# Toxicological Profile for Aldrin/Dieldrin

**Draft for Public Comment**

**July 2021**

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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# FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, 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 the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

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

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

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

# VERSION HISTORY

| Date | Description |
|---|---|
| July 2021 | Draft for public comment toxicological profile released |
| September 2002 | Updated final toxicological profile released |
| September 2000 | Draft for public comment toxicological profile released |
| October 1993 | Final toxicological profile released |

# CONTRIBUTORS & REVIEWERS

## CHEMICAL MANAGER TEAM

Carolyn Harper, Ph.D. (Lead)
Sam Keith, M.S., C.H.P.

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

David W. Wohlers, Ph.D.
Mario Citra, Ph.D.

SRC, Inc., North Syracuse, NY

## REVIEWERS

### Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

### Additional reviews for science and/or policy:

ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

## PEER REVIEWERS

1. David C. Dorman, DVM, PhD, DABVT, DABT; Professor of Toxicology; North Carolina State University- College of Veterinary Medicine; Fulbright- Saastamoinen Foundation Fulbright Scholar; University of Eastern Finland – Kuopio
2. James Klaunig, PhD; Professor and Director of Toxicology; Indiana University School of Medicine; Indianapolis, Indiana
3. Ivan Rusyn, MD, PhD; Professor and Chair; Department of Veterinary Integrative Biosciences; College of Vet Medicine & Biomedical Sciences; Texas A&M University; College Station, Texas

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

# CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

## 1.1 OVERVIEW AND U.S. EXPOSURES

Aldrin and dieldrin were highly chlorinated insecticides designed to control a variety of pests. Aldrin is readily converted to dieldrin under most environmental conditions and in the body. Aldrin was first produced in 1948, and dieldrin was first used in 1950. In 1970, the U.S. Department of Agriculture (USDA) canceled all uses for both aldrin and dieldrin based on concern that these chemicals are serious environmental hazards and are potentially carcinogenic. However, uses of these pesticides were not canceled by EPA until 1989.

Both aldrin and dieldrin are moderately volatile and slow to biodegrade. Large soil adsorption coefficients suggest low mobility in soils and a tendency to partition to suspended solids and sediment in the water column. Low levels of aldrin and dieldrin have been detected in soil, sediment, surface water, groundwater, and public water supplies. Dieldrin has been detected in food, such as root crops, dairy products, and meat.

Ingestion of drinking water or food items containing aldrin and/or dieldrin is the most likely route of exposure by the general population. However, exposure to aldrin and dieldrin is expected to be low since the compounds are no longer manufactured or used in the United States. In the most recently available biomonitoring data (samples taken in 2003–2004), aldrin and dieldrin serum levels were undetectable or very low. People living in areas surrounding hazardous waste sites that contain aldrin and/or dieldrin may be exposed primarily via dermal contact with, or ingestion of, contaminated soil since these compounds bind to soil particles. Aldrin and dieldrin possess high potential for bioaccumulation (based on log $K_{ow}$ values in the range of 4–6). Aldrin and dieldrin have been observed to bioconcentrate in aquatic and terrestrial ecological systems. Aldrin is readily converted to dieldrin by epoxidation in biological systems.

## 1.2 SUMMARY OF HEALTH EFFECTS

Human data regarding the health effects of aldrin and dieldrin come from reports of occupationally-exposed cohorts, studies that employed self-reported use of aldrin or dieldrin and possible associations with health outcomes, studies that evaluated possible associations between dieldrin blood levels and health outcomes, and case reports of accidental or intentional poisonings. Acute high-level exposure to

aldrin or dieldrin in humans has resulted in central nervous system excitation culminating in convulsions and ultimately death. Longer-term exposure of humans in occupational settings has also been associated with adverse effects on the central nervous system. A few case reports have attributed liver and kidney toxicity and hemolytic anemia to intentional or accidental oral exposure to aldrin or dieldrin, but these effects were not observed in larger occupational studies. In general, the epidemiological data are lacking dose-response information.

Available studies in animals employed oral exposure (via diet, gavage, or capsule). As illustrated in Figure 1-1 (aldrin) and Figure 1-2 (dieldrin), the most sensitive common targets of aldrin and dieldrin toxicity appear to be hepatic, neurological, and reproductive endpoints. Body weight and developmental endpoints appear to be sensitive targets of aldrin and/or dieldrin toxicity as well. A systematic review of noncancer endpoints resulted in the following hazard identification conclusions (see Appendix C for more information):

- Body weight effects represent a presumed health effect endpoint for humans (aldrin)
- Hepatic effects represent a presumed health effect endpoint for humans (aldrin, dieldrin)
- Neurological effects represent a presumed health effect endpoint for humans (aldrin, dieldrin)
- Reproductive effects represent a presumed health effect endpoint for humans (aldrin, dieldrin)
- Developmental effects represent a presumed health effect endpoint for humans (aldrin, dieldrin)

***Body Weight Effects.*** Decreases in body weight gain have been observed in rats and dogs exposed to aldrin in the diet for intermediate or chronic durations (Deichmann et al. 1970; NCI 1978a; Treon et al. 1955); weight loss has also been observed in dogs chronically exposed to aldrin (Fitzhugh et al. 1964).

***Hepatic Effects.*** Increased relative liver weight and histopathologic changes were observed among rats administered aldrin or dieldrin in the diet for up to 2 years (Fitzhugh et al. 1964; Treon et al. 1951a; Walker et al. 1969).

***Neurological Effects.*** Single or repeated oral exposure of laboratory animals to aldrin or dieldrin resulted in clinical signs of neurological impairment such as convulsions, tremors, twitching, and hyper-excitability; disrupted operant behavior; impaired learning; and neuronal degeneration (Burt 1975; Kitselman 1953; NCI 1978a, 1978b; Treon et al. 1951b; Walker et al. 1969).

## Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Aldrin

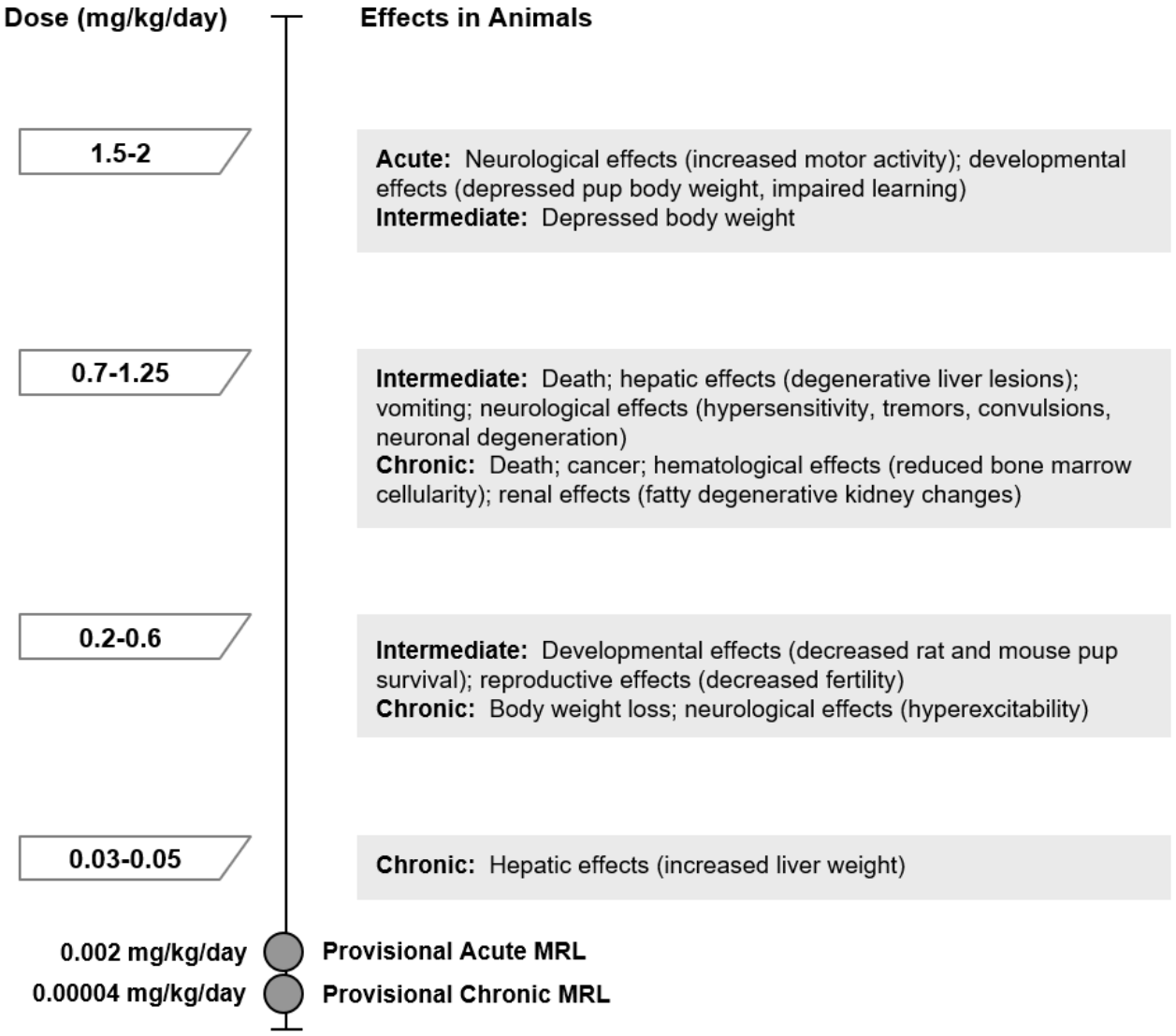
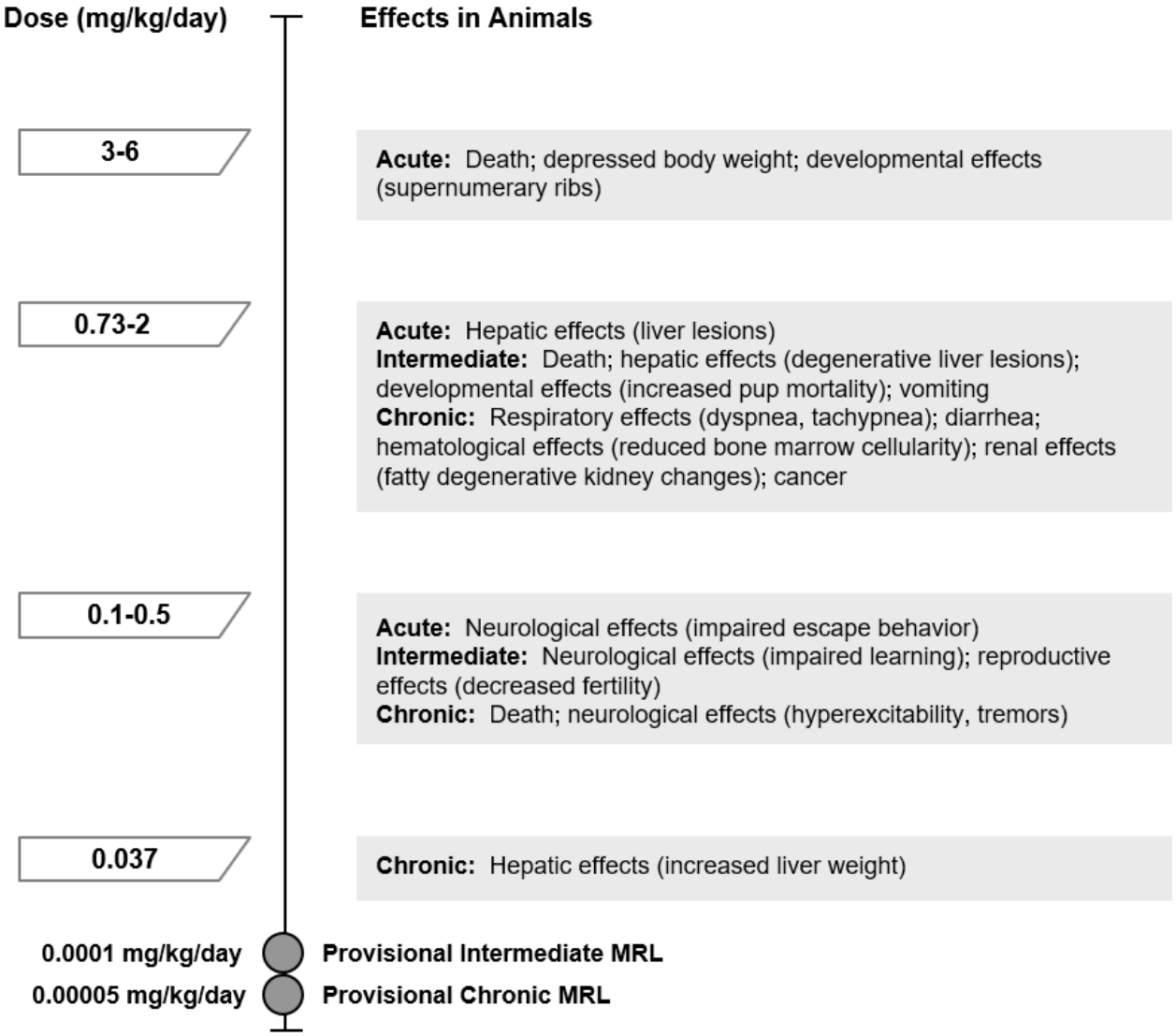


**Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Dieldrin**



***Reproductive Effects.*** In multi-generation reproduction studies in rodents, administration of aldrin or dieldrin in the diet resulted in decreased fertility (Keplinger et al. 1970; Treon et al. 1954a). Reproductive effects such as delayed estrus, reduced libido, lack of mammary function and development, and increased numbers of stillbirths were noted among dogs administered aldrin orally for 14 months prior to mating at doses as low as 0.15 mg/kg/day (Deichmann et al. 1971).

***Developmental Effects.*** Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin in animals (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975). Aldrin or dieldrin exposure during gestation has resulted in some evidence of external malformations or skeletal anomalies in animals (Chernoff et al. 1975; Ottolenghi et al. 1974).

***Cancer Effects.*** Increased incidences of liver tumors were reported in lifetime studies of multiple strains of mice administered aldrin or dieldrin in the diet (Davis and Fitzhugh 1962; Epstein 1975; Lipsky et al. 1989; Meierhenry et al. 1983; NCI 1978a; Reuber 1980; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1973).

## 1.3 MINIMAL RISK LEVELS (MRLs)

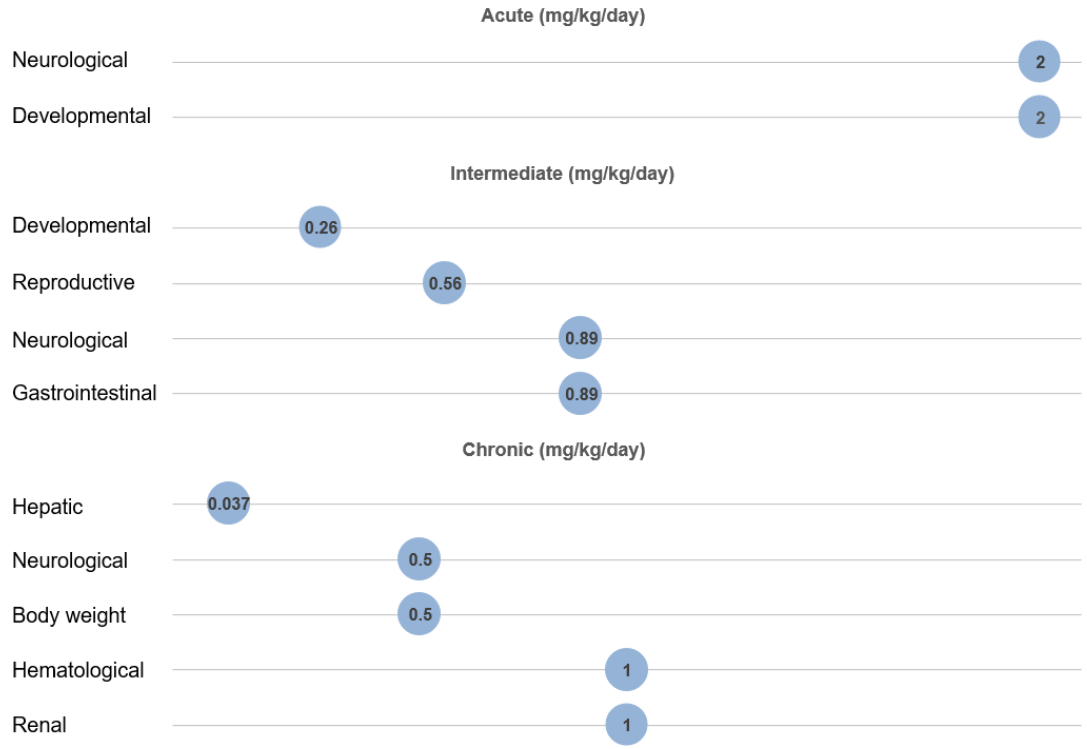
***Aldrin.*** The inhalation database was considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for aldrin.

The oral database was considered inadequate for derivation of an intermediate-duration oral MRL for aldrin. The oral database was considered adequate for derivation of acute- and chronic-duration oral MRLs for aldrin. As presented in Figure 1-3, hepatic, developmental, and neurological endpoints are the most sensitive targets of aldrin toxicity following oral exposure.

## Figure 1-3. Summary of Sensitive Targets of Aldrin – Oral

**The liver, developing organism, and nervous system are the most sensitive target of aldrin oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable exposure-response human data were identified.



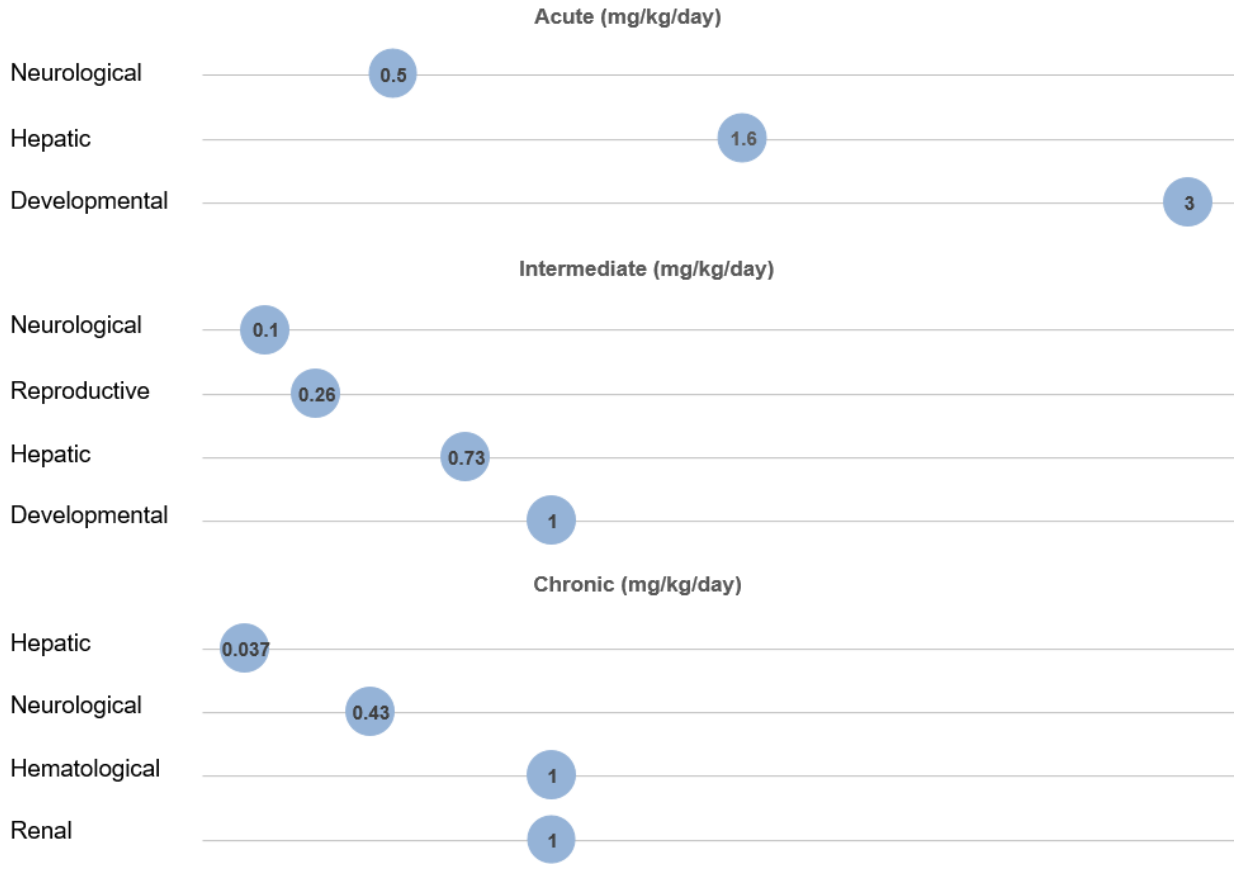

***Dieldrin.*** The inhalation database was considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for dieldrin.

The oral database was considered inadequate for derivation of an acute-duration oral MRL for dieldrin. The oral database was considered adequate for derivation of intermediate- and chronic-duration oral MRLs for dieldrin. As presented in Figure 1-4, hepatic, neurological, and reproductive endpoints are the most sensitive targets of toxicity following oral exposure.

## Figure 1-4. Summary of Sensitive Targets of Dieldrin – Oral

**The nervous system, liver, and reproductive system are the most sensitive target of dieldrin oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable exposure-response human data were identified.



The MRL values for aldrin are summarized in Table 1-1 and discussed in greater detail in Appendix A.

**Table 1-1. Minimal Risk Levels (MRLs) for Aldrin[a]**

| Exposure duration | MRL | Critical effect | Point of departure | Uncertainty factor | Reference |
|---|---|---|---|---|---|
| **Inhalation exposure (ppm)** | | | | | |
| Acute | Insufficient data for MRL derivation | | | | |
| Intermediate | Insufficient data for MRL derivation | | | | |
| Chronic | Insufficient data for MRL derivation | | | | |
| **Oral exposure (mg/kg/day)** | | | | | |
| Acute (provisional) | 0.002 | Neurotoxicity in offspring | 2 (LOAEL) | 1,000 | Al-Hachim 1971 |
| Intermediate | Insufficient data for MRL derivation | | | | |
| Chronic (provisional) | 0.00004 | Increased liver weight and histopathology | 0.037 (LOAEL) | 1,000 | Fitzhugh et al. 1964 |

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

The MRL values for dieldrin are summarized in Table 1-2 and discussed in greater detail in Appendix A.

**Table 1-2. Minimal Risk Levels (MRLs) for Dieldrin[a]**

| Exposure duration | MRL | Critical effect | Point of departure | Uncertainty factor | Reference |
|---|---|---|---|---|---|
| **Inhalation exposure (ppm)** | | | | | |
| Acute | Insufficient data for MRL derivation | | | | |
| Intermediate | Insufficient data for MRL derivation | | | | |
| Chronic | Insufficient data for MRL derivation | | | | |
| **Oral exposure (mg/kg/day)** | | | | | |
| Acute | Insufficient data for MRL derivation | | | | |
| Intermediate (provisional) | 0.0001 | Neurotoxicity | 0.01 (NOAEL) | 100 | Smith et al. 1976 |
| Chronic (provisional) | 0.00005 | Liver effects | 0.005 (NOAEL) | 100 | Walker et al. 1969 |

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

# CHAPTER 2. HEALTH EFFECTS

## 2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of aldrin/dieldrin. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 (aldrin) and Figure 2-2 (dieldrin) provide overviews of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to aldrin or dieldrin, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to aldrin or dieldrin was also conducted; the results of this review are presented in Appendix C.

Animal oral studies are presented in Table 2-1 and Figure 2-3 for aldrin and Table 2-2 and Figure 2-4 for dieldrin. Limited information is available regarding health effects in animals following inhalation or dermal exposure.

Levels of significant exposure (LSEs) 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 endpoint 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 endpoints. 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. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) are indicated in Table 2-1 and Figure 2-3 for aldrin and Table 2-2 and Figure 2-4 for dieldrin.

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

Available human data identify the nervous system as a target of aldrin and dieldrin toxicity following relatively high-level exposures. The human data lack information regarding dose-response characteristics.

Animal studies that employed the oral exposure route suggest that hepatic, neurological, reproductive, and developmental endpoints are most sensitive to aldrin and dieldrin toxicity. Body weight is also a sensitive endpoint for aldrin toxicity.

- **Hepatic effects.** Hepatic effects represent a presumed health effect endpoint for humans. Increased liver weight and histopathologic liver lesions were observed in experimental animals following oral exposure to aldrin or dieldrin.

- **Neurological effects.** Neurological effects represent a presumed health effect endpoint for humans. Clinical signs such as convulsions, tremors, twitching, and hyperexcitability; disrupted operant behavior; impaired learning; and neuronal degeneration were observed in experimental animals following oral exposure to aldrin or dieldrin.

- **Reproductive effects.** Reproductive effects represent a presumed health effect endpoint for humans. Effects such as decreased fertility, delayed estrus, reduced libido, lack of mammary

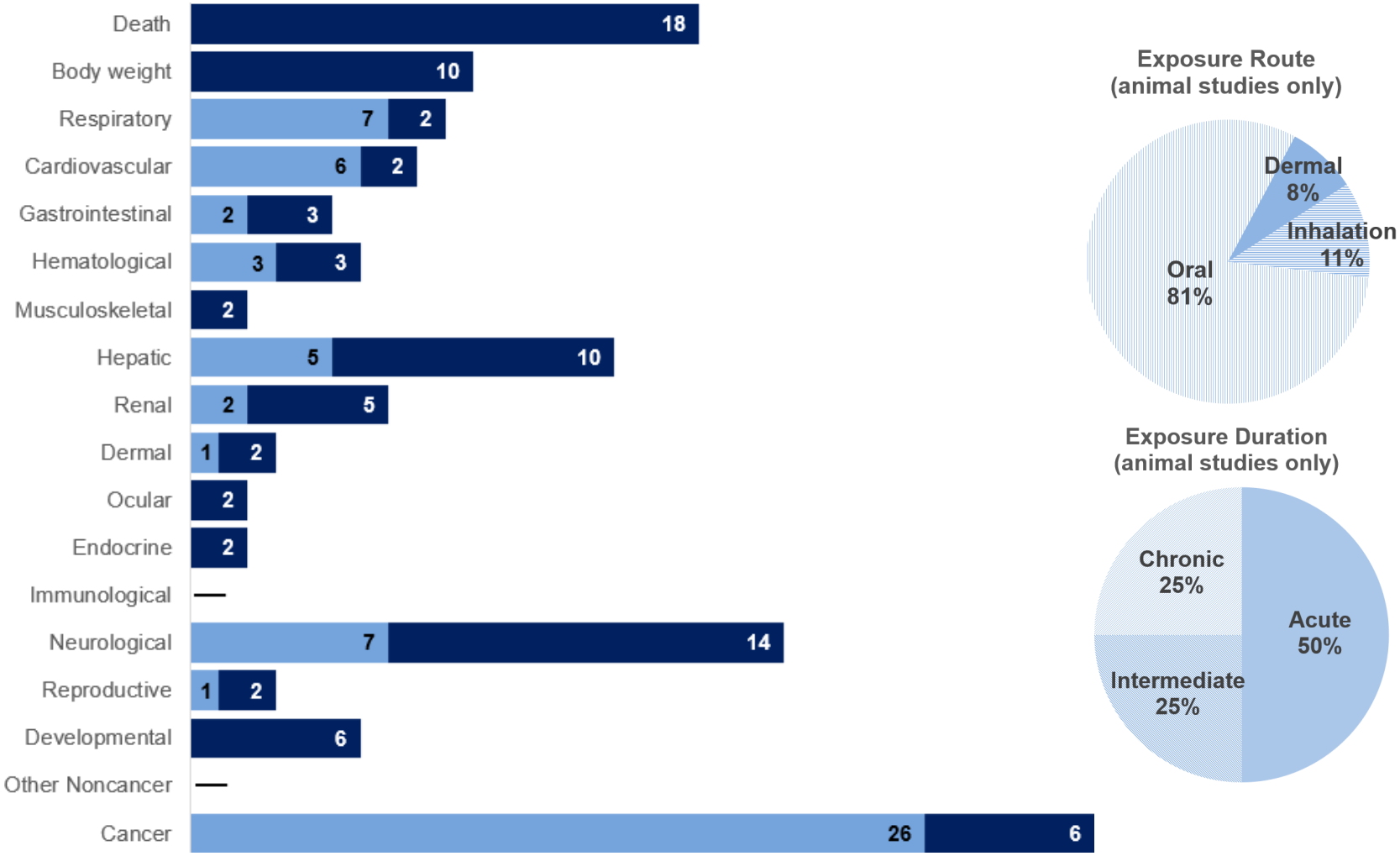
function and development, and increased numbers of stillbirths were reported in animal studies that employed oral exposure to aldrin or dieldrin.

- **Developmental effects.** Developmental effects represent a presumed health effect endpoint for humans. Decreased pup survival was observed in oral studies of maternal animals administered aldrin or dieldrin orally during gestation.

- **Body weight effects.** Body weight effects represent a presumed health effect endpoint for humans exposed to aldrin. Decreases in body weight gain and weight loss have been reported in rats and dogs orally exposed to aldrin.

