarily cancelled in the United States are still being manufactured in large quantities for export abroad (FASE 1996). Unfortunately, only 25% of the pesticides exported from 1992 to 1994 could be definitively identified (FASE 1996). Information as to whether endrin is currently being produced and the export volumes for endrin are needed to evaluate existing routes of exposure for the general population and occupationally exposed individuals.

Endrin and endrin aldehyde are listed as hazardous wastes and disposal of wastes is controlled by a number of federal regulations. Past disposal methods have included landfills (EPA 1987c). Chemical treatment (reductive dechlorination) and incineration are possible disposal methods (HSDB 1995; IRPTC 1985). Existing information on disposal appears adequate. No information was found on disposal of endrin ketone; however, because endrin is no longer used in the United States, current levels of endrin ketone in wastes should be minimal and additional information on disposal is not needed.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1993, became available in 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions. No information was available from the Toxic Release Inventory (TRI) on production because endrin, endrin aldehyde, and endrin ketone are not among the chemicals that facilities are required to report (EPA 1995a).

Environmental Fate. Endrin released to the environment partitions to several environmental compartments; air (Chan et al. 1994; Eisenreich et al. 1981; Nash 1983), soil and sediment (Kenaga 1980; Sharom et al. 1980a; Swann et al. 1983), groundwater (Cohen 1986; EPA 1989; HazDat 1996) and biological organisms (ASTER 1995; EPA 1980a; Metcalf et al., 1973; Leblanc 1995). If released to soils, some endrin partitions to the atmosphere via volatilization from soil surfaces. Once in the

atmosphere, endrin is associated primarily with particulate matter based on its low vapor pressure and high K_{oc} (Kenaga 1980). Small amounts of endrin in the atmosphere may also exist in the vapor phase (Eisenreich et al. 1981). In addition to volatilization, endrin may be lost via photodegradation and heat transformation from soil and plant surfaces exposed to bright sunlight (Burton and Pollard 1974; EPA 1979g; Knoevenagel and Himmelreich 1976; Phillips et al. 1962; Zabik et al. 1971). The remainder is adsorbed strongly to soil where it may persist for extended periods (half-life of months to years), depending on soil conditions (Nash and Woolson 1967). Leaching of endrin into groundwater is not expected to occur very rapidly under most circumstances, due to the compound's high sorption characteristics (Kenaga 1980; Swann et al. 1983).

Endrin released to water will adsorb to sediments or bioaccumulate in fish and other aquatic organisms. Both bioaccumulation and biomagnification of endrin were reported to occur in an aquatic laboratory microcosm system (Metcalf et al. 1973). In terrestrial ecosystems, endrin transformation products (endrin ketone, endrin aldehyde, and endrin alcohol) have been measured in plants grown on endrin-treated soil (Beall et al. 1972; Nash and Harris 1973).

Information on biodegradation of endrin in soil under aerobic conditions exists, but degradation products are not identified (Nash and Woolson 1967; Patil et al. 1970). Anaerobic biodegradation, which may occur in river bottoms and in Superfund sites, has been studied in the laboratory, but not under natural conditions (Gowda and Sethunathan 1976; Maule et al. 1987). Further information on these processes, including identification of degradation products, would be useful in determining potential mechanisms and the potential for contamination of groundwater by endrin released from soils.

No experimental data could be found in the available literature on the environmental fate of endrin aldehyde or endrin ketone, which occur as impurities in or degradation products of endrin. Estimated physical and chemical constants (see Table 3-2) allow some prediction of fate and transport processes for these compounds. However, additional experimental data on the physical and chemical properties of endrin aldehyde and endrin ketone would be useful in providing a clearer picture of their environmental fate.

Bioavailability from Environmental Media. Absorption of endrin following inhalation has been shown to occur in laboratory animals (Treon et al. 1955) and endrin can also be absorbed by humans

following inhalation of contaminated air (Hoogendam et al. 1965). Since endrin has a low volatility, inhalation is probably not a major concern except for potential inhalation of contaminated dust at hazardous waste sites.

Endrin has also been shown to be absorbed after ingestion by humans (Coble et al. 1967; Curley et al. 1970; Kintz et al. 1992; Rowley et al. 1987; Runhaar et al. 1985; Waller et al. 1992; Weeks 1967); however, no studies were located on the rate or extent of absorption that occurs in orally exposed humans or animals. Exposure to endrin through ingestion of contaminated drinking water is not expected to be an important source of concern because the compound has only rarely been detected in drinking water (Schafer et al. 1969; Wnuk et al. 1987). Since endrin is tightly bound to soil particles, ingestion of endrin-contaminated soil, particularly by children, may be an important route of exposure near hazardous waste disposal sites that contain endrin.

Little information was available regarding the absorption of endrin following dermal exposure. Agricultural worker exposure studies demonstrated that dermal exposure was significantly greater than inhalation exposure (Wolfe et al. 1963). Dermal exposure of rats and rabbits to endrin indicates that percutaneous absorption of endrin occurs (Gaines 1960; Treon et al. 1955). Information regarding the bioavailability of endrin from both ingestion of soil-bound endrin and dermal contact with endrin-contaminated soils would be helpful, particularly for population living near hazardous waste sites.

No information could be found in the available literature on the bioavailability of endrin aldehyde or endrin ketone. This information would be useful for assessing the potential for exposure to these compounds from various environmental media, particularly in the vicinity of hazardous waste sites where endrin ketone has been found in surface water, groundwater, leachate, soil, and sediment (HazDat 1996).

Food Chain Bioaccumulation. Endrin has been shown to bioaccumulate significantly in a variety of aquatic organisms (Argyle et al. 1973; ASTER 1995; Hanson et al. 1977; Jarvinen and Tyo 1978; Lowe 1966; Mason and Rowe 1976; Metcalf et al. 1973; Mount and Putnicki 1966; Schimmel et al. 1975; Tyler-Schroeder 1979; Vance and Drummond 1969). The results of an aquatic ecosystem study suggest that biomagnification of endrin is relatively low compared to other organochlorine pesticides (Metcalf et al. 1973). Data on bioaccumulation and bioconcentration of endrin generally appear to be adequate, particularly since endrin has not been used in the United States since the

mid-1980s. Information on its bioconcentration by additional snail species would be useful as the pouch snail exhibited the highest BCF value and may serve as an environmental indicator of endrin contamination.

No experimental information could be found in the available literature on biocdncentration or bioaccumulation of endrin aldehyde or endrin ketone. Estimated BCFs indicate some potential for bioaccumulation for both compounds. No information was found on concentrations of either of these compounds in aquatic systems, but it would be expected that levels would be nondetectable or very low, and that they would continue to decline. Therefore, additional information is not needed at this time.

Exposure Levels in Environmental Media. Endrin has been reported to occur at very low levels in food (Davies 1988; FDA 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995; KAN-DO Office and Pesticides Team 1995; Minyard and Roberts 1991; Roy et al. 1995; Schattenburg and Hsu 1992; Trotter and Dickerson 1993; Yess et al. 1993) and air (Bidleman 1981; Kutz et al. 1976; Nash 1983). It has only rarely been detected in a number of national and regional surveys of drinking water supplies (Schafer et al. 1969; Wnuk et al. 1987). Because endrin is no longer commercially used in the United States, future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low. There are possibilities of exposure from foodstuffs imported from countries that still use endrin (Hundley et al. 1988). There may also be some localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin (Cohen 1986; EPA 1989; HazDat 1996; Plumb 1987). Additional data on environmental concentrations of endrin, endrin aldehyde, and endrin ketone from these possible sources of exposure would be useful.

Reliable monitoring data for the levels of endrin, endrin aldehyde, and endrin ketone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of these substances in the environment can be used in combination with their known body burdens to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Metabolism of endrin in humans is relatively rapid compared with other organochlorine pesticides. Thus, levels in human blood and tissue may not be reliable estimates of exposure except after very high occupational exposures or acute poisonings (Runhaar et al. 1985).

Endrin was not found in adipose tissue samples of the general U.S. population (Stanley 1986), or in adipose breast tissue from breast cancer patients in the United States (Djordjevic et al. 1994). Endrin has been detected in the milk of lactating women (Alawi et al. 1992; Bordet et al. 1993; Dewailly et al. 1993), but no data from the United States could be located. Data on the concentrations of endrin in breast milk from U.S. women would be useful. No information was found on levels of endrin, endrin aldehyde, or endrin ketone in blood and other tissues of people near hazardous waste sites. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for endrin, endrin aldehyde, or endrin ketone were located. These substances are not currently among the compounds for which a subregistry has been established in the National Exposure Registry. These substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances.

5.7.2 Ongoing Studies

A search of the Federal Research in Progress database (FEDRIP 1995) indicates that no research studies are in progress to fill the data needs identified in Section 5.7.1.

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

Endrin is relatively nonvolatile with a vapor pressure (25 (C) of only $2x10^{-7}$ torr. Its water solubility (25 ºC) is 0.20 mg/L, which is much less than the water solubilities of most environmentally and toxicologically significant halogenated alkanes and alkenes, though similar to values for some other common organochlorine pesticides of similar structure. It has a high octanol/water partition coefficient (log K_{ow} = 5.6), implying a strong affinity for lipids. Endrin aldehyde also has a low vapor pressure ($2x10^{-7}$ torr at 25 ºC). Its water solubility (25 ºC) is 50 mg/L and its octanol/water partition coefficient value is approximately the same as that of endrin. There are few corresponding data for endrin ketone; based on its chemical structure, log K_{ow} was calculated to be 4.99 (SRC 1995b) and this is in line with those calculated or measured for endrin aldehyde. These properties affect the manner in which biological samples are analyzed for endrin, endrin aldehyde, and endrin ketone. Specifically, the low volatilities of these compounds preclude their removal from biological samples by purging, and their lipophilicity complicates their removal from lipid fractions of such samples.

Several basic steps are involved in determining high-boiling lipophilic analytes such as endrin and its oxidized derivatives (aldehyde and ketone) in biological materials. The purpose of most of these steps is to remove the analyte(s) from the biological matrix into a concentrated, interference-free form suitable for analysis. Several major steps may be involved.

Tissue may have to be prepared (dried and homogenized) by grinding with sodium sulfate or materials such as reverse phase column packing. Prepared tissue or biological fluids are extracted with an organic solvent to remove analyte, usually with significant amounts of biological matter. The extract may be solvent-exchanged to a solvent more suitable for analysis.

A clean-up step may be employed using gel permeation chromatography, Florisil, silica gel or alumina column fractionation, or solid phase extraction (SPE).

Solvent evaporation/analyte concentration steps may be necessary. Diethyl ether has been a widely used solvent for the extraction of lipophilic organic analytes such as endrin and endrin aldehyde from biological fluids (Zlatkis and Kim 1976). Homogenization of tissue with the extractant, and lysing of cells improves extraction efficiency. When, as is often the case, multiple analytes are determined using solvent extraction, selective extraction and loss of low-boiling compounds can cause errors. The loss of volatile internal standards often results in a recovery of >l00% (Tang et al. 1993). The commercial availability of highly purified solvents has largely eliminated problems with solvent impurities, although high costs, solvent toxicities, and restrictions on spent solvent disposal must be considered. Extraction, the first step in the overall clean-up process, places the analyte in a form and matrix suitable for introduction into the instrument used for analysis. Clean-up of biological samples may often be complex and involve a number of steps (Walters 1986).

In favorable cases, clean-up of biological samples containing endrin and/or endrin aldehyde can be simplified and made faster by using SPE (Marble and Delfino 1988). With this technique, solvent and sample are passed over disposable, prepacked, bonded-phase columns which either retain analyte (for subsequent elution) or retain interfering substances, while allowing for the passage of analyte. Tissue samples ground with reverse phase packing material, placed in a column over activated Florisil, and eluted using acetonitrile resulted in high extraction efficiency and clean-up in one step for crayfish and catfish samples (Long et al. 1991b; Lott and Barker 1993). Long et al. (1991a) also applied this technique to screening of chlorinated pesticides (including endrin) in beef fat. Di Muccio et al. (1990) have shown that sulfuric acid-impregnated Kieselguhr (diatomaceous earth) in SPE columns can improve the chromatography of organochlorine pesticides when the matrix contains fatty materials.

A recent study (Viana et al. 1994) was conducted to examine the impact on recoveries of endrin, endrin aldehyde, and endrin ketone as a result of treatment of extracts with sulfuric acid, potassium

hydroxide, or chromium (VI) oxide. The treatments are sometimes used in clean-up procedures or have been impregnated into adsorbents. Their data showed that endrin is unstable to acid and oxidizing conditions, but is stable in alkali. Endrin aldehyde is stable under acidic conditions, shows some loss with alkali, and is completely decomposed by oxidative conditions. Endrin ketone is stable under acidic and oxidizing conditions, but not to alkaline conditions. It is extremely important that the performance of any preparation scheme be validated with standard compounds before use. An apparently poor recovery for endrin, for example, could be related to its transformation as a result of the procedure.

Procedures for the measurement of endrin and endrin aldehyde in biological samples are the same as those used for other organochlorine pesticides in similar samples. Endrin, endrin aldehyde and endrin ketone are measured by gas chromatography (GC) with electron capture detection (ECD) (EPA 1982a) or GC/MS detection (EPA 1982b). All recently reported work (approximately the past 10 years) used one or both of these techniques. GC/MS should be used to confirm any positive GU/ECD results, since organochlorine pesticides other than endrin respond to the ECD. As already stated, any extraction or processing steps that involve alkaline or acidic conditions may result in the decomposition of endrin or its transformation products (EPA 1982b; Viana et al. 1994). Analytical methods for the determination of endrin, endrin aldehyde, or endrin ketone in human biological samples are given in Table 6-1.

6.2 ENVIRONMENTAL SAMPLES

Endrin and endrin aldehyde are determined in environmental samples by extraction with an organic solvent and GC analysis (e.g., EPA 1982a, 1982b). Various extractions procedures have been evaluated including separatory funnel shake-out and continuous extraction at different pH values (Valkenburg et al. 1989), use of a one-step extractor/concentrator (Harrington-Fowler 1991), and use of a device (“Soxtec”) that has advantages over traditional Soxhlet extraction (Lopez-Avila et al. 1993). Interferences may be eliminated by using silica, Florisil, or alumina column clean-up procedures (e.g., Cruz et al. 1993; Harrington-Fowler 1991). The clean-up of fatty materials as developed by Di Muccio and co-workers (1990) has been applied to vegetable oils (Di Muccio et al. 1991) for analysis of 18 organochlorine pesticides, including endrin. The relatively recent application

Table 6-1. Analytical Methods for Determining Endrin and Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Lipid material	Extraction with pet. ether, partition with acetonitrile, addition of satd. aq NaCl to back-extract pesticides to pet. ether, additional processing	GC/ECD or GC/MS	No data	No data	Walters 1986
Human viscera (endrin)	Extraction of homogenized sample with diethyl ether, volume reduction and clean-up using column chromatography on charcoal, alumina, and sodium sulphate; elution using ethyl ether; solvent removal and redissolution in acetone	TLC	No data	No data	Ganguly and Bhattacharyya 1973
Human serum (endrin)	Combination of serum with methanol followed by extraction with hexane/ethyl ether and clean-up using Florisil	GC/ECD	1 ppb	112.6–121.6 (16.6% RSD)	Burse et al. 1990
Human milk (endrin)	Mixing of milk with Florisil and elution with petroleum ether/dichloromethane (80:20, v/v); solvent removal and redissolution in hexane	GC/ECD, GC/MS	0.003 ppm (3 ppb)	No data	Alawi et al. 1992
Breast adipose (endrin)	Placement of adipose into extraction cell between layers of alumina followed by SFE with CO_2 and CO_2 modified with 5% dichloromethane; analyte recovery into cyclohexane; clean-up using neutral alumina	GC/ECD	10 ppb	73	Djordjevic et al. 1994

Table 6-1. Analytical Methods for Determining Endrin and Metabolites in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (anti-12-hydroxy-endrin glucuronide)	Addition of sodium metaperiodate to urine followed by heating to 70 °C for 45 minutes, addition of carbonate buffer, and extraction with hexane; confirmation of analyte by conversion to 12-ketoendrine with chromium trioxide in pyridine	GC/ECD	No data	92 at 10.5 ppm	Baldwin and Hutson 1980

GC = gas chromatography; GPC = gel permeation chromatography; ECD = electron capture detector; MS = mass spectrometry; MSD = mass selective detector; SFE = supercritical fluid extraction; TLC = thin layer chromatography

of supercritical fluid extraction (SFE) (Hopper and King 1991; Lopez-Avila et al. 1990; Snyder et al. 1992) to a large number of both organochlorine and organophosphorus pesticides (including endrin and its aldehyde and ketone) showed the efficacy of this method, although it was determined to be more expensive than traditional Soxhlet methodology. SFE involves the use of carbon dioxide at high pressure for extraction. The technique is potentially advantageous because of the mildness of the extraction, and because solvent removal is easy (reduced pressure simply allows CO_2 to convert from a supercritical state to a gas). As the emphasis shifts towards reduced use of organic solvents in general, and chlorinated solvents in particular, because of environmental concerns and costs associated with disposal, SFE can provide a quick payback and continued savings.