## Figure 2-1. Overview of the Number of Studies Examining Aldrin Health Effects

**Most studies examined the potential body weight, hepatic, and neurological effects of aldrin**
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)

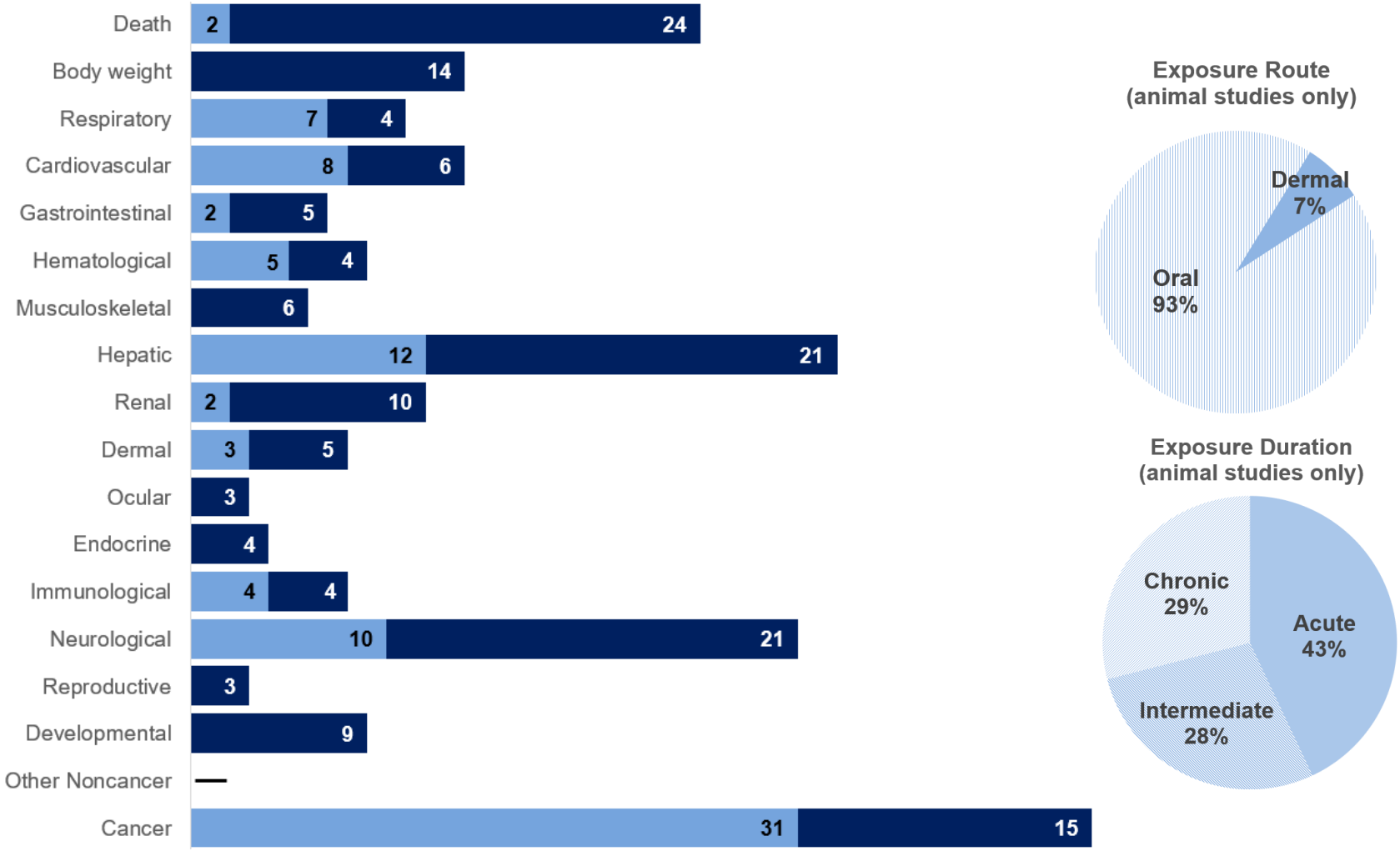



*Includes studies discussed in Chapter 2. A total of 142 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints. Exposure route and duration charts do not include human studies which likely involved multiple exposure routes of unspecified durations.

## Figure 2-2. Overview of the Number of Studies Examining Dieldrin Health Effects

**Most studies examined the potential hepatic and neurological effects of dieldrin**

Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)




*Includes studies discussed in Chapter 2. A total of 239 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints. Exposure route and duration charts do not include human studies which likely involved multiple exposure routes of unspecified durations.

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **ACUTE EXPOSURE** | | | | | | | | | |
| 1 | Rat (Sherman) NS (M, F) | Once (GO) | NS | CS, LE | Death | | | 39 M 60 F | $LD_{50}$ |
| **Gaines 1960 (technical grade; purity not specified)** | | | | | | | | | |
| 2 | Rat (Charles Foster) 6–8 M | Once (GO) | 0, 2, 5, 10 | BH, BI | Neuro | | 2 | | Increased locomotor activity; peak response at 2 hours postdosing |
| **Jamaluddin and Poddar 2001a (grade and purity not specified)** | | | | | | | | | |
| 3 | Rat (Charles Foster) 6–8 M | Once (GO) | 0, 2, 5, 10 | BH, BI | Neuro | | 2 | | Increased locomotor activity; peak response at 2 hours postdosing |
| **Jamaluddin and Poddar 2001b (grade and purity not specified)** | | | | | | | | | |
| 4 | Rat (Charles Foster) 6–8 M | Once (GO) | 0, 1, 2, 5, 10, 15, 20, 25 | BH, BI | Neuro | | 5 | | Increased locomotor activity; peak response at 10 mg/kg |
| **Jamaluddin and Poddar 2001b (grade and purity not specified)** | | | | | | | | | |
| 5 | Rat (Charles Foster) 6–8 M | Up to 30 days 1 time/day (GO) | 0, 2, 5 | BH, BI | Neuro | | 2 | | Increased locomotor activity; peak response at day 12 |
| **Jamaluddin and Poddar 2001b (grade and purity not specified)** | | | | | | | | | |
| 6 | Rat (Charles Foster) 6–8 M | Up to 30 days 1 time/day (GO) | 0, 2, 5 | BH, BI | Neuro | | 2 | | Increased locomotor activity; peak response at day 12 |
| **Jamaluddin and Poddar 2003 (grade and purity not specified)** | | | | | | | | | |

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 7 | Rat (Sprague-Dawley) 4 M | 3 days 1 time/day (GO) | 0, 1, 5, 10 | BI, CS | Neuro | | | 10 | Tremors, convulsions |
| **Mehrotra et al. 1989 (grade and purity not specified)** | | | | | | | | | |
| 8 | Rat (Carworth) 10 M, 10 F | Up to 2 weeks (F) | 0, 55 | CS, GN, HP, LE | Death | | | 55 | 100% mortality |
| | | | | | Hepatic | | | 55 | Severe liver damage |
| | | | | | Neuro | | | 55 | Convulsions, degenerative brain lesions |
| **Treon et al. 1951a (recrystallized 99% purity; technical grade 95% purity)** | | | | | | | | | |
| 9 | Rat (Carworth) 10 F | Once (GO) | NS | CS, LE | Death | | | 48.3 | $LD_{50}$ |
| **Treon et al. 1952 (≥95% purity)** | | | | | | | | | |
| 10 | Mouse (ICR/Ha Swiss) 7 F | Third trimester of pregnancy 1 time/day (GO) | 0, 2, 4 | BW, CS | Develop | | 2[b] | | Depressed pup body weight, increased electroshock seizure threshold |
| **Al-Hachim 1971 (technical grade; purity not specified)** | | | | | | | | | |
| 11 | Mouse (CD1) 9–10 F | GD 9 (GO) | 0, 25 | CS, DX, TG | Develop | | | 25 | Webbed feet |
| **Ottolenghi et al. 1974 (recrystallized; ≥99% purity)** | | | | | | | | | |
| 12 | Hamster NS F | Once GD 7, 8, or 9 (GO) | 0, 50 | CS, DX, TG | Develop | | | 50 | Up to 38% fetal mortality; 19% depressed fetal weight; increased incidences of webbed foot, cleft palate, cleft lip |
| **Ottolenghi et al. 1974 (recrystallized; ≥99% purity)** | | | | | | | | | |

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| 13 | Rat (Osborne-Mendel) 5 M, 5 F | 6 weeks (F) | M: 0, 3.5, 7, 14, 28 F: 0, 3.8, 7.6, 15, 30.2 | BW, LE | Death | | | 28 M 30.2 F | 3/5 males died; 5/5 females died |
| **NCI 1978a (technical grade >85% purity)** | | | | | | | | | |
| 14 | Rat (Carworth) 10 M, 10 F | 6 months (F) | 0, 0.26, 0.53, 2.6, 7.9, 32 | CS, GN, HP, LE | Death | | | 32 | 100% mortality during the first 2 weeks of treatment |
| | | | | | Bd wt | 7.9 | | | |
| | | | | | Hepatic | 0.53 | 2.6 | | Increased liver weight, histopathologic liver lesions |
| **Treon et al. 1951a (recrystallized 99% purity; technical grade 95% purity)** | | | | | | | | | |
| 15 | Rat (Carworth) 40 M, 40 F | 27 weeks (F) | M: 0, 0.25, 1.25, 2.5 F: 0, 0.28, 1.4, 2.8 | BW, HP, LE, OW | Bd wt | 2.5 M 2.8 F | | | |
| | | | | | Hepatic | 2.5 M 2.8 F | | | |
| | | | | | Renal | 2.5 M 2.8 F | | | |
| **Treon et al. 1953a (recrystallized 99% purity)** | | | | | | | | | |
| 16 | Rat (Carworth) 16 M, 16 F | 3 generations (F) | 0, 0.26, 1.3, 2.6 | CS, DX | Repro | 0.26 | | 1.3 | 40% decreased number of litters from first parental mating |
| | | | | | Develop | | | 0.26 | 3.2-fold increased mortality of F1a pups |
| **Treon et al. 1954a** | | | | | | | | | |
| 17 | Mouse (Swiss white) 4 M, 14 F | 6 generations (F) | 0, 0.56, 0.94, 1.88, 4.70 | DX, FX, LE, MX | Repro | | | 0.56 | Decreased number of pregnant dams |
| | | | | | Develop | | | 0.56 | Decreased pup survival to PPD 4 |
| **Keplinger et al. 1970** | | | | | | | | | |

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 18 | Mouse (B6C3F1) 5 M, 5 F | 6 weeks (F) | M: 0, 0.45, 0.9, 1.8, 3.6, 7.2, 14.4 F: 0, 0.49, 1, 2, 3.9, 7.8, 15.6 | BW, LE | Death | | | 7.2 M 7.8 F | 100% mortality |
| **NCI 1978a (technical grade >85% purity)** | | | | | | | | | |
| 19 | Dog (NS) 1 M, 1–2 F | Up to 9 months (F) | 0, 0.89-1.78, 1.25–4.39, 2.07–9.10 | BW, CS, HP, LE | Death | | | 0.89 | Death or moribund sacrifice at 5.7 or 6.7 months |
| | | | | | Gastro | | 0.89 | | Vomiting |
| | | | | | Hepatic | | 1.25 | | Degenerative liver lesions |
| | | | | | Neuro | | | 0.89 | Hypersensitivity, tremors, twitching convulsions prior to death; neuronal degeneration in brain |
| **Treon et al. 1951b (purified, but purity not specified)** | | | | | | | | | |
| 20 | Dog (mixed) 2 M, 1 F | Up to 37 days 5 days/week 1 time/day (C) | 1.5, 3, 4.5 | BW, CS, LE | Death | | | 1.5 | All three pups died |
| | | | | | Bd wt | | 1.5 | | Depressed body weight gain (weight loss prior to death) |
| | | | | | Neuro | | | 1.5 | Lethargy, intoxication |
| **Treon et al. 1955 (recrystallized; purity not specified)** | | | | | | | | | |
| **CHRONIC EXPOSURE** | | | | | | | | | |
| 21 | Rat (Osborne-Mendel) 50 M, 30 F | 25 months (F) | 0, 0.37 | BW, GN, HE, HP, LE, OW | Bd wt | 0.37 | | | |
| | | | | | Hemato | 0.37 | | | |
| **Deichmann et al. 1967 (technical grade; 95% purity)** | | | | | | | | | |
| 22 | Rat (Osborne-Mendel) 50 M, 50 F | 31 months (F) | M: 0, 1.4, 2.1, 3.5 F: 0, 1.54, 2.3, 3.9 | BW, CS, HP, LE | Bd wt | 2.1 M 3.9 F | | 3.5 M | 12–22% depressed body weight gain |
| | | | | | Hepatic | 1.4 M 3.9 F | 2.1 M | | 23% increased relative liver weight |
| **Deichmann et al. 1970 (grade and purity not specified)** | | | | | | | | | |

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 23 | Rat (Osborne-Mendel) 12 M, 12 F | 2 years (F) | 0, 0.037, 0.15, 0.73, 3.65, 7.3, 11 | BW, GN, HP, LE, OW | Death | | | 7.3 | 58% decreased survival |
| | | | | | Bd wt | 11 | | | |
| | | | | | Hepatic | | 0.037[c] | | 34% increased relative liver weight in females, increasing severity of liver lesions at higher doses |
| **Fitzhugh et al. 1964 (recrystallized; ≥99% purity)** | | | | | | | | | |
| 24 | Rat (Osborne-Mendel) 50 M, 50 F | M: 74 weeks F: 80 weeks (F) | M: 0, 2.1, 4.2 F: 0, 2.3, 4.6 | BW, CS, HP, LE | Bd wt | | 2.1 M 2.3 F | | 10–12% depressed mean body weight |
| | | | | | Resp | 4.2 M 4.6 F | | | |
| | | | | | Cardio | 4.2 M 4.6 F | | | |
| | | | | | Gastro | 4.2 M 4.6 F | | | |
| | | | | | Musc/skel | 4.2 M 4.6 F | | | |
| | | | | | Hepatic | 4.2 M 4.6 F | | | |
| | | | | | Renal | 4.2 M 4.6 F | | | |
| | | | | | Dermal | 4.2 M 4.6 F | | | |
| | | | | | Ocular | 4.2 M 4.6 F | | | |
| | | | | | Endocr | 4.2 M 4.6 F | | | |
| | | | | | Neuro | | 2.1 M 2.3 F | | Hyperexcitability |
| **NCI 1978a (technical grade; >85% purity)** | | | | | | | | | |

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 25 | Mouse (C3HeB/Fe) 215 B | 2 years (F) | 0, 1.7 | GN, HP | Cancer | | | 1.7 | CEL (liver tumors) |
| **Davis and Fitzhugh 1962 (grade and purity not specified)** | | | | | | | | | |
| 26 | Mouse (B6C3F1) 50 M, 50 F | 80 weeks (F) | M: 0, 0.7, 1.4<br>F: 0, 0.5, 1 | BW, CS, HP, LE | Death | | | 1 F | Decreased survival |
| | | | | | Bd wt | 1.4 M<br>1 F | | | |
| | | | | | Resp | 1.4 M<br>1 F | | | |
| | | | | | Cardio | 1.4 M<br>1 F | | | |
| | | | | | Gastro | 1.4 M<br>1 F | | | |
| | | | | | Musc/skel | 1.4 M<br>1 F | | | |
| | | | | | Hepatic | 1.4 M<br>1 F | | | |
| | | | | | Renal | 1.4 M<br>1 F | | | |
| | | | | | Dermal | 1.4 M<br>1 F | | | |
| | | | | | Ocular | 1.4 M<br>1 F | | | |
| | | | | | Endocr | 1.4 M<br>1 F | | | |
| | | | | | Neuro | | 0.7 M<br>0.5 F | | Hyperexcitability |
| | | | | | Cancer | | | 0.7 M | Hepatocellular carcinoma |
| **NCI 1978a (technical grade; >85% purity)** | | | | | | | | | |

## Table 2-1. Levels of Significant Exposure to Aldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 27 | Dog (Mongrel) 1–2M, 1–2F | Up to 25 months 6 days/week 1 time/day (C) | 0.2, 0.5, 1, 2, 5 | BW, CS, HP, LE | Death | | | 1 | Decreased survival |
| | | | | | Bd wt | 0.2 | | 0.5 | Body weight loss |
| | | | | | Hemato | 0.5 | 1 | | Reduced bone marrow cellularity |
| | | | | | Hepatic | 0.5 | 1 | | Fatty degenerative changes |
| | | | | | Renal | 0.5 | 1 | | Fatty degenerative kidney changes |
| **Fitzhugh et al. 1964 (recrystallized; ≥99% purity)** | | | | | | | | | |
| 28 | Dog (Beagle) 2 M, 2 F | Up to 15.8 months 7 days/week (F) | 0, 0.04-0.09, 0.12-0.25 | BW, CS, LE, HP, OW | Bd wt | 0.12 | | | |
| | | | | | Hemato | 0.12 | | | |
| **Treon et al. 1955 (recrystallized; purity not specified)** | | | | | | | | | |

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive a provisional acute-duration oral MRL of 0.002 mg/kg/day for aldrin; based on a LOAEL of 2 mg/kg/day and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive a provisional chronic-duration oral MRL of 0.00004 mg/kg/day for aldrin; based on a LOAEL of 0.037 mg/kg/day and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.

B = both sexes; Bd wt or BW = body weight; BH = behavioral; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); (F) = food; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day; (GO) = gavage in oil; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; $LD_{50}$ = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; PPD = postpartum day; Repro = reproductive; Resp = respiratory; TG = teratogenicity

**Figure 2-3. Levels of Significant Exposure to Aldrin – Oral**
Acute (≤14 days)

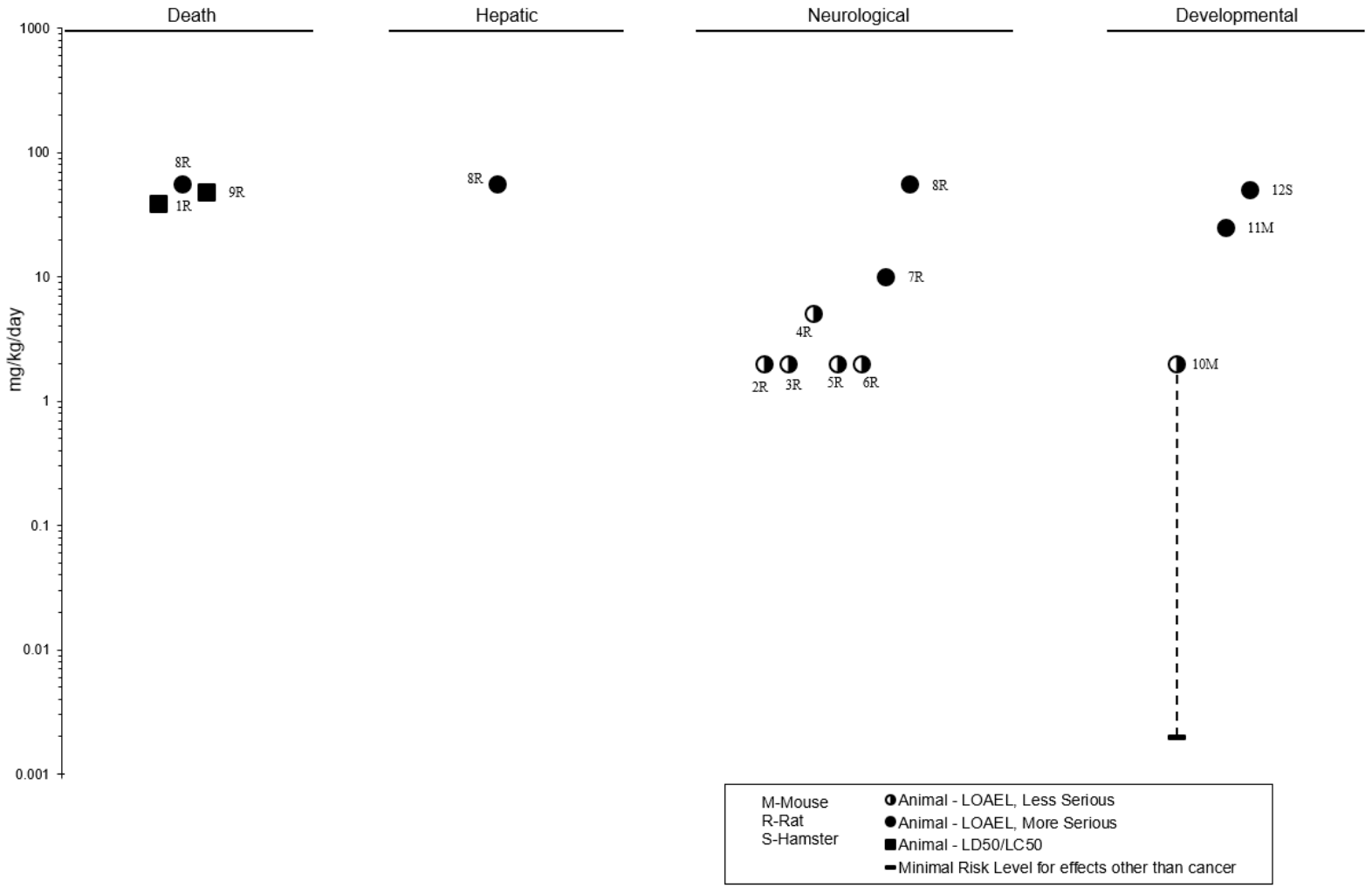


**Figure 2-3. Levels of Significant Exposure to Aldrin – Oral**
Intermediate (15-364 days)

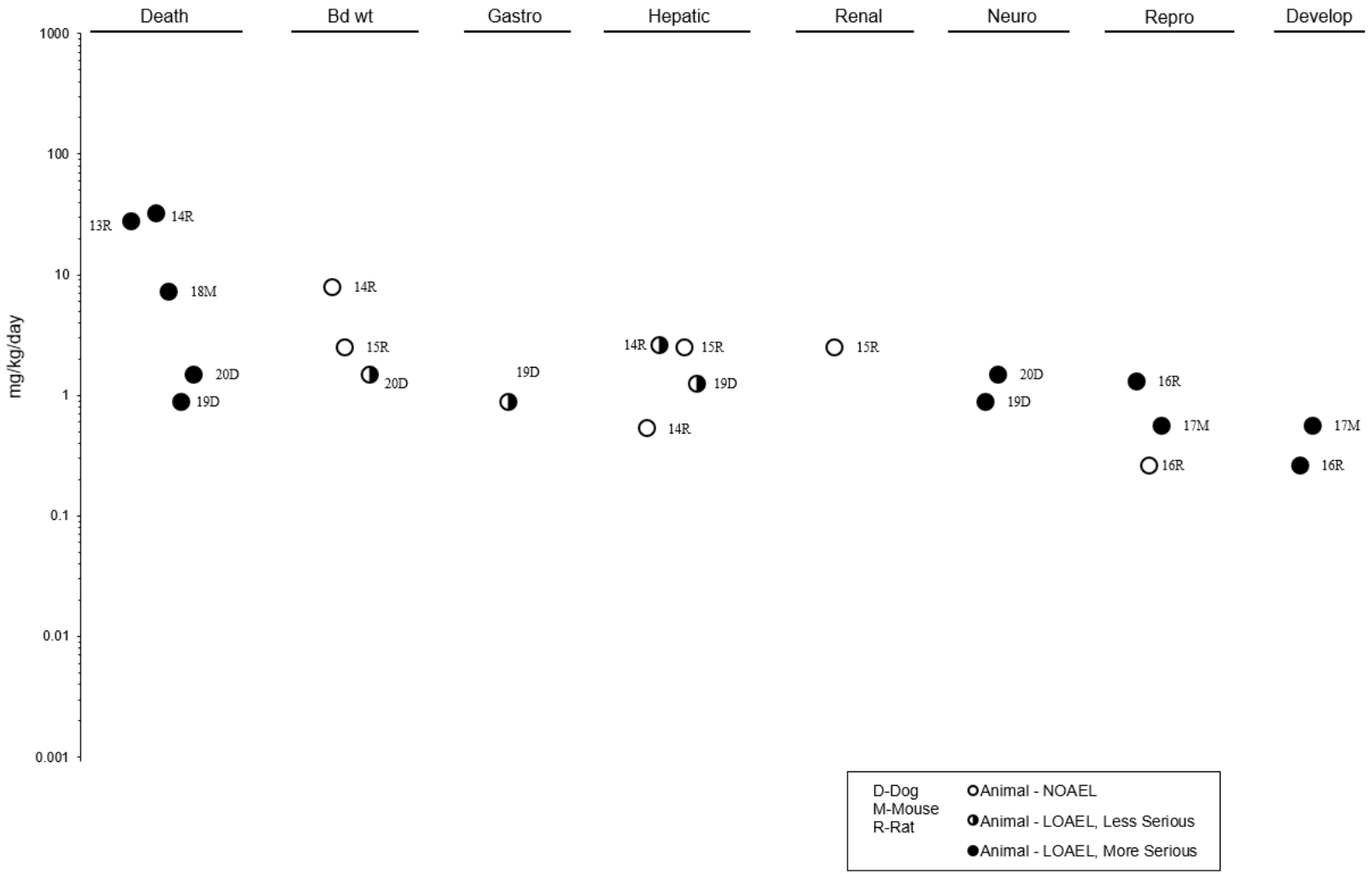
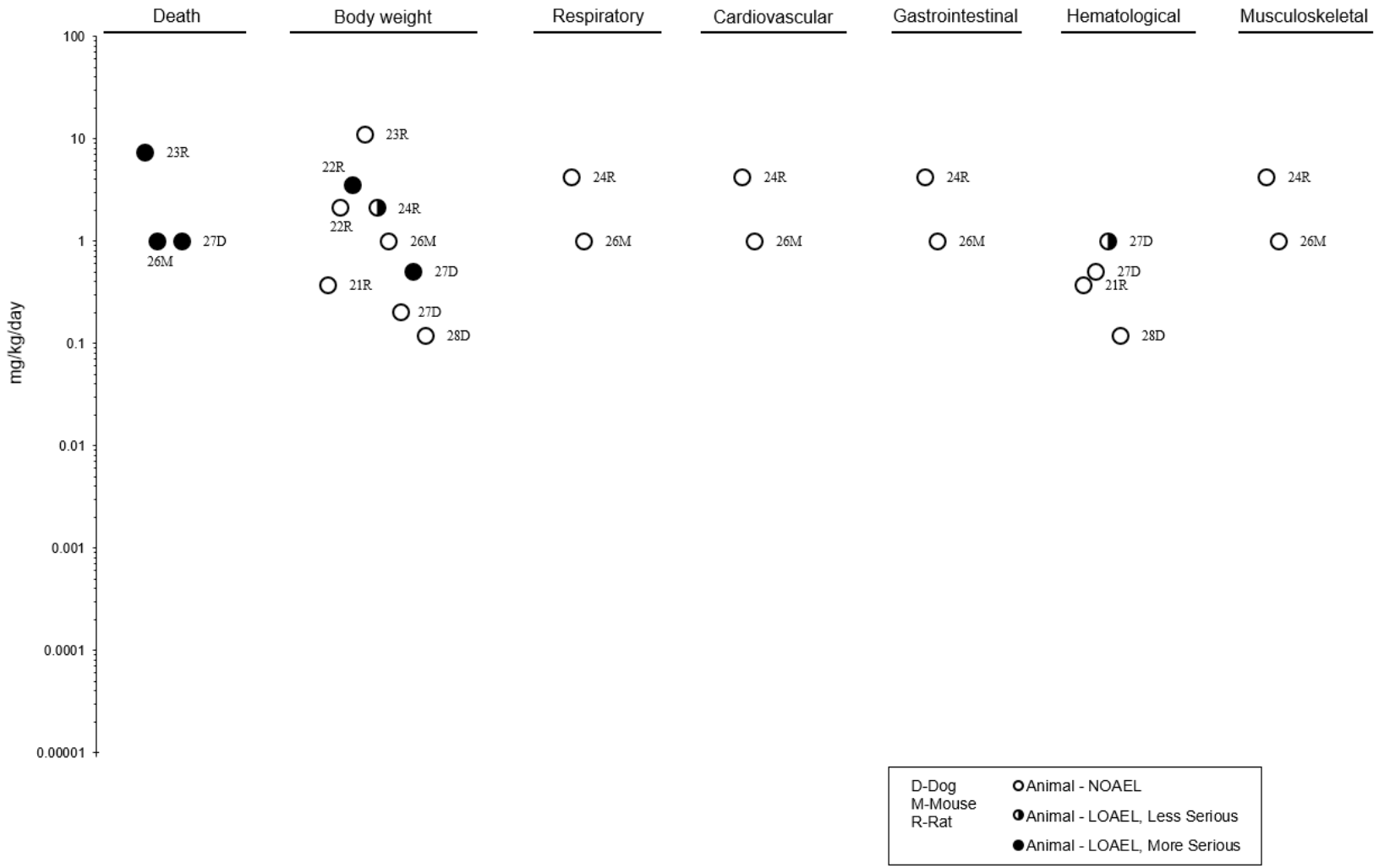
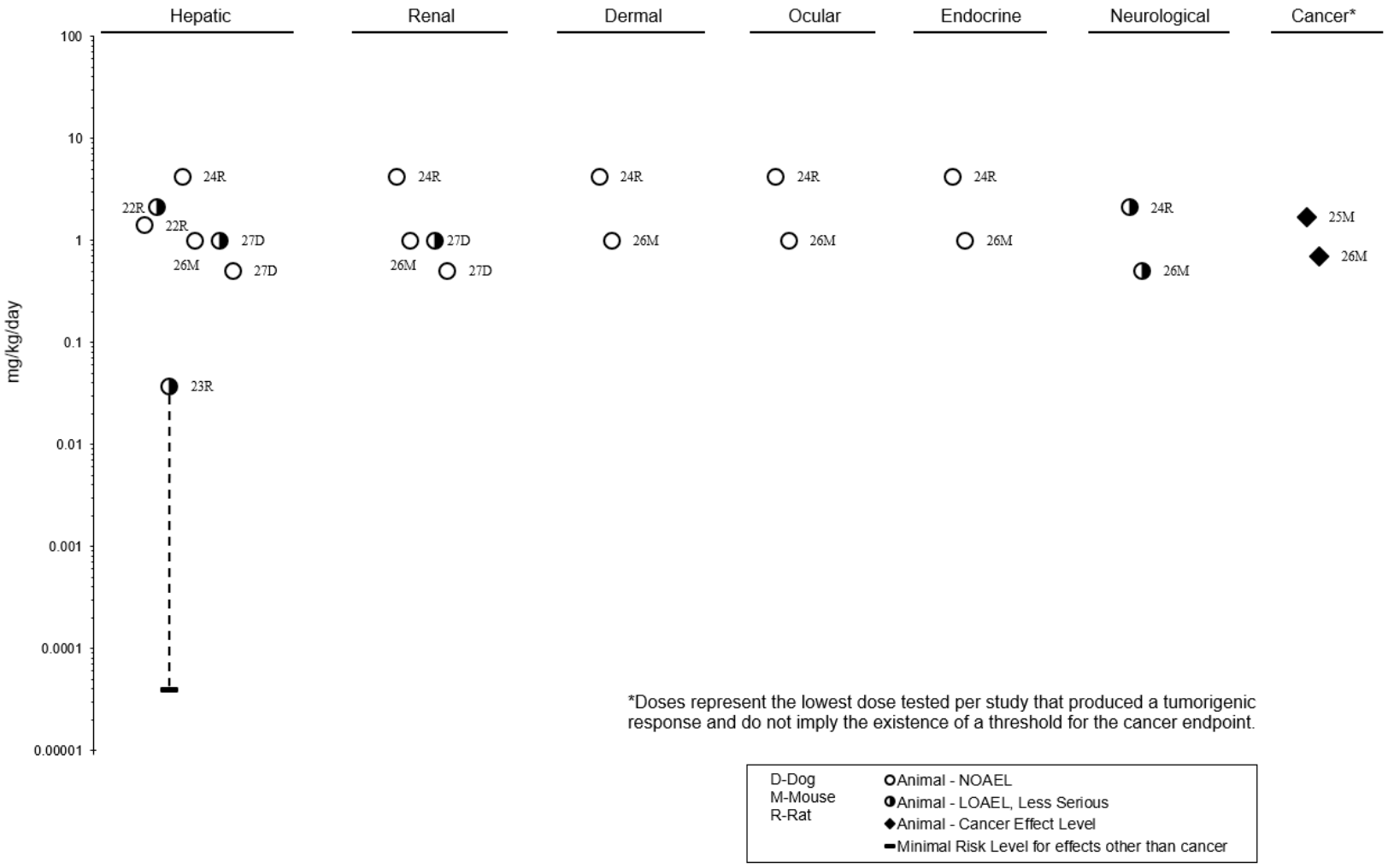


**Figure 2-3. Levels of Significant Exposure to Aldrin – Oral**
Chronic (≥365 days)



## Figure 2-3. Levels of Significant Exposure to Aldrin – Oral

Chronic (≥365 days)



## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **ACUTE EXPOSURE** | | | | | | | | | |
| 1 | Rat (Wistar) 14 or 16 M | Once (GO) | 0, 16.7 | OF | Neuro | | | 16.7 | Impaired maze performance |
| **Burt 1975 (technical grade; 100%)** | | | | | | | | | |
| 2 | Rat (Wistar) NS M | Once (GO) | 2.5, 5 | OF | Neuro | | | 2.5 | Disrupted operant behavior |
| **Burt 1975 (technical grade 100%)** | | | | | | | | | |
| 3 | Rat (Wistar) NS B | Once (GO) | 0, 8.4, 16.7 | OF | Neuro | 8.4 | | 16.7 | Disrupted operant behavior |
| **Burt 1975 (technical grade 100%)** | | | | | | | | | |
| 4 | Rat (Sprague-Dawley) 4 M | Once (GO) | 0, 0.5, 1.5, 4.5 | OF | Neuro | | | 0.5 | Impaired escape behavior |
| **Carlson and Rosellini 1987 (95% purity)** | | | | | | | | | |
| 5 | Rat (CD) 14–32 F | GDs 7–16 1 time/day (GO) | 0, 1.5, 3, 6 | BW, CS, DX, LE, MX | Death | | | 6 | 13 of 32 inseminated females died |
| | | | | | Bd wt | 3 | | 6 | 32% depressed maternal body weight gain |
| | | | | | Develop | 6 | | | |
| **Chernoff et al. 1975 (87% purity)** | | | | | | | | | |
| 6 | Rat (Sherman) NS | Once (GO) | NS | CS | Death | | | 46 | $LD_{50}$ |
| **Gaines 1960 (technical grade; purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 7 | Rat (Sprague-Dawley) 4–8 F | Once (GO) | 0, 26 | BI | Hepatic | | 26 | | 3-fold increase in lipid peroxidation |
| **Goel et al. 1988 (grade and purity not specified)** | | | | | | | | | |
| 8 | Rat (Wistar) 5–10 M | Once (GO) | 0, 30 | BI, OW | Hepatic | | 30 | | 23% increased liver weight, increased lipid peroxidation |
| **Kohli et al. 1977 ("analar" grade; purity not specified)** | | | | | | | | | |
| 9 | Rat (Wistar) 10 M | Once (GO) | NS | LE | Death | | | 167.8 | $LD_{50}$ for newborn male rats |
| **Lu et al. 1965 (grade and purity not specified)** | | | | | | | | | |
| 10 | Rat (Wistar) 10 M | Once (GO) | NS | LE | Death | | | 24.9 | $LD_{50}$ for 14–16-day-old male rats |
| **Lu et al. 1965 (grade and purity not specified)** | | | | | | | | | |
| 11 | Rat (Wistar) 10 M | Once (GO) | NS | LE | Death | | | 37 | $LD_{50}$ for 3–4-month-old male rats |
| **Lu et al. 1965 (grade and purity not specified)** | | | | | | | | | |
| 12 | Rat (Wistar) 10 M | 4 days 1 time/day (GO) | NS | LE | Death | | | 9.04 | 4-day $LD_{50}$ for 14–16-day-old male rats |
| **Lu et al. 1965 (grade and purity not specified)** | | | | | | | | | |
| 13 | Rat (Wistar) 10 M | 4 days 1 time/day (GO) | NS | LE | Death | | | 54.8 | 4-day $LD_{50}$ for 3–4-month-old male rats |
| **Lu et al. 1965 (grade and purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 14 | Rat (Sprague-Dawley) 4 M | 3 days 1 time/day (GO) | 0, 1, 5, 10 | BI, CS | Neuro | | | 10 | Tremors, convulsions |
| **Mehrotra et al. 1989 (grade and purity not specified)** | | | | | | | | | |
| 15 | Rat (Fischer-344) 15 M, 15 F | Up to 2 weeks (F) | 0, 2.6, 5.3, 10.5, 21, 31.6 | CS, HP | Death | | | 21 | 100% mortality |
| **NCI 1978b (purified technical grade)** | | | | | | | | | |
| 16 | Rat (Carworth) 10 F | Once (GO) | NS | CS, LE | Death | | | 38.3 | $LD_{50}$ |
| **Treon et al. 1952 (99% purity)** | | | | | | | | | |
| 17 | Rat (Carworth) 10 M, 10 F | Up to 2 weeks (F) | 0, 55 | CS, GN, HP, LE | Death | | | 55 | 100% mortality |
| | | | | | Hepatic | | | 55 | Severe liver damage |
| | | | | | Neuro | | | 55 | Hypersensitivity, degenerative brain lesions |
| **Treon et al. 1951a (recrystallized 99% purity; technical grade 85% purity)** | | | | | | | | | |
| 18 | Rat (NS) NS | Once (GO) | 0, 12.5, 25, 40 | CS, OF | Neuro | 12.5 | 25 | | Increased evoked potentials |
| **Woolley et al. 1985** | | | | | | | | | |
| 19 | Mouse (CD-1) 12–23 F | GDs 7–16 1 time/day (GO) | 0, 1.5, 3, 6 | BW, CS, DX, MX, OW | Bd wt | 3 | | 6 | Essentially no maternal body weight gain |
| | | | | | Hepatic | 1.5 | 3 | | 25% increased mean maternal liver weight |
| | | | | | Develop | 1.5 | 3 | | Increased incidence of supernumerary ribs (42 versus 6% among controls) |
| **Chernoff et al. 1975 (87% purity)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 20 | Mouse (CD-1) 30–86 NS | Once (GO) | 2-200 | LE | Death | | | 27 | $LD_{50}$ |
| **Costella and Virgo 1980 (technical grade; 86.1% purity)** | | | | | | | | | |
| 21 | Mouse (BALB/c) 24 F | Up to 2 weeks 1 time/day (GO) | 0, 0.45, 2.25, 4.5, 22.5 | CS, LE | Death | | | 22.5 | Unspecified number of high-dose mice died during the first week |
| | | | | | Neuro | | | 22.5 | Seizures, hypersalivation, loss of consciousness |
| **Foster et al. 2008 (grade and purity not specified)** | | | | | | | | | |
| 22 | Mouse (BALB/c) 12 or 13 F | 5 days prior to mating 1 time/week from gestation day 9 to weaning (GO) | 0, 0.45, 2.25, 4.5 | BW, CS, DX, FX, GN, HP, MX | Bd wt | 4.5 | | | |
| | | | | | Neuro | 2.25 | 4.5 | | Mild seizures in postweaning female pups |
| **Foster et al. 2008 (grade and purity not specified)** | | | | | | | | | |
| 23 | Mouse (C57B1/6) 4-5 F | Twice 7 days apart (GO) | 0, 16.6 | OF | Immuno | | 16.6 F | | Impaired T-cell activity |
| **Fournier et al. 1988 (99% purity)** | | | | | | | | | |
| 24 | Mouse (three strains) 10 F | Once (GO) | 0, 4, 12, 18, 30 | CS, LE, OF | Immuno | 12 | | 18 | Increased lethality in two strains following viral infection |
| **Krzystyniak et al. 1985 (99.9% purity)** | | | | | | | | | |
| 25 | Mouse (BALB/c) 10 M | 2 weeks (F) | 0, 0.09, 0.9, 9 | OF | Immuno | | 0.09 | | Impaired antigen processing by macrophages |
| **Loose et al. 1981 (grade and purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 26 | Mouse (CD1) 10 F | GD 9 (GO) | 0, 15 | CS, TG | Develop | | | 15 | Webbed foot; cleft palate |
| **Ottolenghi et al. 1974 (recrystallized; ≥99% purity)** | | | | | | | | | |
| 27 | Mouse (C57BL/6J) NS F | 2 weeks prior to mating and during gestation and lactation; every 3 days | 0, 0.3, 1, 3 | BW, CS, DX | Bd wt | 3 | | | |
| **Richardson et al. 2006 (≥98% purity)** | | | | | | | | | |
| 28 | Mouse (Carworth Farm No. 1) NS F | Up to 10 days (F) | 0, 0.16, 1.6, 7.5 | HP, LE, OW, | Death | | | 7.5 | 4/4 mice died during the first 10 days of treatment |
| | | | | | Hepatic | 0.16 | 1.6 | | Liver lesions after 7 days of treatment |
| **Wright et al. 1972 (recrystallized; >99.5% purity)** | | | | | | | | | |
| 29 | Hamster (Syrian golden) NS F | Once GD 7, 8, or 9 (GO) | 0, 30 | CS, DX, TG | Develop | | | 30 | Up to 25% fetal mortality; 26% depressed fetal weight; increased incidences of webbed foot, cleft palate, cleft lip |
| **Ottolenghi et al. 1974 (recrystallized; ≥99% purity)** | | | | | | | | | |
| 30 | Sheep (NS) 4 F | 4 days 1 time/day (C) | 20 | CS, OF | Neuro | | | 20 | Impaired operant behavior, EEG changes |
| **Sandler et al. 1969 (technical grade; purity not specified)** | | | | | | | | | |
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| 31 | Monkey (Squirrel) 2–4 M | 55 days 1 time/day (F) | 0, 0.01, 0.1 | CS, OF | Neuro | 0.01[b] | | 0.1 | Learning deficit |
| **Smith et al. 1976 (technical grade; purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 32 | Rat (NS) 65 M, 65 F | 6 months (F) | 0, 22 | HP | Hepatic | | 22 | | Increased serum AST and AP, decreased serum cholesterol and total protein, necrosis in Kupffer cells |
| | | | | | Renal | | | 22 | Degenerative changes in kidney epithelial cells; focal aggregation of lymphocytes and macrophages associated with edema and fibroblastic proliferation |
| **Ahmed et al. 1986 (technical grade; 85.6% purity)** | | | | | | | | | |
| 33 | Rat (Wistar) 5 M | 15 days (GO) | 0, 5 | HP | Hepatic | | 5 | | Diffuse necrosis in the liver |
| | | | | | Renal | | 5 | | Glomerulonephritis; renal tubular nephrosis |
| **Bandyopadhyay et al. 1982b (grade and purity not specified)** | | | | | | | | | |
| 34 | Rat (Wistar) 8–15 M | 60–120 days (F) | 0.046, 0.46, 1.8 | OF | Neuro | 0.046 | | 0.46 | Disrupted operant behavior |
| **Burt 1975 (technical grade 100%)** | | | | | | | | | |
| 35 | Rat (Osborne-Mendel) 5 M, 5 F | 6 weeks (F) | M: 0, 4, 8, 16, 32 F: 0, 4.5, 9, 18, 36 | BW, LE | Death | | | 32 M 36 F | 2/5 males died; 5/5 females died |
| **NCI 1978a (technical grade; >85% purity)** | | | | | | | | | |
| 36 | Rat (Fischer-344) 15 M, 15 F | Up to 8 weeks (F) | 0, 2.6, 5.3, 10.5, 21, 31.6 | CS, HP | Neuro | 5.3 | | 10.5 | Neuronal necrosis of brain |
| **NCI 1978b (purified technical grade)** | | | | | | | | | |
| 37 | Rat (Albino) 3–6 M | 1–6 months (F) | 0, 2 | BI, HP | Hepatic | | 2 | | Decreased hepatic protein; hepatocellular necrosis |
| **Shakoori et al. 1982 (grade and purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 38 | Rat (Carworth) 10 M, 10 F | 6 months (F) | 0, 0.26, 0.53, 2.6, 7.9, 32 | CS, GN, HP, LE | Bd wt | 7.9 | | | |
| | | | | | Hepatic | 0.53 | 2.6 | | Increased liver weight, histopathologic liver lesions |
| **Treon et al. 1951a (recrystallized 99% purity; technical grade 95% purity)** | | | | | | | | | |
| 39 | Rat (Carworth) 40 M, 40 F | 27 weeks (F) | M: 0, 0.25, 1.25, 2.5 F: 0, 0.28, 1.4, 2.8 | BW, HP, LE, OW | Bd wt | 2.5 M 2.8 F | | | |
| | | | | | Hepatic | 2.5 M 2.8 F | | | |
| | | | | | Renal | 2.5 M 2.8 F | | | |
| **Treon et al. 1953a (recrystallized 99% purity)** | | | | | | | | | |
| 40 | Rat (Carworth) 16 M, 16 F | 3 generations (F) | 0, 0.26, 1.3, 2.6 | CS, DX | Repro | | | 0.26 | 34% decreased number of litters from first parental mating |
| | | | | | Develop | 0.26 | | 1.3 | 1.9-fold increased 5-day mortality of F3a pups |
| **Treon et al. 1954a** | | | | | | | | | |
| 41 | Mouse (FVB-MMTV) 29–30 F | 5 days premating 1 time/week during gestation and lactation | 0, 0.45, 2.25, 4.5 | BW, CS, DX, FX, GN, HP, MX | Cancer | | | 4.5 | CEL (mammary tumor burden) |
| **Cameron and Foster 2009** | | | | | | | | | |
| 42 | Mouse (CFW Swiss) 101 B | 120 days (F) | 0, 0.93 | CS | Repro | 0.93 | | | |
| **Good and Ware 1969 (technical grade; 85% purity)** | | | | | | | | | |
| 43 | Mouse (BALB/c) 10 M | 3, 6, or 18 weeks (F) | 0, 0.18, 0.9 | OF | Immuno | | | 0.18 | Increased lethality following tumor implant |
| **Loose et al. 1981 (grade and purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 44 | Mouse (B6C3F1) 5 M, 5 F | 6 weeks (F) | M: 0, 0.45, 0.9, 1.8, 3.6; F: 0, 0.49, 1, 2, 3.9 | BW, LE | Death | | | 3.6 M<br>3.9 F | M: 3/5 died<br>F: 4/5 died |
| **NCI 1978a (technical grade >85% purity)** | | | | | | | | | |
| 45 | Mouse (B6C3F1) 4 M | 28 days (F) | 0, 0.18, 0.54, 1.8 | BC, BW, EA, FI, HP, OF, OW | Hepatic | 1.8 M | | | |
| **Stevenson et al. 1995 (grade and purity not specified)** | | | | | | | | | |
| 46 | Mouse (Swiss-Vancouver) 18–19 F | 4 weeks premating to postpartum day 28 (F) | 0, 0.5, 1, 2, 2.9, 3.9, 4.9 | CS, DX, LE, OF | Death | | | 3.9 | 7/18 maternal mice died prior to mating |
| | | | | | Repro | 1 | | 2 | 18% of bred females did not become pregnant |
| | | | | | Develop | 0.5 | | 1 | Increased pup mortality |
| **Virgo and Bellward 1975 (technical grade; 86.1% purity)** | | | | | | | | | |
| 47 | Dog (NS) 1 M, 1–2 F | Up to 9 months (F) | 0, 0.73–1.85, 1.95–4.24, 2.45–9.80 | BW, CS, HP, LE | Death | | | 1.95 | 3/3 died |
| | | | | | Gastro | 0.73 | 1.95 | | Vomiting |
| | | | | | Hepatic | | 0.73 | | Degenerative liver lesions |
| | | | | | Neuro | | | 0.73 | Hypersensitivity, tremors, twitching convulsions prior to death; neuronal degeneration in brain |
| **Treon et al. 1951b (purified, but purity not specified)** | | | | | | | | | |
| **CHRONIC EXPOSURE** | | | | | | | | | |
| 48 | Human 3-4 M | 18 months 1 time/day (C) | 0, 0.00014, 0.00071, 0.003 | BC, BI | Hemato | 0.003 M | | | |
| | | | | | Hepatic | 0.003 M | | | |
| | | | | | Neuro | 0.003 M | | | |
| **Hunter and Robinson 1967** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 49 | Rat (Osborne-Mendel) 50 M, 50 F | 31 months (F) | M: 0, 1.4, 2.1, 3.5 F: 0, 1.54, 2.3, 3.9 | BW, CS, HP, LE | Death | | | 2.3 F | Decreased survival |
| | | | | | Bd wt | 3.5 M 3.9 F | | | |
| | | | | | Hepatic | 3.5 M 3.9 F | | | |
| **Deichmann et al. 1970 (grade and purity not specified)** | | | | | | | | | |
| 50 | Rat (Osborne-Mendel) 12 M, 12 F | 2 years (F) | 0, 0.037, 0.15, 0.73, 3.65, 7.3, 11 | BW, GN, HP, LE, OW | Death | | | 3.65 | 42% decreased survival |
| | | | | | Bd wt | 11 | | | |
| | | | | | Hepatic | | 0.037 | | 34% increased relative liver weight in females; dose-related increasing incidence and severity of liver lesions |
| **Fitzhugh et al. 1964 (recrystallized; ≥99% purity)** | | | | | | | | | |
| 51 | Rat (Osborne-Mendel) 50 M, 50 F | 59–80 weeks (F) | M: 0, 2.0, 4.6 F: 0. 2.2, 5.0 | BW, CS, HP, LE | Bd wt | 4.6 M 5.0 F | | | |
| | | | | | Resp | | 2 M 2.2 F | | Dyspnea, tachypnea |
| | | | | | Cardio | 4.6 M 5.0 F | | | |
| | | | | | Gastro | | 2 M 2.2 F | | Diarrhea |
| | | | | | Musc/skel | 4.6 M 5.0 F | | | |
| | | | | | Hepatic | 4.6 M 5.0 F | | | |
| | | | | | Renal | 4.6 M 5.0 F | | | |
| | | | | | Dermal | | 2 M 2.2 F | | Rough coat, discolored hair coat, alopecia |
| | | | | | Ocular | 4.6 M 5.0 F | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Endocr | 4.6 M<br>5.0 F | | | |
| **NCI 1978a (technical grade; >85% purity)** | | | | | | | | | |
| 52 | Rat (Fischer-344)<br>24 M, 24 F | 104–105 weeks (F) | 0, 0.17, 0.85, 4.25 | CS | Neuro | 0.85 | | 4.25 | Convulsions |
| **NCI 1978b (purified technical grade)** | | | | | | | | | |
| 53 | Rat (Carworth Farm E)<br>25 M, 25 F | 2 years (F) | 0, 0.005, 0.05, 0.5 | BC, BW, CS, FI, GN, HP, LE, OW | Bd wt | 0.5 | | | |
| | | | | | Resp | 0.5 | | | |
| | | | | | Cardio | 0.5 | | | |
| | | | | | Gastro | 0.5 | | | |
| | | | | | Hemato | 0.5 | | | |
| | | | | | Musc/skel | 0.5 | | | |
| | | | | | Hepatic | 0.5 M<br>0.005[c] F | 0.05 F | | 13% increased liver weight; parenchymal cell changes at 0.5 mg/kg/day |
| | | | | | Renal | 0.5 | | | |
| | | | | | Dermal | 0.5 | | | |
| | | | | | Endocr | 0.5 | | | |
| | | | | | Neuro | 0.05 | | 0.5 | Tremors and occasional convulsions |
| **Walker et al. 1969 (>99% purity)** | | | | | | | | | |
| 54 | Mouse (C3HeB/Fe)<br>218 B | 2 years (F) | 0, 1.7 | GN, HP | Cancer | | | 1.7 | CEL (liver tumors) |
| **Davis and Fitzhugh 1962 (grade and purity not specified)** | | | | | | | | | |
| 55 | Mouse (BALB/c)<br>90 M | 75 weeks (F) | 0, 1.7 | HP | Cancer | | | 1.7 | CEL (liver tumors) |
| **Lipsky et al. 1989 (grade and purity not specified)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 56 | Mouse (three strains) 50–75 M | 85 weeks (F) | 0, 1.7 | GN, HP | Cancer | | | 1.7 | CEL (liver tumors) |
| **Meierhenry et al. 1983 (98.5% purity)** | | | | | | | | | |
| 57 | Mouse (B6C3F1) 50 M, 50 F | 80 weeks (F) | 0, 0.43, 0.86 | BW, CS, HP, LE | Bd wt | 0.86 | | | |
| | | | | | Resp | 0.86 | | | |
| | | | | | Cardio | 0.86 | | | |
| | | | | | Gastro | 0.86 | | | |
| | | | | | Musc/skel | 0.86 | | | |
| | | | | | Hepatic | 0.86 | | | |
| | | | | | Renal | 0.86 | | | |
| | | | | | Dermal | 0.86 | | | |
| | | | | | Ocular | 0.86 | | | |
| | | | | | Endocr | 0.86 | | | |
| | | | | | Neuro | | 0.43 | | Hyperexcitability, tremors |
| | | | | | Cancer | | | 0.86M | CEL (liver tumors) |
| **NCI 1978a (technical grade; >85% purity)** | | | | | | | | | |
| 58 | Mouse (C3H) 11–21 M | 2 years (F) | 0, 1.7 | HP | Cancer | | | 1.7 | CEL (hepatocellular adenomas) |
| **Ruebner et al. 1984 (>99% purity)** | | | | | | | | | |
| 59 | Mouse (Carworth Farm No. 1) 19–82 M | Up to 92 weeks (F) | 0, 1.7 | BW, GN, HP, OF, OW | Bd wt | 1.7 | | | |
| | | | | | Cancer | | | 1.7 | CEL (liver tumors) |
| **Tennekes et al. 1981 (>99% purity)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 60 | Mouse (CF1) 30–45 M 30–45 F | 2 years (F) | 0, 1.7 | CS, GN, HP, LE | Death | | | 1.7 | Decreased survival in latter portion of the treatment period |
| | | | | | Cancer | | | 1.7 | CEL (liver tumors) |
| **Thorpe and Walker 1973 (>99% purity)** | | | | | | | | | |
| 61 | Mouse (Carworth Farm No. 1) 58 NS | Up to 64 weeks (F) | 0, 1.7 | HP | Cancer | | | 1.7 | CEL (liver tumors) |
| **Walker et al. 1973 (>99% purity)** | | | | | | | | | |
| 62 | Mouse (Carworth Farm No. 1) 60 B | Up to 128 weeks (F) | 0, 0.2, 0.43, 0.86, 1.7, 3.4 | CS | Death | | | 1.7 | Decreased survival |
| | | | | | Neuro | 1.7 | | 3.4 | Body tremors, convulsions |
| | | | | | Cancer | | | 0.43 | CEL: Liver tumors |
| **Walker et al. 1973 (>99% purity)** | | | | | | | | | |
| 63 | Mouse (Carworth Farm No. 1) 250–600 B | Up to 132 weeks (F) | 0, 0.017, 0.17, 1.7 | CS, GN, HP, LE | Death | | | 1.7 | (50% mortality reached at 15 months versus 20–24 months in controls) |
| | | | | | Cancer | | | 1.7 | CEL (liver tumors) |
| **Walker et al. 1973 (>99% purity)** | | | | | | | | | |
| 64 | Dog (Mongrel) 1–2 M, 1–2 F | Up to 25 months 6 days/week (C) | 0.2, 0.5, 1, 2, 5, 10 | BW, CS, HP, LE | Death | | | 0.5 | Decreased survival |
| | | | | | Hemato | 0.5 | 1 | | Reduced bone marrow cellularity |
| | | | | | Hepatic | 0.5 | 1 | | Fatty degenerative changes in liver |
| | | | | | Renal | 0.5 | 1 | | Fatty degenerative changes in kidney |
| **Fitzhugh et al. 1964 (recrystallized; ≥99% purity)** | | | | | | | | | |

## Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 65 | Dog (Beagle) 2 M, 2 F | Up to 15.8 months 7 days/week (F) | 0, 0.03–0.10, 0.14–0.23 | BW, CS, LE, HP, OW | Bd wt | 0.14 | | | |
| | | | | | Hemato | 0.14 | | | |
| **Treon et al. 1955 (recrystallized; purity not specified)** | | | | | | | | | |
| 66 | Dog (Beagle) 5 M, 5 F | 2 years 1 time/day (C) | 0, 0.005, 0.05 | BC, BH, BW, CS, FI, GN, HP, LE, OW, UR | Bd wt | 0.05 | | | |
| | | | | | Resp | 0.05 | | | |
| | | | | | Cardio | 0.05 | | | |
| | | | | | Gastro | 0.05 | | | |
| | | | | | Hemato | 0.05 | | | |
| | | | | | Musc/skel | 0.05 | | | |
| | | | | | Hepatic | 0.05 | | | |
| | | | | | Renal | 0.05 | | | |
| | | | | | Dermal | 0.05 | | | |
| | | | | | Ocular | 0.05 | | | |
| | | | | | Endocr | 0.05 | | | |
| | | | | | Neuro | 0.05 | | | |
| **Walker et al. 1969 (>99% purity)** | | | | | | | | | |

[a]The number corresponds to entries in Figure 2-4.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.0001 mg/kg/day for dieldrin; based on a NOAEL of 0.01 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive a provisional chronic-duration oral MRL of 0.00005 mg/kg/day for dieldrin; based on a NOAEL of 0.005 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

AP = alkaline phosphatase; AST = aspartate aminotransferase; B = both sexes; BC = serum (blood) chemistry; BH = behavioral; Bd wt or BW = body weight; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; EEG = electroencephalogram; Endocr = endocrine; F = female(s); (F) = food; FI = food intake; Gastro = gastrointestinal; GD = gestation day(s); (GO) = gavage in oil; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; $LD_{50}$ = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; TG = teratogenicity; UR = urinalysis

**Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral**
Acute (≤14 days)

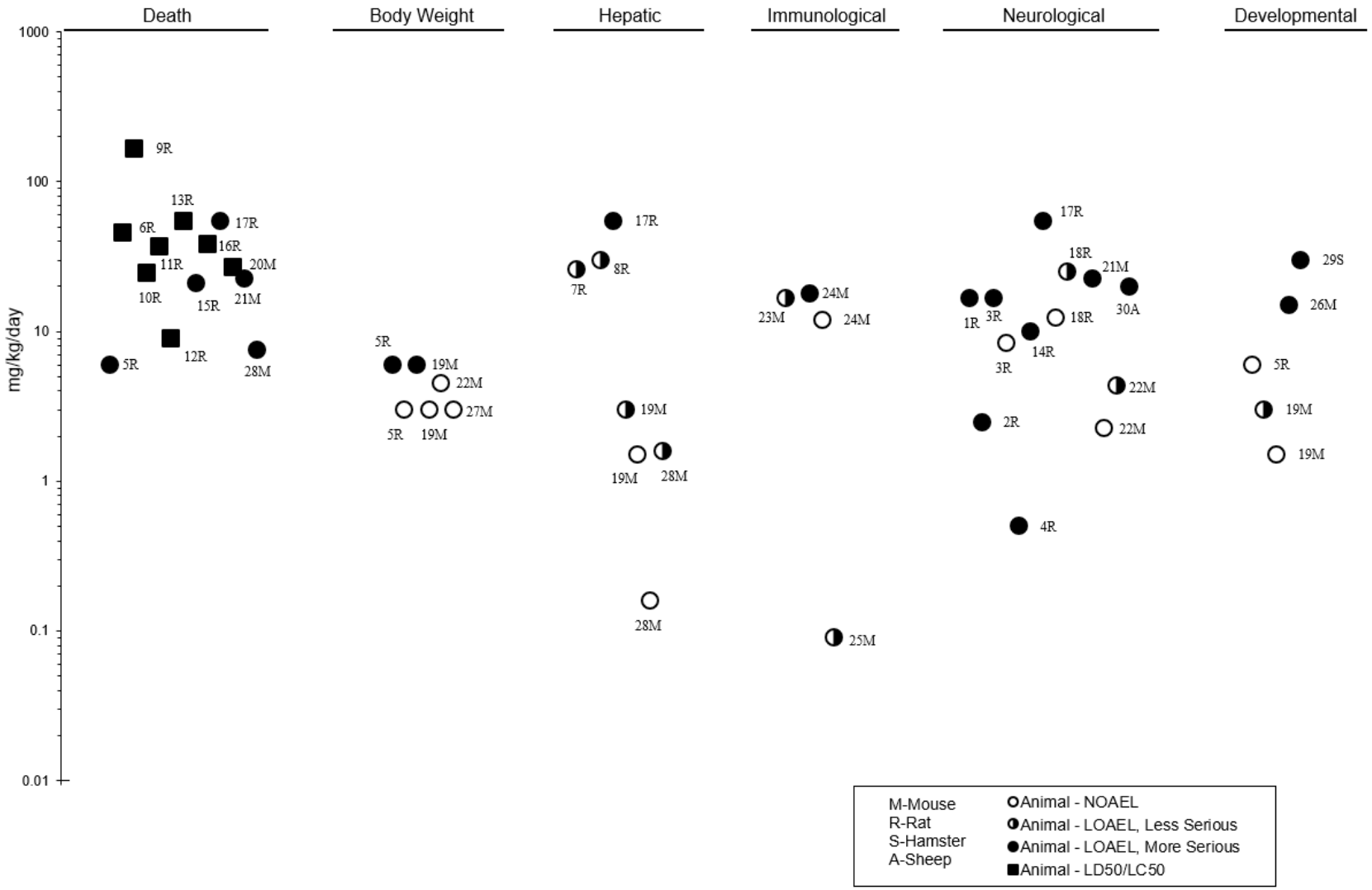


**Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral**
Intermediate (15-364 days)

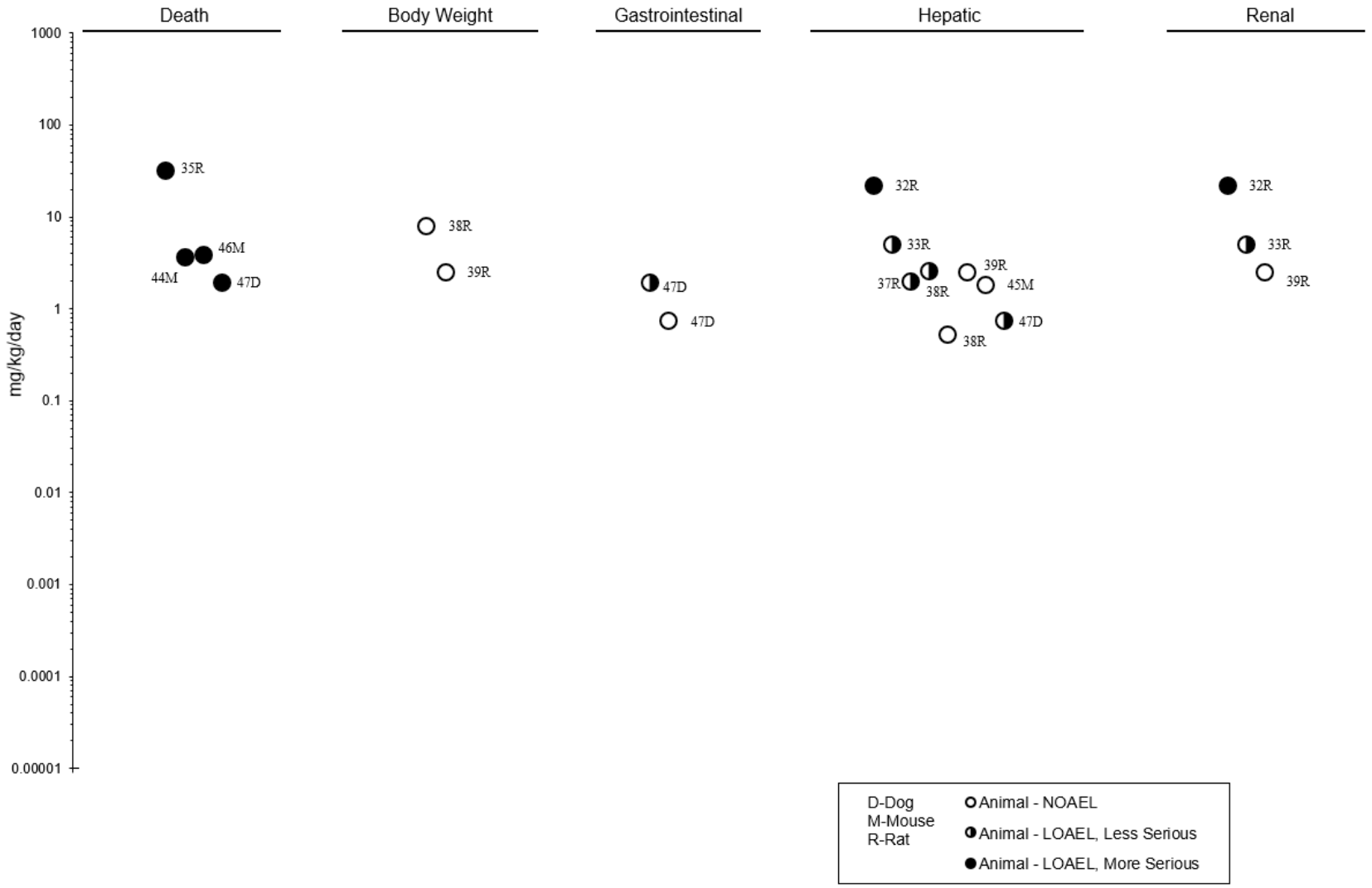


**Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral**
Intermediate (15-364 days)

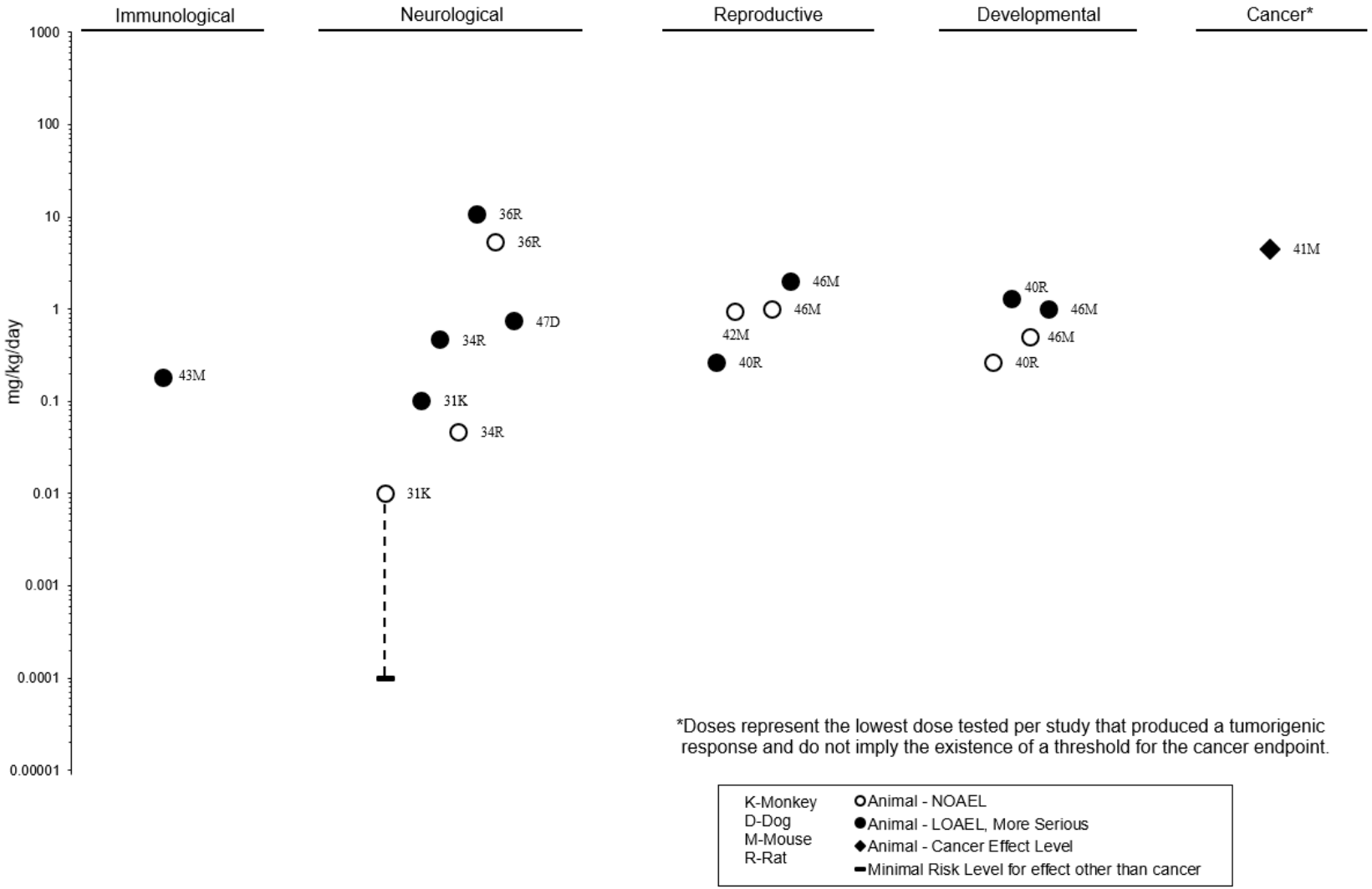


**Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral**
Chronic (≥365 days)

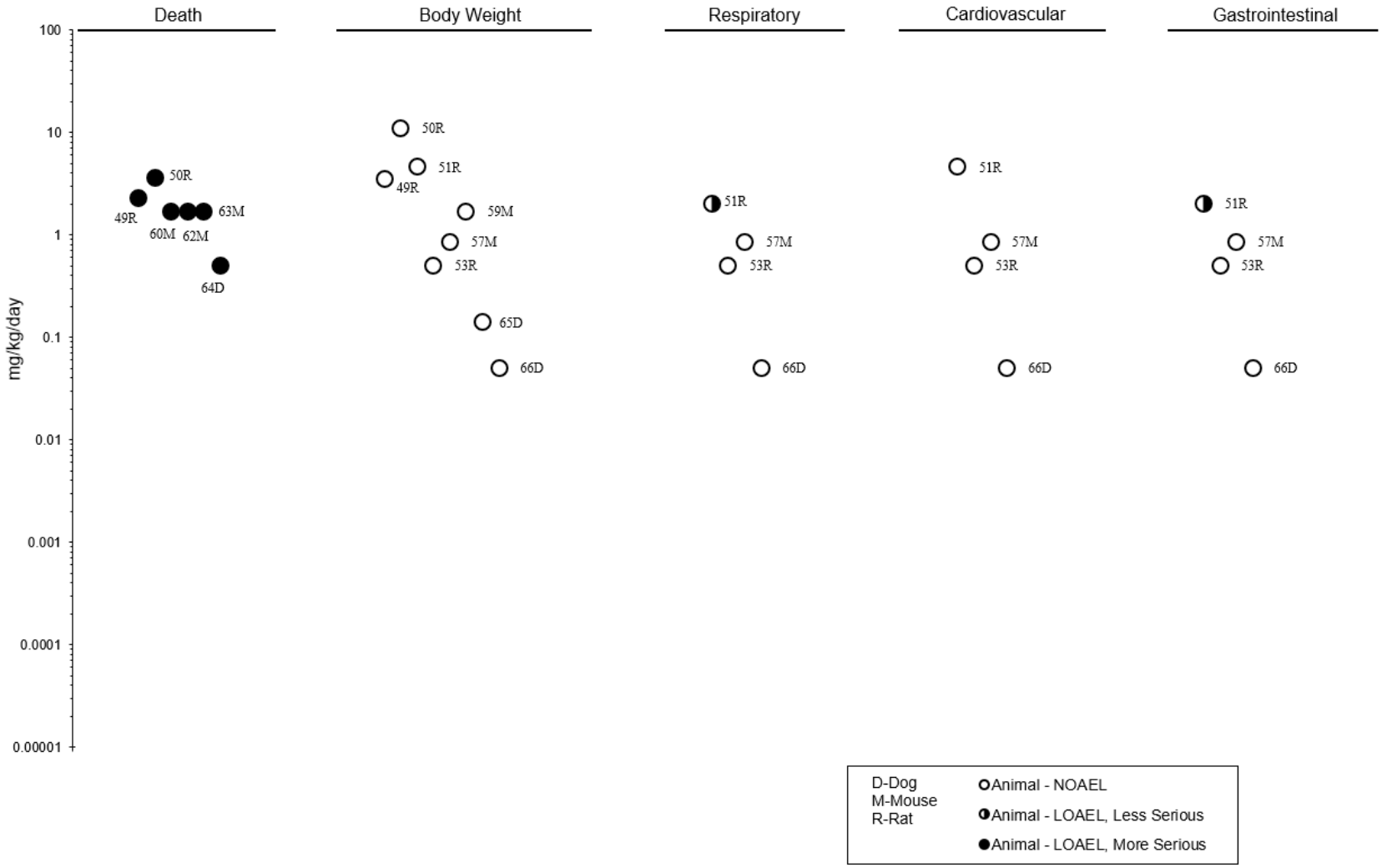


**Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral**
Chronic (≥365 days)

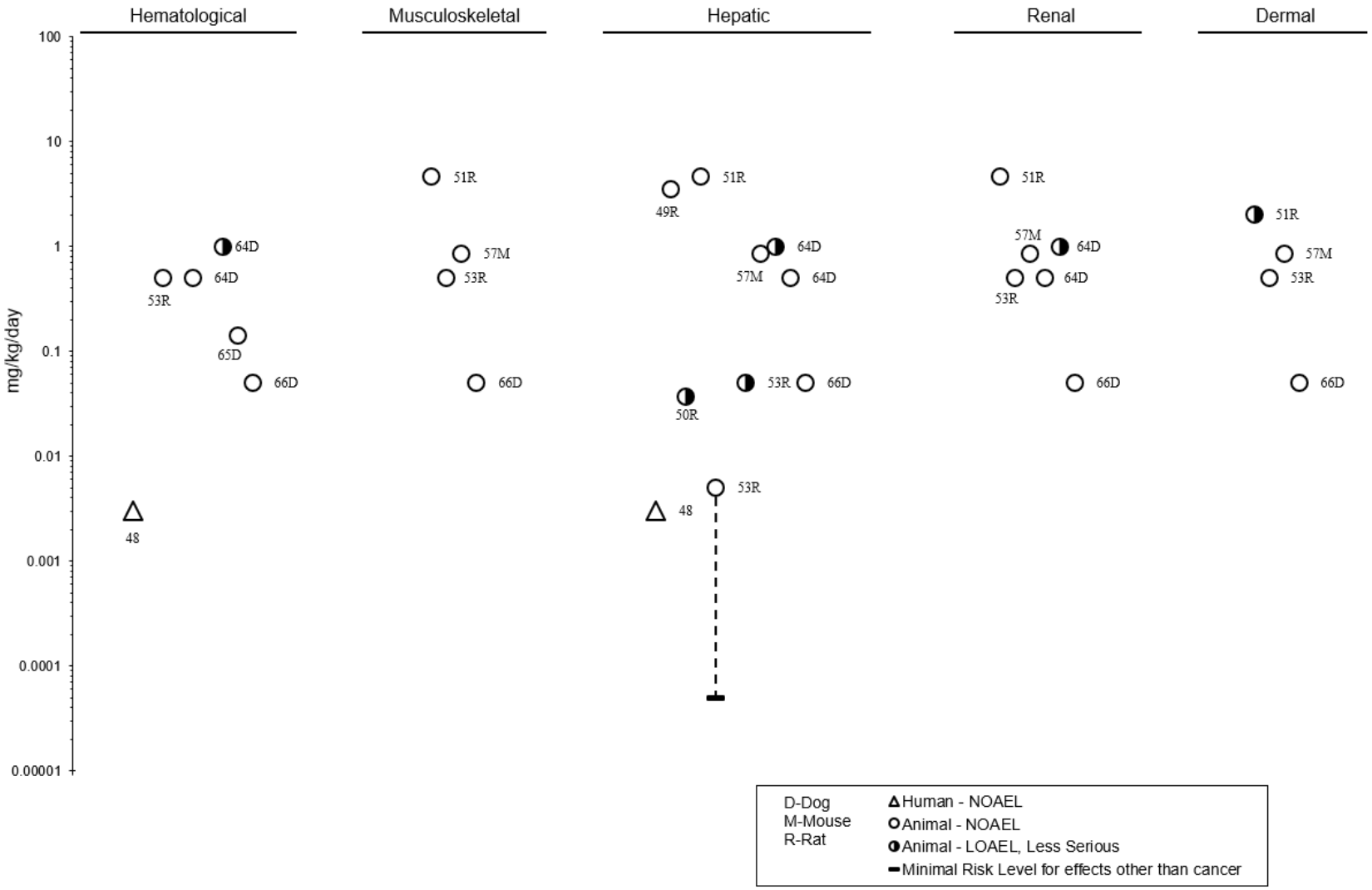
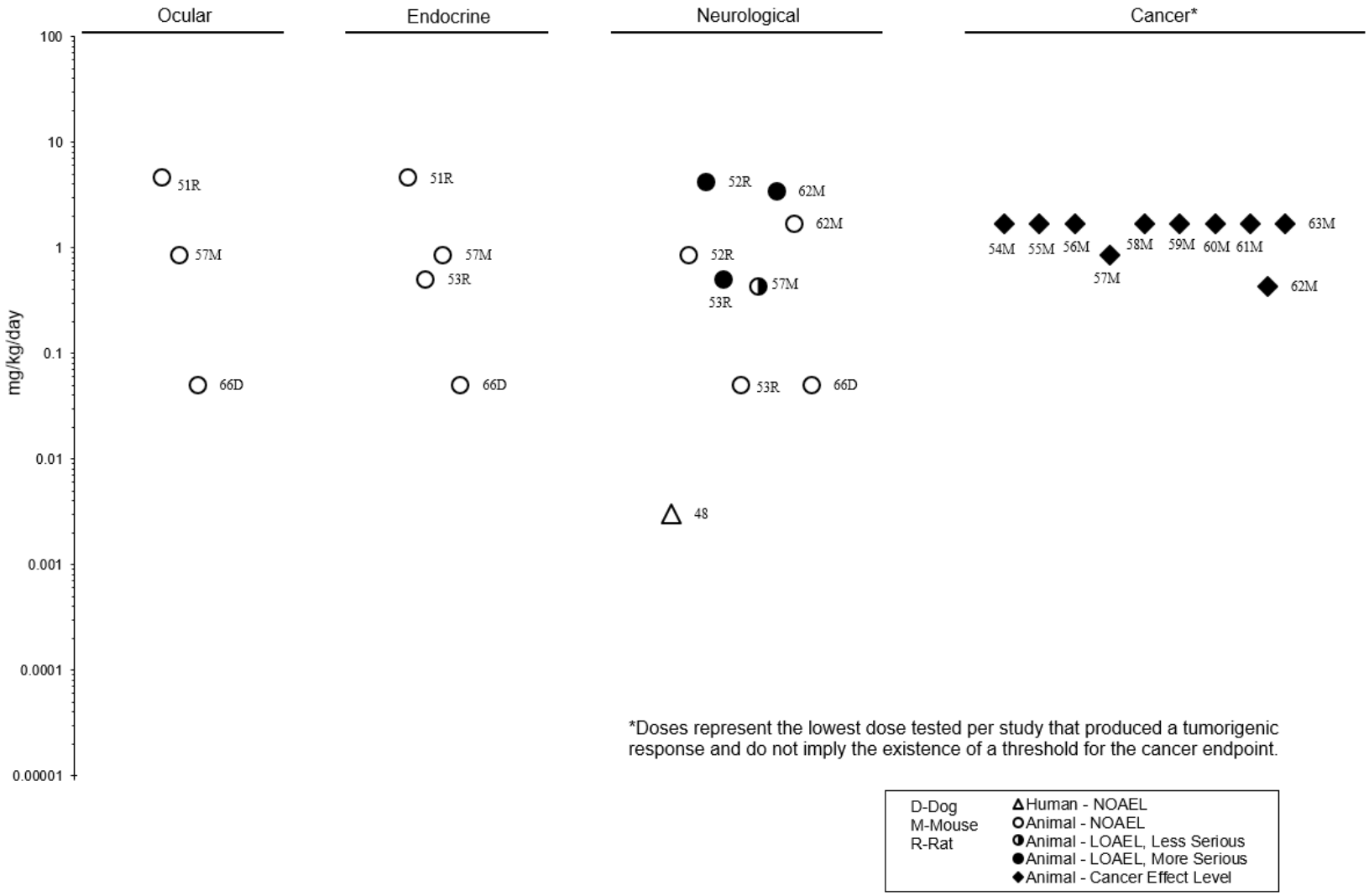


**Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral**
Chronic (≥365 days)



## 2.2 DEATH

***Epidemiological Studies.*** A lower than expected overall incidence of mortality was observed in a cohort of 570 workers who had been employed in the manufacture of aldrin, dieldrin, endrin, and/or telodrin at a facility in the Netherlands for at least 1 year between 1954 and 1970 (de Jong 1991). Although the workers represented a unique population because they had been under observation for at least 18 years, the evaluations are limited by uncertainty regarding exposure levels, and the potential exposure of the subjects to more than one of these pesticides and/or to other chemicals at the chemical manufacturing complex.

Only two case studies were located regarding deaths that may have been attributable to occupational exposure to aldrin or dieldrin. One of these studies concerned a farmer with multiple exposures to insecticides that contained dieldrin (Muirhead et al. 1959). The farmer died in hemolytic crisis after developing immunohemolytic anemia. Immunologic testing revealed a strong antigenic response to red blood cells coated with dieldrin. The other study concerned a worker from an orange grove who developed aplastic anemia and died following repeated exposures to aldrin during spraying (Pick et al. 1965).

Limited human data are available for the oral exposure route. A 2-year-old child died a short time after consuming an unknown quantity of a 5% solution of dieldrin (Garrettson and Curley 1969). This child's 4-year-old brother, who also consumed an unknown quantity of the 5% dieldrin solution, experienced severe convulsions but recovered completely. Of several persons who consumed wheat that had been mixed with aldrin and lindane, an infant female child died within a few hours after experiencing a severe generalized convulsion (Gupta 1975).

***Aldrin.*** Only very limited data were located regarding death in animals following inhalation exposure to aldrin. Cats, guinea pigs, rats, rabbits, and mice were exposed to airborne aldrin generated by sublimation at 200°C (Treon et al. 1957). Aldrin exposure for 1 hour at 108 mg/m$^3$ resulted in death of 9/10 rats, 3/4 rabbits, and 2/10 mice. A single cat exposed for 4 hours at 215 mg/m$^3$ died; guinea pigs survived this exposure scenario. Interpretation of the results of this study is limited in that sublimation may have resulted in the generation of atmospheres containing a higher proportion of volatile contaminants and thermal decomposition products than would be expected in atmospheres typical of most occupational exposures.

In experimental animals, acute oral $LD_{50}$ values in adult rats are in the range of 39–60 mg/kg (Gaines 1960; Treon et al. 1952). Aldrin was lethal in females at a slightly lower dose when it was administered in oil ($LD_{50}$=48 mg/kg) than when it was administered in a kerosene vehicle ($LD_{50}$=64 mg/kg) (Treon et al. 1952). When aldrin was widely used as an insecticide, several incidents were reported in which livestock died as the result of accidental mixing of unspecified amounts of aldrin with livestock feed (Buck and Van Note 1968). In an incident involving both calves and adult cattle, mortality occurred exclusively among the calves.

Lethality was reported in intermediate-duration rat and mouse studies at doses ranging from 8 to 30 mg/kg/day (NCI 1978a). Following chronic-duration oral exposure, deaths were reported in rats at 3.9 mg/kg/day (Deichmann et al. 1970) and 7.3 mg/kg/day (Fitzhugh et al. 1964). Decreased survival was reported in mice chronically exposed to 1 mg/kg/day (NCI 1978a). In dogs, deaths were reported at oral aldrin doses as low as 0.89 mg/kg/day (Fitzhugh et al. 1964; Treon et al. 1951b) for intermediate or chronic durations.

Limited information was located regarding lethality in experimental animals following dermal exposure to aldrin. Reported acute dermal $LD_{50}$ values for rats were in the range of 98 mg/kg (Gaines 1960). However, the rats were not restrained, oral intake could not be eliminated, and the xylene vehicle has intrinsic dermal toxicity. A single 24-hour dermal exposure of rabbits to dry crystallized aldrin resulted in 100% mortality at 1,250 mg/kg (Treon et al. 1953b). Similar results were obtained when these chemicals were prepared as oil solutions and maintained in contact with the skin for 24 hours. Repeated dermal applications of aldrin in the range of 19–125 mg/kg/day were lethal to rabbits (Treon et al. 1953b). Mortalities were more prevalent when aldrin was dissolved in oil or kerosene than when applied in crystallized form.

***Dieldrin.*** A single-dose exposure to dieldrin resulted in an $LD_{50}$ values of 37–168 mg/kg in rats (Gaines 1960; Lu et al. 1965). Age appeared to influence the acute oral lethality of dieldrin. Reported $LD_{50}$ values were 168 mg/kg for newborn rats, 25 mg/kg for 2-week-old rats, and 37 mg/kg for 3–4-month-old rats (Lu et al. 1965). In a repeated exposure study, 100% mortality was observed in rats exposed to 21 mg/kg/day (NCI 1978b) or 55 mg/kg/day (Treon et al. 1951a) for up to 2 weeks. In a developmental toxicity study, approximately 40% of the rat dams died from administration of 6 mg/kg/day on gestation days (GDs) 7–16 (Chernoff et al. 1975). An $LD_{50}$ of 27 mg/kg was estimated in mice receiving a single

gavage dose of dieldrin (Costella and Virgo 1980). Repeated oral exposure resulted in deaths in mice administered 7.5–22.5 mg/kg/day (Foster et al. 2008; Wright et al. 1972)

Dieldrin was lethal to experimental animals during repeated intermediate-duration oral exposure at doses of 32 mg/kg/day in rats (NCI 1978a), 3.6–3.9 mg/kg/day in mice (NCI 1978a; Virgo and Bellward 1975), and 1.95 mg/kg/day in dogs (Treon et al. 1951a). Chronic-duration oral exposures were lethal at estimated doses in the range of 2.3–3.65 mg/kg/day in rats (Deichmann et al. 1970; Fitzhugh et al. 1964), 1.7 mg/kg/day in mice (Thorpe and Walker 1973; Walker et al. 1973), and 0.5 mg/kg/day in dogs (Fitzhugh et al. 1964). However, survival was not affected among hamsters orally-exposed to dieldrin for 120 weeks at 14.9 mg/kg/day (Cabral et al. 1979).

A dermal $LD_{50}$ of 60 mg/kg was estimated in rats following a single dermal exposure (Gaines 1960); as noted for aldrin, the animals were not restrained, oral exposure cannot be ruled out, and the xylene vehicle may have influenced the toxicity. Dermal exposure to dieldrin as a dry powder resulted in 1/4 deaths in rabbits (Treon et al. 1953b). In a 10-week dermal exposure study, 100% mortality was observed in rats exposed to 97–174 mg/kg dieldrin in a dry powder and 43–57 mg/kg dieldrin in peanut oil; 2/3 rabbits died when exposed to 4–5 mg/kg dieldrin in kerosene (Treon et al. 1953b).

Sheep dipped in a solution of 200 mg dieldrin/L (twice the recommended dose) experienced an 11% mortality rate within the first month following exposure (Glastonbury et al. 1987). This study is limited because the preparation of dieldrin was unsuitable for use in emulsions and may have been stripped from the bath during the dipping of the first sheep, resulting in much higher doses for some animals than others. In addition, wool biting was observed among these sheep; this type of oral exposure may have contributed to the lethal effects.

## 2.3 BODY WEIGHT

***Epidemiological Studies.*** No information was located regarding body weight effects in humans exposed to aldrin or dieldrin.

***Aldrin.*** Treon et al. (1955) reported depressed body weight gain in dogs treated with aldrin for up to 37 days at a lethal dose level of 1.5 mg/kg/day. In two chronic-duration studies of rats administered aldrin in the diet, approximately 10–12% depressed body weight was observed at doses as low as 2.1–2.3 mg/kg/day (NCI 1978a) and up to 22% depressed body weight gain was observed at 3.5 mg/kg/day

(Deichmann et al. 1970). Actual body weight loss was observed at 0.5 mg aldrin/kg/day in chronically-treated dogs (Fitzhugh et al. 1964).

***Dieldrin.*** Chernoff et al. (1975) observed 32% depressed maternal body weight in rats gavaged at 6 mg dieldrin/kg/day during GDs 7–16.

## 2.4 RESPIRATORY

***Epidemiological Studies.*** Extremely limited information is available regarding the respiratory effects of aldrin and dieldrin in humans. In a study that examined 1,155 workers involved in the manufacture of aldrin, dieldrin, and/or endrin for at least 6 months during the time period of 1946 until the 1970s (follow-up through December 1976), a significantly increased incidence of pneumonia and other pulmonary diseases was observed when compared to the incidence in U.S. white males (Ditraglia et al. 1981). Significantly increased incidence of death from respiratory disease was noted in follow-up evaluation of this cohort through 1987 (Brown 1992). Amoateng-Adjepong et al. (1995) expanded the cohort to include all employees who ever worked at the plant during 1952 through 1982 and for whom social security numbers and dates of employment and birth were known (n=2,384). The expanded cohort was followed through 1990 and included workers involved in production of other chemicals/pesticides as well. There was no apparent increased incidence of death from respiratory diseases. However, these studies are limited by small sample size and potential for exposure to other chemicals and/or pesticides.

A study of workers with at least 4 years of employment in the manufacture of aldrin, dieldrin, endrin, or telodrin in the Netherlands found no evidence of exposure-related pulmonary disease or deterioration of existing pulmonary disease (Jager 1970). No increase in mortality from respiratory diseases was noted among 570 of these workers employed for at least 1 year during 1954–1970 and followed until January 1, 1987 (de Jong 1991), until January 1, 1993 (de Jong et al. 1997), January 1, 2001 (Swaen et al. 2002), and until April 30, 2006 (van Amelsvoort et al. 2009). However, these studies are limited by small sample size and exposure to multiple pesticides.

***Aldrin.*** Cats, guinea pigs, rats, rabbits, and mice exposed to aldrin vapors and particles generated by sublimating aldrin at 200°C were reported to have exhibited symptoms indicative of mucous membrane irritation (Treon et al. 1957). However, the exposure levels associated with these effects were not reported and the contribution of thermal decomposition products or other volatile contaminants other than

aldrin cannot be eliminated. No information was located regarding respiratory effects in experimental animals following inhalation exposure to dieldrin.

There was no evidence of treatment-related respiratory effects in routine gross and microscopic examinations of respiratory tract tissues from rats or mice following intermediate- or chronic-duration oral exposure to aldrin at the doses in the range of 1-4.2 mg/kg/day (NCI 1978a).

***Dieldrin.*** In chronic exposure studies, no histological alterations were observed in rats orally exposed to 0.5–4.6 mg/kg/day (NCI 1978a; Walker et al. 1969), mice exposed to 0.86 mg/kg/day (NCI 1978a), or dogs exposed to 0.05 mg/kg/day (Walker et al. 1969).