As noted above for biological sample analysis, detection of endrin and its derivatives may be accomplished using either ECD or mass spectrometry (MS). The same concerns about chemical transformation of endrin, endrin aldehyde, and endrin ketone during sample preparation as discussed for biological samples are valid for environmental samples. Bentabol and Jodral (1995) showed that the use of sulfuric acid completely destroyed endrin during its isolation from cheese. Many of the EPA methods, such as Method 508 for drinking water (EPA 1988e), include steps to measure the degradation of endrin into endrin aldehyde and endrin ketone that results from the procedure. Active sites within the GC injector or column can also impact conversions (Grob and Wagner 1993). An immunoassay method has been reported as a screening procedure for endrin in selected vegetables (Wigfield and Grant 1992). Table 6-2 gives the analytical methods for the determination of endrin and the aldehyde and ketone in environmental samples.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of endrin is available. Where adequate information is not available, ATSDR, in conjunction with the 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 endrin.

Table 6-2. Analytical Methods for Determining Endrin and Transformation Products in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air[a]	Low volume sampler with glass fiber filter and ethylene glycol trap	GC/ECD	No data	No data	Harkov 1986
Air[a]	Adsorption/solvent extraction with polyurethane foam plug	HRGC/MS	No data	No data	Ligocki and Pankow 1985
Water	Extracted with dichloromethane/hexane, dry with sodium sulfate, concentrated.	GC/ECD	0.05 ppb	No data	ASTM 1988
Water	Extracted with dichloromethane, exchanged to hexane, concentrated.	GC/ECD	0.006 ppb	95±2.1[b]	EPA 1982a
Water	Extracted with dichloromethane at pH 11 and 2, concentrated.	GC/MS	No data	No data	EPA 1982b
Water	Solid phase extraction with Empore disk. Eluted with ethyl acetate. Dried with sodium sulfate, concentrated.	GC/ECD	4 ppt	86	Tomkins et al.1992
Water	Solid phase extraction. Eluted with pentane, concentrated.	GC/ECD	0.1 ppb	100	Russo et al. 1993
Water	Solid phase extraction followed by supercritical fluid extraction.	GC/MS	No data	136	Tang et al. 1993
Water	Acidified water. Extracted through Empore Disk with ethyl acetate followed by dichloromethane. Dried with sodium sulfate, concentrated.	GC/MS	No data	126–128	Kraut-Vass and Thoma 1991
Well water	Extracted/concentrated using reverse phase SPE columns. Eluted analytes withmethanol.	GC (detection not specified)	No data	58–67	Hogmire et al. 1990
Runoff water	Samples solvent extracted with methylene chloride, concentrated and cleaned up with Florisil.	GC/ECD	No data	No data	Marsh 1993

Table 6-2. Analytical Methods for Determining Endrin and Transformation Products in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sea water	Samples filtered then extracted with pentane. Solvent dried then partitioned with sodium hydroxide. Organic fraction cleaned up with alumina and silica.	GC/ECD	<0.1 ppt	97	Cruz et al. 1993
Soil and solid	Extracted from sample, waste clean-up	GC/MS	No data	No data	EPA 1986b
Soil and solid	Extracted from sample, waste clean-up	HRGC/MS	No data	No data	EPA 1986c
Soils	1) Supercritical fluid extraction with CO_2 premixed with 3% methanol.	GC/MS	No data	97	Snyder et al. 1992
	2) Soil mixed with sodium sulfate. Soxhlet extracted with 1:1 hexane/acetone. Dried extracts with sodium sulfate, concentrated. Solvent exchanged to MTBE.	GC/ECD		97	
	3) Sonication extraction with 1:1 dichloromethane/acetone. Dried extracts with sodium sulfate, concentrated. Solvent exchanged to MTBE.				
Soils	Liquid extraction by concentric rotation. Extract dried with anhydrous sodium sulfate.	GC/ECD	2–30 ppb	90–110	Carey et al. 1976
Milk	Extraction with ethyl acetate-methanol-acetone (2:4:4). Clean-up with solid-phase extraction.	GC/ECD	≈2 ppb	108–116	Prapamontol and Stevenson 1991

Table 6-2. Analytical Methods for Determining Endrin and Transformation Products in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Milk	Solid phase extraction of milk mixed with 0.5% toluene. Eluted with hexane.	GC/ECD	No data	75.55	Barcarolo et al. 1988
Human milk	Homogenized sample with Florisil. Eluted with 80:20 pet, ether/ dichloromethane. Evaporated eluate. Dissolved residue in hexane.	GC/ECD	No data	No data	Alawi et al. 1992
Human milk (?)	Sample previously cleaned up by Florisil added to sulfuric acid-impregnated Kieselguhr SPE. Eluted with pet. ether. Transferred to isooctane.	GC/ECD	No data	Endrin converted to ketone	Di Muccio et al. 1990
Food	Food was chopped, then homogenized with dichloromethane. Dried with sodium sulfate. Solvent exchanged to cyclohexane. Sample cleaned up by GPC. Concentrated to 1.0 mL isooctane.	GC/ECD	10 ppt	No data	Davies 1988
Food	Blended food mixed with pelletized diatomaceous earth. Added mixture to extraction column. Extracted with SC-CO_2. Eluted nonfat samples from Florisil trap with acetone.	GC/ECD	No data	82–99	Hopper and King 1991
Olive oil	Oil dissolved in hexane, then transferred to SPE column. Eluted with acetonitrile. Residue after drying cleaned up using Florisil. Hexane/benzene/ethyl acetate used to elute fraction for analysis.	GC/ECD	No data	101	Di Muccio et al. 1991

Table 6-2. Analytical Methods for Determining Endrin and Transformation Products in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Apple	Samples blended/filtered and brought up in acetone. Partitioned into methylene chloride, dried and concentrated.	ELISA	10–30 ppm	23–82 (spiked samples)	Wigfield and Grant 1992

[a] Method applicable to chlorinated pesticides similar to endrin, such as aldrin and dieldrin
[b] Relative recovery, percent ± standard deviation, percent

ECD = electron capture detector; ELISA = enzyme-linked immunosorbent assay; GC = gas chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; MTBE = methyl-*tert*-butyl ether; ppb = parts per billion; ppm = parts per million; ppt = parts per trillion; SPE = solid phase extraction

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Endrin has been measured in various human samples including tissues, blood, and breast milk (Alawi et al. 1992; Burse et al. 1990; Djordjevic et al. 1994; Ganguly and Bhattacharyya 1973). Methods have been published for use with animal tissues and could serve as the basis for work with human samples (see Table 6-l). The determination of the glucuronide of anti-12-hydroxyendrin in urine (Baldwin and Hutson 1980) provides for a biomarker of exposure that might be specific to endrin; anti-12-hydroxyendrin can undergo dehydrogenation to form 12-ketoendrin. If a concurrent exposure to keto-endrin occurred, 12-hydroxyendrin could be formed by an *in vivo* reduction of 12-ketoendrin. The extent to which this could occur is not known. Baldwin and Hutson (1980) claimed 92% recovery for the method and did not detect any interferences in its application to urine from workers in an endrin synthesis plant. Based on this information, the method appears to be reliable. Work has been conducted to show that, as a result of endrin-induced oxidative stress, certain lipid metabolites are excreted in the urine of rats. Thus the levels of formaldehyde, acetaldehyde, malondialdehyde, and acetone were excreted in significantly increased quantities following exposure to endrin. These data probably reflect the response of the organism to a general xenobiotic-induced oxidative stress, and are not endrin-specific. In addition, various neurological effects can result from exposure to endrin (see Section 2.6.2), but these are not specific to endrin, endrin aldehyde, or endrin ketone.

Cyclodiene pesticides, of which endrin and its oxidized analogs are representative, can also be estimated by receptor-assay technique. Cyclodiene pesticides exert their mode of action by altering central nervous system membrane ion transport. In work reported by Saleh et al. (1993), a labeled amino acid, GABA, that binds to the chloride channel receptor is displaced by endrin (and other similar molecules), and thus serves as an assay for these pesticides. The GABA receptor was shown to be a potentially useful biomarker for organochlorine pesticides such as lindane, toxaphene, endrin, chlordane, and others. The assay involves small quantities of blood (0.1 mL), and requires only that

the plasma be separated from the blood for direct analysis. Sensitivity for several cyclodiene pesticides was in the low-to-mid-picomole range.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The MRL for chronic oral exposure to endrin is 0.0003 mg/kg/day. Assuming a 70-kg individual and oral intakes of either 2 L/day of water or 2 kg/day of food, analytical methods would need to have sensitivities below 10.5 ppb (10.5 (μg /L or 10.5 (μg /kg) in either medium. The methods reported for drinking water have limits of detection (LODs) far below this value and are adequate (ASTM 1988; EPA 1982a, 1988e; Russo et aI. 1993; Tomkins et al. 1992). The needed sensitivities can be achieved for some foods (Alawi et al. 1992; Davies 1988; Nakamura et al. 1994; Prapamontol and Stevenson 1991; Schmitt et al. 1985). The LODs of FDA methods (1994a, 1994b) are within a factor of 2-3 of those needed to measure chronic exposure but can be used to monitor intermediate acute exposure (MRL = 0.002 mg/kg/day) where LODs of 70 ppb are needed. Additional methods for foods are needed to measure concentrations relevant to the chronic oral MRL. Many of the reported methods have not been validated for the oxygenated derivatives of endrin (endrin aldehyde and endrin ketone). Although many of the methods should work for these derivatives, this needs to be shown. No MRLs have been established for inhalation exposures.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of endrin and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution CG and magnetic sector MS which gives detection limits in the low parts per trillion (ppt) range.

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of endrin and phenolic compounds in urine. These methods use high resolution GC and magnetic sector MS which gives detection limits in the low parts per trillion (ppt) range.

No ongoing studies concerning techniques for measuring and determining endrin, endrin aldehyde, or endrin ketone in biological and environmental samples were reported.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding endrin in air, water, and other media are summarized in Table 7-1.

ATSDR has derived an intermediate oral MRL of 0.002 mg/kg/day based on a laboratory animal study showing neurotoxic effects in dogs (Treon et al. 1955).

ATSDR has derived a chronic oral MRL of 0.0003 mg/kg/day based on a laboratory animal study showing neurotoxic effects in dogs (Kettering Lab 1969). The EPA reference dose for endrin is $3x10^{-4}$ mg/kg/day, and the critical dose is 0.025 mg/kg/day (IRIS 1995). Critical effects were occasional convulsions and mild histological lesions in the liver (Kettering Lab 1969). No EPA reference concentration exists for the compound.

The EPA has determined that endrin is not classified as to its human carcinogenicity (Group D) because the available information is inadequate to allow the classification (IRIS 1995). No cancer classifications exist for the IARC (no adequate data) (IARC 1987). The National Toxicology Program (NTP) has assigned endrin the carcinogen code N (negative) (NTP 1995).

Endrin is on the list of chemicals regulated based on "The Emergency Planning and Community Rightto-Know Act of 1986" (EPCRA) (EPA 1988a). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to endrin to institute engineering controls and work practices to reduce and maintain employee exposure at or below PELs. The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour TWA of 0.1 mg/m^3. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1989). Also, to prevent or reduce skin absorption, an employee's skin exposure to endrin must be prevented or reduced to the extent necessary in the circumstances through the use of gloves, coveralls, goggles, or other appropriate personal protective equipment, engineering controls, or work practices.

7. REGULATIONS AND ADVISORIES

Endrin is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Section 400-475, of the Code of Federal Regulations. For each point source category, endrin may be regulated as a group of chemicals controlled as Total Toxic Organics or may have a Zero Discharge Limitation. The point source categories for which endrin is controlled as a Total Toxic Organic include electroplating (EPA 1981), metal finishing (EPA 1983a), and aluminum forming (EPA 1983b). The point source category for which endrin has a specific Regulatory Limitation is endrin manufacturing (EPA 1977a). There are no point source categories for which endrin has a Zero Discharge Limitation.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), a 0 ppm food tolerance restriction is in place for endrin (EPA 1977b).

The Resource Conservation and Recovery Act (RCRA) identifies endrin as a hazardous waste in two ways: (1) when it exceeds a toxicity characteristic leaching procedure test concentration of 0.02 mg/L (EPA 1980a); and (2) when it is discarded as a commercial chemical product, off-specification species, container residue, or spill residue (EPA 1980a).

Table 7-1. Regulations and Guidelines Applicable to Endrin, Endrin Aldehyde, and Endrin Ketone

Agency	Description	Information	Reference
INTERNATIONAL			
WHO		NA	
IARC	Group (cancer ranking)	Yes	
NATIONAL			
Regulations:			
a. Air:			
OSHA	Permissible Exposure Limit (TWA)	0.1 mg/m^3 ($6.4x10^{-3}$ ppm)	29 CFR 1910.1000 OSHA 1974
	Short-term Exposure Limit (STEL)	0.3 mg/m^3 ($1.9x10^{-2}$ ppm) (15 min)	
	Skin Designation	Yes	29 CFR 1910.1000 OSHA 1974
b. Water:			
EPA/OW	Ambient Water Quality Criterion	$1x10^0$ µg/L (water & fish)	45 FR 79318 IRIS 1994
	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978a
	Reportable Quantities of Hazardous Substances: Section 311 of Clean Water Act	1 lb.	40 CFR 117.3 EPA 1979a
	Appendix D--NPDES Permit Application Testing Requirements (122.21)	Yes	40 CFR 122 EPA 1983c
	Form 2D	Yes	40 CFR 122 EPA 1983c
	Instructions - Form 2C	Yes	40 CFR 125 EPA 1979b
	Toxic Pollutant Effluent Standards	Yes	40 CFR 129.4 EPA 1977a
	Endrin Effluent Standards	0.004 µg/L 1.5 µg/L	40 CFR 129.102 EPA 1977a
	Identification of Test Procedures	Yes	40 CFR 136.3 EPA 1973
	Method 608 - Organochlorine Pesticides and PCBs	Yes	40 CFR 136 EPA 1973
	Method 625 - Base/Neutrals and Acids	Yes	40 CFR 136 EPA 1973
	Effluent Guidelines and Standards: Toxic Pollutants	Yes	40 CFR 401 EPA 1979c
	Pretreatment Regulations: Appendix B - 65 Toxic Pollutants	Yes	40 CFR 403 EPA 1986a

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)			
	Effluent Guidelines and Standards: Electroplating - Definitions of Total Toxic Organics	>0.01 mg/L	40 CFR 413.02 EPA 1981
	Effluent Guidelines and Standards: Steam Electric Power Generation - Appendix A - 126 Priority Pollutants	Yes	40 CFR 423 EPA 1982
	Effluent Guidelines and Standards: Metal Finishing - Definition of Total Toxic Organics	>0.01 mg/L	40 CFR 433.11 EPA 1983a
	Applicability: Description of the Organic Pesticide Chemicals Manufacturing Subcategory	Yes	40 CFR 455.20 EPA 1978b
	Effluent Guidelines and Standards: Aluminum Forming - Definition of Total Toxic Organics	>0.01 mg/L	40 CFR 467.02 EPA 1983b
EPA/ODW	National Primary Drinking Water Regulations: Effective Dates	Yes	40 CFR 141.6 EPA 1975
	Organic Chemicals Other Than Total Trihalomethanes, Sampling and Analytical Requirements	Yes	40 CFR 141.24 EPA 1975
	Public Notification	NA	40 CFR 141.32 EPA 1975
	National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels for Synthetic Organic Contaminants - Endrin	0.002 mg/L	40 CFR 141.61 EPA 1991a
	Variances and Exemptions From the Maximum Contaminant Levels for Organic and Inorganic Chemicals	NA	40 CFR 142.62 EPA 1976b
c. Food:			
d. Other:			
CPSC	Consumer product limits	NA	
EPA/OERR/CEPP	Reportable Quantity	1 lb.	40 CFR 302.4 EPA 1985a
	Emergency Planning and Notification: Appendix A - Extremely Hazardous Substances and Threshold Planning Quantities	500/10,000 lbs.	40 CFR 355 EPA 1987a

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA/OPTS	Pesticides Classified for Restricted Use	≥2%	40 CFR 152.175 EPA 1988b
	TSCA Reporting and Recordkeeping Hexachloronorbornadiene	Yes	40 CFR 704.102 EPA 1985b
	Fish Bioconcentration Test	Yes	40 CFR 797.1520 EPA 1985c
	Hazardous Waste Constituents Subject to Testing	Yes	40 CFR 799.5055 EPA 1984
	Standards for Pesticide Containers and Contaminants (Proposed)	Yes	54 FR 6712 EPA 1994a
EPA/OSW	Criteria for Classification of Solid Waste Disposal Facilities and Practices: Appendix I - Maximum Contaminant Levels (MCLs)	0.0002 mg/L	40 CFR 257 EPA 1979d
	Design Criteria	0.0002 mg/L	40 CFR 258.40 EPA 1991b
	Municipal Solid Waste Landfills: Appendix II - List of Hazardous Inorganic and Organic Constituents	0.1–20 µg/L (Practical Quantitation Limits for 2 Methods)	40 CFR 258 EPA 1991b
	Toxicity Characteristic	0.02 mg/L	40 CFR 261.24 EPA 1980a
	Discarded Commercial Chemical Products, Off-specification Species, Container Residues, and Spill Residues Thereof	Yes	40 CFR 261.33 EPA 1980a
	Identification and Listing of Hazardous Wastes: Appendix III - Chemical Analysis Test Methods	Yes	40 CFR 261 EPA 1980a
	Identification and Listing of Hazardous Wastes: Appendix VIII - Hazardous Constituents	Yes	40 CFR 261 EPA 1980a
	Identification and Listing of Hazardous Wastes: Appendix IX -- Wastes Excluded Under 260.20 and 260.22	Yes	40 CFR 261 EPA 1980a
	Maximum Concentration of Constituents for Ground-water Protection	0.0002 mg/L	40 CFR 264.94 EPA 1980b
	Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities: Appendix IX - Ground-water Monitoring List	0.1–10 µg/L (Practical Quantitation Limits for 2 Methods)	40 CFR 264 EPA 1980b

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)			
	Interim Status Standards for Owners and Operators of Hazardous Waste Treatment, Storage and Disposal Facilities: Appendix III - EPA Interim Primary Drinking Water	0.0002 mg/L	40 CFR 265 EPA 1980c
	Standards for the Management of Specific Hazardous Wastes and Specific Types of Hazardous Waste Management Facilities: Appendix VII - Health-Based Limits for Exclusion of Waste-Derived Residues	0.0002 mg/kg	40 CFR 266 EPA 1985d
	Identification of Wastes to be Evaluated by May 8, 1990	Yes	40 CFR 268.12 EPA 1986b
	Applicability of Treatment Standards	Yes	40 CFR 268.40 EPA 1987b
	Treatment Standards Expressed as Specified Technologies	Yes	40 CFR 268.42 EPA 1987b
	Treatment standards expressed as waste concentrations	0.13 mg/kg (non-waste waters)	40 CFR 268.43 EPA 1988c
	Land Disposal Restrictions: Appendix III - List of Halogenated Organic Compounds Regulated Under 268.32	Yes	40 CFR 268 EPA 1986d
	Universal Treatment Standards		40 CFR 268.48 60 FR 242 EPA 1995a
	Endrin	0.0028 mg/L (wastewater) 0.13 mg/kg(non wastewater)	
	Endrin aldehyde	0.025 mg/L (wastewater) 0.13 mg/kg(non wastewater)	
Guidelines:			
a. Air:			
ACGIH	Ceiling limit for Occupational Exposure (TLV-TWA)	0.1 mg/m^3 (skin) (6.4x10^{-3} ppm)	ACGIH 1988
NIOSH	Recommended Exposure Limit for Occupational exposure (TWA)	0.1 mg/m^3 (skin) (6.4x10^{-3} ppm)	NIOSH 1992
	Immediately Dangerous to Life and Health	2,000 mg/m^3 (128.4 ppm)	NIOSH 1990

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)			
b. Water:			
EPA	1-d Health Advisory	0.02 mg/L (child)	EPA 1995
	10-d Health Advisory	0.02 mg/L (child)	EPA 1995
	Longer-term Health Advisory	0.003 mg/L (child) 0.01 mg/L (adult)	EPA 1995
	Lifetime Health Advisory	0.002 mg/L (adult)	EPA 1995
	Maximum Contaminant Level	0.002 mg/L	40 CFR 141.61 EPA 1991a
	Maximum Contaminant Level Goal	0.002 mg/L	40 CFR 141.50 EPA 1991a
	Proposed Water Quality Guidance for the Great Lakes System (proposed rule)	Yes	40 CFR 132 58 FR 20802 EPA 1993f
	Acute criteria for protection of aquatic life in ambient water (CMC)	0.09 µg/L	
	Chronic criteria for protection of aquatic life in ambient water (CCC)	0.037 µg/L	
	Bioaccumulative chemicals of concern (BCCs)	Endrin aldehyde	
c. Other			
CPSC	Consumer products limit	NA	
EPA	Cancer classification	Group D[a]	IRIS 1994
	Hazard Ranking	NA	
	RfD (Oral)	0.0003 mg/kd/d	IRIS 1994
NTP	Cancer classification	NA	
STATE			
Regulations and Guidelines a. Air:			
	Acceptable Ambient Air Concentration Guidelines or Standards		NATICH 1992
AZ	1 hr avg. time	2.50 $\mu g/m^3$ (1.60×10^{-4} ppm)	
	24 hr avg. time	7.90×10^{-1} $\mu g/m^3$ (5.07×10^{-5} ppm)	
CT	8 hr avg. time	2.00 $\mu g/m^3$ (1.28×10^{-4} ppm)	

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
FL-PINELLA	8 hr avg. time	1.00x10 µg/m^3 (6.42x10^{-5} ppm)	
	24 hr avg. time	2.40x10^{-1} µg/m^3 (1.54x10^{-5} ppm)	
	Annual avg. time	3.00x10^{-1} µg/m^3 (1.93x10^{-5} ppm)	
KS	Annual avg. time	2.38x10^{-1} µg/m^3 (1.53x10^{-5} ppm)	
ND	8 hr avg. time	1.00x10^{-3} mg/m^3 (6.42x10^{-5} ppm)	
NV	8 hr avg. time	2.00x10^{-3} mg/m^3 (1.28x10^{-5} ppm)	
OK	24 hr avg. time	1.00 µg/m^3 (6.42x10^{-5} ppm)	
PA-PHIL.	1 yr avg. time	7.00x10^{-2} µg/m^3 (4.49x10^{-6} ppm)	
	Annual avg. time	7.00 µg/m^3 (4.49x10^{-4} ppm)	
TX	30 min avg. time	1.00 µg/m^3 (6.42x10^{-5} ppm)	
	Annual avg. time	1.00x10^{-1} µg/m^3 (6.42x10^{-6} ppm)	
VA	24 hr avg. time	1.70 µg/m^3 (1.09x10^{-4} ppm)	
WA-SWEST	24 hr avg. time	3.00x10^{-1} µg/m^3 (1.93x10^{-5} ppm)	
b. Water:			
	Water Quality: Human Health		
AL	Drinking water standard	0.2 µg/L	FSTRAC 1990
AZ	Domestic water source	0.2 µg/L	CELDs 1993
	Drinking water guideline	0.32 µg/L	FSTRAC 1990
	Fish consumption	1.1 µg/L	CELDs 1993
CT	*Consumption of organisms only**	0.81	CELDs 1993
	Consumption of water and organisms*	0.76	CELDs 1993

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
DE	Freshwater fish ingestion only	1.0 µg/L	CELDs 1993
	Freshwater fish and water ingestion	0.2 µg/L	CELDs 1993
	Marine/estuarine fish/shellfish ingestion	0.14 µg/L	CELDs 1993
DC	Raw water source for public water supply	1.0 µg/L	CELDs 1993
FL	Domestic/Drinking water	2.0 µg/L	Sittig 1994
IL	Public and food processing water supply standard	0.0002 mg/L	CELDs 1993
IN	Pt. of water intake - continuous conc. [4 d avg.]	1.0 µg/L	CELDs 1993
KY	Domestic water source	0.001 mg/L	CELDs 1993
LA	Drinking water supply	0.26 µg/L	CELDs 1993
	Non-drinking water supply	0.26 µg/L	CELDs 1993
MA	Drinking water standard	0.2 µg/L	FSTRAC 1990
	Domestic/Drinking water	2.0 µg/L	Sittig 1994
MD	Drinking water	0.2 µg/L	CELDs 1993
ME	Drinking water guideline	0.2 µg/L	FSTRAC 1990
MI	Domestic/Drinking water	1.2 µg/L	Sittig 1994
MN	Drinking water standard	0.2 µg/L	FSTRAC 1990
MS	Organisms only	0.814 µg/L	CELDs 1993
	Water and organisms	0.2 µg/L	CELDs 1993
MO	Fish consumption	0.0023 µg/L	CELDs 1993
	Drinking water supply	0.75 µg/L	CELDs 1993
NE	Water supply	0.0002 mg/L	CELDs 1993
NJ	Domestic/Drinking water	2.0 µg/L	Sittig 1994
NV	Municipal or domestic supply	0.0002 mg/L	CELDs 1993
NY	Class A, A-5, AA, AA-S (Not detectable) Class GA	0.2 µg/L	CELDs 1993
	Class A, A-S, AA, AA-S, B, C, D, SA, SB, SC, SD	0.002 µg/L	CELDs 1993
OH	Public water supply	1 µg/L	EPA 1988d
OK	Public and private water supply	0.0002 mg/L	EPA 1988d

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OR	Water and fish ingestion	1 µg/L	CELDs 1993
	Drinking water	0.0002 mg/L	CELDs 1993
RI	Drinking water standard	0.2 µg/L	FSTRAC 1990
	Class A - upper value	0.18 µg/L	EPA 1988d
	Class A - secondary upper limit	0.0023 µg/L	EPA 1988d
SD	Domestic water	0.2 µg/L	CELDs 1993
TN	Domestic raw water supply and industrial water supply	0.2 µg/L	CELDs 1993
	Drinking water	0.0002 mg/L	CELDs 1993
UT	Domestic source	0.2 µg/L	CELDs 1993
VA	Surface public water supply - upper value	0.0002 mg/L	EPA 1988d
VT	Class A or B waters	1 µg/L	CELDs 1993
	Drinking water guideline	0.32 µg/L	FSTRAC 1990
WV	Criterion based on body burden 1.0 µg/L	0.0023	CELDs 1993
	Water Quality: Aquatic Life		
AL	Acute-fresh water acute	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-marine*	0.037	CELDs 1993
	Chronic-marine*	0.0023	CELDs 1993
AR	All classes - upper value	0.18 µg/L	EPA 1988d
	All classes - secondary upper limit	0.0023 µg/L	EPA 1988d
AZ	Acute-cold water fishery*	0.18	CELDs 1993
	Acute-warm water fishery*	0.2	CELDs 1993
	Acute-effluent dominated water*	0.2	CELDs 1993
	Acute-ephemeral*	0.7	CELDs 1993
	Chronic-cold water fishery*	0.002	CELDs 1993
	Chronic-warm water fishery*	0.08	CELDs 1993
	Acute-effluent dominated*	0.08	CELDs 1993
	Acute-ephemeral*	0.3	CELDs 1993

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CT	Acute-fresh water*	0.09	CELDs 1993
	Chronic-fresh water*	0.0023	CELDs 1993
	Acute-salt water*	0.0185	CELDs 1993
	Chronic-salt water*	0.0023	CELDs 1993
DE	Acute-fresh water	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-marine	0.037 µg/L	CELDs 1993
	Chronic-marine	0.0023 µg/L	CELDs 1993
DC		0.0023 µg/L	CELDs 1993
HI	Acute-fresh water	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-salt water	0.037 µg/L	CELDs 1993
	Chronic-salt water	0.0023 µg/L	CELDs 1993
ID	All classes - upper value	0.0002 mg/L	EPA 1988d
IN	Acute- aquatic-max	0.09 µg/L	CELDs 1993
	Continuous conc. 4-d avg. outside of mixing zone; chronic aquatic for aquatic life*	0.0023	CELDs 1993
KS	Special aquatic life waters - upper value	0.0023 µg/L	EPA 1988d
KY	Acute-warm water	0.18 µg/L	CELDs 1993
	Chronic-warm water	0.0023 µg/L	CELDs 1993
LA	Acute-fresh water	0.18 µg/L	CELDs 1993
	Acute-marine	0.037 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Chronic-marine	0.0023 µg/L	CELDs 1993
MD	Acute-fresh water	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-salt water	0.037 µg/L	CELDs 1993
	Chronic-salt water	0.0023 µg/L	CELDs 1993
	All waters - upper value	0.004 µg/L	EPA 1988d

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MS	Acute-fresh water	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-salt water*	0.037	CELDs 1993
	Chronic-salt water*	0.0023	CELDs 1993
NC	All fresh surface waters (WS-I-III) - upper value	0.002 µg/L	EPA 1988d
NE	All classes - upper value	0.0002 mg/L	EPA 1988b
NV	"Aquatic Use"	0.00018 mg/L	CELDs 1993
	"Propagation of Wildlife"	0.002 mg/L	CELDs 1993
NJ	Classes FW2, SE, & SC	0.0023 µg/L	CELDs 1993
	Fresh water	0.0023 µg/L	CELDs 1993
	Salt water	0.0023 µg/L	CELDs 1993
ND	Acute	0.18 µg/L	CELDs 1993
	Chronic	0.0023 µg/L	CELDs 1993
OH	Warm water outside mixing zone 30-d avg.	0.002 µg/L	CELDs 1993
	Aquatic life habitat; limited resource-cold water, outside mixing zone, human health	0.002 µg/L	CELDs 1993
OK	Acute	0.18 µg/L	CELDs 1993
	Chronic*	0.0023	CELDs 1993
OR	Acute-fresh water	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-marine	0.037 µg/L	CELDs 1993
	Chronic-marine	0.0023 µg/L	CELDs 1993
PR	All coastal water classes - upper value	0.001 µg/L	EPA 1988d
	Coastal estuarine waters	0.0023 µg/L	CELDs 1993
RI	Freshwater Classes D and E - upper level	0.18 µg/L	EPA 1988d
	Freshwater Classes D and E - secondary upper limit	0.0023 µg/L	EPA 1988d
	Saline Classes SA, SB and SC - upper level	0.037 µg/L	EPA 1988d
	Saline Classes SA, SB and SC - secondary upper limit	0.0023 µg/L	EPA 1988d