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

## 2.5 CARDIOVASCULAR

***Epidemiological Studies.*** Very limited information is available regarding the cardiovascular effects of aldrin or dieldrin in humans. Suggestive evidence of an association between dieldrin and hypertension was obtained in a study examining disease incidence in patients with elevated fat levels of dieldrin (Radomski et al. 1968). However, the number of patients with hypertension in this study was low (eight cases), and elevated fat levels of other pesticide residues also correlated with hypertension. A slight, but significant, increase in serum cholesterol was observed in pesticide-exposed workers with elevated serum dieldrin (Morgan and Lin 1978). Other studies did not support the correlation of hypertension with dieldrin exposure. A study examining disease incidence in 2,620 pesticide-exposed workers reported no increase in the incidence of hypertension in workers with elevated serum dieldrin (Morgan et al. 1980). Workers involved in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years in the Netherlands had normal blood pressure (Jager 1970). Follow-up evaluations of 570 of these workers employed for at least 1 year during 1954–1970 until January 1, 1987 (de Jong 1991), until January 1, 1993 (de Jong et al. 1997), until January 1, 2001, and until April 30, 2006 (van Amelsvoort et al. 2009) revealed no evidence of increased risk of death from cardiovascular disease. However, these studies are limited by small sample size and exposure to multiple pesticides.

A young man who survived an attempted suicide by consuming approximately 25.6 mg/kg of aldrin had extremely labile blood pressure upon admission to the hospital (Spiotta 1951). His electrocardiogram was normal. Another man who ingested 120 mg/kg of dieldrin had tachycardia and elevated blood pressure at the time of his admission to the hospital (Black 1974). Both men were also suffering from convulsions; thus, it is possible that these cardiovascular effects may have been the result of altered activity in the central nervous system. In the case of the man who ingested 120 mg/kg of dieldrin, the cardiovascular effects (tachycardia and hypertension) were controlled with β-adrenergic blocking drugs (Black 1974). The investigator suggested that the cardiovascular effects were due to sympathetic overstimulation; this hypothesis has not been confirmed with supporting data.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to aldrin or dieldrin. Gavage administration of aldrin or dieldrin to rats caused significantly decreased cardiac calmodulin levels at doses as low as 5 mg aldrin/kg/day and 1 mg dieldrin/kg/day, and significant inhibition of $Ca^{2+}$ATPase activity in heart sarcoplasmic reticulum at 10 mg/kg/day aldrin or dieldrin (Mehrotra et al. 1989). The authors suggested that such changes could adversely affect cardiac contractility by altering calmodulin-regulated $Ca^{2+}$-pump activity in neurons, but no measurements of cardiac function were performed to support this hypothesis.

***Aldrin.*** Routine gross and microscopic examinations showed no adverse cardiovascular effects in rats or mice administered aldrin orally for 6 months to 2 years at doses in the range of 1–4.2 mg/kg/day (NCI 1978a).

***Dieldrin.*** Chronic oral exposure to doses ranging from 0.05 to 4.6 mg/kg/day did not result in histological alterations in the heart of rats, mice, or dogs (NCI 1978a; Treon et al. 1951a; Walker et al. 1969).

Harr et al. (1970) reported that chronic exposure of rats to dieldrin at dietary doses as low as 0.016 mg/kg/day resulted in fibrinoid degeneration, inflammation, endothelial proliferation, and perivascular edema in small-to-medium-size arteries (Harr et al. 1970). However, this condition is known to occur spontaneously, no dose-response information was provided, and incidence data and/or statistical analyses of these data were not presented.

No effects on heart weight or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study

is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

## 2.6 GASTROINTESTINAL

***Epidemiological Studies.*** Human data regarding possible gastrointestinal effects related to aldrin or dieldrin exposure are limited. No increased mortality from digestive system causes was observed in a mortality study of 570 workers employed in the manufacture of aldrin and dieldrin for at least 1 year between 1954 and 1970 and followed up until January 1, 1987 (de Jong 1991) and January 1, 2001 (Swaen et al. 2002).

***Aldrin.*** No adverse gastrointestinal effects were observed in rats or mice administered aldrin orally for up to 80 weeks at doses in the range of 1–4.2 mg/kg/day (NCI 1978a). Vomiting was reported in dogs exposed to 0.89 mg/kg/day aldrin in the diet for up to 9 months (Treon et al. 1951b); this dose was also associated with death or morbidity.

***Dieldrin.*** Diarrhea was reported in rats exposed to approximately 2 mg/kg/day dieldrin in the diet for up to 80 weeks (NCI 1978a); no histological alterations were observed in the gastrointestinal tract. Similarly, chronic oral exposure to 0.5 mg/kg/day in rats (Walker eta l. 1969) or 0.86 mg/kg/day in mice (NCI 1978a) did not result in histological alterations. Dogs that ingested lethal doses of dieldrin (as low as 1.95–4.24 mg/kg/day over a period of 11 days–1.3 months) during a 9-month study vomited and became emaciated several days prior to death (Treon et al. 1951b). It is unclear whether the vomiting was directly due to gastrointestinal irritation. There was no evidence of gastrointestinal effects in dogs administered dieldrin for up to 2 years at doses up to 0.05 mg/kg/day (the highest dose level tested) (Walker et al. 1969).

## 2.7 HEMATOLOGICAL

***Epidemiological Studies.*** No abnormal values for hemoglobin, white blood cells, or erythrocyte sedimentation rate were found in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years (Jager 1970). No increase in blood diseases was observed in a morbidity study of workers employed at the plant described by Jager (1970) over the period of 1979–1990 (de Jong 1991). Workers who had been involved in either the manufacture or application of pesticides

and who had elevated blood levels of dieldrin exhibited no hematological effects of clinical significance (Morgan and Lin 1978; Warnick and Carter 1972).

Groups of 3–4 volunteers who consumed dieldrin in capsules at doses as high as 0.003 mg/kg/day over a period of 18 months experienced no adverse effects on cellular components of the blood (hemoglobin, packed cell volume, total and differential white blood cell count) or plasma proteins (Hunter and Robinson 1967). Blood coagulation tests were normal in the case of a man who ingested 120 mg/kg of dieldrin followed by repeated stomach lavage in an effort to limit absorption (Black 1974). A case of immunohemolytic anemia attributed to multiple dieldrin exposures was reported (Muirhead et al. 1959). Also, a worker from a grove where aldrin was sprayed developed aplastic anemia (Pick et al. 1965); one person employed in the manufacture of aldrin and dieldrin between 1954 and 1970 died from aplastic anemia (de Jong 1991). However, it is unclear whether these cases of aplastic anemia were directly due to aldrin or dieldrin exposures because exposure to a variety of other chemicals was possible. Also, three cases of pancytopenia and one case of thrombocytopenia associated with exposure to dieldrin were reported during 1961 (AMA 1962). However, no assessment of whether dieldrin was the causative agent was provided in the report.

***Aldrin.*** Routinely-examined hematological indices were normal in dietary studies of rats chronically exposed to aldrin at doses as high as 0.37 mg/kg/day (Deichmann et al. 1967). Some histological changes in blood-forming tissues of exposed animals have been reported. Rats that were exposed to 0.37 mg/kg/day aldrin for 25 months had moderate to marked congestion of the red pulp with slight hemolysis in the spleen (Deichmann et al. 1967), but the significance of this finding is unclear due a lack of incidence data and the report of normal hematology results.

***Dieldrin.*** There was no evidence of hematological effects in rats or dogs administered dieldrin for up to 2 years at doses up to 0.5 mg/kg/day or 0.05 mg/kg/day, respectively (Walker et al. 1969). Dogs given doses as low as 1 mg/kg/day dieldrin for 25 months had a reduced number of mature granulocytes and erythroid cells in the bone marrow (Fitzhugh et al. 1964); these data are limited by small numbers of animals (1–2 /sex/dose).

## 2.8 MUSCULOSKELETAL

***Epidemiological Studies.*** No human studies were located regarding musculoskeletal effects associated with exposure to aldrin or dieldrin. No studies were located regarding musculoskeletal effects in experimental animals following inhalation or dermal exposure to aldrin or dieldrin.

***Aldrin.*** Routine gross and microscopic examinations showed no adverse musculoskeletal effects in rats or mice administered aldrin orally for up to 80 weeks at doses in the range of 1–4.2 mg/kg/day (NCI 1978a).

Muscular lesions, including focal edema, coagulative necrosis, and chronic myositis (inflammation), were observed in rats fed aldrin at doses of 0.016 mg/kg/day for 750 days or 0.032 mg/kg/day for 546 days (Harr et al. 1970). Although these effects were not observed in controls, interpretation of the findings is complicated by study limitations, which include small numbers of animals (2/sex/dose) and the lack of incidence data.

***Dieldrin.*** No musculoskeletal alterations were observed in chronic oral studies in rats exposed to doses of 0.5–4.6 mg/kg/day (NCI 1978a; Walker et al. 1969), mice exposed to 0.86 mg/kg/day (NCI 1978a), or dogs exposed to 0.05 mg/kg/day (Walker et al. 1969).

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

## 2.9 HEPATIC

***Epidemiological Studies.*** Although a slight increase in serum hepatic enzymes (serum alanine aminotransferase [ALT] and serum aspartate aminotransferase [AST]) has been observed to correlate with serum dieldrin levels in one study of pesticide-exposed workers (Morgan and Lin 1978), no evidence of any hepatic effects of aldrin or dieldrin exposure has been observed in other studies of workers involved in either the manufacture (de Jong 1991; Hoogendam et al. 1965; Hunter et al. 1972; Jager 1970; van Sittert and de Jong 1987) or the manufacture or application (Morgan and Roan 1974; Warnick and Carter 1972) of these pesticides. Parameters examined in the negative studies include serum hepatic enzyme

activity (Hoogendam et al. 1965; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987; Warnick and Carter 1972), hepatic enlargement (Jager 1970), and tests intended to detect microsomal enzyme induction (Hunter et al. 1972; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987). All of the studies are limited by the potential exposure of the workers to other chemicals, including other organochlorine pesticides.

Healthy male subjects who consumed up to 0.003 mg/kg/day of dieldrin in capsules for 18 months showed no clinical signs and had no adverse hepatic effects as indicated by normal serum levels of liver enzymes (ALT, AST, alkaline phosphatase [AP]); however, no other liver function tests or biopsies were performed (Hunter and Robinson 1967). A child who drank an unknown quantity of a 5% dieldrin solution and experienced severe convulsions had evidence of liver dysfunction (Garrettson and Curley 1969). Six months post-exposure, serum AP and thymol turbidity test results were elevated. It is likely that the solution ingested by the child contained solvents and possibly emulsifiers. Evidence of liver damage (elevated serum aminotransferases) was also observed in a man 5 days after ingesting 120 mg/kg of dieldrin (in toluene) despite vigorous intervention to limit absorption (Black 1974). It is possible that the other ingredients in the dieldrin solutions contributed to the hepatic toxicity.

***Adaptive Responses.*** A number of adaptive changes characteristically produced by halogenated hydrocarbon pesticides were observed in livers of dogs, mice, and rats exposed to aldrin and/or dieldrin. These changes include increased liver weight and/or size (Bandyopadhyay et al. 1982b; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; Kohli et al. 1977; Olson et al. 1980; Tennekes et al. 1981; Treon et al. 1951a, 1953a, 1955; Walker et al. 1969; Walton et al. 1971; Wright et al. 1972), liver cell enlargement (Olson et al. 1980; Treon et al. 1951a, 1954b; Walker et al. 1973), cytoplasmic eosinophilia with migration of basophilic granules (Fitzhugh et al. 1964; Treon et al. 1951a, 1954b; Walker et al. 1969, 1973), increased smooth endoplasmic reticulum (Wright et al. 1972), increased microsomal protein (Wright et al. 1972), increased cytochrome P-450 content (Walton et al. 1971; Wright et al. 1972, 1978), and/or increased microsomal enzyme activity (Den Tonkelaar and van Esch 1974; Kohli et al. 1977; Tennekes et al. 1981; Walton et al. 1971; Wright et al. 1972, 1978).

Within 1 week, alterations of liver cell ultrastructure (an increase in cytoplasmic vacuoles and smooth endoplasmic reticulum) and increased microsomal protein and mixed-function oxidase activity were observed in rats and mice exposed to dieldrin orally at 8 or 1.6 mg/kg/day, respectively (Wright et al. 1972). After 4 weeks of exposure to dieldrin at 2 mg/kg/day, similar effects were observed in dogs. The rats and mice also exhibited liver cell enlargement and increased levels of cytochrome P-450 after

4 weeks of treatment; cessation of dosing with dieldrin allowed the reversal of hepatic changes (Wright et al. 1972). Dieldrin elicited a more limited response in monkeys than dogs, mice, or rats. Oral exposure of monkeys to dieldrin for 5–6 years at a dose level as high as 0.1 mg/kg/day resulted in increased mixed-function oxidase activity and cytochrome P-450 content in livers, but no observable histologic changes (Wright et al. 1972, 1978). In virtually all of these studies, no other evidence of hepatic toxicity was reported; thus, these adaptive changes were not considered to be adverse.

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

***Aldrin.*** Increases in relative liver weight and histopathological alterations were observed in rats exposed to 2.6 mg/kg/day aldrin in the diet for 6 months (Treon et al. 1951a); at a higher, lethal dose (55 mg/kg/day), severe liver damage was observed within the first 2 weeks of the study. In another study by this group, no histological alterations were observed in the livers of rats exposed to 2.5 mg/kg/day for 27 weeks (Treon et al. 1953a). Degenerative liver lesions were observed in dogs exposed to 1.25 mg/kg/day for up to 9 months (Treon et al. 1951b).

Rats receiving aldrin from the diet for up to 2 years exhibited increased relative liver weight and hepatic histopathological changes consistent with exposure to chlorinated hydrocarbons (Fitzhugh et al. 1964). The liver effects were characterized as hypertrophy of centrilobular hepatocytes, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation; these changes are consistent with an adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. Significant increases in relative liver weight was observed at ≥0.037 mg/kg/day in males and ≥0.15 mg/kg/day in females. The incidences of specific liver lesions were not included in the paper; significant increases in the total number of liver lesions were observed at ≥0.15 mg/kg/day. At 3.65 mg/kg/day, gross enlargement of the liver was observed; the histopathological changes were marked and included increased severity of hepatic cell vacuolation. NCI (1978a) did not report histological alterations in the liver of rats and mice exposed to doses of ≥4.2 and 1 mg/kg/day, respectively, for 80 months.

***Dieldrin.*** Limited evidence for adverse hepatic effects has been observed in rats following 1–6 months of exposure to dieldrin at 2 mg/kg/day (Shakoori et al. 1982) or 6 months of exposure to 22 mg dieldrin/kg/day (Ahmed et al. 1986a). At 2 mg /kg/day, adverse effects were limited to decreased hepatic protein and some incidences of necrosis (Shakoori et al. 1982). At 22 mg/kg/day, there was an increase in serum hepatic enzyme activity (AP and/or AST) with decreases in hepatic protein and areas of necrosis (Ahmed et al. 1986a). The statistical significance of the incidence of necrotic areas was not presented. Both studies are limited because only one dose of dieldrin was used.

Treon et al. (1951a) reported increased relative liver weight and histopathologic liver lesions in rats receiving dieldrin in food at 2.6 mg/kg/day for 6 months. Rats receiving dieldrin from the diet at 0.092 or 0.92 mg/kg/day for 2 years exhibited increased absolute and relative liver weights; the highest dose level resulted in liver parenchymal cell changes characteristic of organochlorine exposure, as well as indications of focal hyperplasia (Walker et al. 1969). Rats fed dieldrin at doses in the range of 0.016–0.063 mg/kg/day throughout their lifetime were reported to have developed hepatic lesions consisting of centrilobular degeneration and peripheral hyperplasia (Harr et al. 1970). Pyknosis of hepatocellular nuclei was also reported; however, no statistics, dose-response data, or incidence data were presented to support this conclusion.

Mice receiving dieldrin from the diet at 1.3 mg/kg/day for 2 years had livers with occasional necrotic areas (Thorpe and Walker 1973); however, this study is limited because it is unclear whether the necrotic areas were secondary to tumor development, the incidence of these areas was not reported, and only one dose of dieldrin was tested. Routine histological examinations revealed no evidence of nonneoplastic liver changes in other studies of mice administered dieldrin chronically at doses as high as 0.86–1.7 mg/kg/day (NCI 1978a; Tennekes et al. 1981).

Dogs that ingested doses as low as 0.73–1.85 mg dieldrin/kg/day for 9 months had moderate parenchymatous degeneration (Treon et al. 1955). Although the degeneration appeared to increase in severity with dose, this study is limited by a small number of animals. In dogs treated at 1 mg/kg/day of dieldrin for 25 months, slight-to-moderate fatty degeneration was observed (Fitzhugh et al. 1964). Also, in dogs given dieldrin at doses as low as 0.2 mg/kg/day for up to 1 year, degeneration was observed (Kitselman 1953). The degree of necrosis increased with dose. However, these studies are limited in that too few animals were tested (Fitzhugh et al. 1964; Kitselman 1953; Treon et al. 1955). Both male and female dogs receiving dieldrin orally at 0.05 mg/kg/day for 2 years had elevated serum AP levels, and males at this dose exhibited decreased serum proteins (Walker et al. 1969). The decrease in total serum

proteins was slight and considered to have no clinical or toxicological significance since the electrophoretic pattern of the proteins was unchanged. The possibility that increased serum AP may not necessarily represent hepatic damage in dogs was also raised by El-Ahraf et al. (1972), who showed that dogs exposed to dieldrin orally at 0.05–0.20 mg/kg/day for 1 year had increased serum AP of hepatic origin, but no increase in serum levels of 5'-nucleotidase (a hepatic membrane enzyme that should be elevated in the serum as a result of hepatic damage). Because hepatic levels of AP increased in parallel with serum levels of AP, these authors suggested that AP may be transferred directly from the hepatocyte to the sinusoidal blood.

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

## 2.10 RENAL

***Epidemiological Studies.*** No evidence of renal damage was seen in workers employed for ≥4 years in the manufacture of aldrin or dieldrin (Jager 1970). A man who attempted suicide by consuming an estimated 25.6 mg/kg of aldrin had elevated blood urea nitrogen, gross hematuria, and albuminuria upon admission to the hospital (Spiotta 1951). By 17 days after admission, levels of nitrogen, blood, and protein in the urine had returned to normal. Six weeks after the suicide attempt, the ability to concentrate the urine was poor. Another man who reportedly ingested 120 mg/kg of dieldrin exhibited no evidence of renal damage (Black 1974). In both of these case reports, the actual dose available for absorption was unknown because efforts were made to limit absorption of the chemicals from the gastrointestinal tract.

***Aldrin.*** Adverse effects on the kidneys have been observed following oral exposure of rats and dogs to aldrin. No histological alterations were observed in the kidneys of rats exposed to 2.5 mg/kg/day aldrin in the diet for 27 weeks (Treon et al. 1953a), rats exposed to 4.2 mg/kg/day in the diet for 74–80 weeks (NCI 1978a), or mice exposed to 1 mg/kg/day for 80 weeks (NCI 1978a). In contrast, fatty degenerative changes were observed in the kidneys of dogs exposed to 1 mg/kg/day aldrin administered via a capsule (Fitzhugh et al. 1964). The results of this study should be interpreted cautiously because due to the small number of dogs per dose group.

***Dieldrin.*** Gavage treatment of rats at 5 mg/kg/day dieldrin for 15 days resulted in membranous glomerulonephritis, nephrosis in the proximal convoluted tubules, vacuolated cytoplasm, necrotic cells in the tubular lumen, and large intertubular spaces (Bandyopadhyay et al. 1982b). Oral exposure of rats to dieldrin at 22 mg/kg/day for 6 months resulted in degenerative changes in the epithelial cells of the kidney and lymphocyte and macrophage infiltration (Ahmed et al. 1986a). Rats receiving dieldrin from the diet at 0.37 mg/kg/day for 25 months exhibited slight lymphocyte infiltration, vascular congestion in the renal cortex, and hyaline casts in the renal tubules (Deichmann et al. 1967). Dogs receiving dieldrin from the diet at doses as low as 0.2–1 mg/kg/day also exhibited degeneration of the renal tubules (Fitzhugh et al. 1964; Kitselman 1953), but these studies are limited by the absence of sufficient experimental detail, lack of histopathological data on many of the animals, and small number of animals tested. The study by Fitzhugh et al. (1964) employed only one or two dogs/sex/dose; the study by Kitselman (1953) employed three dogs/dose. Slight vacuolation of the renal tubules was also reported in dogs at dietary doses as low as 0.14–0.23 mg dieldrin/kg/day or 0.04–0.09 mg aldrin/kg/day for 15.7 months, but this study was also limited by the small number of dogs used (Treon et al. 1955).

Routine gross and microscopic examinations showed no adverse renal effects in rats or mice administered dieldrin orally for 6 months to 2 years at doses in the range of 0.5–4.6 mg/kg/day (NCI 1978a; Treon et al. 1951a, 1953a; Walker et al. 1969). There was no evidence of renal effects in dogs administered dieldrin for up to 2 years at doses up to 0.05 mg/kg/day (the highest dose level tested) (Walker et al. 1969).

## 2.11 DERMAL

***Epidemiological Studies.*** No evidence of dermatitis was seen in workers employed for ≥4 years in the manufacture of aldrin, dieldrin, endrin, or telodrin (Jager 1970). Contact dermatitis was observed in police recruits wearing socks that had been moth-proofed with a solution containing dieldrin (Ross 1964). Several recruits had a positive patch test when tested against the moth-proofing agent. The outbreak of the dermatitis appeared to have been exacerbated by the presence of the particular dye used in the socks and the fact that the recruits' feet had perspired heavily. No evidence of dermatitis was seen in volunteers who wore patches of cotton broadcloth or wool flannel impregnated with up to 0.5% dieldrin by weight for 4 days (Suskind 1959).

***Aldrin.*** Limited data were located regarding dermal effects in animals after inhalation exposure to aldrin. Cats, guinea pigs, rats, rabbits, and mice exposed to aldrin vapors and particles generated by sublimating

aldrin at 200°C were reported to have exhibited symptoms indicative of mucous membrane irritation (Treon et al. 1957). However, the exposure levels associated with these effects were not reported and the contribution of thermal decomposition products or other volatile contaminants other than aldrin cannot be eliminated.

Routine gross and microscopic examinations showed no adverse dermal effects in rats or mice exposed to aldrin in the diet for 74–80 weeks at doses in the range of 1–4.2 mg/kg/day (NCI 1978a).

A single dermal application of aldrin as a dry powder resulted in very slight erythema in rabbits (Treon et al. 1953b). The doses resulting in erythema were not reported; the tested doses ranged from 600 to 6,000 mg/kg. In an intermediate-duration study, no skin irritation was noted in rabbits exposed to doses of 221–320 mg /kg/day aldrin for 10 weeks (2 hours/day, 5 days/week) (Treon et al. 1953b).

***Dieldrin.*** Rough coat, discolored hair coat, and alopecia were noted in rats exposed to approximately 2 mg/kg/day dieldrin in the diet for 59–80 weeks (NCI 1978a). No dermal effects were noted in other oral studies in rats (Walker et al. 1969) and mice (NCI 1978a). There was no evidence of dermal effects in dogs administered dieldrin orally for up to 2 years at doses up to 0.05 mg/kg/day (the highest dose level tested) (Walker et al. 1969).

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

## 2.12 OCULAR

***Epidemiological Studies.*** No information was located regarding ocular effects in humans following inhalation, oral, or dermal exposure to aldrin or dieldrin.

***Aldrin.*** No ocular gross or histological alterations were observed in rats and mice chronically exposed to 1–4.2 mg/kg/day aldrin in the diet for 74–80 weeks (NCI 1978a).

***Dieldrin.*** Routine gross and microscopic examinations showed no adverse ocular effects in rats, mice, or dogs administered dieldrin orally for 6 months to 2 years at doses in the range of 0.05–4.6 mg/kg/day (NCI 1978a; Walker et al. 1969).

## 2.13 ENDOCRINE

***Epidemiological Studies.*** No studies were located regarding endocrine effects in humans following inhalation, oral, or dermal exposure to aldrin or dieldrin.

***Aldrin.*** No histological alterations of endocrine tissues were observed in the in rats and mice exposed to 1–4.2 mg/kg/day aldrin in the diet for 74–80 weeks (NCI 1978a).

***Dieldrin.*** Histological examination of endocrine tissues in intermediate- and chronic-duration oral studies revealed no evidence of dieldrin-related non-neoplastic changes in rats, mice, and dogs orally exposed to 0.05–4.6 mg/kg/day (NCI 1978a; Walker et al. 1969).

## 2.14 IMMUNOLOGICAL

***Epidemiological Studies.*** Limited information is available regarding the possible immunological effects of aldrin or dieldrin in humans. In one case report, a pesticide sprayer developed immunohemolytic anemia after multiple exposures to dieldrin, heptachlor, and toxaphene (Muirhead et al. 1959). Antibodies for dieldrin-coated or heptachlor-coated red blood cells were found in the subject's serum. However, this study is limited because the subject was exposed to other pesticides as well. In another case report, a man developed immunohemolytic anemia after eating fish that contained high levels of dieldrin (Hamilton et al. 1978). Testing of the patient's serum revealed a positive antibody test for dieldrin-coated red blood cells. No sensitization was observed in volunteers challenged with fabric containing up to 0.5% dieldrin 2 weeks following 4-day induction exposure (Suskind 1959). In a study of 98 breastfed and 73 bottle-fed Inuit infants from Nunavik (Arctic Quebec, Canada), risk of experiencing otitis media (three or more episodes) over the first year of life was reportedly increased with prenatal exposure to dieldrin (Dewailly et al. 2000). No clinically relevant differences were noted between breastfed and bottle-fed infants with regard to immunologic parameters.

***Dieldrin.*** Immunosuppression by dieldrin has been reported in a number of studies in mice. An increase in lethality of mouse hepatitis virus 3 and a decrease in the antigenic response to the virus were observed in mice given a single oral dose of dieldrin (≥18 mg/kg) (Krzystyniak et al. 1985). An increase in lethality of infections with the malaria parasite, *Plasmodium berghei*, or *Leishmania tropica* in mice was produced by treatment of the mice with dieldrin in the diet for 10 weeks at doses as low as 0.18 mg/kg/day (Loose 1982). A decrease in tumor cell killing in mice was observed after dieldrin treatment with oral doses as low as 0.13 mg/kg/day for 3–18 weeks (Loose et al. 1981).

Since resistance to intracellular organisms and tumor cell killing require induction of cell-mediated immunity through thymus-derived lymphocyte (T-lymphocyte) interactions with macrophages, the effects of dieldrin consumption on the activity of these components of the response were tested. A decrease in antigen processing by alveolar macrophages was observed in mice following consumption of dieldrin for 2 weeks at an estimated dose of 0.09 mg/kg/day (Loose et al. 1981). Macrophages that ingested sheep red blood cell antigen manifested a significantly impaired ability to transfer an adequate immunogen to naive control mice. Splenic and alveolar macrophages were the most sensitive cell types as the decrease occurred following exposure to dieldrin doses as low as 0.09 mg/kg/day (lowest tested dose). Peritoneal macrophage antigen processing was significantly depressed at 0.9 mg/kg/day, and Kupffer cell antigen processing was depressed at 9 mg/kg/day. This effect was observed in the absence of effects on macrophage respiration, phagocytic activity or capacity, or microbicidal activity. In addition, macrophages from dieldrin-treated (0.9 mg/kg/day for 10 weeks) mice produced a soluble factor that induced T-lymphocyte suppressor cells (Loose 1982). Inhibition of lymphocyte proliferation was also seen in a mixed lymphocyte reaction test in which splenic cells from mice treated twice with 16.6 mg dieldrin/kg (the only dose tested) were combined with stimulator cells from control animals (Fournier et al. 1988).

I*n vitr*o studies have shown dieldrin to cause increased superoxide production in human neutrophils (Pelletier and Girard 2002; Pelletier et al. 2001), presumably via protein kinases C and tyrosine kinases, and apoptotic alterations in human peripheral blood lymphocytes (Michalowicz et al. 2013). Cytotoxicity and oxidative stress were observed in BALB/c 3T3 fibroblasts exposed to aldrin (Lonare et al. 2016).

## 2.15 NEUROLOGICAL

***Epidemiological Studies.*** Central nervous system excitation culminating in convulsions was the principal adverse effect noted in occupational studies of workers employed in either the application or manufacture

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

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

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

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

Results from a comprehensive neurological examination of 27 workers involved in either the manufacture or application of dieldrin were compared to those of a group of unexposed workers (Sandifer et al. 1981).

Scores on five psychological tests were significantly different from those of the unexposed controls. However, the importance of the results was questioned by the authors because of differences in the degree of literacy between the two groups. Also, three exposed workers had abnormal electromyograms (EMGs), suggesting a peripheral neuropathy. However, EMGs were not obtained in the control group; thus, the significance of these results is unknown.

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

A small group of persons who consumed wheat mixed with aldrin and lindane over a period of 6–12 months developed a variety of central nervous system symptoms (Gupta 1975); exposure levels were not estimated. These included bilateral myoclonic jerks, generalized seizures, auditory and visual auras, hyperexcitability, and irritability. In some cases, the onset of symptoms was abrupt. EEGs showed spike and wave activity and abnormal bursts of slow delta-wave discharges. After exposure was discontinued, the symptoms slowly improved. However, 1 year after exposure, infrequent myoclonic jerks were observed in several of the subjects. One subject also complained of memory loss and irritability, and a 7-year-old child was believed to have developed mild mental retardation as a result of the exposure. Although both aldrin and lindane had been mixed with the wheat, the author concluded that the effects observed were due to the aldrin exposure because in previous years wheat had been routinely mixed with lindane and consumed with no apparent adverse effects.