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
SD	Acute	0.18 µg/L	CELDs 1993
	Chronic	0.0023 µg/L	CELDs 1993
TN	Maximum	0.18 µg/L	CELDs 1993
	Continuous	0.0023 µg/L	CELDs 1993
TX	Acute-fresh water	0.18 µg/L	CELDs 1993
	Chronic-fresh water	0.0023 µg/L	CELDs 1993
	Acute-marine	0.037 µg/L	CELDs 1993
	Chronic-marine	0.0023 µg/L	CELDs 1993
UT	4 d avg.	0.0023 µg/L	CELDs 1993
	1 hr avg.	0.09 µg/L	CELDs 1993
	Aquatic Wildlife Classes 3A-D	0.004 µg/L	EPA 1988d
VT	Acute	0.18 µg/L	CELDs 1993
	Chronic	0.0023 µg/L	CELDs 1993
VA	Chronic-all waters	0.0023 µg/L	CELDs 1993
WI	Great Lakes	0.101 µg/L	CELDs 1993
	Cold water	0.101 µg/L	CELDs 1993
	Warm water sport fish	0.158 µg/L	CELDs 1993
	All others	0.158 µg/L	CELDs 1993
	Water Quality: Agricultural Uses		
AZ	Agri irrigation*	0.004	CELDs 1993
	Livestock watering*	0.004	CELDs 1993
NV	Irrigation	0.0002 mg/L	CELDs 1993
	Livestock watering*	0.00018	CELDs 1993
OH	Agri water supply	0.2 µg/L	CELDs 1993
	Water Quality: Recreational Use		
AZ	Full and partial body contact	40 µg/L	CELDs 1993
RI	Classes B and C - upper value	0.18 µg/L	EPA 1988d
	Classes B and C - secondary upper limit	0.0023 µg/L	EPA 1988d
	Groundwater Quality Standards		CELDs 1993
AZ		0.0002 mg/L	
CO		0.0002 mg/L	
MA		0.0002 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MN	Standards for groundwater at hazardous waste mgt. facilities	0.0002 mg/L	
MO		0.75 mg/L	
NJ	Classes GW1 through 3	0.004 µg/L	
NY		Yes	
NC	Class GS	0.0002 mg/L	
ND		0.0002 mg/L	
OR		0.0002 mg/L	
TN		0.0002 mg/L	
UT		0.0002 mg/L	
WI	Enforcement standard	0.2 µg/L	
	Hazardous waste facility standard	0.0002 mg/L	
	Groundwater Quality Monitoring Parameters		CELDs 1993
CO		0.0002 mg/L	
		Yes	
IL		0.0002 mg/L	
		Yes	
IN		0.0002 mg/L	
LA		0.0002 mg/L	
		Yes	
MN		Yes	
NJ		0.0002 mg/L	
VA		Yes	
WV		Yes	
WI		Yes	
	Preventive action	0.01 µg/L	
	Discharge Limits		CELDs 1993
AR	Chronic toxicity [24 hr avg.]	0.0023 µg/L	
	Acute toxicity [never to exceed]	0.18 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CA	6-mo median	2 ng/L	
	Daily maximum	4 ng/L	
	Instantaneous maximum	6 ng/L	
NJ	NPDES Permits: Testing Requirements for Organic Toxic Pollutants	Yes	CELDs 1993
CA	Restricted Pesticides	Yes	CELDs 1993
	Toxic Discharge		CELDs 1993
WI	Maximum allowable concentrations for organochlorides and other persistent pesticides (preservation of species dependent on waterbody)	Yes	
OK	Alert	0.3 mg/kg	
SD	Surface Water Discharge Permit Application Requirements: Test Requirements for Organic Toxic Pollutants	Yes	CELDs 1993
c. Other			CELDs 1993
	Hazardous Waste Constituents		
CA		20 wt • wt in mg/kg (total threshold limit conc. in extremely hazardous wastes)	
		Yes	
CO		Yes (App. VIII)	
IL		Yes (App. H)	
LA		Yes	
MA		Yes	
		Yes (LDR)	
MN		Yes	
NH		Yes	
ND		Yes	
WV		Yes (App. VIII)	
WI		Yes (App. IV)	
	Hazardous Waste Toxicity Characteristics		CELDs 1993

Table 7-1. Regulations and Guidelines Applicable to Endrin/Endrin Aldehyde and Endrin Ketone (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CA	Maximum conc. for toxicity characteristics	0.02 mg/L	
CO		0.02 mg/L	
IL		0.02 mg/L	
LA		0.02 mg/L	
MA		0.02 mg/L	
MN		0.02 mg/L	
ND		0.02 mg/L	
PA		0.02 mg/L	
WV		0.02 mg/L	
WI		0.02 mg/L	

NOTE: Update of drinking water guidelines and other areas in progress.
Units in table reflect values and units of measure designated by each agency in its regulations or advisories.

[a] Not classifiable as a human carcinogen
* Unit of measure not specified.

ACGIH = American Conference of Governmental and Industrial Hygienists; CELDs = Computer-aided Environmental Legislative Database; CPSC = Consumer Product Safety Commission; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; LDR = Land Disposal Restrictions; MCL = Maximum Contaminant Level ; NA = Not available at the present time; NATICH = National Air Toxics Information Clearninghouse; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; OW = Office of Water; PCB = Polychlorinated Biphenyl; RfD = Reference Dose; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TSCA = Toxic Substances Control Act; TWA = Time Weighted Average; WHO = World Health Organization

8. REFERENCES

*ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1988. Threshold limit values for chemical substances and physical agents and biological exposure indices (1988-1989). American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH. 1991. Threshold limit values for chemical substances and physical agents and biological exposure indices (199 I-1992). American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Ahmed FE, Hattis D, Wolke RE, et al. 1993. Risk assessment and management of chemical contaminants in fishery products consumed in the USA. J Appl Toxicol 13(6):395-410.

*Akubue PI, Stohs SJ. 1992. Endrin-induced production of nitric oxide by rat peritoneal macrophages. Toxicol Letters 62:311-316.

*Alawi MA, Ammari N, Al-Shuraiki. 1992. Organochlorine pesticide contaminations in human milk samples from women living in Amman, Jordan. Arch Environ Contam Toxicol 23:235-239.

*Ali SS, Shakoori R. 1993. Short-term toxicity of endrin in Sprague Dawley rats: Biochemical and histological changes in liver. Punjab Univ J Zool 8: l-l 3.

*Ambrns A, Lantos J, Visi E, et al. 1981. General method for determination of pesticide residues in samples of plant origin, soil and water: I. Extraction and cleanup. J Assoc Off Anal Chem 64:733-742.

*Ames BN, McCann J, Yamasaki E. 1975. Methods for detecting carcinogens and mutagens with the salmonella/mammalian - microsome mutagencity test. Mutation Res 3:347-364.

*Andersen RL, DeFoe DL. 1980. Toxicity and bioaccumulation of endrin and methoxychlor in aquatic invertebrates and fish. Environmental Pollution 22:11-121.

*Argyle RL, Williams GC, Dupree HK. 1973. Endrin uptake and release by fingering channel (Ictalurus punctatus). J Fish Res Board Can 30:1743-1744.

*ASTER. 1995. ASTER (Assessment Tools for the Evaluation of Risk) ecotoxicity profile. U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory. Mid-Continent Ecology Division.

*ASTM. 1988. Method D 3086-85. Standard test method for organochlorine pesticides in water. 1988 annual book of ASTM standards. Vol. 11.02: Water and environmental technology. American Society for Testing and Materials, Philadelphia, PA 163-178.

*Cited in text

8. REFERENCES

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta, GA.

*ATSDR/CDC. 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.

*Bagchi M, Hassoun EA, Stohs SJ. 1992a. Endrin-induced increases in hepatic lipid peroxidation, membrane microviscosity, and DNA damage in rats. Arch Environ Contam Toxicol 23:1-5.

*Bagchi D, Bagchi M, Hassoun E, et al. 1992b. Endrin-induced urinary excretion of formaldehyde, acetaldehyde, malondialdehyde and acetone in rats. Toxicology 75:81-89.

*Bagchi D, Bagchi M, Hassoun E, et al. 1992c. Effect of endrin on the hepatic distribution of iron and calcium in female Sprague-Dawley rats. J Biochem Toxicology 7(1):37-42.

*Bagchi D, Hassoun EA, Bagchi M, et al. 1993c. Protective effects of antioxidants against endrin-induced hepatic lipid peroxidation, DNA damage, and excretion of urinary lipid metabolites. Free Radical Biology & Medicine 15:217-222.

*Bagchi E, Hassoun E, Akubue P, et al. 1993d. Comparative effects of endrin on hepatic lipid peroxidation and DNA damage, and nitric oxide production by peritoneal macrophages from C57BW6J and DBA/2 mice. Comp Biochem Physiol 105C(3):525-529.

*Bagchi M, Hassoun EA, Bagchi D, et al. 1993a. Production of reactive oxygen species by peritoneal macrophages and hepatic mitochondria and microsomes from endrin-treated rats. Free Radical Biology & Medicine 14:149-155.

*Baldwin MK, Crayford JV, Hutson DH, et al. 1976. The metabolism and residues of [14C] endrin in lactating cows and laying hens. Pestic Sci 7:575-594.

*Baldwin MK, Hutson DH. 1980. Analysis of human urine for a metabolite of endrin by chemical oxidation and gas-liquid chromatography as an indicator of exposure to endrin. Analyst 105:60-65.

*Baldwin MK, Robinson J, Parke DV. 1970. Metabolism of endrin in the rat. Agric Food Chem 18:1117-1123.

*Bandyopadhyay SK, Tiwari RK, Mitra P, et al. 1982. Effects of L-ascorbic acid supplementation on dieldrin toxicity in rats. Arch Toxicol 50:227-232.

*Barcarolo R, Tealdo E, Tutta C. 1988. Multiresidue determination of organochlorine and triazine pesticides in homogenized milk. J High Resolution Chromatography & Chromatography Comm 11:10746-10748.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regulatory Toxicology and Pharmacology 8:471-486.

*Bartha R, Lanzilotta RP, Pramer D. 1967. Stability and effects of some pesticides in soil. Appl Microbial 15:67-75.

8. REFERENCES

*Bason CW, Colborn T. 1992. U.S. application and distribution of pesticides and industrial chemicals capable of disrupting endocrine and immune systems. In: Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection, Vol XXI, M.A. Mehlman, Princeton Scientific Publishing Co.

*Beall M Jr, Harris WG, Nash RG. 1972. Endrin transformations in soil. J Environ Qual 1(4):391-394.

*Bedford CT, Hutson DH, Natoff IL. 1975a. The acute toxicity of endrin and its metabolites to rats. Toxicol Appl Pharmacol 33:115-121.

*Bedford CT, Harrod RK, Hoadley EC, et al. 1975b. The metabolic fate of endrin in the rabbit. Xenobiotica 5:485-500.

*Bentabol A, Jodral M. 1995. Determination of organochlorine pesticides in cheese. J AOAC International 78(1):94-98.

*Beyer WN, Stafford C. 1993. Survey and evaluation of contaminants in earthworms and in soils derived from dredged materials at confined disposal facilities in the Great Lakes region. Environmental Monitoring and Assessment 24:151-165.

*Bidleman TF. 1981. Interlaboratory analysis of high molecular weight organochlorines in ambient air. Atmos Environ 15:619-24.

*Bishop FS. 1984. Written communication (August 29) to Velsicol Chemical Company, regarding notice of intent to cancel registration: Velsicol technical endrin. EPA registration No. 876-20. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs, Registration Division.

*Bishop FS. 1985. Written communication (July 29) to Velsicol Chemical Company, regarding final cancellation notice: Velsicol technical endrin. EPA registration No. 876.20. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs, Registration Division.

*Bishop FS. 1986. Written communication (July 2) to Velsicol Chemical Corporation, Chicago, IL, regarding notice of intent to cancel the registration of certain pesticide products: Velsicol endrin 1.6 EC. EPA registration No. 876-153. Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

*Bloomquist JR. 1992. Intrinsic lethality of chloride-channel-directed insecticides and convulsants in mammals. Toxicology Letters 60:289-298.

*Blus LJ, Henny CJ, Grove RA. 1989. Rise and fall of endrin usage in Washington State fruit orchards: effects on wildlife. Environmental Pollution 60:331-349.

*Bordet F, Mallet J, Maurice L, et al. 1993. Organochlorine pesticide and PCB congener content of French human milk. Bull Environ Contam Toxicol 50:425-432.

*Burse VW, Head SL, Korver MP, et al. 1990. Determination of selected organochlorine pesticides and polychlorinated biphenyls in human serum. J Anal Toxicol 14:137-142.

8. REFERENCES

*Burton WB, Pollard GE. 1974. Rate of photochemical isomerization of endrin in sunlight. Bull Environ Contam Toxicol 12:113-116.

*Buttner JK, Makarewicz JC, Lewis TW. 1995. Concentration of selected priority organic contaminants in fish maintained on formulated diets in lake Ontario waters. Progressive Fish-Culturist 57:141-146.

*Carbajal-Rodriguez L, Oldak-Skvirsky D, Loredo-Abdala A, et al. 1990. Intoxicación por endrin. Bol Med Hosp Infant Mex. 47(2):100-102.

*Carey AE, Gowen JA, Tai H, et al. 1979. Pesticide residue levels in soils and crops from 37 states, 1972 National Soils Monitoring Program (IV). Pestic Monit J 12:209-229.

*Carey AE, Kutz FW. 1985. Trends in ambient concentrations of agrochemicals in humans and the environment of the United States. Environmental Monitoring and Assessment 5:155-163.

*Carey AE, Wiersma GB, Tai H. 1976. Pesticide residues in urban soils from 14 United States cities, 1970. Pestic Monit J 10(2):54-60.

*Carey AE, Yang HSC, Wiersma GB, et al. 1980. Residual concentrations of propanil, TCAB and other pesticides in rice-growing soils in the United States, 1972. Pestic Monit J 14:23-25.

Carrero I, Fernandez-Moreno MD, Perez-Albarsanz MA, et al. 1989. Lindane effect upon the vasoactive intestinal peptide receptor-effector system in rat enterocytes. Biochem Biophys Res Comm 159(3):1391-1396.

Carrero I, Perez-Albarsanz MA, Carmena MJ, et al. 1990. Lindane inhibits b-adrenergic stimulation of cyclic AMP accumulation in rat prostatic epithelial cells. Pesticide Biochem Physiol 38:197-203.

*CELDs. 1993. Computer-assisted Environmental Legislative Database. University of Illinois at Urbana.

*Chan CH, Bruce G, Harrison B. 1994. Wet deposition of organochlorine pesticides and polychlorinated biphenyls to the great lakes. J Great Lakes Res 20(3):546-560.

Chernoff N, Kavlock RJ, Gray LE, et al. 1979b. Teratogenic effects of endrin in the golden hamster [Abstract]. Toxicol Appl Pharmacol 48:A201.

*Chernoff N, Kavlock RJ, Hanisch RC, et al. 1979a. Perinatal toxicity of endrin in rodents. I. Fetotoxic effects of prenatal exposure in hamsters. Toxicology 13:155-165.

*Clayton GD, Clayton FE. 1981. Patty's industrial hygiene and toxicology. Volume 2B: Toxicology. 3rd ed. New York, NY: John Wiley & Sons, 3685.

*Coble Y, Hildebrandt P, Davis J, et al. 1967. Acute endrin poisoning. JAMA 202:489-493.

*Cohen DB. 1986. Ground water contamination by toxic substances, California Assessment. Pollutant Investigations Branch, State Water Resources Control Board, Sacramento, CA: American Chemical Society.

6. REFERENCES

Cole JF, Klevay LM, Zavon MR. 1970. Endrin and dieldrin: a comparison of hepatic excretion in the rat. Toxicol and Applied Pharmacology 16547-555.

*Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. J Water Pollut Control Fed 56(7):898-908.

Cook WO, Casteel SW. 1985. A suspected case of endrin toxicosis in a cat. Vet Hum Toxicol 27(2):111-114.

*Crespo C, Marce RM, Borrull F. 1994. Determination of various pesticides using membrane extraction discs and gas chromatography mass spectrometry. J Chromatogr 670(1-2):135-144.

*Cruz I, Wells DE, Mat-r IL. 1993. Determination of organochlorines in sea water: An assessment. Analytica Chimica Acta 283:280-286.

*Curley A, Jennings RW, Mann HT, et al. 1970. Measurement of endrin following epidemics of poisoning. Bull Environ Contam Toxicol 5:24-29.

*Davies GM, Lewis I. 1956. Outbreak of food poisoning from bread made of chemically contaminated flour. Br Med J 11:393-398.

*Davies K. 1988. Concentrations and dietary intake of selected organochlorines, including PCBs, PCDDs and PCDFs in fresh food composites grown in Ontario, Canada. Chemosphere 17(2):263-276.

*De Bruijin J, Busser F, Seinem W, et al. 1989. Determination of octanol water partition coefficients for hydrophobic organic chemicals with the “slow-stirring” method. Environmental Toxicology and Chemistry 8:499-512.

*De Peyster A, Donohoe R, Slymen DJ. 1993. Aquatic biomonitoring of reclaimed water for potable use: The San Diego health effects study. Journal of Toxicology and Environment Health 39:121-142.

*Deichmann WB, MacDonald WE, Blum E, et al. 1970. Tumorigenicity of aldrin, dieldrin and endrin in the albino rat. Industrial Medicine 39:37-45.

*Dewailly E, Ayotte P, Bruneau S, et al. 1993. Inuit exposure to organochlorines through the aquatic food chain in arctic Quebec. Environmental Health Perspectives 101:618-620.

*Di Muccio A, Ausili A, Dommarco R, et al. 1991. Solid-matrix partition for separation of organochlorine pesticide residues from fatty materials. J Chromatog 552:241-247.

*Di Muccio A, Santilio A, Dommarco R, et al. 1990. Behaviour of 23 persistent organochlorine compounds during sulphuric acid clean-up on a solid-matrix column. J Chromatog 513:333-337.

*Dikshith TSS, Datta KK. 1973. Endrin induced cytological changes in albino rats. Bull Environ Contam Toxicol 9(2):65-69.

*Ditraglia D, Brown DP, Namekata T, et al. 1981. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Stand J Work Environ Health 7:140-146.

8. REFERENCES

*Djordjevic MV, Hofmann D, Fan J. 1994. Assessment of chlorinated pesticides and polychlorinated biphenyls in adipose breast tissue using a supercritical fluid extraction method. Carcinogenesis 15(11):2581-2585.

*Doherty FG, Evans DW, Neuhauser EF. 1993. An assessment of total and leachable contaminants in Zebra mussels (Dreissena polymorpha) from Lake Erie. Ectotoxicology and Environmental Safety 25:328-340.

*Eichelberger JW, Lichtenberg JJ. 1971. Persistence of pesticides in river water. Environ Sci Technol 5(6):541-544.

*Eisenlord G, Loquvam GS, Leung S. 1968. Results of reproduction study of rats fed diets containing endrin over three generations. Prepared by Hine Laboratories for Shell Chemical Co. and Velsicol Chemical Corp.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

*Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology diagnosis and treatment of human poisoning. New York, NY: Elsevier, 1078-1080.

*EPA. 1971. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.

*EPA. 1973. Guidelines establishing test procedures for the analysis of pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136.

*EPA. 1975. National primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.

EPA. 1976a. Endrin: Position Document I. Arlington, VA: U.S. Environmental Protection Agency, Special Pesticide Review Division. EPA/SPRD-80/37. NTIS No. PB81-112690.

*EPA. 1976b. National primary drinking water regulations implementation. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 142.62.

*EPA. 1977a. Regulatory limitation. U.S. Environmental Protection Agency. Code of FeGeral Regulations. 40 CFR 129.102.

*EPA. 1977b. Tolerances for residues. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.131.

*EPA. 1977c. Toxic pollutant effluent standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 129.

*EPA. 1978a. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

8. REFERENCES

*EPA. 1978b. Pesticide chemicals. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 455.20.

*EPA. 1979a. Determination of reportable quantities for hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

*EPA. 1979b. Criteria and standards for the national pollutant discharge elimination system. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 125.

*EPA. 1979c. Toxic pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

*EPA. 1979d. Criteria for classification of solid waste disposal facilities and practices. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 257.

*EPA. 1979e. U.S. Environmental Protection Agency: Part II. Federal Register 44:43632-43657.

*EPA. 1979f. Endrin: Position document 4. Washington, DC: U.S. Environmental Protection Agency, Special Pesticide Review Division. EPA/SPRD-80/39. NTIS No. PB81-109480.

*EPA. 1979g. Water-related environmental fate of 129 priority pollutants. Vol I: Introduction and technical background, metals and inorganics, pesticides and PCBs. U.S. Environmental Protection Agency, Office of Water Planning and Standards, Washington, DC. (authors: Callahan et al.) EPA-440/4-79-029a.

*EPA. 1980a. Ambient water quality criteria document for endrin. U.S. Environmental Protection Agency. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards, Washington, DC.

*EPA. 1980b. Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.

*EPA. 1980c. Standards for owners and operators of hazardous waste treatment, storage, and disposal facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264.

*EPA. 1980d. Interim status standards for owners and operators of hazardous waste treatment, storage, and disposal facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 265.

EPA. 1980e. Chemical contaminants in nonoccupationally exposed U.S. residents. U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. (authors: Holleman et al.). EPA-600/l-80-001.

*EPA. 1981a. Aquatic fate process data for organic priority pollutants. U.S. Environmental Protection Agency, Office of Water Regulations and Standards, Washington, DC. (authors: Mabey et al.). EPA-440/4-81-014.

8. REFERENCES

*EPA. 1981 b. Electroplating point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.

*EPA. 1982a. Test method: Organochlorine pesticides and PCBs - method 608. In: Longbottom JE, Lichtenberg JJ, eds. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA-600/4-82-057.

*EPA. 1982b. Test method: Base/neutrals and acids - method 625. In: Longbottom JE, Lichtenberg JJ, eds. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA-600/4-82-057.

*EPA. 1982c. Steam electric power generating point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 423.

*EPA. 1983a. EPA administered permit programs: The National Pollutant Discharge Elimination System. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122.

*EPA. 1983b. Total toxic organics: Metal finishing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433.11.

*EPA. 1983c. Aluminum forming. Total toxic organics. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467.02.

EPA. 1983d. Treatability manual: Vol I. Treatability data. Washington DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-82-00l a.

*EPA. 1983e. Status of pesticides in reregistration and special review. U. S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Washington, DC. EPA 738-R-93-009.

*EPA. 1984a. Analytical reference standards and supplemental data: The pesticides and industrial chemicals repository. U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory - Las Vegas. EPA-600/4-84-082.

*EPA. 1984b. Identification of specific chemical substance and mixture testing requirements. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 799.5055.

*EPA. 1984c. Method T04 for the determination of organochlorine pesticides and polychlorinated biphenyls. In: Winberry et al. Compendium of methods for the determination of toxic organic compounds in ambient air. U. S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. (authors: Winberry, et al). EPA-600/4-84-041.

*EPA. 1985a. Designation of reportable quantities and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.

*EPA. 1985b. Reporting and recordkeeping requirements. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 704.102.

8. REFERENCES

*EPA. 1985c. Environmental effects testing guidelines. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 797.1520.

*EPA. 1985d. Standards for the management of specific hazardous wastes and specific types of hazardous waste management facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266.

*EPA. 1985e. Drinking water criteria document for endrin. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water. EPA-600/X-84-176.

EPA. 1985f. Suspended, cancelled and restricted pesticides. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs.

*EPA. 1986a. General pretreatment regulations for existing and new sources of pollution. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 403, Appendix B.

*EPA. 1986b. Method 8250: Gas chromatography/mass spectrometry for semivolatile organics: Packed column technique. In: Test methods for evaluating solid waste. Volume IC: Laboratory manual: Physical/chemical methods. SW-846. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986c. Method 8270: Gas chromatography/mass spectrometry for semivolatile organics: Capillary column technique. In: Test methods for evaluating solid waste. Volume IC: Laboratory manual: Physical/chemical methods. SW-846. 3rd ed. Washington DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986d. Land disposal restrictions. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.

EPA. 1986e. Reference values for risk assessment. Final draft. U.S. Environmental Protection Agency, Office of Solid Waste, Cincinnati, OH. ECAO-CIN-477.

*EPA. 1987a. Emergency planning and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355.

*EPA. 1987b. Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.

*EPA. 1987c. U.S. Environmental Protection Agency: Part V. Federal Register 52:25760-25763, 25791.

EPA. 1987d. Endrin health advisory. U.S. Environmental Protection Agency, Office of Drinking Water, Washington, DC.

EPA. 1987e. Health effects assessment of endrin. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/8-881035.

*EPA. 1988a. Toxic chemical release reporting: Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.

EPA. 1988b. Pesticide registration and classification procedures. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 152.175.

*EPA. 1988c. Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.

*EPA. 1988d. State water quality standards summaries. U.S. Environmental Protection Agency, Office of Water, Washington, DC. EPA-440/5-88-031.

*EPA. 1988e. Method 508 Determination of chlorinated pesticides in water by gas chromatography with an electron capture detector. In: Methods for the determination of organic compounds in drinking water (rev 3.0). U. S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington DC. SW 846.

*EPA. 1989. Pesticides in ground water data base:1988 interim report. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs. EPA-540/09-89-036.

*EPA. 1990. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency. EPA-600/8-90/066A.

*EPA. 1991a. National primary drinking water regulations: Maximum contaminant levels and goals. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50 and 141.61.

*EPA. 1991b. Criteria for municipal solid waste landfills (Eff. 10-9-93). U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 258.

EPA. 1992a. National primary drinking water regulations: Synthetic organic chemicals and inorganic chemicals. Final rule. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141 and 142.

*EPA. 1992b. National study of chemical residues in fish. Volume I. Office of Science and Technology, Washington, DC. EPA-823-R-92-008A.

EPA. 1992c. Drinking water criteria document for endrin. ECAO-CIN-423.

*EPA. 1993. Proposed water quality guidance for the great lakes system. U.S. Environmental Protection Agency. Federal Register 40 CFR 122,123,131,132.

*EPA. 1994a. Standards for pesticide containers and containment. Proposed rule. U.S. Environmental Protection Agency. Federal Register 59:6712-6789.

*EPA. 1994b. Drinking water regulations and health advisories. U.S. Environmental Protection Agency, Office of Water. Washington, DC.

*EPA. 1995a. Toxic chemical release inventory reporting form R and instructions. Revised 1994 version. Washington DC. U. S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA-745-K-95-051.

8. REFERENCES

* EPA. 1995b. The national listing of fish consumption advisories and bans. Washington DC: U.S. Environmental Protection Agency, Office of Water. EPA-823-C-95-001.

*EPA. 1995c. Method 8270C Semivolatile organic compounds by gas chromatography mass spectrometry (GC/MS): Capillary column technique. In: Test methods for evaluating solid waste, revision 3, January 1995. Washington DC. U. S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, SW 8465.

*EPA. 1995d. Method 8081A: Organochlorine pesticides by capillary column gas chromatography, revision 1, January 1995. In: Test methods for evaluating solid waste, revision 3, January 1995. U. S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, SW 846.

*Ert MV, Sullivan, JP. 1992. Organochlorine pesticides in hazardous materials toxicology: clinical principles of environmental health. Baltimore, MD: William & Wilkins, 1047-1048.

Farm Chemicals Handbook. 1994. Berg GL, ed. Willoughby, OH: Meister Publishing Co.

*FASE. 1996. Pesticide exports from US ports, 1992-1994. Foundation for Advancements in Science and Education. Park Mile Plaza, LA, CA.

*Fazzalari FA. 1978. ASTM/DS-48A: Compilation of odor and taste threshold values. 58

*FDA. 1988. Residues in foods-1987. Food and Drug Administration Program. J Assoc Off Anal Chem 71(6):156A-174A.

* FDA. 1989. Residues in foods -1988 (2nd Annual FDA Pesticide Residue Montitoring Program Repport). J Assoc Off Anal Chem 72(5):133A-152A.

*FDA. 1990. Residues in foods-1989 (3rd Annual FDA Pesticide Residue Monitoring Program Report). J Assoc Off Anal Chem 73(5):127A-146A.

*FDA. 1991. Residues in foods-1990 (4th Annual FDA Pesticide Residue Monitoring Program Report). J Assoc Off Anal Chem 74(5):121A-140A.

*FDA. 1992. Residue monitoring-1991 (5th Annual FDA Pesticide Residue Monitoring Program Report). J of AOAC International 75(5):135A-157A.

*FDA. 1993. Residue monitoring 1992 (6th Annual FDA Pesticide Residue Monitoring Program Report). J of AOAC International 76(5):127A-147A.

*FDA. 1994a. Residue monitoring 1993 (7th Annual FDA Pesticide Residue Monitoring Program Report). J of AOAC International 77(5):163A-185A.

*FDA. 1994b. 302 and 303 Methods for nonfatty foods. In: Pesticides Analytical Manual, 3rd edition, vol. 1: Multiresidue methods. U. S. Department of Health and Human Services, Food and Drug Administration.

8. REFERENCES

*FDA. 1994c. 304: Method for fatty foods. In: Pesticide Analytical Manual, 3rd edition vol. 1: Multiresidue Methods. U. S. Department of Health and Human Services, Food and Drug Administration.

*FDA. 1995. Residue monitoring -1994 (8th Annual FDA Pesticide Residue Monitoring Program Report). J of AOAC International 78(5):119A-142A.

*FEDRIP. 1995. Summary of federal research. Federal Research in Progress (FEDRIP) data base, 1995.

*Finkel AJ. 1983. Hamilton and Hardy's industrial Toxicology, 4th ed. Littleton, MA: John Wright, 295-297.

*Fleming L, Mann JB, Bean J, et al. 1994. Parkinson's disease and brain levels of organochlorine pesticides. Annals of Neurology 36(1):98-103.

*Ford M. 1993. Insecticides and pesticides. In: Vicellio P. Handbook of medical toxicology. Boston, MA: Little Brown and Company, 303-313.

*Ford WM, Hill EP. 1991. Organochlorine pesticides in soil sediments and aquatic animals in the Upper Steele Bayou watershed of Mississippi. Archives of Environmental Contamination and Toxicology 20:161-167.

* Foster GD, Gates PM, Foreman WT. 1993. Determination of dissolved-phase pesticides in surface water from the Yakima River Basin, Washington, using the goulden large-sample extractor and gas chromatography/mass spectrometry. Environ Sci Tech 27(9):1911-1917.

*FSTRAC. 1990. Summary of State and Federal Drinking Water Standards and Guidelines. U.S. Environmental Protection Agency. Chemical Communication Subcommittee, Federal and State Toxicology and Regulatory Alliance Committee (FSTRAC), Washington, DC.

*Gaines TB. 1960. The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 2:88-99.

*Gaines TB. 1969. Acute toxicity of pesticides. Toxicol Appl Pharmacol 14:515-534.

*Ganguly SK, Bhattacharyya J. 1973. Detection of small amounts of pesticides in human biological material by thin-layer chromatography. Forensic Sci 2:333-338.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:146-161.

*Ghadiri H, Rose CW, Connell DW. 1995. Degradation of organochlolrine pesticides in soils under controlled environment and outdoor conditions. Journal of Environmental Management 43:14 l-l 51.

*Gianessi LP. 1986. A national pesticide usage data base, summary of report submitted to the office of standards and regulations, U.S. EPA under cooperative agreement CR 811858-01-0 by Resources for the Future, Washington, DC.

8. REFERENCES

*Giesy JP, Verbrugge DA, Othout RA, et al. 1994. Contaminants in fishes from Great Lake influenced sections and above dams of three Michigan rivers. I: Concentrations of organochlorine insecticides, polychlorinated biphenyls, dioxin equivalents, and mercury. Arch Environ Contam Toxicol 27:202-212.

*Glatt H, Jung R, Oesch F. 1983. Bacterial mutagenicity investigation of epoxides: Drugs, drug metabolites, steroids and pesticides. Mutat Res 11:99-l 18.

*Goldenthal EI. 1978a. Endrin: Teratology study in rats. Prepared by International Research and Development Corp. for Velsicol Chemical Corp.

*Goldenthal EI. 1978b. Endrin: Teratology study in hamsters. Prepared by International Research and Development Corp. for Velsicol Chemical Corp.

*Good EE, Ware GW. 1969. Effects of insecticides on reproduction in the laboratory mouse: IV. Endrin and dieldrin. Toxicol Appl Pharmacol 14:201-203.

Gosselin RE, Smith RP, Hodge HC, et al. 1984. Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, 11-285.

*Gowda TK, Sethunathan N. 1976. Persistence of endrin in Indian rice soils under flooded conditions. J Agric Food Chem 24:750-753.