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

Although case-control studies have provided evidence of associations between exposure to pesticides and risk of Parkinson's disease, no information specific to aldrin was located and only extremely limited data were located for dieldrin. Postmortem brain tissue from 14 cases of Parkinson's disease contained dieldrin concentrations 3 times higher than levels measured in brain tissue from 12 age-matched controls (Pennell et al. 2006). In another study, dieldrin was not detected in postmortem brain tissue from 50 Parkinson's disease patients (Richardson et al. 2009). In a nested case-control study of 101 Parkinson's disease cases and 349 matched controls, increasing serum concentrations of dieldrin trended toward higher risk of Parkinson's disease (Weisskopf et al. 2010). However, the study authors noted that chance or exposure correlation with other pesticides may have contributed to the findings.

***Aldrin.*** Single or repeated gavage dosing of rats with aldrin at 2–25 mg/kg/day resulted in increased locomotor activity (Jamaluddin and Poddar 2001a, 2001b, 2003). Peak responses occurred at 2 hours postdosing. In a study designed to evaluate dose-response characteristics following single dosing at 1–25 mg/kg, the greatest increase in locomotor activity occurred at 10 mg/kg; there was no significant difference in locomotor activity between controls and rats dosed at 25 mg/kg (Jamaluddin and Poddar 2001b). In studies that employed dosing at 5 or 10 mg/kg/day for up to 30 days, the peak of aldrin-induced increased locomotor activity occurred at treatment day 12; by treatment day 30, locomotor activity had returned to near control levels (Jamaluddin and Poddar 2001b, 2003). Tremors and convulsions were observed in rats administered 10 mg/kg/day aldrin for 3 days (Mehrotra et al. 1989). Neurotoxic signs observed in cattle poisoned with unspecified dietary concentrations of aldrin included tremors, running, hyperirritability, and seizures (Buck and Van Note 1968).

Irritability, tremors, and/or convulsions were observed in rats exposed to 2.1 mg/kg/day aldrin in the diet for 74–80 weeks (NCI 1978a, 1978b). In 80-week bioassays of mice, hyperexcitability, fighting, and/or tremors were reported at oral doses of 0.5 mg/kg/day aldrin (NCI 1978a).

Dogs orally administered aldrin at 0.89–1.78 mg/kg/day for up to 9 months experienced convulsions and neuronal degeneration in the cerebral cortex (Treon et al. 1951b). At this dose, aldrin-treated dogs also exhibited hypersensitivity to stimulation, twitching, and tremors. At higher doses, degenerative changes were observed in basal ganglia and cerebellum. In another chronic dog study, moderate neuronal

degeneration was reported in dogs following 1 year of oral exposure to aldrin at 0.2 mg/kg/day (Kitselman 1953). The small number of animals tested and the poor reporting of the results limit the interpretation of this study.

***Dieldrin.*** Convulsions were observed in rats given single oral doses of dieldrin ranging from 40 to 50 mg/kg (Wagner and Greene 1978; Woolley et al. 1985). When dieldrin was administered to rats for 3 days, tremors and convulsions were observed at a dose of 10 mg/kg/day (Mehrotra et al. 1989). Transient hypothermia and anorexia were also observed in rats following a single oral dose of 40 mg/kg (Woolley et al. 1985). Long-term potentiation of limbic evoked potentials was observed in rats following a single oral dose of 25 mg/kg, and subthreshold limbic stimulation caused convulsions following a single oral dose of 40 mg/kg (Woolley et al. 1985).

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

In studies of intermediate duration, operant behavior was disrupted at somewhat lower doses of dieldrin. Following 60–120 days of exposure of rats to 0.46 mg/kg/day, dieldrin significantly impaired maze training (Burt 1975). Monkeys orally administered 0.1 mg dieldrin/kg/day for 55 days demonstrated impaired learning (difficulty learning a successive discrimination reversal task) (Smith et al. 1976). Sheep appeared to be somewhat less sensitive to the effects of dieldrin on behavior, although a small number of animals was used in these studies (Van Gelder 1975). The lowest dose at which sheep exhibited impaired operant behavior was 2.5 mg/kg/day for 12 weeks. This was determined using an auditory signal detection test. Visual discrimination was not impaired until doses of 10 mg/kg/day were administered, and maze training and extinction of a conditioned avoidance response were not impaired at 15 mg/kg/day (Van Gelder 1975).

Chronic-duration oral exposure of rats resulted in irritability, tremors, and/or convulsions at 0.5–4.25 mg/kg/day (NCI 1978a, 1978b; Walker et al. 1969). In 80-week bioassays of mice, hyper-excitability, fighting and/or tremors were reported at oral doses of 0.43 mg dieldrin/kg/day (NCI 1978a).

Body tremors and convulsions were also reported in mice exposed to 3.4 mg/kg/day dieldrin in the diet for up to 128 weeks (Walker et al. 1973).

Convulsions and neuronal degeneration in the cerebral cortex were observed in dogs administered 0.73–1.85 mg/kg/day dieldrin for up to 9 months (Treon et al. 1951b). Convulsions and neuronal degeneration in the cerebral cortex were observed in dogs orally administered at 0.73–1.85 mg/kg/day dieldrin for up to 9 months (Treon et al. 1951b). EEGs taken from dogs administered dieldrin in capsule for 2 years at 0.05 mg/kg/day were normal (Walker et al. 1969).

Histopathologic evidence of dieldrin treatment-related neurological effects was reported in two chronic-duration oral studies. Slight neuronal degeneration was reported in dogs following 1 year of oral exposure to dieldrin at 0.2 mg/kg/day (Kitselman 1953). Cerebral edema and small foci of degeneration were reported in rats administered dieldrin orally for 2 years at 0.016 mg/kg/day (Kitselman 1953). However, no statistical analysis of these results was presented and no incidence data were reported.

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

Facilitation of neurotransmitter release by dieldrin has been proposed to occur as the result of the ability of aldrin or dieldrin to inhibit brain calcium ATPases (Mehrotra et al. 1988, 1989). These enzymes are involved in pumping calcium out of the nerve terminal. By inhibiting their activity, aldrin and dieldrin would cause a build-up of intracellular levels of calcium and an enhancement of neurotransmitter release. Heusinkveld and Westerlink (2012) demonstrated that nanomolar concentrations of dieldrin interrupted intracellular calcium homeostasis in rat dopaminergic pheochromocytoma PC-12 cells (an established model system for neurosecretion and neuronal differentiation) by inhibiting depolarization-evoked influx of $Ca^{2+}$.

The role of aldrin and dieldrin in blocking inhibitory activity within the brain has received a great deal of attention as the probable mechanism underlying the central nervous system excitation. Based on the

observed interaction of other cyclodiene insecticides with the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) (Matsumura and Ghiasuddin 1983), numerous studies were undertaken to assess the effects of aldrin and dieldrin on GABA receptor function. Both *in vivo* experiments in rats and mice and *in vitro* experiments using rat or mouse brain membranes or cell lines have shown that aldrin and dieldrin are capable of blocking the activity of GABA by blocking the influx of chloride through the $GABA_A$ receptor-ionophore complex (Abalis et al. 1986; Babot et al. 2007; Bloomquist 1992, 1993; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Ikeda et al. 1998; Jamaluddin and Poddar 2001a, 2001b; Lawrence and Casida 1984; Liu et al. 1997a, 1997b; Nagata and Narahashi 1994, 1995; Narahashi et al. 1992, 1995, 1998; Obata et al. 1988; Pomes et al. 1994; Vale et al. 2003). Overall, based on good correlations of effects from the molecular level to whole animal toxicity, the preponderance of evidence indicates that the convulsant and other neurotoxic effects of aldrin and dieldrin could be consequent to a blocking action on the $GABA_A$ receptor-chloride channel complex. Vale et al. (2003) demonstrated that dieldrin also inhibited glycine-gated chloride channels in primary cultures of mouse cerebellar granule cells.

Oral exposure of pregnant mice to dieldrin (0.3, 1, or 3 mg/kg every 3 days) during gestation and lactation resulted in dose-related increased messenger ribonucleic acid (mRNA) levels of the dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) in the 12-week-old offspring (Richardson et al. 2006).

Slotkin and Seidler (2008, 2009a, 2009b) performed a series of *in vitro* mechanistic studies that employed rat dopaminergic pheochromocytoma PC-12 cells. Collectively, the studies demonstrated that dieldrin caused upregulation of tryptophan hydrolase (an enzyme involved in the synthesis of the neurotransmitter serotonin), suppressed the expression of eight subtypes of serotonin receptor transporter genes, both up- and downregulated selected genes involved in oxidative stress responses and glutathione-related genes, and both up- and downregulated selected subtypes of protein kinase c (involved in controlling the function of other proteins).

Results from a number of studies indicate a potential role for dieldrin in the etiology of Parkinson's disease that includes oxidative damage and/or apoptosis (e.g., Hatcher et al. 2007; Kanthasamy et al. 2008; Kitazawa et al. 2001, 2003; Saminathan et al. 2011; Schmidt et al. 2017; Sharma et al. 2010; Sun et al. 2005). Possible underlying mechanisms in aldrin and/or dieldrin-induced oxidative damage and/or apoptosis in dopaminergic neuronal cells include changes such as increased expression of α-synuclein

resulting in proteosomal dysfunction, mitochondrial dysfunction, promotion of caspase-3-dependent proteolytic cleavage of protein kinase c, and activation of a nonreceptor tyrosine kinase.

Kochmanski et al. (2019) administered dieldrin (0.3 mg/kg every 3 days) to female mice prior to mating and throughout gestation and lactation. At 12 weeks of age, offspring were sacrificed for evaluation of mesencephalic deoxyribonucleic acid (DNA). The results indicated that developmental dieldrin exposure altered DNA methylation at genes related to dopaminergic neuron development and Parkinson's disease. In another mouse study, dieldrin administration resulted in oxidative stress evidenced by increased lipid peroxidation in all brain regions and strong antioxidative and DNA repair responses (Sava et al. 2007).

Pesticides have also been implicated in the etiology of the Lewy body diseases, which involve intracellular deposits consisting of fibrils of α-synuclein. Dieldrin has been shown to stimulate α-synuclein fibril formation *in vitro* (Uversky et al. 2001). While α-synuclein is a natively unfolded protein, dieldrin induces a conformational change in α-synuclein, a time-dependent increase in secondary structure, which precedes the increase in fibril formation. The natively unfolded state of α-synuclein arises from the large net negative charge at neutral pH and the low intrinsic hydrophobicity. Uversky et al. (2001) proposed that nonpolar dieldrin binds to α-synuclein and shifts the equilibrium from the unfolded state to a folded intermediate conformation. The intermediate then associates, leading to fibril formation.

## 2.16 REPRODUCTIVE

***Epidemiological Studies.*** Limited information was located regarding aldrin or dieldrin exposure-related reproductive effects in humans. Aldrin levels in blood and placental tissues of women who had premature labor or spontaneous abortions were significantly higher than in women with normal deliveries (Saxena et al. 1980). However, interpretation of this study is limited because levels of six other organochlorine pesticides were also significantly elevated. Furthermore, other potential distinctions between the two groups that might have contributed to premature labor or abortion (e.g., smoking, alcohol consumption) were not addressed. Nevertheless, this observation suggests that aldrin can pass through the human placenta and accumulate in the developing fetus. Accumulation of dieldrin in the amniotic fluid and in the developing fetus has been reported by Polishuk et al. (1977a).

***Aldrin.*** Acute exposure of male mice to aldrin produced no adverse effects on reproduction. Male mice treated with doses of aldrin up to 1 mg/kg/day for a period of 5 days showed no significant effects in a dominant lethal study (Epstein et al. 1972).

In a 6-generation reproduction study, decreased fertility (decreased number of mated dams that delivered pups) was noted at dietary aldrin levels resulting in estimated doses as low as 0.56 mg/kg/day (the lowest level tested) (Keplinger et al. 1970). A decrease in fertility was also observed in a 3-generation study (Treon et al. 1954a). Dietary exposure to aldrin doses as low as 1.3 mg/kg/day resulted in decreased fertility (decreased number of litters) during the first mating of the parental generation. A subsequent mating of the parental rats receiving aldrin showed no reproductive effects.

***Dieldrin.*** In a dominant lethal assay, no significant effect on the number of pregnancies produced by male mice following single oral doses of dieldrin ranging from 12.5 to 50 mg/kg was observed (Dean et al. 1975).

A significant but slight decrease in fertility was observed in female mice receiving dieldrin from the diet at 2 or 2.9 mg/kg/day from 4 weeks prior to mating through weaning (Virgo and Bellward 1975). In this study, males were exposed to test material only during the 2-week mating period. In a 3-generation reproduction study, male and female weanling rats receiving test substance from the diet at doses as low as 0.26 mg/kg/day dieldrin exhibited decreased fertility (decreased number of litters) during the first mating of the parental generation (Treon et al. 1954a). A subsequent mating of the parental rats receiving dieldrin failed to show a consistent dose-related effect on fertility. At matings of the offspring, no effect on fertility (number of litters) was observed at 0.26 mg dieldrin/kg/day; effects on fertility due to higher doses were difficult to assess because few offspring survived to be mated. No consistent effect of doses as high as 2 mg/kg/day dieldrin was found on the conception rate of male and female rats exposed from the time they were 28 days old through the period of mating (initiated when the rats were 146 days old) (Harr et al. 1970). These results are limited in that no statistical analysis of the data was presented. In addition, male and female mice exposed to 0.93 mg/kg/day dieldrin for 30 days prior to mating and then for 90 days thereafter exhibited no adverse effects on fertility, fecundity, or length of gestation (Good and Ware 1969). The only adverse reproductive effect observed in this study was a slight decrease in litter size. However, this study is limited in that only one dose level of dieldrin was tested.

A number of adverse reproductive effects were observed in dogs administered aldrin orally (males and females) at 0.15 or 0.30 mg/kg/day for 14 months prior to mating (Deichmann et al. 1971). The effects

included delayed estrus, reduced libido, lack of mammary function and development, and an increased number of stillbirths. However, this study is limited by the small number of animals tested.

Maternal behavior was adversely affected by dieldrin when mice were treated orally from 4 weeks prior to delivery until weaning. At 2 mg/kg/day, Virgo and Bellward (1975) observed a delay in the time before mice nursed their pups. At doses ≥2.9 mg/kg/day, some dieldrin-treated maternal animals violently shook the pups, ultimately killing them, and others neglected their litters (Virgo and Bellward 1975). Maternal mortality was noted at dieldrin doses >2.9 mg/kg/day.

## 2.17 DEVELOPMENTAL

***Epidemiological Studies.*** No studies were located regarding aldrin or dieldrin treatment-related developmental effects in humans, although dieldrin has been detected in placenta, amniotic fluid, and fetal blood (Polishuk et al. 1977a).

***Aldrin.*** Several studies have evaluated the potential developmental toxicity in animals orally exposed to aldrin. The most consistently reported effect was increased postnatal mortality.

Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin. Increased mortality of offspring during the first 5 days postpartum was observed at 0.26 mg/kg/day of aldrin in the first mating of a 3-generation reproduction study in rats (Treon et al. 1954a). Decreased pup survival to postpartum day 4 was observed in a multigeneration study in which mice were exposed to 0.56 mg/kg/day aldrin (Keplinger et al. 1970). Poor litter survival was also reported in a study of dogs treated orally for up to 1 year at doses of aldrin as low as 0.2 mg/kg/day (Kitselman 1953). In some instances, apparently normal puppies died after a few days of nursing. Although maternal toxicity was not specifically addressed in this study, dogs receiving similar doses of aldrin exhibited histopathologic evidence of hepatic and renal toxicity. This study is limited because too few dogs were tested, pregnancies were incidental to the study protocol, and adequate controls were not used. Dogs mated 2 weeks to 9 months after 14 months of oral exposure to aldrin at doses as low as 0.15 mg/kg/day also exhibited high levels of offspring mortality (Deichmann et al. 1971). However, this study was also limited by the small number of animals tested. An increase in fetal mortality was observed in hamsters administered single gavage doses of 50 mg/kg aldrin on GD 7, 8, or 9 (Ottolenghi et al. 1974).

Offspring of mice administered aldrin orally for 5–7 days during the third trimester of pregnancy at 2 or 4 mg/kg/day exhibited 18% depressed body weight and a significantly increased electroconvulsive shock brain seizure threshold, although there was no disruption of the acquisition of a conditioned avoidance response (Al-Hachim 1971). Increased incidence of webbed feet and the number of fetuses with open eyes were observed in the offspring of mice administered 25 mg/kg on GD 9 (Ottolenghi et al. 1974).

***Dieldrin.*** As with aldrin, increased postnatal mortality is the most consistently reported developmental effect of dieldrin. Decreased pup survival was reported in a study of mice administered dieldrin in the diet from 4 weeks prior to mating through weaning at doses as low as 1 mg/kg/day (Virgo and Bellward 1975). A similar decrease in postnatal survival was observed in rats exposed to dieldrin by the oral route. Increased mortality of F3a rat offspring during the first 5 days postpartum was observed at 1.3 mg/kg/day of dieldrin (Treon et al. 1954a). Decreased postnatal pup survival was reported in a study of rats exposed to dieldrin from 28 days of age to mating at 146 days of age at a dose level as low as 0.125 mg/kg/day (Harr et al. 1970). Maternal mortality in this study was unaffected at doses <0.5 mg/kg/day. This study is limited, however, in that no statistical analysis of the data was presented to confirm this assertion.

To test whether the decrease in pup survival was dependent on maternal postnatal care, a cross-fostering experiment was performed (Virgo and Bellward 1977). Mice born to dieldrin-exposed dams were nursed by untreated dams. Significantly decreased pup survival was also observed in this study at 1 mg/kg/day irrespective of whether pups were nursed by birth or foster maternal animals. In a single-dose level study of mice exposed via their mothers administered dieldrin orally at 2 mg/kg/day on GDs 6–18, pups that were examined at varying times after birth exhibited a rapid decrease in blood glucose and depletion of tissue glycogen stores (Costella and Virgo 1980). These decreases occurred despite apparently normal gluconeogenesis. Cardiac failure, secondary to cardiac glycogen depletion, has been proposed as the cause of death (Costella and Virgo 1980).

Conflicting results have been obtained in animal studies designed to evaluate the ability of dieldrin to cause external malformations or skeletal anomalies. Such effects have been observed in mice and hamsters following a single very large dose of dieldrin in mid-gestation (Ottolenghi et al. 1974). Significant increases in cleft palate and webbed foot were observed in mice following a dose of 15 mg/kg dieldrin on GD 9. Significant increases in cleft palate, open eye, and webbed foot were observed in fetuses from hamsters dosed once on gestation day 7, 8, or 9 at 30 mg/kg dieldrin. Other developmental effects included increased fetal mortality and depressed fetal weight. A significant increase in supernumerary ribs was observed in mice from dams administered dieldrin orally on GDs 7–16 at 3 or

6 mg/kg/day (Chernoff et al. 1975). No developmental defects were observed in studies of rats administered dieldrin orally during GDs 7–16 at doses as high as 6 mg/kg/day (Chernoff et al. 1975) or in mice exposed to 1–4 mg/kg/day on GDs 6–14 (Dix et al. 1977).

Olson et al. (1980) reported significant improvement in swimming and maze running performance by rat pups exposed via their mothers to dieldrin during gestation and lactation followed by oral treatment from weaning to 70 days of age at a dose of 0.00035 mg/kg/day. This dose of dieldrin is several orders of magnitude below any other dose at which developmental effects have been observed. Interpretation of these results is difficult because the significance of improved performance in behavioral paradigms is unknown; the study is limited because only one dose of dieldrin was tested.

Histopathologic examination of pups born to treated maternal animals was performed in two studies. Neural lesions consisting of cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration were reported among rat pups born to dams administered dieldrin orally at doses as low as 0.004–0.008 mg/kg/day (Harr et al. 1970). Hepatic degeneration was seen in the pups of dams fed doses of dieldrin as low as 0.016 mg/kg/day. However, no information regarding dose-dependency or the relative numbers of animals affected was reported. Degeneration of hepatic and renal tissues was reported among offspring of dogs treated orally with aldrin at doses as low as dieldrin at doses as low as 0.6 mg/kg/day (Kitselman 1953). Both studies are limited by the lack of supporting clinical chemistry data and the absence of statistical analyses of the histopathological data. Furthermore, in the study by Kitselman (1953), not all offspring were examined histopathologically.

## 2.18 OTHER NONCANCER

No data were located regarding other noncancer effects in humans or animals exposed to aldrin or dieldrin.

## 2.19 CANCER

***Epidemiological Studies.*** The database of information regarding the potential human carcinogenicity of aldrin and dieldrin includes evaluation of cohorts involved in aldrin and dieldrin production, cohort or case-control studies employing self-reported usage of aldrin and/or dieldrin, and case-control studies using blood or tissue aldrin or dieldrin levels as evidence of exposure. A major limitation common to the epidemiological studies for aldrin and dieldrin is the lack of quantitative measures of exposure. Other

limitations include exposure to other pesticides, relatively small numbers of cases for selected cancer types, and possible exposure to known human carcinogens.

The potential carcinogenicity of aldrin and dieldrin was evaluated in a cohort of 1,155 workers at an organochlorine manufacturing plant in Colorado (Ditraglia et al. 1981). All workers in the study had been employed for at least 6 months prior to December 31, 1964. Vital status was ascertained through December 31, 1976. There was no increased risk of death from all malignant neoplasms, or cancers of the esophagus, stomach, intestines, rectum, liver, pancreas, respiratory system, bladder and urinary system, or lymphatic and hematopoietic system. Numbers of observed deaths from these selected cancer types ranged from one to seven. Follow-up evaluation of this cohort through December 31, 1987 revealed 5 deaths from liver biliary/gallbladder cancer (1.27 expected) (Brown 1992). Amoateng-Adjepong et al. (1995) expanded the cohort to include all employees who ever worked at the plant during 1952 through 1982 and for whom social security numbers and dates of employment and birth were known (n=2,384). Among white male workers in hourly jobs, five deaths from hepatobiliary cancer were observed (two expected). Observed deaths from other cancers (digestive system, colon/rectum, respiratory system, lung, brain and central nervous system, lymphopoietic) and all cancer types were similar to those expected based on Colorado rates. A major limitation of this cohort is the production of numerous other pesticide compounds at the plant in addition to aldrin and dieldrin, which limits the usefulness of the results.

The potential carcinogenicity of aldrin and dieldrin was also evaluated in a study of workers with at least 4 years of employment in the manufacture of aldrin, dieldrin, endrin, or telodrin in the Netherlands (Jager 1970). Follow-up evaluations were performed using 570 workers employed for at least 1 year during 1954–1970 and followed until January 1, 1987 (de Jong 1991), until January 1, 1993 (de Jong et al. 1997), until January 1, 2002 (Swaen et al. 2002), and until April 30, 2006 (van Amelsvoort et al. 2009). There was no apparent increased risk for stomach, intestinal, liver, pancreas, lung, prostate, bladder, multiple myeloma, leukemia, or kidney cancer. De Jong et al. (1997) reported increased risk of death from rectal cancer (6 deaths versus 1.6 expected). Swaen et al. (2002) reported increased risk of death from rectal cancer, but only in the low-intake group (based on measured dieldrin blood levels). The latest follow-up of this population (van Amelsvoort et al. 2009) found a nonstatistical increase in rectal cancer in the low exposure group, but no increases in the moderate or high exposure groups.

A number of cohort or case-control studies have used data collected as part of the Agricultural Health Study of pesticide applicators in Iowa and North Carolina to evaluate possible associations between self-reported use of aldrin or dieldrin and risk of non-Hodgkin's lymphoma (Alavanja et al. 2014; Cantor et al.

1992; De Roos et al. 2003; Lee et al. 2004a; McDuffie et al. 2001; Purdue et al. 2006; Schroeder et al. 2001); multiple myeloma (Alavanja et al. 2014); female breast cancer (Engel et al. 2005; Louis et al. 2017); prostate cancer (Koutros et al. 2013a, 2013b; Purdue et al. 2006); bladder cancer (Koutros et al. 2016; Purdue et al. 2006); leukemia (Brown et al. 1990; Purdue et al. 2006); lung cancer (Bonner et al. 2017; Purdue et al. 2006); stomach/esophageal cancer (Lee et al. 2004b); pancreatic cancer (Clary and Ritz 2003); colon cancer (Purdue et al. 2006); rectal cancer (Purdue et al. 2006); melanoma (Dennis et al. 2010; Purdue et al. 2006); soft tissue sarcoma (Pahwa et al. 2011); or childhood cancer (Flower et al. 2004). As shown in Table 2-3, most studies found no association between self-reported aldrin or dieldrin use and risk of selected cancer types.

**Table 2-3. Summary of Epidemiological Studies Evaluating Possible Associations between Self-Reported Aldrin or Dieldrin Use and Risk of Selected Cancer Types**

| Cancer type | Association[a] | No association[b] |
|---|---|---|
| **Aldrin** | | |
| Non-Hodgkin's lymphoma | McDuffie et al. 2001 | Alavanja et al. 2014<br>Cantor et al. 1992<br>De Roos et al. 2003<br>Lee et al. 2004a<br>Purdue et al. 2006<br>Schroeder et al. 2001 |
| Lung | | Purdue et al. 2006 |
| Multiple myeloma | | Alavanja et al. 2014 |
| Female breast cancer | Engel et al. 2005[c] | Engel et al. 2005<br>Louis et al. 2017 |
| Prostate cancer | Koutros et al. 2013b[d] | Koutros et al. 2013a[e]<br>Purdue et al. 2006 |
| Bladder cancer | | Koutros et al. 2016<br>Purdue et al. 2006 |
| Leukemia | | Brown et al. 1990<br>Purdue et al. 2006 |
| Stomach/esophageal cancer | | Lee et al. 2004b |
| Colon | | Purdue et al. 2006 |
| Rectum | | Purdue et al. 2006 |
| Melanoma | | Dennis et al. 2010<br>Purdue et al. 2006 |
| Soft tissue sarcoma | | Pahwa et al. 2011 |
| Childhood cancers | Flower et al. 2004[f] | |

**Table 2-3. Summary of Epidemiological Studies Evaluating Possible Associations between Self-Reported Aldrin or Dieldrin Use and Risk of Selected Cancer Types**

| Cancer type | Association[a] | No association[b] |
|---|---|---|
| **Dieldrin** | | |
| Non-Hodgkin's lymphoma | Schroeder et al. 2001[g] | Alavanja et al. 2014<br>Cantor et al. 1992<br>De Roos et al. 2003<br>Lee et al. 2004a<br>Purdue et al. 2006 |
| Lung | | Bonner et al. 2017<br>Purdue et al. 2006 |
| Multiple myeloma | | Alavanja et al. 2014 |
| Female breast cancer | Engel et al. 2005[c] | Louis et al. 2017 |
| Prostate cancer | | Koutros et al. 2013a<br>Purdue et al. 2006 |
| Bladder cancer | | Koutros et al. 2016<br>Purdue et al. 2006 |
| Leukemia | | Brown et al. 1990<br>Purdue et al. 2006 |
| Stomach/esophageal cancer | | Lee et al. 2004b |
| Colon | | Purdue et al. 2006 |
| Rectum | | Purdue et al. 2006 |
| Melanoma | | Purdue et al. 2006 |

[a]Increased risk.
[b]No increased risk.
[c]Increased risk among women who never used pesticides, but whose husbands used pesticides.
[d]Increased risk among men carrying two A alleles at rs7679673 of the *TET*2 (Tet Methylcytosine Dioxygenase 2) gene, but only for the highest level of estimated aldrin use.
[e]No increased risk for total prostate cancer; increased risk for aggressive prostate cancer among workers in the highest estimated category of exposure duration.
[f]Paternal use of aldrin during prenatal period.
[g]The reported association between self-reported use of dieldrin and risk of non-Hodgkin's lymphoma was observed only among those agricultural workers expressing the chromosomal translocation t(14;18).

Clary and Ritz (2003) evaluated possible association between living in California zipcodes associated with "high" pesticide usage and risk of pancreatic cancer. No association was found between dieldrin and risk of pancreatic cancer after adjusting for usage of 17 other pesticides.

Some studies evaluated possible associations between dieldrin in blood or adipose tissue and risk of non-Hodgkin's lymphoma (Cantor et al. 2003; De Roos et al. 2005; Quintana et al. 2004); female breast cancer (Gammon et al. 2002; Hoyer et al. 1998, 2001, 2002; Mathur et al. 2002; Ward et al. 2000); or prostate cancer (Ritchie et al. 2003). Table 2-4 provides a summary list of reported association/lack of association between dieldrin in blood or adipose tissue and risk of selected cancer types. The most

convincing evidence for an association between blood or adipose tissue dieldrin levels and cancer risk was for female breast cancer among estrogen receptor negative ($ER^-$) breast cancer cases (Hoyer et al. 2001). Two studies examined the possible association between blood aldrin levels and the risk of female breast cancer. Ward et al. (2000) did not find an association in a case control study of women aged 18–60 years. Ibarluzea et al. (2004) found an association among postmenopausal women.

**Table 2-4. Summary of Epidemiological Studies Evaluating Possible Associations between Dieldrin Levels in Blood or Adipose Tissue and Risk of Selected Cancer Types**

| Cancer type | Association[a] | No association[b] |
|---|---|---|
| Non-Hodgkin's lymphoma | Quintana et al. 2004 | Cantor et al. 2003<br>De Roos et al. 2005 |
| Female breast cancer | Hoyer et al. 1998<br>Hoyer et al. 2001[c]<br>Ibarluzea et al. 2004[d] | Gammon et al. 2002<br>Hoyer et al. 2002<br>Ibarluzea et al. 2004[e]<br>Ward et al. 2000 |
| Prostate cancer | | Ritchie et al. 2003 |

[a]Increased risk.
[b]No increased risk.
[c]Increased risk only among estrogen receptor negative ($ER^-$) breast cancer cases in the highest quartile of serum dieldrin levels (>57.11 ng/mL).
[d]Increased risk among postmenopausal women.
[e]No increased risk among premenopausal women.