*Gray LE Jr, Kavlock RJ, Chemoff N, et al. 1981. Perinatal toxicity of endrin in rodents. III. Alterations of behavioral ontogeny. Toxicology 21:187-202.

*Greenberg AE, Clesceri LS, Easton AD, eds. 1992. Method 6630c9: Standard methods for the examination of water and wastewater, 18th edition, American Public Health Association, Washington DC.

*Grab K, Wagner C. 1993. Procedure for testing inertness of inserts and insert packing materials for GC injectors. J High Resolut Chromatogr 16:464-568.

*Gunderson EL. 1988. Chemical contaminants monitoring: FDA total diet study, April 1982-April 1984, dietary intakes of pesticides, selected elements, and other chemicals. J Assoc Off Anal Chem 71(6):1200-1209.

*Hansen DJ Schimmel SC, Forester J. 1977. Endrin: Effects on the entire life-cycle of saltwater fish, Cyprinbdon variegatus. J Toxicol Environ Health 3:721-733.

*Harkov R. 1986. Semivolatile organic compound in the atmosphere: A review. J Environ Sci Health 409-433.

*Harrington-Fowler L. 1991. Application of a one-step extractor/concentrator in environmental testing. American Laboratory (August 1991):39-42.

*Hartgrove RW Jr., Hundley SG, Webb RE. 1977. Characterization of the hepatic mixed function oxidase system in endrin-resistant and -susceptible pine vol. Pesticide Biochemistry and Physiology 7:146-153.

8. REFERENCES

*Hassan MQ, Numan IT, Al-Nasiri N, et al. 1991. Endrin-induced histopathological changes and lipid peroxidation in livers and kidneys of rats, mice, guinea pigs and hamsters. Toxicologic Pathology 19(2):108-l 14.

*Hassoun E, Bagchi M, Bagchi D, et al. 1993. Comparative studies on lipid peroxidation and DNA-single strand breaks induced by lindane, DDT, chlordane and endrin in rats. Comp Biochem Physiol 104C(3):427-431.

Hayes JR, Hartgrove RW, Hundley SG, et al. 1975. Interaction of endrin and dieldrin with hepatic microsomal cytochrome 450 from the rat, mouse, and endrin-susceptible and resistant pine voles. Toxicol Appl Pharmacol 32:559-565.

*Hayes WJ Jr. 1963. Clinical handbook on economic poisons: Emergency information for treating poisoning. Atlanta, GA: U.S. Department of Health, Education, and Welfare, Public Health Service, Communicable Disease Center -Toxicology Section.

*HAZDAT. 1995. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HAZDAT. 1996. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HeIlou J, Warren WG, Payne JF. 1993. Organochlorines including polychlorinated biphenyls in muscle, liver, and ovaries of cod, Gadus morhua. Arch Environ Contam Toxicol 25:497-505.

*Hermanutz R. 1978. Endrin and malathion toxicity to flagfish (Jordanella floridae). Arch Environ Contam Toxicol 7:159-168.

*Hermmanutz RO, Eaton JG, Mueller LH. 1985. Toxicity of endrin and malathion mixtures to Flagfish (Jordanella floridae). Arch Environ Contam Toxicol 14:307-314.

*Hogmire HW, Weaver JE, Brooks JL. 1990. Survey for pesticides in wells associated with apple and peach orchards in West Virginia. Bull Environ Contam Toxicol 44:81-86.

*Hoogendam I, Versteeg JPJ, DeVlieger M. 1962. Electroencephalograms in insecticide toxicity Arch Environ Health 4:92-100.

*Hoogendam I, Versteeg JPJ, DeVlieger M. 1965. Nine years' toxicity control in insecticide plants. Arch Environ Health IO:441448

*Hopper M, King JW. 1991. Enhanced supercritical fluid carbon dioxide extraction of pesticides from foods using pelletized diatomaceous earth. J Assoc Off Anal Chem 74(4):661-666.

*Howard PH. 1991. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Vol 3: Pesticides Lewis Publishers. 349-361.

*HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. November 1994.

8. REFERENCES

*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. November 1995.

*Hundley HK, Cairns T, Luke MA, et al. 1988. Pesticide residue findings by the Luke method in domestic and imported foods and animal feeds for fiscal years 1982-1986. J Assoc Off Anal Chem 71(5):875-892.

*Hunter J, Maxwell JD, Stewart DA, et al. 1972. Increased hepatic microsomal enzyme activity from occupational exposure to certain organochlorine pesticides. Nature 237:399-401,

*Hutson DH. 1981. The metabolism of insecticides in man. Prog Pestic Biochem 1:247-285.

*Hutson DH, Baldwin MK, Hoadley EC. 1975. Detoxication and bioactivation of endrin in the rat. Xenobiotica 5:697-714.

*IARC. 1974. IARC monographs on the evaluation of carcinogenic risk of chemicals to man: Some organochlorine pesticides. Vol 5. World Health Organization, Lyon, France.

*IARC. 1987. IARC monographs on the evaluation of carcinogenic risk to humans. Supplement 7. World Health Organization, Lyon, France.

*IRIS. 1994. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. May 1994.

*IRPTC. 1985. Treatment and disposal methods for waste chemicals. International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland. December 1985.

IRPTC. 1989. IRPTC data profile on: Endrin. International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland. January 1989.

*Janik F, Wolf HU. 1992. The Ca2+-transport-ATPase of human erythrocytes as an *in vitro* toxicity test system--acute effects of some chlorinated compounds. J Appl Toxicol 12:351-358.

*Jaquess AB, Winterlin W, Peterson D. 1989. Feasibility of toxaphene transport through sandy soil. Bull Environ Contam Toxicol 42:417-423.

*Jarvinen AW, Tyo RM. 1978. Toxicity to fathead minnows of endrin in food and water. Arch Environ Contam Toxicol 7:409-421.

*KAN-DO Office and Pesticides Team. 1995. Accumulated pesticides and industrial chemical findings from a ten-year study of ready-to-eat foods. Journal of AOAC International.

Kanja LW, Skaare JU, Ojwang SBO, et al. 1992. A comparison of organochlorine pesticide residues in maternal adipose tissue, maternal blood, cord blood, and human milk from mother/infant pairs. Arch Environ Contam Toxicol 22:21-24.

8. REFERENCES

*Kavlock RJ, Chemoff N, Hanisch RC, et al. 1981. Perinatal toxicity of endrin in rodents. II. Fetotoxic effects of prenatal exposure in rats and mice. Toxicology 21:141-150.

*Kavlock RJ, Chemoff N, Rogers EH. 1985. The effect of acute maternal toxicity on fetal development in the mouse. Teratogenesis Carcinogen Mutagen 5:3-13.

*Kawamura Y, Sekita H, Sasaki K, et al. 1982. Analytical method for ethoprop (mocap) in agricultural crops. J Food Hyg Sot Japan 23:81-85.

*Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol Environ Safety 4:26-38.

*Kennicutt MC, Wade BJ, Presley AG, et al. 1994. Sediment contaminants in Casco Bay, Maine: Inventories, sources, and potential for biological impact. Environ Sci Technol 28(1):1-15.

*Kettering Laboratory. 1969. Effects exerted upon beagle dogs during a period of two years by the introduction of 1,2,3,4,10, 10-hexachloro- 6,7,- epoxy-1,4,4a,5,6,7,8,8a-octahydro -1,4-endo, endo-5,8-dimethanonaphthalene into their daily diets. Cincinnati, OH. Report to Velsicol Chemical Corporation.

*Kettering Laboratory. 1971. The reproductive capacity among dogs fed diets containing endrin. Prepared by The Kettering Laboratory in the Dept. of Environmental Health, College of Medicine, Univ. of Cincinnati for Velsicol Chemical Corp.

*Kintz P, Baron L, Tracqui A, et al. 1992. A high endrin concentration in a fatal case. Forensic Sci Int 54(2):177-180.

*Klaasen CD, Amdur MD, Doull J. 1986. Casarett and Doull’s toxicology. 3rd ed. New York, NY: MacMillan Publishing, 547-549.

*Klevay LM. 1971. Endrin excretion by the isolated perfused rat liver: A sexual difference (35385) Department of Environmentat Health, University of Cincinnati, College of Medicine, Cincinnati, OH.

*Knoevenagel K, Himmelreich R. 1976. Degradation of compounds containing carbon atoms by photooxidation in the presence of water. Arch Environ Contam Toxicol 4:324-333.

*Kodavanti PRS, Mehrota BD, Chetty SC, et al. 1988. Effect of selected insecticides on rat brain synaptosomal adenylate cyclase and phospodiesterase. J Toxicol Environ Health 25:207-215.

*Korte F, Klein W, Weisgerber, et al. 1970. Recent results in studies on the fate of chlorinated insecticides. Inter-American Conference on Toxic and Occupational Medicine, 6th Pesticides Symposia, 51-56.

*Kraut-Vass A, Thoma J. 1991. Performance of an extraction disk in synthetic organic chemical analysis using gas chromatograph-mass spectrometry. J Chromatog 538:233-240.

*Kutz FW, Yobs AR, Yang HSC. 1976. National pesticide monitoring programs. In: Lee RE Jr., ed. Air pollution from pesticides and agricultural processes. Cleveland, OH: CRC Press.

8. REFERENCES

*Leblanc GA. 1995. Trophic-level differences in the bioconcentration of chemicals: Implications in assessing environmental biomagnification. Environ Sci Technol 29:154-160.

*Lee RF Jr. 1977. Fate of petroleum components in estuarine waters of the southeastern United States. Proceedings of 1977 Oil Spill Conference: Prevention, behavior, control, cleanup, March 8-10, 1977. American Pesticide Institute, 611-616.

*Lee TP, Moscati R, Park BH. 1979. Effects of pesticides on human leukocyte functions. Res Comm in Chem Pathol and Pharmacol 23(3):597-609.

*Lewis RG, Lee RE. 1976. Air pollution from pesticides: Sources, occurrences and dispersions. In: Lee RE, ed. Air pollution from pesticides and agricultural processes. Cleveland, OH: CRC Press.

*Ligocki MP, Pankow JF. 1985. Assessment of adsorption/solvent extraction with polyurethane foam and adsorption/thermal desorption with Tenax-GC for the collection and analysis of ambient organic vapors. Anal Chem 57:1138-1144.

*Ling Y-C, Huang I-P. 1995. Multiresidue matrix solid phase dispersion method for determining 16 organochlorine pesticides and polychlrinated biphenyls in fish. Chromatographia 40(5-6):259-266.

Long AR, Crouch MD, Barker SA. 1991b. Multiresidue matrix solid phase dispersion (MSPD) extraction and gas chromatographic screening of nine chlorinated pesticides in catfish (Ictalurus punctatus) muscle tissue. J Assoc Off Anal Chem 74:667-670.

*Long AR, Soliman MM, Barker SA. 1991. Matrix solid phase dispersion (MSPD) extraction and gas chromatographic screening of nine chlorinated pesticides in beef fat. J Assoc Off Anal Chem 74:493-496.

*Lopez-Avila V, Bauer K, Milanes J, et al. 1993. Evaluation of Soxtec extraction procedure for extracting organic compounds from soils and sediments. J AOAC International 76:864-880.

*Lopez-Avila V, Dodhiwala NS, Becker WF. 1990. Supercritical fluid extraction and its application to environmental analysis. J Chromatographic Sci 28:468-476.

*Lott HM, Barker SA. 1993. Extraction and gas chromatographic screening of 14 chlorinated pesticides in crayfish (Procambarus clarkii) hepatopancreas. J AOAC International 76:663-668.

*Lowe JI. 1966. Some effects of endrin on estuarine fishes. In: Proceedings 19th Annual Conference of Southeastern Association of Game and Fish Commissioners, 271-276.

*Ludke JL. 1976. Organochlorine pesticide residues associated with mortality: Additivity of chlordane and endrin. Bull Environ Contam Toxicol 16:253-260.

Luke MA, Masumoto HT, Cairns T, et al. 1988. Levels and incidences of pesticide residues in various foods and animal feeds analyzed by the Luke Multiresidue methodology for fiscal year 1982-1986. J Assoc Off Anal Chem 71:415-433.

*Lyman WJ. 1990. Handbook of Chemical Property Estimation Methods. American Chemical Society, Washington, DC, 4-l-4-9.

8. REFERENCES

*Marble LK, Delfino JJ. 1988. Extraction and solid phase cleanup methods for pesticides in sediment and fish. American Laboratory 23-32.

*Marsh JM. 1993. Assessment of nonpoint source pollution in stormwater runoff in Louisville, (Jefferson County) Kentucky, USA. Arch Environ Contam Toxicol 25:446-455.

*Maslansky CJ, Williams GM. 1981. Evidence for an epigenetic mode of action in organochlorine pesticide hepatocarcinogenicity: A lack of genotoxicity in rat, mouse, and hamster hepatocytes. J Toxicol Environ Health 8:121-130.

*Mason JW, Rowe DR. 1976. The accumulation and loss of dieldrin and endrin in the eastern oyster. Arch Environ Contamin Toxicol 4:349-360.

*Mathews TD. 1994. Contaminants in recreationally important estuarine finfish from South Carolina. Bull Environ Contam Toxicol 53:412-419.

*Maule A, Plyte S, Quirk V. 1987. Dehalogenation of organochlorine insecticides by mixed anaerobic microbial populations. Pesticide Biochemistry and Physiology 27:229-236.

*McGregor DB, Brown AG, Howgate S, et al. 19 91 . Responses of the L5178Y mouse lymphoma cell forward mutation assay V: 27 Coded chemicals. Environmental and Molecular Mutagenesis 17:196-219.

*Meena K, Gupta PK, Bawa SR. 1978. Endrin-induced toxicity in normal and irradiated rats. Environ Res 16:373-382.

*Mehorta BD, Moorthy KS, Ravichandra R, et al. 1989. Effects of cyclodiene compounds on calcium pump activity in rat brain and heart. Toxicology 54:17-29.

*Merck Index. 1989. Merck index: An encyclopedia of chemicals, drugs, and biologicals. 1lth ed. Budavari S, ed. Rahway NJ: Merck & Co., Inc.

Mes J, Davies DJ, Turon D, et al. 1986. Levels and trends of chlorinated hydrocarbon contaminants in the breast milk of Canadian women. Food Add Contam 3:313-322.

Mes J, Doyle JA, Adams BR, et al. 1984. Polychlorinated biphenyls and organochlorine pesticides in milk and blood of Canadian women during lactation. Arch Environ Contam Toxicol 13:217-223.

*Metcalf RL, Kapoor IP, Lu P-Y, et al. 1973. Model ecosystem studies of the environmental fate of six organochlorine pesticides. Environ Health Perspect June: 35-44.

Michael LC, Pellizari ED, Wiseman RW. 1988. Development and evaluation of a procedure for determining volatile organics in water. Environ Sci Technol 22:565-570.

*Miller PE, Fink GB. 1973. Brain serotonin level and pentylenetetrazol seizure threshold in dieldrin and endrin treated mice. Proc West Pharmacol Sot 16:195-197.

*Minyard JP Jr, Roberts WE. 1991. State findings on pesticide residues in foods--l 988 and 1989. J Assoc Off Anal Chem 74:438-452.

8. REFERENCES

*Molto JC, Lejeune B, Prognon P, et al. 1994. GC-MS determination of organochlorine pesticide in five medicine plants. Int J Environ Anal Chem 54:81-91.

*Moriya M, Ohta T, Watanbe K, et al. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185-216.

Moser GJ, Smart RC. 1989. Hepatic tumor-promoting chlorinated hydrocarbon stimulate protein kinase C activity. Carcinogenesis 10(5):851-856.

*Mount DI, Putnicki GJ. 1966. Summary report of 1963 Mississippi fish kill. In: Trefethen JB, ed. Transactions of the thirty-first North American wildlife and natural resources conference. Washington, DC: Wildlife Management Institute 177-184.

Murayama J-I, Ishiwata M, Fukui M, et al. 1990. Comparative acute cytotoxicities of 37 xenobiotics detected in drinking water to rat hepatocyte primary culture. Eisei Kagaku 36(4):267-276.

*Murray HE, Beck JN. 1990. Concentrations of selected chlorinated pesticides in shrimp collected from the Calcasieu River/Lake complex, Louisiana. Bull Environ Contam Toxicol 44:798-804.

Mussalo-Rauhamaa H, Hasanen E, Pyysalo H, et al. 1990. Occurrence of beta-hexachlorocyclohexane in breast cancer patients. Cancer 66(10):2124-2128.

Nagelsmit A, van Vliet PW, van der Wiel-Wetzels WAM, et al. 1979. Porphyrins as possible parameters for exposure to hexachlorocyclopentadiene, allylchloride, epichlorohydrin and endrin. In: Strik JJTWA and Koeman JH, eds. Chemical porphyria in man. Elsevier/North Holland Biomedical Press, 55-61.

*Nakamura Y, Tonogai Y, Sekiguchi Y, et al. 1994. Multiresidue analysis of 48 pesticides in agricultural products by capillary gas chromatography. J Agric Food Chem 42(11):2508-2518.

*Narahashi T. 1991. Transmitter-activated ion channels as the target of chemical agents. Adv Exp Med Biol 287:61-72.

NAS. 1977. Drinking water and health. Washington, DC: National Academy of Sciences, 556-568.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*Nash RG. 1983. Comparative volatilization and dissipation rates of several pesticides from soil. J Agric Food Chem 31:210-217.

*Nash RG. 1984. Extraction of pesticides from environmental samples by steam distillation. J Assoc Off Anal Chem 67:199-203.

*Nash RG, Harris WG. 1973. Chlorinated hydrocarbon insecticide residues in crops and soil. J Environ Qual 2:267-273.

8. REFERENCES

Nash RG, Wells MJ, Smith AE, et al. 1986. Pesticide residues in environmental samples. In: Zweig G, Sherma J, eds. Analytical methods for pesticides and plant growth regulators. Vol 15. New York, NY: Academic Press, 247-286.

*Nash RG, Woolson EA. 1967. Persistence of chlorinated hydrocarbon insecticides in soils. Science 157:924-927.

*NATICH. 1992. NATICH data base report of federal, state, and local air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, National Air Toxics Information Clearinghouse. EPA-453\R-92-008.

*NCI. 1978. Bioassay of technical-grade endrin for possible carcinogenicity. Bethesda, MD: National Cancer Institute, Division of Cancer Cause and Prevention. NCI-CG-TR 12.

*NIOSH. 1990. NIOSH pocket guide to chemical hazards. Washington, DC: US. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute of Occupational Safety and Health.

*NIOSH. 1992. Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements. U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health, Cincinnati, OH.

*NLM. 1988. Chemline. National Library of Medicine, Bethesda, MD. December 1988.

*Numan IT, Hassan MQ, Stohs SJ. 1990a. Endrin-induced depletion of glutathione and inhibition of glutathione peroxidase activity in rats. Gen Pharmac 21(5):625-628.

*Numan IT, Hassan MQ, Stohs SJ. 1990b. Protective effects of antioxidants against endrin-induced lipid peroxidation, glutathione depletion, and lethality in rats. Arch Environ Contam Toxicol 19:302-306.

*OSHA. 1974. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 1989. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*Osowski SL, Brewer LW, Baker OE, et al. 1995. The decline of mink in Georgia, North Carolina, and South Carolina: The role of contaminants. Arch Environ Contam Toxicol 29:418-423.

*OTA:1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Office of Technology Assessment, Washington, DC. OTA-BA-438.

*Ottevanger CF, Van Sittert NJ. 1979. Relation between anti-12-hydroxy-endrin excretion and enzyme induction in workers involved in the manufacture of endrin. In: Strik JJ, Koeman JH, eds., Chemical porphyria in man. Amsterdam: Elsevier/North-Holland Biomedical Press, 123-129.

*Ottolenghi AD, Haseman JK, Suggs F. 1974. Teratogenic effects of aldrin, dieldrin, and endrin in hamsters and mice. Teratology 9:11-16.

8. REFERENCES

*Pandey BB. 1978. A note on endrin poisoning in bullocks. Indian Vet J 55:253.

*Parkinson RW, Wang TC, White JR, et al. 1993. Distribution and migration of pesticide residues in mosquito control impoundments. St. Lucie County, Florida, USA. Environmental Geology 22:26-32.

*Patil KC, Matsumura F, Boush GM. 1970. Degradation of endrin, aldrin, and DDT by soil microorganisms. Appl Microbial 19:879-881.

*Patil KC, Matsumura F, Boush GM. 1972. Metabolic transformation of DDT, dieldrin, aldrin, and endrin by marine microorganisms. Environ Sci Technol 6:629-632.

Pawar SS, Kachole MS. 1978. Hepatic and renal microsomal electron transport reactions in endrin treated female guinea pigs. Bull Environ Contam Toxicol 20:199-205.

Petrella VJ, Fox JP, Webb RE. 1975. Endrin metabolism in endrin-susceptible and resistant strains of pine mice. Toxicol Appl Pharmacol 34:283-291.

*Petty JD, Huckins JN, Martin DB. 1995. Use of semipermeable membrane devices (SPMDS) to determine bioavailable organochlorine pesticide residues in streams receiving irrigation drainwater. Chemosphere 30(10):1891-1903.

*Phillips DD, Pollard GE, Soloway SB. 1962. Thermal isomerization of endrin and its behavior in gas chromatography. J Agric Food Chem 10(3):217-221.

*Plumb RH. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. GWMR 7:94-100.

*Prapamontol T, Stevenson D. 1991. Rapid method for the determination of organochlorine pesticides in milk. J Chromatog 552:249-257.

*Probst GS, McMahon RE, Hill LE, et al. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ Mutagen 3:11-32.

*Proctor NH, Hughes JP, Fischman ML. 1988. Chemical hazards of the workplace. 2nd ed. Philadelphia, PA: J.B. Lippincott Co.

*Quick MP, Shaw IC, Manser PA. 1989. A surprising case of endrin poisoning in dogs. Journal of the Forensic Science Society 29(5):331-338.

R.U.P. 1994. EPA Pesticide Information Network Restricted Use Products (RUP) File. Office of Pesticide Programs (On-line BBS Database), Washington, DC.

*Ressang AA, Titus I, Andar RS, et al. 1959. Aldrin, dieldrin and endrin intoxication in cats. Communicationes Veterinariae 2:71-88.

*Reuber MD. 1978. Carcinomas, sarcomas and other lesions in Osborne-Mendel rats ingesting endrin. Exp Cell Biol 46:129-145.

8. REFERENCES

*Ribbens PH. 1985. Mortality study of industrial workers exposed to aldrin, dieldrin and endrin. Int Arch Occup Environ Health 5675-79.

*Richardson LA, Lane JR, Gardner WS, et al. 1967. Relationship of dietary intake to concentration of dieldrin and endrin in dogs. Bull Environ Cont & Toxicol 2(4):207-219.

Rotenberg SA, Weinstein IB. 1991. Two polychlorinated hydrocarbons cause phospholipid-dependent protein kinase C activation *in vitro* in the absence of calcium. Molecular Carcinogenesis 4:477-481.

*Rowley DL, Rab MA, Hardjotanojo W, et al. 1987. Convulsions caused by endrin poisoning in Pakistan. Pediatrics 79:928-934.

*Roy RR, Albert RH, Wilson P, et al. 1995. U. S. food and drug administration pesticide program: Incidence level monitoring of domestic and imported pears and tomatoes. Journal of AOAC International 78(4):930-940.

*Roylance KJ, Jorgensen CD, Booth GM, et al. 1985. Effects of dietary endrin on reproduction of mallard ducks (Anas platyrhynchos). Arch Environ Contam Toxicol 14:705-711.

*RTECS. 1994. Registry of Toxic Effects of Chemical Substances (RTECS). National Institute for Occupational Safety and Health (NIOSH). Computer database online.

*Runhaar EA, Sangster B, Greve PA, et al. 1985. A case of fatal endrin poisoning. Hum Toxicol 4:241-247.

*Russo MV, Goretti G, Liberti A. 1993. Rapid determination of chlorinated pesticides using CN-bonded cartridges followed by GC-ECD. Chromatographia 35:290-294.

*Saleh MA, Abou Zied M, El-Baroty G, et al. 1993. Gamma aminobutyric acid radioreceptor-assay, a possible biomarker for human exposure to certain agrochemicals. J Environ Sci Health B28:687-699.

Sax NI, Lewis RJ Sr. 1987. Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Company, 462.

*Schafer ML, Peeler JT, Gardner WS, et al. 1969. Pesticides in drinking water: Waters from the Mississippi and Missouri Rivers. Environ Sci Technol 3:1261-1269.

*Schattenberg HJ III, Hsu J-P. 1992. Pesticide residue survey of produce from 1989 to 1991. Journal of AOAC International 75(5):925-933.

Scheufler E, Rozman K. 1986. Industrial and environmental chemicals. In: Rozman K, Hanninen 0, eds. Gastrointestinal toxicology. Amsterdam: Elsevier, 404-405.

*Schimmel SC, Parrish PR, Hansen DJ, et al. 1975. Endrin: Effects on several estuarine organisms. In: Proceedings 28th Annual Conference of Southeastern Association of Game and Fish Commissioners, 187-194.

*Schmitt CJ, Zajicek JL, Peterman PH. 1990. National contaminant biomonitoring program: Residues of organochlorine chemicals in U.S. freshwater fish, 1976-1984. Arch Environ Contam Toxicol 19:748-781.

*Schmitt CJ, Zajicek JL, Ribick MA. 1985. National pesticide monitoring program: Residues of organochlorine chemicals in freshwater fish, 1980-81. Arch Environ Contam Toxicol 14:225-260.

*Schneider JF, Schneider KR, Spiro SE, et al. 1991. Evaluation of gas chromatography/matrix isolation-infrared spectroscopy for the quantitative analysis of environmental samples. Applied Spectroscopy 45:566-571.

Seidenberg JM, Becker RA. 1987. A summary of the results of 55 chemicals screened for developmental toxicity in mice. Teratogenesis Carcinog Mutagen 7:17-28.

Seifert J. 1989. Teratogenesis of polychlorocycloalkane insecticides in chicken embryos resulting from their interactions at the convulsant recognition sites of the GABA (pro)receptor complex. Bull Environ Contam Toxicol 42:707-715.

Shara MA, Dickson PH, Bagchi D, et al. 1992. Excretion of formaldehyde, malondialdehyde, acetaldehyde and acetone in the urine of rats in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin, paraquat, endrin and carbon tetrachloride. J Chromatography 576:221-233.

*Sharom MS, Miles JR, Harris CR, et al. 1980a. Behavior of 12 insecticides in soil and aqueous suspensions of soil and sediment. Water Res 14:1095-l100.

*Sharom MS, Miles JR, Harris CR, et al. 1980b. Persistence of 12 insecticides in water. Water Res 14:1089-1093.

*Singh AJ, Renzi FP. 1993. Drug withdrawal syndromes. In: Viccellio P. Handbook of Medical Toxicology. Boston, MA: Little Brown and Company, 631-635.

*Sittig M, ed. 1980. Pesticide manufacturing and toxic materials control encyclopedia. Park Ridge, NJ: Noyes Data Corporation, 366-373.

*Sittig M. ed. 1994. Domestic drinking water. World wide limits for toxic and hazardous chemicals in air, water, and soil. Park Ridge, NJ: Noyes Data Corporation, 338-339.

*Snyder JL, Grob RL, McNally ME, et al. 1992. Comparison of supercritical fluid extraction with classical sonication and soxhlet extractions for selected pesticides. Anal Chem 64:1940-1946.

*Sobti RC, Krishan A, Davies J. 1983. Cytokinetic and cytogentic effect of agricultural chemicals on human lymphoid cells *in vitro*. II. Organochlorine pesticides. Arch Toxicol 52:221-231.

*Speck LB, Maaske CA. 1958. The effects of chronic and acute exposure of rats to endrin. AMA Arch Ind Health 18:268-272.

*Spicer PE, Kereu RK. 1993. Organochlorine insecticide residues in human breast milk: A survey of lactating mothers from a remote area in Papua New Guinea. Bull Environ Contam Toxicol 50:540-546.

8. REFERENCES

*SRC. 1994a. Syracuse Research Center. Henry's Law Constant Program (HENRYWIN, version 2.50, serial H0142). Chemical Hazard Assessment Division, Environmental Chemistry Center, Syracuse, NY.

*SRC. 1994b. Syracuse Research Center. Aqueous Hydrolysis Rate Program (HYDROWIN, version lSOa, serial HOY0126). Chemical Hazard Assessment Division, Environmental Chemisty Center, Syracuse, NY.

*SRC. 1995a. Syracuse Research Center. Atmospheric Oxidation Program (AOPWIN, version 1.65, serial 0156). Chemical Hazard Assessment Division, Environmental Chemistry Center, Syracuse, NY.

*SRC. 1995b. Syracuse Research Center. Octanol-Water Partition Coefficient Program (KOWWIN, Version 1.37, Serial L0148). Chemical Hazard Assessment Division, Environmental Chemistry Center, Syracuse, NY.

*SRI. 1987. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 847.

SRI International. 1981. National screening program for organics in drinking water: Part II. Report to U.S. Environmental Protection Agency, Office of Drinking Water, Washington, DC by SRI International, Menlo Park, CA (author, Boland PA).

*Stalling DL, Tindle RC, Johnson JL. 1972. Cleanup of pesticide and polychlorinated biphenyl residues in fish extracts by gel permeation chromatography. J Assoc Off Anal Chem 55:32.

*Stanley JS. 1986. Broad scan analysis of the FY82 national human adipose tissue survey specimens: Volume I - executive summary. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA/560/5-86/037.

*Staples CA, Werner AF, Hoogheem TJ. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environmental Toxicology and Chemistry 4:131-142.

*Storm DL. 1994. Chemical monitoring of California's public drinking water sources: Public exposures and health impacts. In: Wang RGM, ed. Water Contamination and Health New York, NY: Marcel Dekker, Inc, 67-124.

*Strachan WMJ. 1988. Toxic contaminants in rainfall in Canada:1984. Environmental Toxicology and Chemistry 7:871-877.

*Swarm RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res Rev 85:17-28.

*Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-1518.

*Tang PH, Ho JS, Eichelberger JW. 1993. Determination of organic pollutants in reagent water by liquid-solid extraction followed by supercritical fluid elution. J AOAC International 76:72-82.

8. REFERENCES

*Tatken RL, Lewis RJ Sr, eds. 1983. Registry of toxic effects of chemical substances. 1981-1982 ed. Vol 2. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute of Occupational Safety and Health.

*Teshke K, Kelly SJ, Wiens M, et al. 1993. Concentrations of organochlorine pesticides in the adipose tissue of British Columbia. Canadian Journal of Public Health 84(3):192-196.

*Tewari SN, Sharma IC. 1978. Study of the distribution of chlorinated organic pesticides in different autopsy materials of human poisoning cases using TLC and UV spectrophotometric techniques. Chemical Era 215-218.

*Thomas RG. 1982. Volatilization from water. Handbook of Chemical Proper Estimation Methods, 15-1-15-34.

*Thomas RG. 1990. Volatilization from water. Handbook of Chemical Proper Estimation Methods, 15-1-15-17.

*TOMES. 1994. TOMES (Toxicology, Occupational Medicine and Environmental Series) electronic database. Endrin; Endrin metabolites. Micromedex, Inc. Vol. 78.

*Tomkins BA, Merriweather R, Jenkins RA. 1992. Determination of eight organochlorine pesticides at low nanogram/liter concentrations in groundwater using filter disk extraction and gas chromatography. J AOAC International 75:1091-1099.

*Treon JF, Cleveland FP, Cappel J. 1955. Toxicity of endrin for laboratory animals. Agricultural and Food Chemistry 3:842-848.

*TRI. 1991. Toxic chemical release inventory reporting form R and instructions. Revised 1990 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Super-fund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC. EPA-560/4-91-007.

*Trotter WJ. 1993. Pesticide residues in cornposited milk collected through the U. S. Pasteurized Milk Network. Journal of AOAC International 76(6):1220-1225,

*Tyler-Schroeder DB. 1979. Use of the grass shrimp (Palaemonetes pugio) in a life-cycle toxicity test. In: Marking LL and RA Kimerle, eds. Aquatic Toxicology, ASTM STP 667. American Society for Testing and Materials, 159-170.