***Aldrin.*** Davis and Fitzhugh (1962) reported significantly increased incidences of hepatic cell adenoma in C3HeB/Fe mice exposed to 1.7 mg/kg/day aldrin in the diet for up to 2 years. Re-evaluation of the histopathology data indicated that most tumors were actually hepatocellular carcinomas (Epstein 1975; Reuber 1976). Epstein (1975) also summarized a 1965 unpublished study conducted by Davis. In this study, an increase in the incidence of benign hepatoma was observed in male and female mice exposed to 1.7 mg/kg/day aldrin in the diet for up to 2 years. As with the Davis and Fitzhugh (1962) study, a partial re-evaluation indicated that the tumors classified as benign hepatomas were hepatocellular carcinomas (Reuber 1976). Increased incidences of hepatocellular carcinoma were reported in male B6C3F1 mice administered 0.7 and 1.4 mg/kg/day aldrin in the diet for up to 80 weeks (NCI 1978a). Incidences at the highest dose were 25/45 compared to 3/20 among matched controls and 17/92 among pooled controls obtained from the study of aldrin and other contemporary studies.

NCI (1978a) observed significantly increased incidences of follicular cell adenoma and carcinoma of the thyroid in Osborne-Mendel male rats receiving 2.1 mg/kg/day aldrin in the diet for up to 74–80 weeks,

but not at 4.2 mg/kg/day. Similarly-treated female rats exhibited significantly increased incidences of adrenal cortical adenoma and combined adenoma and carcinoma at 2.3 mg/kg/day; however, incidences of these tumor types were not significantly increased at 4.6 mg/kg/day. The study authors considered the lack of a dose-response to suggest the lack of a carcinogenic response.

Carcinogenicity studies of aldrin in rats have produced mostly negative results (Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; NCI 1978a). However, several of these studies were based on limited microscopic examination of animals (Fitzhugh et al. 1964) and/or high levels of early mortality with insufficient numbers of animals surviving until study termination (Deichmann et al. 1970; Fitzhugh et al. 1964). It is noted that the Fitzhugh et al. (1964) study found an increase in total tumors at the lowest dose tested (0.037 mg/kg/day), but not at higher doses.

The Department of Health and Human Services (HHS) has not evaluated the carcinogenicity of aldrin (NTP 2016a).

EPA classified aldrin as Group B2 (probable human carcinogen) based on sufficient evidence in animals (significantly increased liver tumor responses in three strains of male and female mice and noted that tumor induction was also observed in structurally related chemicals (including dieldrin, a pesticide and metabolite of aldrin) (EPA 2003; IRIS 1987). EPA considered the human carcinogenicity data for aldrin to be inadequate.

EPA calculated human potency estimates for aldrin using liver tumor responses in mice (EPA 2003; IRIS 1987). The potency estimates ($q_1^*$) represent a 95% upper confidence limit of the extra lifetime human risks. Using potency estimates calculated from three data sets in two mouse strains and both sexes (Epstein 1975; NCI 1978a), a geometric mean of 17 $(mg/kg/day)^{-1}$ was chosen for the oral cancer risk estimate for aldrin (EPA 2003; IRIS 1987). The unit risk estimate for drinking water exposures (the excess cancer risk associated with lifetime exposure to 1 µg/L) is $4.9x10^{-4}$. Based on the oral data, a unit risk estimate of $4.9x10^{-3}$ was calculated for inhalation exposures (the excess cancer risk associated with lifetime exposure to 1 $µg/m^3$) to aldrin (IRIS 1987).

Based on evaluation of available human and animal data, IARC determined that there is *inadequate evidence* in humans and *sufficient evidence* in experimental animals for the carcinogenicity of aldrin (IARC 2019). The overall evaluation was that aldrin metabolized to dieldrin is *probably carcinogenic to humans* (Group 2A). As rationale for its determination, IARC stated that "because aldrin is rapidly

metabolized to dieldrin in humans and experimental animals, exposure to aldrin always leads to internal exposure to dieldrin. Therefore, for the evaluation of aldrin, the evidence on the carcinogenicity of dieldrin was taken into account."

***Dieldrin.*** Bioassays in BALB/c, $CF_1$, $B6C3F_1$, C3HeB/Fe, C3H/He, and C57BL/6J mice have also shown increased incidences of hepatocellular adenoma and/or carcinoma with chronic oral exposure. NCI (1978a) reported significantly increased incidence of hepatocellular carcinoma in male B6C3F1 mice exposed to 0.86 mg/kg/day dieldrin in the diet for 80 weeks; incidences were not increased in males at 0.43 mg/kg/day or similarly-treated females at either dose level.

Eight other studies employed chronic-duration dietary exposure of mice to 1.7 mg/kg/day dieldrin and reported treatment-related increased incidences of liver tumors (Davis and Fitzhugh 1962; Epstein 1975; Lipsky et al. 1989; Meierhenry et al. 1983; Ruebner et al. 1984; Tennekes et al. 1979, 1981; Thorpe and Walker 1973; Walker et al. 1973). Increased incidences of hepatocellular carcinomas were reported in male C3H/He, B6C3F1, and C57BL/6J mice treated for up to 85 weeks (Meierhenry et al. 1983) and in male CF1 mice treated for up to 92 weeks (Tennekes et al. 1979, 1981). These studies employed male mice only. Thorpe and Walker (1973) reported increases in both hepatocellular adenomas and hepatocellular carcinomas in CF1 mice treated for up to 2 years. Increased incidence of hepatocellular carcinomas and combined incidence of both hepatocellular adenomas and carcinomas were observed in CF1 mice (both sexes) treated for up to 132 weeks (Walker et al. 1973). In a 75-week study of BALB/c mice (Lipsky et al. 1989) and 2-year studies in C3HeB/Fe mice (Davis and Fitzhugh 1962; Epstein 1975), increased incidences of hepatic cell adenoma were reported. However, reexamination of the histopathology data by Reuber (1980) and other pathologists showed an increase in the incidence of hepatocellular carcinomas (Epstein 1975). An increase in hepatocellular adenomas was also observed in a study of male C3H/He mice exposed for 54 weeks followed by an approximate 1-year recovery period (Ruebner et al. 1984); however, there were no increases in adenomas in a second group exposed for 64 weeks followed by the recovery period. Although reanalysis of the data presented in the Walker et al. (1973) study by Reuber (1980) also indicated significant increases in pulmonary adenomas and carcinomas in female mice administered dieldrin in the diet and a significant increase in lymphoid and other tumors in female mice at 0.17 mg/kg/day (Epstein 1975), these conclusions were based on errors in the reporting of the number of females examined at the 0.017 and 0.17 mg/kg/day treatment levels (Hunt et al. 1975). Increased incidence of hepatocellular adenoma and carcinoma (combined) was also observed among CF1 mice administered dieldrin in the diet for up to 128 weeks at 0.43 mg/kg/day (Walker et al. (1973).

In addition to producing an increase in the incidence of hepatocellular carcinomas in mice, dieldrin was also shown to significantly decrease time-to-tumor development in mice at doses as low as 0.017 mg/kg/day in females and 0.17 mg/kg/day in males (Tennekes et al. 1982). A study of transgenic mouse model of spontaneous mammary tumor formation found an increase in the total mammary tumor burden in female mice administered 4.5 mg/kg dieldrin via gavage (Cameron and Foster 2009). The dams were exposed 5 days/week for 2 weeks prior to mating, throughout lactation until weaning; the female offspring were exposed 1 day/week until 9 weeks of age.

In general, increases in cancer incidence have not been reported in rat and hamster studies (Cabral et al. 1979; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; NCI 1978b; Walker et al. 1969). However, several of these studies were based on limited microscopic examination of animals (Fitzhugh et al. 1964; Walker et al. 1969), small numbers of animals employed (Fitzhugh et al. 1964; NCI 1978b), and/or high levels of early mortality with insufficient numbers of animals surviving until study termination (Deichmann et al. 1970; Fitzhugh et al. 1964). NCI (1978a) reported an increase in the incidence of adrenal cortical adenomas and carcinomas in female rats administered 2.2 mg/kg/day aldrin, when compared to the incidence in pooled controls. However, the incidence was not significantly different from concurrent controls and no increase in tumor incidence was observed in females administered 5 mg/kg/day; NCI (1978a) noted that the tumor was not clearly associated with treatment.

There is evidence that dieldrin can act as a liver tumor promoter in mice, but not rats (Kolaja et al. 1996a). Preneoplastic focal hepatic lesions were initiated by intraperitoneal treatments with diethylnitrosamine (two injections separated by 2 weeks in male F344 rats, two injections/week for 8 weeks in male B6C3F1 mice). After the preneoplastic lesions developed, dieldrin was administered in the diet for 7, 30, or 60 days at 0.1, 1, or 10 ppm. Dieldrin induced significant increases in the number, volume, and DNA labeling index of the diethylnitrosamine-induced preneoplastic foci in mice at 10 ppm after 30 and 60 days. The lower concentrations (≤1 ppm) did not produce these promotional effects at any time point. The results of this study are consistent with findings of other studies of generally-similar design by the same investigators (Kolaja et al. 1995a, 1995b, 1998).

The HHS has not evaluated the carcinogenicity of dieldrin (NTP 2016a).

EPA classified dieldrin as Group B2 (probable human carcinogen) based on sufficient evidence of carcinogenicity (liver tumors) in seven strains of mice treated orally (IRIS 1988). EPA noted that dieldrin

is structurally related to other compounds (including aldrin) that produce tumors in rodents. EPA considered the human carcinogenicity data for dieldrin to be inadequate.

EPA calculated human potency estimates for dieldrin using liver tumor responses in mice (EPA 2003; IRIS 1988). Using potency estimates calculated from 13 data sets in five mouse strains and both sexes (Epstein 1975; Meierhenry et al. 1983; NCI 1978a, 1978b; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1973), a geometric mean of 16 $(mg/kg/day)^{-1}$ was chosen for the oral cancer risk estimate for dieldrin (EPA 2003; IRIS 1988). The unit risk estimate for drinking water exposures to dieldrin is $4.6x10^{-4}$. Based on the oral data, a unit risk estimate of $4.6x10^{-3}$ was calculated for inhalation exposures (the excess cancer risk associated with lifetime exposure to 1 $\mu g/m^3$) to dieldrin (IRIS 1988).

Based on evaluation of available human and animal data, IARC determined that there is *limited evidence* in humans and *sufficient evidence* in experimental animals for the carcinogenicity of dieldrin (IARC 2019). The overall evaluation was that dieldrin is *probably carcinogenic to humans* (Group 2A).

***Mechanisms of Action.*** Most mechanistic studies designed to evaluate possible modes of action for aldrin or dieldrin carcinogenicity have been performed with dieldrin. Several bioassays indicate that the response in mice to prolonged ingestion of aldrin or dieldrin differs from that in other species in that a generalized hepatomegaly observed in rats (Cleveland 1966; Fitzhugh et al. 1964; Hodge et al. 1967; Treon and Cleveland 1955; Walker et al. 1969), mice (Davis and Fitzhugh 1962; Walker et al. 1973), and dogs (Fitzhugh et al. 1964; Hodge et al. 1967; Walker et al. 1969) appears to progress to liver tumors only in mice.

A preponderance of evidence from studies in a variety of mammalian species indicates a unique sensitivity of the mouse liver to aldrin- and dieldrin-induced hepatocarcinogenicity; mechanistic studies suggest a nongenotoxic mode of action (Stern 2014; Stevenson et al. 1999; WHO 1989) via promotion of spontaneously initiated (background) liver cells. The cellular and molecular mechanisms involved in the promotion of liver tumors have not been fully elucidated, but appear to mainly involve species-specific susceptibility of the mouse to dieldrin-induced oxidative stress and inhibition of gap junctional communication (Jone et al. 1985; Klaunig and Ruch 1987; Klaunig et al. 1990, 1995, 1998; Kurata et al. 1982; Ruch and Klaunig 1986; Stevenson et al. 1999; Trosko et al. 1987; van Ravenzwaay and Kunz 1988; Wade et al. 1986; Lin et al. 1986). As discussed by Stevenson et al. (1999), the production of reactive oxygen species, depletion of hepatocyte antioxidant defenses such as vitamin E, and peroxidation of liver lipid have been shown to accompany oxidative metabolism of dieldrin in mice, apparently

resulting in modulation of gene expression that favors the clonal expansion of spontaneously initiated cells.

Bachowski et al. (1998) examined possible associations between dieldrin-induced hepatic DNA synthesis and modulation of biomarkers of oxidative damage to lipids and DNA in male rats and mice administered dieldrin in the food for up to 90 days. Dieldrin induced oxidative damage in the mice, but not the rats. Based on these findings, the investigators suggested that dieldrin-induced oxidative stress in the mice (but not rats) may be involved in early events in dieldrin-induced hepatocarcinogenesis and that rats may be protected from dieldrin-induced oxidative stress by a more effective antioxidant defense system.

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

The ability of chlorinated hydrocarbons to disrupt estrogen homeostasis by upregulating selected gene transcription has also been hypothesized as a mechanism of carcinogenesis. Neither aldrin nor dieldrin showed evidence of estrogenicity as evidenced by lack of induction of transcriptional activation of an estrogen-responsive reported gene in transfected HeLa cells (Tully et al. 2000). There is evidence of a synergistic estrogenic effect of dieldrin and toxaphene on the bone mass density in rats. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 µmol/kg/day (5 days/week for 9 months), when administered with toxaphene (30 µmol toxaphene/kg/day and 7.5 µmol/kg/day), bone mass density was significantly increased (Syversen et al. 2000). In contrast, the results of several estrogen-responsive assays in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based reporter gene assays indicate that the activities of both dieldrin and toxaphene, as well as a binary mixture of the two, were minimally estrogenic (Ramamoorthy et al. 1997a). A single dose of dieldrin (37 mg/kg), administered to female rats by gavage significantly increased expression of the cytochrome P-450 enzymes CYP1A1, CYP1A2, and CYP1B1, which are involved in estrogen metabolism, in the liver, kidney, and mammary tissues (Badawi et al. 2000).

## 2.20 GENOTOXICITY

Aldrin and dieldrin have been evaluated for potential genotoxicity in a variety of test systems both *in vivo* and *in vitro*. Results from *in vivo* and *in vitro* testing of aldrin are summarized in Tables 2-5 and 2-6, respectively.

**Table 2-5. Genotoxicity of Aldrin *In Vivo***

| Species (exposure route) | Endpoint | Results | Reference |
|---|---|---|---|
| Human | | | |
| Lymphocytes (occupational) | Sister chromatid exchange | + | Dulout et al. 1985 |
| Lymphocytes (occupational) | Chromosomal aberrations | – | Dulout et al. 1985 |
| Blood, lymphocytes (pest-control workers) | Sister chromatid exchange | – | Edwards and Priestly 1994 |
| Blood, lymphocytes (mother-infant pairs) | DNA strand breaks | – | Alvarado-Hernandez et al. 2013 |
| Blood, lymphocytes (mother-infant pairs) | Micronuclei | – | Alvarado-Hernandez et al. 2013 |
| Rat | | | |
| Bone marrow (i.p.) | Chromosomal aberrations | + | Georgian 1975 |
| Mouse+ | | | |
| Bone marrow (i.p.) | Chromosomal aberrations | + | Markaryan 1966 |
| Bone marrow (i.p.) | Chromosomal aberrations | + | Georgian 1975 |
| Bone marrow (oral) | Micronuclei | + | Usha Rani et al. 1980 |
| Germinal tissue (oral) | Dominant lethality | – | Epstein et al. 1972 |
| Germinal tissue (i.p.) | Dominant lethality | – | Epstein et al. 1972 |

– = negative result; + = positive result; i.p. = intraperitoneal injection

**Table 2-6. Genotoxicity of Aldrin *In Vitro***

| | | Results | | |
|---|---|---|---|---|
| | | Activation | | |
| Species (test system) | Endpoint | With | Without | Reference |
| Prokaryotic organisms: | | | | |
| *Salmonella typhimurium* | | | | |
| TA98, TA1535, TA 1537, TA1538 | Gene mutation | – | – | NTP 2016b |
| TA100 | Gene mutation | – | +/– | NTP 2016b |
| TA98, TA 100, TA1535, TA1537, TA1538 | Gene mutation | – | – | Moriya et al. 1983 |

**Table 2-6. Genotoxicity of Aldrin *In Vitro***

| Species (test system) | Endpoint | Results: Activation With | Results: Activation Without | Reference |
|---|---|---|---|---|
| TA1535, TA1536, TA1537, TA1538 | Gene mutation | | – | Shirasu et al. 1975, 1976 |
| TA98, TA 100, TA1535, TA1537, TA1538 | Gene mutation | – | | EPA 1977 |
| *Escherichia coli* | | | | |
| WP2, WP67, CM871 | Gene mutation | – | – | De Flora et al. 1984 |
| WP2 *hcr* | Gene mutation | – | – | Moriya et al. 1983 |
| WP2 | Gene mutation | | – | Shirasu et al. 1975, 1976 |
| *Bacillus subtilis* | | | | |
| H17 $Rec^+$, M45 $Rec^-$ | DNA damage | – | – | De Flora et al. 1984 |
| H17 $Rec^+$, M45 $Rec^-$ | DNA damage | | – | Shirasu et al. 1976 |
| Mammalian cells: | | | | |
| Human | | | | |
| Lymphocytes | Chromosomal aberrations | | (+) | Georgian 1975 |
| Lymphocytes | Unscheduled DNA synthesis | | (+) | Rocchi et al. 1980 |
| SV-40 transformed fibroblasts | Unscheduled DNA synthesis | + | + | Ahmed et al. 1977a |

– = negative result; + = positive result; (+) = weakly positive result; +/– = equivocal result; DNA = deoxyribonucleic acid

Limited information was located regarding the genotoxicity of aldrin *in vivo* (see Table 2-5). Studies in humans are limited by lack of information regarding the exposure scenarios and potential for exposure to other potentially genotoxic agents. Aldrin did not induce sister chromatid exchange in blood samples from pest-control workers (Edwards and Priestly 1994), chromosomal aberrations in lymphocytes from floriculturists occupationally-exposed to aldrin and other pesticides (Dulout et al. 1985), DNA strand breaks or micronuclei in blood samples from mother-infant pairs in a rural agricultural region (Alvarado-Hernandez et al. 2013), or dominant lethality in mice treated orally or by intraperitoneal injection (Epstein et al. 1972). Dulout et al. (1985) reported increased sister chromatid exchange in lymphocytes from floriculturists; however, the specific contribution of aldrin could not be determined and there was no correlation between rates of sister chromatid exchange and individuals exhibiting at least one symptom of intoxication compared to asymptomatic individuals.

Aldrin did not induce mutagenicity in a variety of *in vitro* test systems (see Table 2-6) or DNA damage in *Bacillus subtilis* in the presence (De Flora et al. 1984) or absence (De Flora et al. 1984; Shirasu et al.

1976) of exogenous metabolic activation. Ahmed et al. (1977a) reported unscheduled DNA synthesis in SV-40 transformed human fibroblasts. *In vitro* assays that employed human lymphocytes provided equivocal results for chromosomal aberrations (Georgian 1975) and unscheduled DNA synthesis (Rocchi et al. 1980).

Results from *in vivo* and *in vitro* testing of dieldrin are summarized in Tables 2-7 and 2-8, respectively.

**Table 2-7. Genotoxicity of Dieldrin *In Vivo***

| Species/test substance (exposure route) | Endpoint | Results | Reference |
|---|---|---|---|
| Human | | | |
| Lymphocytes (dieldrin plant workers) | Chromosomal aberrations | – | Dean et al. 1975 |
| Mouse | | | |
| Liver (oral) | Gene mutation | – | Bauer-Hofmann et al. 1990 |
| Liver (oral) | Gene mutation | – | Bauer-Hofmann et al. 1992 |
| Liver tumors (oral) | Gene mutation | – | Bauer-Hofmann et al. 1990 |
| Liver tumors (oral) | Gene mutation | – | Bauer-Hofmann et al. 1990 |
| Bone marrow (oral) | Unscheduled DNA synthesis | – | Bachowksi et al. 1998 |
| Bone marrow (i.p.) | Chromosomal aberrations | + | Majumdar et al. 1976 |
| Bone marrow (i.p.) | Chromosomal aberrations | + | Markaryan 1966 |
| Bone marrow (i.p.) | Micronuclei | + | Cicchetti et al. 1999 |
| Germinal tissue (oral) | Dominant lethality | – | Dean et al. 1975 |
| Germinal tissue (oral) | Dominant lethality | – | Epstein et al. 1972 |
| Germinal tissue (i.p.) | Dominant lethality | – | Epstein et al. 1972 |
| Chinese hamster | | | |
| Bone marrow (oral) | Chromosomal aberrations | – | Dean et al. 1975 |
| *Drosophila melanogaster* | | | |
| Wing spot test (oral) | Gene mutation | – | Osaba et al. 1999 |

– = negative result; + = positive result; DNA = deoxyribonucleic acid; i.p. = intraperitoneal injection

**Table 2-8. Genotoxicity of Dieldrin *In Vitro***

| Species (test system) | Endpoint | Results: Activation With | Results: Activation Without | Reference |
|---|---|---|---|---|
| Prokaryotic organisms: | | | | |
| *Salmonella typhimurium* | | | | |
| TA98, TA 100, TA1535, TA1537, TA1538 | Gene mutation | – | – | De Flora et al. 1984 |
| TA98, TA100 | Gene mutation | | – | De Flora et al. 1989 |
| TA98, TA100 | Gene mutation | | – | Glatt et al. 1983 |
| TA98, TA100, TA1535, TA1538 | Gene mutation | – | | Anderson and Styles 1978 |
| TA1535, TA1537 | Gene mutation | | – | Glatt et al. 1983 |
| TA98, TA100, TA1535, TA1537 | Gene mutation | – | – | Haworth et al. 1983 |
| TA98, 100 | Gene mutation | + | + | Majumdar et al. 1977 |
| TA1535 | Gene mutation | + | – | Majumdar et al. 1977 |
| TA1535, TA1536, TA1537, TA1538 | Gene mutation | – | – | Marshall et al. 1976 |
| TA98, TA 100, TA1535, TA1537, TA1538 | Gene mutation | – | – | Moriya et al. 1983 |
| TA98, TA100, TA1535, TA1537 | Gene mutation | – | – | NTP 2016c |
| TA1535, TA1536, TA1537, TA1538 | Gene mutation | | – | Shirasu et al. 1975, 1976 |
| TA98, TA100 | Gene mutation | – | – | Wade et al. 1979 |
| *Escherichia coli* | | | | |
| WP2 *Try*$^-$ | Gene mutation | | – | Ashwood-Smith et al. 1972 |
| WP2, WP67, CM871 | Gene mutation | – | – | De Flora et al. 1984 |
| Strain not specified | Gene mutation | | – | Fahrig et al. 1974 |
| WP2 *hcr* | Gene mutation | – | – | Moriya et al. 1983 |
| WP2 | Gene mutation | | – | Shirasu et al. 1975, 1976 |
| ColE1 plasmid DNA | DNA strand breaks | | – | Griffin and Hill 1978 |
| *Bacillus subtilis* | | | | |
| H17 Rec$^+$, M45 Rec$^-$ | DNA damage | – | – | De Flora et al. 1984 |
| H17 Rec$^+$, M45 Rec$^-$ | DNA damage | | – | Shirasu et al. 1976 |
| Eukaryotic organisms: | | | | |
| *Saccharomyces cerevisiae* | | | | |
| D4 | Mitotic gene conversion | | – | Dean et al. 1975 |
| RS112 | Mitotic gene conversion | | – | Fahrig et al. 1974 |
| *Aspergillus nidulans* | | | | |
| 35 (haploid) | Gene mutation | | – | Crebelli et al. 1986 |
| P1 (diploid) | Aneuploidy | | – | Crebelli et al. 1986 |

**Table 2-8. Genotoxicity of Dieldrin *In Vitro***

| Species (test system) | Endpoint | Results: Activation With | Results: Activation Without | Reference |
|---|---|---|---|---|
| Mammalian cells: | | | | |
| Human | | | | |
| Lymphocytes | Unscheduled DNA synthesis | | (+) | Rocchi et al. 1980 |
| SV-40 transformed fibroblasts | Unscheduled DNA synthesis | + | + | Ahmed et al. 1977a |
| Embryonic lung WI-38 | Chromosomal aberrations | + | | Majumdar et al. 1976 |
| Rat | | | | |
| Hepatocytes | DNA damage | | – | Stedeford et al. 2001 |
| Hepatocytes | Unscheduled DNA synthesis | | – | Probst et al. 1981 |
| Adrenal gland pheochromocytoma | DNA damage | | + | Klaunig et al. 1995 |
| Mouse | | | | |
| L5178Y lymphoma cells | Gene mutation | | + | McGregor et al. 1991 |
| Hepatocytes | DNA damage | | + | Klaunig et al. 1995 |
| Hepatocytes | Unscheduled DNA synthesis | | – | Klaunig et al. 1984 |
| Lung fibroblasts | Micronuclei | | + | Cicchetti and Argentin 2003 |
| Embryo fibroblasts | Focus formation | | + | Kowalski et al. 2000 |
| Chinese hamster | | | | |
| V79 lung fibroblasts | Gene mutation | | + | Ahmed et al. 1977b |
| V79 lung fibroblasts | DNA damage | – | – | Swenberg et al. 1976 |
| CHO-W-B1 | Chromosomal aberrations | – | – | Galloway et al. 1987 |
| CHO-W-B1 | Sister chromatid exchange | + | + | Galloway et al. 1987 |
| Calf | | | | |
| Thymus DNA | DNA adducts | | – | Decloitre et al. 1975 |

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid

Dieldrin has been evaluated for potential genotoxicity in a number of *in vivo* evaluations. There was no evidence of dieldrin-related increases in chromosomal aberrations in cultured lymphocytes from workers at a dieldrin production facility (Dean et al. 1975). Negative results were obtained from tests of dieldrin-induced gene mutations in livers or liver tumors from orally-exposed mice (Bauer-Hofmann et al. 1990, 1992) or orally-exposed *Drosophila melanogaster* (Osaba et al. 1999). Dieldrin did not induce chromosomal aberrations in bone marrow from orally-exposed Chinese hamsters (Dean et al. 1975). Dieldrin did not induce dominant lethality in mice exposed via oral or intraperitoneal injection routes (Dean et al. 1975; Epstein et al. 1972). However, dieldrin induced chromosomal aberrations (Majumdar

et al. 1976) and micronuclei (Cicchetti et al. 1999) in bone marrow from mice exposed by intraperitoneal injection.

*In vitro* assays for dieldrin-induced mutagenicity in a variety of bacterial test systems were predominantly negative. Dieldrin did not induce mutagenicity in the fungus, *Aspergillus nidulans* (Crebelli et al. 1986). However, positive results were obtained for gene mutation in mouse L5178Y lymphoma cells (McGregor et al. 1991) and Chinese hamster V79 lung fibroblasts (Ahmed et al. 1977b) in the absence of exogenous metabolic activation. Dieldrin did not induce mitotic gene conversion in two strains of *Saccharomyces cerevisiae* (Dean et al. 1975; Fahrig et al. 1974).

Mixed results were obtained from *in vitro* assays designed to evaluate nonmutagenic endpoints. Dieldrin did not induce chromosomal aberrations in Chinese hamster CHO-W-B1 cells in the presence or absence of exogenous metabolic activation (Galloway et al. 1987), but was positive for chromosomal aberrations in human embryonic lung WI-38 cells in the presence of exogenous metabolic activation (Majumdar et al. 1976). Positive results were obtained for sister chromatid exchange in Chinese hamster CHO-W-B1 cells in the presence or absence of exogenous metabolic activation (Galloway et al. 1987). Cicchetti and Argentin (2003) reported dieldrin-induced micronucleus formation in mouse lung fibroblasts. Kowalski et al. (2000) reported dieldrin-induced focus formation in mouse embryo fibroblasts.

In assays for dieldrin-induced unscheduled DNA synthesis, negative results were obtained using rat or mouse hepatocytes (Klaunig et al. 1984; Probst et al. 1981), but weakly positive or positive results were obtained using human lymphocytes (Rocchi et al. 1980) or SV-40 transformed human fibroblasts (Ahmed et al. 1977a). Dieldrin did not induce DNA damage in *B. subtilis* (De Flora et al. 1984; Shirasu et al. 1976), rat hepatocytes (Stedeford et al. 2001), or Chinese hamster V79 lung fibroblasts (Swenberg et al. 1976). However, positive results were obtained using rat adrenal gland pheochromocytoma preparations or mouse hepatocytes (Klaunig et al. 1995). Dieldrin did not induce DNA adduct formation in calf thymus DNA (Decloitre et al. 1975).

Based on available information, aldrin does not appear to be a genotoxic agent. Available information for dieldrin is mixed. Although dieldrin does not appear to induce mutagenicity via point or frameshift mutations, the findings of dieldrin-related effects on chromosomes (possibly via DNA damage) suggest a mutagenic role for dieldrin. Stern (2014) provided evidence for an oxidative stress-related effect on chromosomes.

# CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

## 3.1 TOXICOKINETICS

- Aldrin and dieldrin are readily absorbed from the gastrointestinal tract; limited data indicate that aldrin or dieldrin are also absorbed from the lung and skin.
- Absorbed aldrin is rapidly converted to dieldrin (primarily in the liver); distribution is initially widespread, but quickly redistributed mainly to adipose tissue.
- Dieldrin and its metabolites are mainly excreted in the feces (via bile) and to a lesser extent in the urine.

### 3.1.1 Absorption

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

Absorption of orally-administered dieldrin has been demonstrated in volunteers fed dieldrin at concentrations of 0.0001, 0.0007, or 0.003 mg/kg/day for 18–24 months. Dose-related increased levels of dieldrin were observed in blood and adipose tissue (Hunter and Robinson 1967; Hunter et al. 1969).

Although data are limited regarding absorption of aldrin or dieldrin following dermal exposure in humans, it appears to occur rapidly. Aldrin and dieldrin were first detected in urine 4 hours after dermal application of a single dose (0.004 mg/cm$^2$) of $^{14}$C-labeled aldrin or dieldrin to the forearm of six volunteers. Based on urinary radioactivity, it was estimated that 7.8% of aldrin and 7.7% of dieldrin was absorbed over a 5-day period (Feldmann and Maibach 1974). The accuracy of these values is questionable since the dose used was small, recovery of radioactivity in the urine was low, the major route of excretion was in the feces (not the urine), and a large individual variation in data was reported.