*USDA. 1995. U. S. Department of Agriculture, National Agricultural Pesticide Impact Assessment Program (NAPIAP), Reregistration Notification Network (RNN). 3(11):l-l,l-4.

*Valkenburg CA, Munslow WD, Butler LC. 1989. Evaluation of modifications to extraction procedures used in analysis of environmental samples from Superfund sites. J Assoc Off Anal Chem 72:602-608.

*Vance BD, Drummond W. 1969. Biological concentration of pesticides by algae. J Am Water Works Assoc 61:360-362.

8. REFERENCES

*Veith GD, Defoe DL, Bergstedt BV. 1979. Measuring and estimating the bioconcentration factor of chemical in fish. Environ Sci Technol 16(5):1040-1048.

*Veith GD, Kosian P. 1983. Estimating bioconcentration potential from octanol/water partition coefficients, In: Mackay et al., eds. Physical Behavior of PCAEs in the Great Lakes. Ann Arbor, MI: Ann Arbor Science Publishers, 269-282.

Velsicol Chemical Corporation. 1969. MRID No. 00030198. Available from U.S. EPA. Write Freedom of Information Office, U.S. Environmental Protection Agency, Washington, DC 20460.

*Venkat JA, Shami S, Davis K, et al. 1995. Relative genotoxic activities of pesticides evaluated by a modified SOS microplate assay. Environmental and Molecular Mutagenesis 25:67-76.

*Verschueren K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Company, 606-611.

*Versteeg JP, Jager KW. 1973. Long-term occupational exposure to the insecticides aldrin, dieldrin, endrin, and telodrin. Br J Ind Med 30:201-202.

*Viana E, Molto JC, Manes J, et al. 1994. Clean up confirmatory procedures for gas chromatographic analysis of pesticide residues, Part II. J Chromatogr 678(1):109-l 17.

*Vrij-Standhardt WC, Strik JJ, Ottevanger CF. 1979. Urinary D-glucaric acid and urinary total porphyrin excretion in workers exposed to endrin. In: Strik JJ, Koeman JH, eds. Chemical porphyria in man. Amsterdam: Elsevier/North Holland Biomedical Press, 113-121.

*Wafford KA, Sattelle DB, Gant DB, et al. 1989. Noncompetitive inhibition of GABA receptors in insect and vertebrate CNS by endrin and lindane. Pesticide Biochem Physiol 33:213-219.

Walker CH. 1981. The correlation between *in vivo* and *in vitro* metabolism of pesticides in vertebrates. In: Hutson DH, Roberts TR, eds. The metabolism of insecticides in man. Prog Pestic Biochem 1:247-285.

Walker JJ, Philips DE. 1987. An electron microscopic study of endrin induced alterations in unmyelinated fibers of mouse sciatic nerve. Neurotoxicology 8:55-64.

*Wailer K, Prendergast TJ, Slagle A, et al. 1992. Seizures after eating a snack food contaminated with the pesticide endrin: The tale of the toxic taquitos. The Western Journal of Medicine 157(6):648-651.

*Walters SM. 1986. Cleanup of samples. In: Zweig G, Sherma J. eds. Analytical methods for pesticides and plant growth regulators, Vol 15, Chap. 3. New York, NY: Academic Press:67-110.

*Webb RE, Hartgrove RW, Randolph WC, et al. 1973. Toxicity studies in endrin-susceptible and resistant strains of pine mice. Toxicol Appl Pharmacol 25:42-47.

*Weeks DE. 1967. Endrin food-poisoning: A report on four outbreaks caused by two separate shipments of endrin-contaminated flour. Bull WHO 37:499-512.

8. REFERENCES

*Wieboldt RC, Adams GE, Later DW. 1988. Sensitivity improvement in infrared detection for supercritical fluid chromatography. Anal Chem 60:2422-2427.

*Wigfield YY, Grant R. 1992. Evaluation of an immunoassay kit for the detection of certain organochlorine (cyclodiene) pesticide residues in apple, tomato, and lettuce. Bull Environ Contam Toxicol 49:342-347.

*Williams DT, LeBel GL, Junkins E. 1984. A comparison of organochlorine residues in human adipose tissue autopsy samples from two Ontario municipalities. J Toxicol Environ Health 13:19-29.

*Williams DT, LeBel GL, Junkins E. 1988. Organohalogen residues in human adipose autopsy samples from six Ontario municipalities. J Asso Off Anal Chem 71(2):410-414.

*Williams GM. 1980. Classification of genotoxic and epigenetic hepatocarcinogens using liver culture assays. Ann NY Acad Sci 349:273-282.

Williams GM, Mori H, McQueen CA. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutation Research 221:263-286.

*Wnuk M, Kelley R, Breuer G, et al. 1987. Pesticides in water samples using surface water sources. Des Moines, IA: Iowa Dept. of Natural Resources and Iowa University Hygienic Laboratory. PB88-136916.

*Wolfe HR, Durham WF, Armstrong JF. 1963. Health hazards of the pesticides endrin and dieldrin: Hazards in some agricultural uses in the Pacific Northwest. Arch Environ Health 6:458-464.

*Woo OF. 1990. Chlorinated hydrocarbon pesticides in poisoning and drug overdose. Olson K, ed. Norwalk, CT: Appleton & Lange, 117-l 18.

*Worthington CR, Walker SB. 1983. The Pesticide manual. The British Crop Protection Council. 7th edition, 235.

*Yess NJ, Gunderson EL, Roy RR. 1993. U. S. Food and Drug Administration monitoring of pesticide residues in infant foods and adult foods eaten by infants/children. J AOAC International 76(3):492-507.

Yess NJ, Houston MG, Gunderson EL. 1991. Food and Drug Administration pesticide residue monitoring of foods:1983-1986. J Assoc Off Anal Chem 74(2):273-280.

*Young RA, Mehendale HM. 1986. Effect of endrin and endrin derivatives on hepatobiliary function and carbon tetrachloride-induced hepatotoxicity in male and female rats. Food Chem Toxicol 24:863-868.

*Zabik MJ, Schuetz RD, Burton WL, et al. 1971. Photochemistry of bioactive compounds: Studies of a major photolytic product of endrin. J Agric Food Chem 19:308-313.

Zavon MR, Hine CH, Parker KD. 1965. Chlorinated hydrocarbon insecticides in human body fat in the United States. JAMA 193(10):837-839.

8. REFERENCES

*Zeiger E, Anderson B, Haworth S, et al. 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environmental Mutagetiesis 9:1-18.

*Zlatkis A, Kim K. 1976. Column elution and concentration of volatile compounds in biological fluids. J Chromatogr 126:475-485.

9. GLOSSARY

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

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

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

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.

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.

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.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

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.

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

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

9. GLOSSARY

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

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

In Vivo-Occurring within the living organism.

Lethal Concentration $_{(Lo)}$ (LC_{Lo})-The lowest concentration of a chemical in air which has been reported to have cause 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 is expected to have caused death in humans or animals.

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

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

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose 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.

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

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to.be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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

No-Observed-Adverse-Effect Level (NOAEL)-The dose of 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.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

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).

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 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 CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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

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

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

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

Toxic Dose (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.

Uncertainty Factor (UF)- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

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 a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endrin/Endrin Aldehyde
CAS Number: ID1575000/PC8580000
Date: August 1996
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key To Figure: 47
Species: Dog

MRL: 0.002 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Treon et al. 1955

Experimental Design: (Human study details or strain, number of animals per exposure/control group, sex, dose administration details): Endrin was administered at doses of 0.15, 0.20, 0.25, 0.29, 0.49,0.53, 1.21, and 2.50 mg/kg/day in the diet of dogs for 18 days to 9.9 months, 6 days per week.

Effects Noted in Study and Corresponding Doses: Doses of 0.20 mgikg/day and greater resulted in neurotoxicity evidenced by convulsions, tremors, and degenerative lesions in the brain and systemic toxicity which included renal tubular necrosis, respiratory distress and pulmonary edema, and diffuse degenerative lesions of the heart. One animal administered diet corresponding to 0.20-0.27 mg/kg/day died after 47 days of feeding.

Dose End noint Used for MRL Derivation: Doses of 0.20 mg/kg/day and greater resulted in neurotoxicity, systemic toxicity, and death.

[X] NOAEL [ ] LOAEL 0.15 mg/kg/day

Uncertainty Factors Used in MRL Derivation:

[ ] 1 [ ] 3 [ ] l0(For use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (For extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (For human variability)

Was a Conversion Factor used from prim in food or water to a mg/body weight dose?
If so, explain: The food concentrations were presented in terms of ppm (mg endrin/kg food) and as ranges for daily dosages in relationship to body weight (mg/kg). If the minimum of each mg/kg/day range is used as a conservative estimate of dose, then the respective dose levels are: 0.15, 0.20, O-25,0.29, 0.49,0.53, 1.21, and 2.50 for the 4, 5,2/8, 8, 10,5/20, 25, and 50 ppm groups, respectively. The 0.25 mg/kg/day dose was calculated as the time-weighted average (TWA) of the 2 ppm diet (0.09 mg/kg/day) for 2.9 months and the 8 ppm diet (0.29 mg/kg/day) for the remaining 7 months. The 0.53 ppm dose was calculated as the TWA of the 5 ppm diet (0.25 mg/kg/day) for 2.9 months and the 20 ppm diet (0.97 mg/kg/day) for the remaining 1.8 months.

APPENDIX A

If an inhalation study in animals, list Conversion Factors used in determining human eauivalent dose: None.

Was a Conversion used from intermittent to continuous exnosure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL: The central nervous system is the primary target system for endrin as evidenced by reports of neurologic effects including convulsions and tremors in humans and other animal species (e.g., Curley et al. 1970; Waller et al. 1992; Deichmann et al. 1970; Treon et al. 1955).

Anency Contract (Chemical Manager): Jessilyn Taylor

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endrin/Endrin Aldehyde
CAS Number: I D1575000/PC8580000
Date: August 1996
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key To Figure: 64
Species: Dog

MRL: 0.0003 [Xl mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Kettering 1969

Experimental Design: (Human study details or strain, number of animals per exposure/control group, sex, dose administration details): Beagle dogs were fed diets containing 0, 0.0025, 0.0125, 0.025, 0.05, or 0.1 mg/kg/day endrin for 2 years.

Effects Noted in Study and Corresponding Doses: Concentrations less than 0.05 mg/kg/day endrin in the daily diet did not elicit changes in the rate of growth, food consumption, usual activities, or any of the hematologic, biochemical or pathologic criteria evaluated. One female and 2 male dogs at 0.1 mg/kg/day dietary level and one female dog at the 0.05 mg/kg/day dietary level showed evidence of, or were observed having, convulsions. Concentrations of 0.05 mg/kg/day and 0.1 mg/kg/day endrin were associated with slight to moderate vacuolation of hepatic cells. Petechial hemorrhages and cerebral edema were observed in the brain of one dog having convulsions at the time of necropsy. There were occasional slight increases in the weight of livers from dogs fed diets containing endrin at 0.05 and 0.1 mg/kg/day.

Dose End point Used for MRL Derivation: 0.025 mg/kg/day

[X] NOAEL [ ] LOAEL

Uncertainty Factors Used in MRL Derivation:
[ ] 1 [ ] 3 [ ] 10 (For use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (For extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (For human variability)

Was a Conversion Factor used from num in food or water to a mg/body weight dose?
If so, explain.

No.

If an inhalation study in animals, list Conversion Factors used in determining human equivalent dose:
None.

Was a conversion used from intermittent to continuous exposure?:
If so, explain: No.

Other additional studies or Dertinent information that lend support to this MRL:

Agencv Contract (Chemical Manager): Jessilyn Taylor

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15364 days), andchronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions'help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious

effects The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NQAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health 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, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(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 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Reference
2 □ INTERMEDIATE EXPOSURE						
	5	6	7	8	9	10
3 □ Systemic	□	□	□	□	□	□
4 □ 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE					11	
Cancer					□	
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

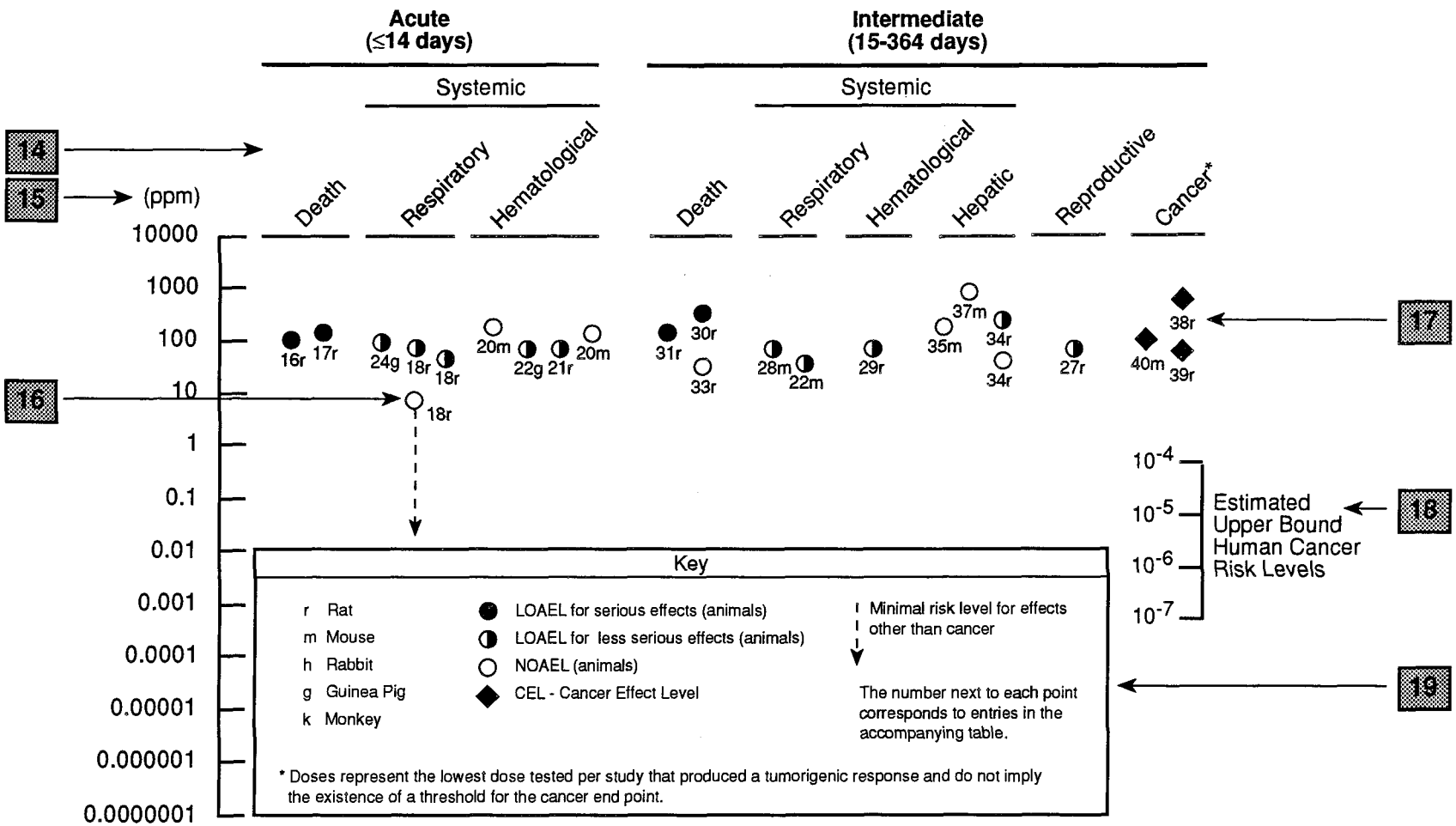
[a] The number corresponds to entries in Figure 2-1.

12 □ [b] uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section, If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk Ievels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans) In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmhg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit

STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
	alpha
	beta
	delta
	gamma
μm	micron
μg	microgram

• U.S. GOVERNMENT PRINTING OFFICE: 1996-739-324