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

Aldrin and dieldrin are readily absorbed by the gastrointestinal tract following oral exposure of a variety of experimental animals, including rats, mice, and dogs (Brown et al. 1964; Furusawa 2002; Hayes 1974; Korte and Kochen 1966; Müller et al. 1979). Following oral dosing with radiolabeled aldrin or dieldrin, high levels of radioactivity were detected in the liver, blood, and stomach and/or duodenum of dosed rats within 1–5 hours (Heath and Vandekar 1964; Iatropoulos et al. 1975). Twenty-four hours following a single oral administration of dieldrin to rats at 10 mg/kg, approximately 50% of the dose was found in fat (Hayes 1974). Several metabolic studies indicate that dieldrin is absorbed from the gastrointestinal tract and is transported via the hepatic portal vein (Heath and Vandekar 1964).

Aldrin was rapidly absorbed into the skin of female rats following dermal application at doses of 0.006, 0.06, and 0.6 mg/cm$^2$ (Graham et al. 1987). Both aldrin and dieldrin were detected in the skin 1 hour after aldrin application. The amount absorbed was proportional to the dose applied. *In vitro* studies of rat skin strips incubated with aldrin showed absorption of aldrin was complete by 80 minutes (Graham et al. 1987). Absorption of dieldrin from fabric that had been impregnated with up to 0.04% dieldrin was also demonstrated in rabbits (Witherup et al. 1961).

Due to the high lipophilic nature of aldrin and dieldrin, they are likely absorbed via passive diffusion.

### 3.1.2 Distribution

Aldrin is rapidly converted to dieldrin in environmental and biological systems. Distribution of dieldrin is initially general, but within a few hours, it is redistributed primarily to fat. A study was conducted on volunteers who ingested dieldrin in doses of 0, 0.0001, 0.0007, or 0.003 mg/kg/day for 24 months (Hunter and Robinson 1967; Hunter et al. 1969). Dieldrin concentrations in blood and adipose tissue increased in a dose-related manner with a finite upper limit for the storage of dieldrin corresponding to a balance between the amount ingested and the amount eliminated daily. This was observed at about 15 months with the eventual body burden characteristic of a person and his particular daily intake (Hunter et al.

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

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

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

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

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

Species differences in tissue distribution of dieldrin in rodents have been reported (Hutson 1976). When male rats and mice were subjected to a single dose of $^{14}$C-dieldrin (3 mg/kg), liver and fat residues were higher in the mice than in the rats 8 days after ingestion. The liver concentration in mice (0.94 mg/kg) was about nine times higher than in rats (0.11 mg/kg). Fat samples in mice contained dieldrin levels (11.6 mg/kg) that were twice as high as the levels in rats (5.6 mg/kg) (Hutson 1976). Sex differences in tissue distribution of dieldrin in rodents have also been reported (Davison 1973; Walker et al. 1969). Female rats fed dieldrin (0.002, 0.01, and 0.1 mg/kg/day) in their diet for 39 weeks had a higher proportion of the total dose in their carcasses than male rats that were treated similarly (Davison 1973). Also, female rats fed dieldrin (0, 0.005, and 0.5 mg/kg/day) in their diet for 2 years had tissue concentrations of dieldrin between 2 and 10 times that of male rats fed the same dietary concentration (Walker et al. 1969).

Following repeated dosing (2–104 weeks), an equilibrium or steady state is reached between the intake, storage, and excretion of dieldrin in various strains of rats and beagle dogs. Steady-state kinetics were

determined by measuring both the level of radioactivity retained in fat, blood, liver, and brain and the percentage of the administered dose excreted at sublethal doses. The steady-state tissue concentration of dieldrin was dose- and time-dependent. In dogs receiving daily oral doses of 0.005 or 0.05 mg/kg/day dieldrin for 2 years, the steady-state blood residue levels were reached in 12–18 or 18–30 weeks, respectively (Walker et al. 1969). In rats receiving 0.002–0.10 mg/kg/day dieldrin from the diet, steady state was reached by 6 weeks ( Davison 1973); time to steady state was similar at the tested dose levels. In rats receiving daily oral doses of 0.012 mg/kg/day $^{14}$C-aldrin for 3 months, steady state was reached in 53 days (Ludwig et al. 1964).

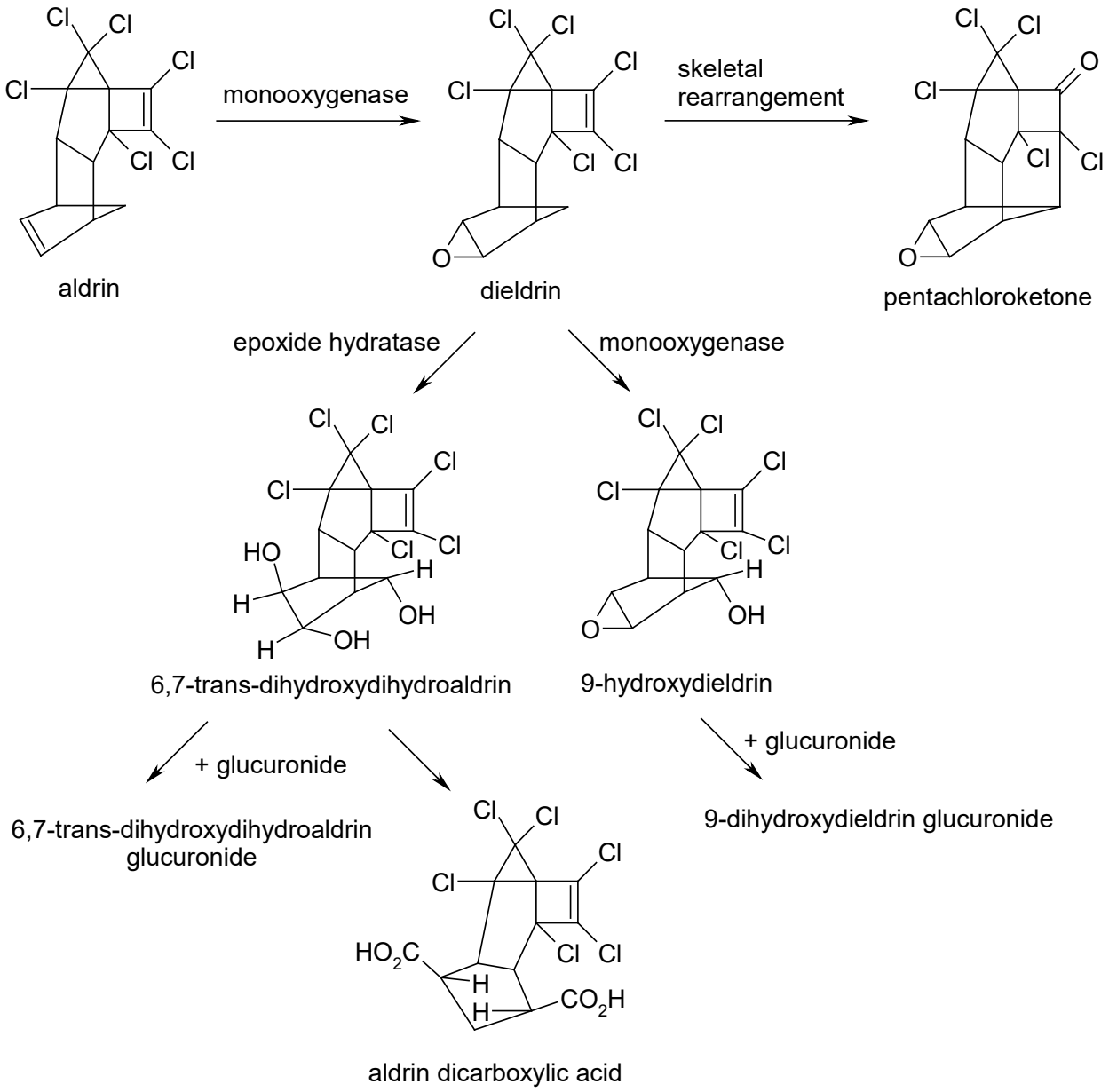
In another study, the steady-state concentration in adipose tissues of rats receiving dietary concentrations of 1.25 mg/kg/day dieldrin for 8 weeks was reported to be 50 mg/kg dieldrin (Baron and Walton 1971). The elimination of dieldrin residues from the adipose tissue of rats subsequently placed on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

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

### 3.1.3 Metabolism

The initial and major step in the biotransformation of aldrin in experimental animals is the formation of the corresponding epoxide dieldrin (Wong and Terriere 1965). Aldrin is readily converted to dieldrin primarily in the liver by mixed-function oxidases (Wong and Terriere 1965) and to a lesser extent in the lung (Lang et al. 1986) and skin (Graham et al. 1987; Lang et al. 1986). The known metabolic pathways of aldrin and dieldrin in laboratory animals are presented in Figure 3-1.

**Figure 3-1. Proposed Metabolic Pathway for Aldrin and Dieldrin**




Source: EPA 1987a

The formation of dieldrin by epoxidation of aldrin is a reaction catalyzed by monooxygenases in liver and lung microsomes. Aldrin epoxidation was studied in rat liver microsomes (Wolff et al. 1979). Microsomes from phenobarbital-treated rats showed a 3-fold increase in dieldrin formation, whereas 3-methylcholanthrene treatment markedly depressed enzyme activity. Thus, cytochrome P-450 seems to be involved in epoxidation. *In vitro* studies compared the oxidation of aldrin to dieldrin in extrahepatic

and hepatic tissues of rats (Lang et al. 1986). The authors tried to identify the pathway by which aldrin is metabolized in liver, lung, seminal vesicle, and subcutaneous granulation tissue. Many organs and tissues possess low cytochrome P-450 content. In these cases, an alternative oxidative pathway mediated by prostaglandin endoperoxide synthase (PES) might be more important. PES consists of a cyclooxygenase, which catalyzes the bis-dioxygenation of arachidonic acid to prostaglandin $G_2$ ($PGG_2$). In a second step, a reduction by hydroperoxidase to prostaglandin $H_2$ ($PGH_2$) occurs. The aldrin epoxidation was completely nicotine adenine dinucleotide phosphate (NADPH)-dependent in liver microsomes and hepatocytes. In lung microsomes, two pathways were involved. The NADPH-dependent activity was 1.5% and the arachidonic acid-dependent aldrin epoxidation was 0.3% of the activity found in the liver. In seminal vesicle microsomes and granulation tissue microsomes, aldrin epoxidation was stimulated by arachidonic acid and inhibited by indomethacin (a specific inhibitor of cyclooxygenase). These results suggest that aldrin was epoxidized by a prostaglandin synthase-mediated pathway in extrahepatic tissues as an alternative enzyme in the cytochrome P-450-dependent monooxygenases (Lang et al. 1986).

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

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

Dieldrin is also metabolized by epoxide hydrolase to form 6,7-*trans*-dihydroxydihydroaldrin, which was originally isolated and identified in rabbits and mice (Korte and Arent 1965) and later found also to form in other animals, including Rhesus monkeys and chimpanzees (Müller et al. 1975). The 6,7-*trans*-dihydroxydihydroaldrin glucuronide is formed *in vitro* in hepatic microsomal preparations from rabbits or rats in the presence of uridine diphosphoglucuronic acid and NADPH (Matthews and Matsumura 1969). 6,7-*trans*-Dihydroxydihydroaldrin can be further oxidized to aldrin dicarboxylic acid or conjugated to glucuronic acid (Baldwin et al. 1972; Hutson 1976).

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

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

### 3.1.4 Excretion

Excretion in humans is primarily in the feces via the bile. 9-Hydroxydieldrin was found in the feces of seven workers occupationally exposed to aldrin and dieldrin (Richardson and Robinson 1971). A half-life for dieldrin elimination was estimated to be 369 days (Hunter et al. 1969). Dieldrin is also excreted via lactation in nursing mothers. Dieldrin concentrations of 19–26 ppb were found in breast milk (Schecter et al. 1989a).

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

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

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

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

Pentachloroketone is the major component in rat urine (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971). The mouse, unlike the rat, does not appear to excrete pentachloroketone as a urinary metabolite.

Pretreatment of CFE rats with dieldrin caused an enhancement of the urinary excretion of pentachloroketone, but no effect on the pattern of excretion of urinary metabolites could be detected when $CF_1$ mice were given similar treatments (Baldwin et al. 1972). Aldrin dicarboxylic acid, unchanged dieldrin, and 9-hydroxydieldrin glucuronide have also been found in lower concentrations in the urine of rats (Hutson 1976; Müller et al. 1975).

### 3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

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

No PBPK models for aldrin or dieldrin were located.

### 3.1.6 Animal-to-Human Extrapolations

Most of the available human data come from cases of acute oral exposure to relatively high levels of aldrin or dieldrin (Black 1974; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951) or from chronically-exposed workers (Amoateng-Adjepong et al. 1995; Brown 1992; de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; Van Raalte 1977; Van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). In both humans and animals, high doses of aldrin or dieldrin result primarily in neurotoxicity. Epidemiologic studies involving chronic exposure to aldrin and/or dieldrin similarly indicate that the central nervous system is a major organ of toxicity. Chronic-duration animal studies additionally demonstrate adverse effects in the kidney and liver; the liver being the most sensitive target. Liver effects are indicated in limited reports of humans exposed to levels of aldrin or dieldrin that result in neurotoxic symptoms (Black 1974; Garrettson and Curley 1969). Although the human data are extremely limited, at present, there is no evidence to suggest that noncancer effects seen in animal studies would be different from those in humans. Available information is suggestive of general similarity in the metabolic

pathways and disposition of aldrin and dieldrin in humans and experimental animals (Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974; Hunter and Robinson 1967; Hunter et al. 1969; Iatropoulus et al. 1975). However, elimination rates vary among animal species and between males and females, thus contributing to uncertainty in extrapolation of toxicokinetic data from animals to humans.

## 3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to aldrin or dieldrin are discussed in Section 5.7, Populations with Potentially High Exposures.

Neurological symptoms (for example, convulsions, abnormal EEGs, hyperexcitability, restlessness) have been reported in adults and children following ingestion (accidental or intentional) of aldrin or dieldrin (Black 1974; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951). Two young children (2 and 4 years of age) experienced severe convulsions within 15 minutes after consuming an unknown quantity of a 5% solution of dieldrin; the younger child died, whereas the older brother recovered completely after exhibiting evidence of liver dysfunction (Garrettson and Curley 1969). The observed effects could not be attributed solely to dieldrin because the ingested solution likely also contained solvents and emulsifiers. Among 11 people experiencing evidence of neurotoxicity associated with the consumption of wheat mixed with aldrin and lindane for a period of 6–12 months, a female infant was reported to suffer a severe convulsion, followed by death a few hours later (Gupta 1975). Since no symptoms had been observed among individuals previously consuming wheat mixed only with lindane, it was assumed that the neurotoxic effects were the result of aldrin poisoning. A 7-year-old child in this same group was thought

to have developed mild mental retardation as a result of the poisoning. However, these limited oral human data do not conclusively indicate age-related differences in susceptibility to aldrin or dieldrin poisoning.

Signs of neurotoxicity have also been reported in occupational studies of workers employed in the application or manufacture of aldrin or dieldrin where exposures may have been predominantly by inhalation (Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). No data were located regarding adverse effects in humans dermally exposed to aldrin or dieldrin, although both aldrin and dieldrin have been shown to pass through the skin and enter the blood of adults (Feldmann and Maibach 1974). It is expected that children and adults would be similarly affected by dermal exposure to aldrin or dieldrin, although no data were available to substantiate this assumption.

Limited oral $LD_{50}$ studies indicate that newborn rats may be less sensitive than adult rats to high acute doses of dieldrin, while 2-week-old rats may be somewhat more sensitive than adults (Lu et al. 1965). In a study of adult cattle and calves given feed that was inadvertently mixed with aldrin, mortality occurred exclusively among calves (Buck and Van Note 1968); however, information regarding the amount of aldrin in the feed and relative consumption rates of calves and adult cattle was not available. No other information was available to suggest that children may be more susceptible than adults to aldrin or dieldrin.

It is generally believed that the neurotoxicity of both aldrin and dieldrin is based on alterations in synaptic activity within the central nervous system (Joy 1982; Shankland 1982). As discussed in Section 2.21 (Mechanisms of Action), *in vitro* and *in vivo* animal studies have shown that aldrin and dieldrin are capable of blocking the activity of the inhibitory neurotransmitter GABA, an indication that both chemicals may exert their neurotoxic effects via blockage of inhibitory activity within the brain.

There is conflicting information regarding the developmental toxicity of aldrin and dieldrin. In some cases, increased incidences of external malformations or skeletal anomalies were observed following oral exposure of pregnant laboratory animals to aldrin or dieldrin in mid-gestation (Chernoff et al. 1975; Ottolenghi et al. 1974); no significant malformations or anomalies were seen in other studies (Chernoff et al. 1975; Dix et al. 1977). These studies were limited in design and study details. A more consistently reported developmental effect was that of decreased postnatal survival in laboratory animals following *in utero* exposure to dieldrin (Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975, 1977). Dieldrin has been detected in human placenta, amniotic fluid, and fetal blood, and may be

found in higher concentration in fetal blood than in the mother's blood (Polishuk et al. 1977a). Furthermore, dieldrin is excreted in the breast milk of nursing mothers (Schecter et al. 1989a). In an animal study designed to test whether decreased pup survival might be related to maternal postnatal care, mice born to dieldrin-exposed dams and then nursed by untreated dams exhibited similar survival rates to those nursed by their exposed dams, suggesting that decreased pup survival was correlated with *in utero*, rather than postnatal, exposure (Virgo and Bellward 1977). Intraperitoneal injection of aldrin in male rats resulted in plasma decreases in luteinizing hormone, follicular hormone, and testosterone, as well as decreases in testicular testosterone (Chatterjee et al. 1988a, 1988b, 1988c). In an *in vitro* study using rat interstitial testicular cells, dieldrin caused a significant increase in testosterone production (Ronco et al. 1998). There is some evidence that aldrin and dieldrin may be estrogenic. Oral administration of aldrin resulted in delayed estrous in dogs (Deichmann et al. 1971). Subcutaneous injection of aldrin resulted in a persistent vaginal estrous in ovariectomized rats (Chatterjee et al. 1992). Dieldrin slightly decreased binding of 17β-estradiol to the estrogen receptor in extracts of uterine tissue from immature female rats intraperitoneally administered dieldrin (Wade et al. 1997). Dieldrin weakly induced both cellular proliferation and slight increases in the levels of estrogen and progesterone receptors within MCF-7 human breast cancer cells (Soto et al. 1994, 1995). The overall evidence indicates that aldrin and dieldrin may be disruptive of reproductive hormone levels in male animals and weakly estrogenic in females; the developmental significance of these findings is not clear at present.

Two studies evaluated with polymorphisms and cancer risk. In a study of single nucleotide polymorphisms, Koutros et al. (2013b) found an increased risk of prostate cancer risk among men with aldrin use and two A alleles at rs7679673 in TET2 region. The second study examined mutations in the p53 suppressor gene and breast cancer risk associated with dieldrin exposure (Høyer et al. 2002). Although no significant alterations in breast cancer risk was associated with this polymorphism, women with 'wild-type' p53 had an increased risk of dying.

The pharmacokinetics of aldrin and dieldrin are expected to be similar in children and adults. No studies were located to indicate any age-dependent differences in absorption rates. As discussed in detail in Section 3.1 (Toxicokinetics), aldrin is rapidly converted to dieldrin. Dieldrin (either absorbed or converted from aldrin) is found mainly in the liver during the first 3 hours following absorption, but is quickly distributed to fat and eliminated primarily in the feces (via the bile) with a calculated half-time of elimination of 369 days. The slow elimination may play a role in the delayed onset of neurotoxicity symptoms seen in some cases of repeated exposure to relatively low doses of aldrin or dieldrin. Although there are no data to indicate age-related differences in the pharmacokinetics of aldrin or dieldrin, any age-

related increases in average body fat could conceivably result in increased susceptibility. Aldrin is readily converted to dieldrin, primarily in the liver, through epoxidation catalyzed by monooxygenases (Wong and Terriere 1965). Available information indicates that cytochrome P-450 is involved (Wolff et al. 1979); however, specific enzymes have not been identified. In the rat, it has been shown that dieldrin is largely hydroxylated to 9-hydroxydieldrin by liver microsomal monooxygenases, which is then conjugated with glucuronide, to some extent, before excretion (Matthews and Matsumura 1969). Enzyme systems responsible for these metabolic pathways may operate in the very young at levels below those in adults (Calabrese 1978). This could result in increased toxic effects due to decreased rates of excretion in the young.

There is some indication that aldrin and dieldrin may impair cellular immunity (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981). Aldrin- or dieldrin-induced impairment of the immature immune system of infants and children (Calabrese 1978) might result in a lower level of resistance to infections than adults.

There are no biomarkers of exposure or effect for aldrin or dieldrin that are unique to children or that have been validated in children or adults exposed as children. No studies were located regarding interactions of aldrin or dieldrin with other chemicals in children. Limited data concerning interactions with other chemicals in adults (see Section 3.4, Interactions With Other Chemicals) did not suggest that such interactions would be different in children.

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

## 3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to aldrin or dieldrin are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for aldrin and dieldrin from this report are discussed in Section 5.6, General Population Exposure.

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 effect caused by aldrin or dieldrin are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

### 3.3.1 Biomarkers of Exposure

Exposure to aldrin and dieldrin is measured almost exclusively by determining the level of dieldrin in the blood. Because aldrin is rapidly converted to dieldrin in the body, the detection of aldrin in body tissues is rare. Blood levels of dieldrin are specific for aldrin and dieldrin.

Detection of dieldrin in the blood may indicate either recent or past exposure to aldrin or dieldrin. Dieldrin would be detected in the blood either immediately after inhalation, oral, or dermal absorption or as stores of dieldrin are slowly released from adipose tissue. In humans, dieldrin has a relatively long

half-life in the body (Hunter and Robinson 1967; Hunter et al. 1969; Jager 1970). Hunter et al. (1969) calculated a mean half-life of 369 days, and Jager (1970) estimated a mean half-life of 266 days. Thus, exposures of sufficient magnitude occurring several years earlier may still be detected in the blood. A GABA radioreceptor assay has been developed that could serve as a sensitive biomarker for exposure to dieldrin (Saleh et al. 1993). GABA is the major inhibitory neurotransmitter in the central nervous system (see Section 2.15). Although potentially useful for reproducibly detecting nanogram levels of dieldrin in minute blood samples (0.1 mL), this method is not specific for aldrin and dieldrin because it would also detect other nervous system toxicants with high specific binding affinity to the chloride channel of $GABA_A$ receptor-ionophore sites (e.g., endosulfan and other cyclodiene insecticides, hexachlorocyclohexanes, pyrethroids, bicyclophosphates, and bicycloorthocarboxylate insecticides).

Because dieldrin rapidly redistributes to adipose tissue, the highest levels of dieldrin are found in fat (except immediately after exposure). Thus, fat levels of dieldrin are also a good source for identifying exposure to aldrin or dieldrin. However, obtaining fat samples requires at least minor surgery; therefore, this method is not commonly used.

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

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

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

Prior to the use of blood levels to monitor exposure to aldrin and dieldrin, EEGs were used to monitor workers for possible overexposure to these substances (Hoogendam et al. 1962, 1965; Jager 1970). However, this technique is most reliable when a baseline EEG recording from each subject has been

obtained prior to exposure. Also, any centrally acting neuroexcitatory substance could produce EEG changes similar to those produced by aldrin or dieldrin.

### 3.3.2 Biomarkers of Effect

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

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

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

## 3.4 INTERACTIONS WITH OTHER CHEMICALS

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

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

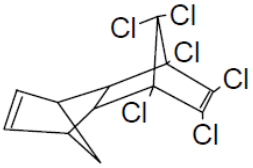
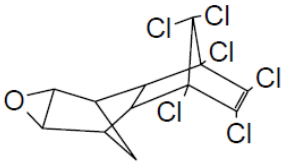
The ability of chlorinated hydrocarbons to disrupt estrogen homeostasis, by upregulating selected gene transcription, has been hypothesized to be responsible for their oncogenic effects. Neither aldrin nor dieldrin showed evidence of estrogenicity as evidenced by lack of induction of transcriptional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

# CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

## 4.1 CHEMICAL IDENTITY

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

**Table 4-1. Chemical Identity of Aldrin and Dieldrin[a]**

| Characteristic | Information | |
|---|---|---|
| Chemical name | Aldrin | Dieldrin |
| Synonym(s) and registered trade name(s) | 1,2,3,4,10,10-Hexachloro-1,4,4α 5,8,8α-hexahydro-exo-1,4-endo-5,8-dimethano-naphthalene; HHDN[b]<br>Aldrec; Aldrex; Drinox; Octalene; Seedrin; Compound 118 | 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4α,5,6,7,8,8α-octa-hydro-1,4-endo,exo-5,8-dimethano-naphthalene; HEOD[b]<br>Alvit; Dieldrix; Octalox; Quintox; Red Shield[c] |
| Chemical formula | $C_{12}H_8Cl_6$ | $C_{12}H_8Cl_6O$ |
| Chemical structure |  |  |
| CAS Registry Number | 309-00-2 | 60-57-1 |

[a]All information obtained from NLM (2020a, 2020b), except where noted.
[b]Tomlin 1997
[c]EPA 2007a

CAS = Chemical Abstracts Service

## 4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

**Table 4-2. Physical and Chemical Properties of Aldrin and Dieldrin[a]**

| Property | Aldrin | Dieldrin |
|---|---|---|
| Molecular weight | 364.91 | 380.91 |
| Color | White (pure); tan to brown (technical grade) | White (pure); light brown (technical grade) |
| Physical state | Crystalline solid[b] | Crystalline solid[b] |
| Melting point | 104–105.5°C[c];<br>49–60°C (technical grade)[c] | 176–177°C[c];<br>95°C (technical grade)[d] |

## Table 4-2. Physical and Chemical Properties of Aldrin and Dieldrin[a]

| | | |
|---|---|---|
| Boiling point | Decomposes[e] | Decomposes[e] |
| Density | 1.6 g/L at 20°C[f] | 1.75 g/L at 25°C[f] |
| Odor | Mild chemical odor[e] | Mild chemical odor[e] |
| Odor threshold: | | |
| Water | No data | No data |
| Air | 0.017 mg/kg[c] | 0.041 mg/kg[c] |
| Solubility: | | |
| Water at 20°C | 0.011 mg/L[g] | 0.110 mg/L[g] |
| Organic solvents | Very soluble in most organic solvents[b] | Moderately soluble in common organic solvents except aliphatic petroleum solvents and methyl alcohol[b] |
| Partition coefficients: | | |
| Log $K_{ow}$ | 6.50[h] | 6.2[c] |
| Log $K_{oc}$ | 7.67[i] | 6.67[i] |
| Vapor pressure at 20°C | $7.5 \times 10^{-5}$ mmHg[b] | $3.1 \times 10^{-6}$ mmHg[b] |
| Henry's law constant at 25°C | $4.9 \times 10^{-5}$ atm-$m^3$/mol[j] | $5.2 \times 10^{-6}$ atm-$m^3$/mol[j] |
| Autoignition temperature | No data | No data |
| Flashpoint | No data | No data |
| Flammability limits | Nonflammable[f] | Nonflammable[f] |
| Conversion factors | 1 ppm=14.96 mg/$m^3$ at 25°C, 1 atm | 1 ppm=15.61 mg/$m^3$ at 25°C, 1 atm[k] |
| Explosive limits | Stable[f] | Stable[f] |

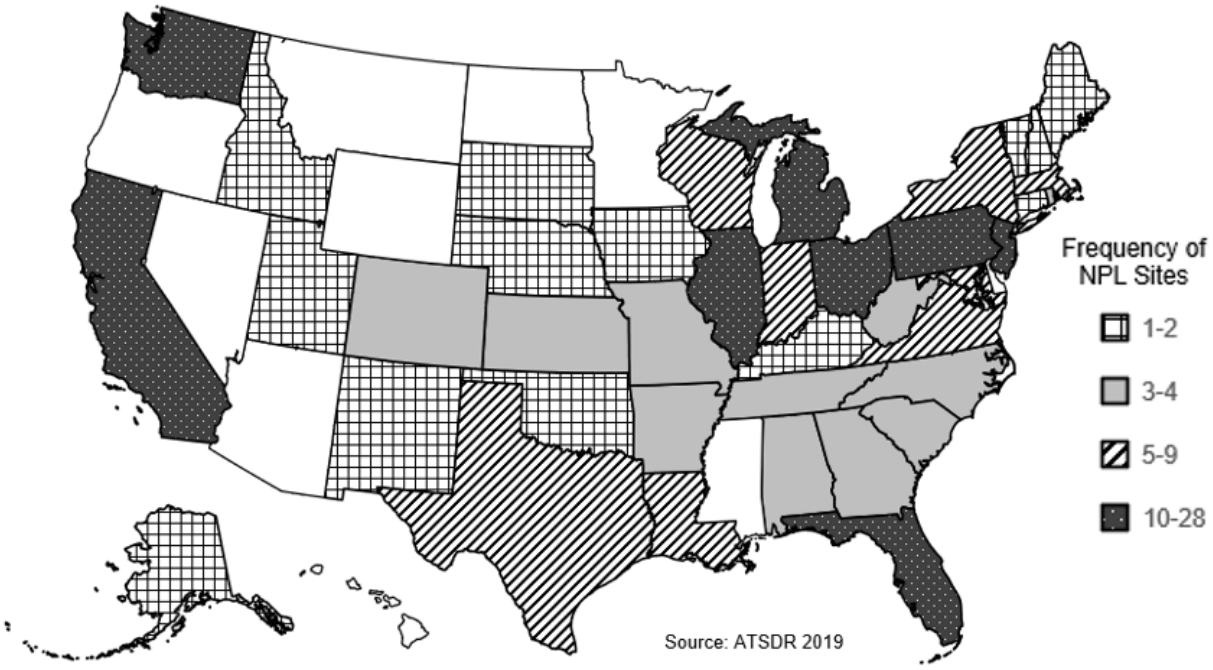
[a]All information obtained from NLM (2020a, 2020b) unless otherwise noted.
[b]Budavari et al. 2001.
[c]Verschueren 2001.
[d]Hayes 1982.
[e]NIOSH 1997.
[f]Weiss 1986.
[g]Bus and Leber 2001.
[h]Hansch et al. 1995.
[i]Briggs 1981.
[j]Guerin and Kennedy 1992.
[k]EPA 1987a.

# CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

## 5.1 OVERVIEW

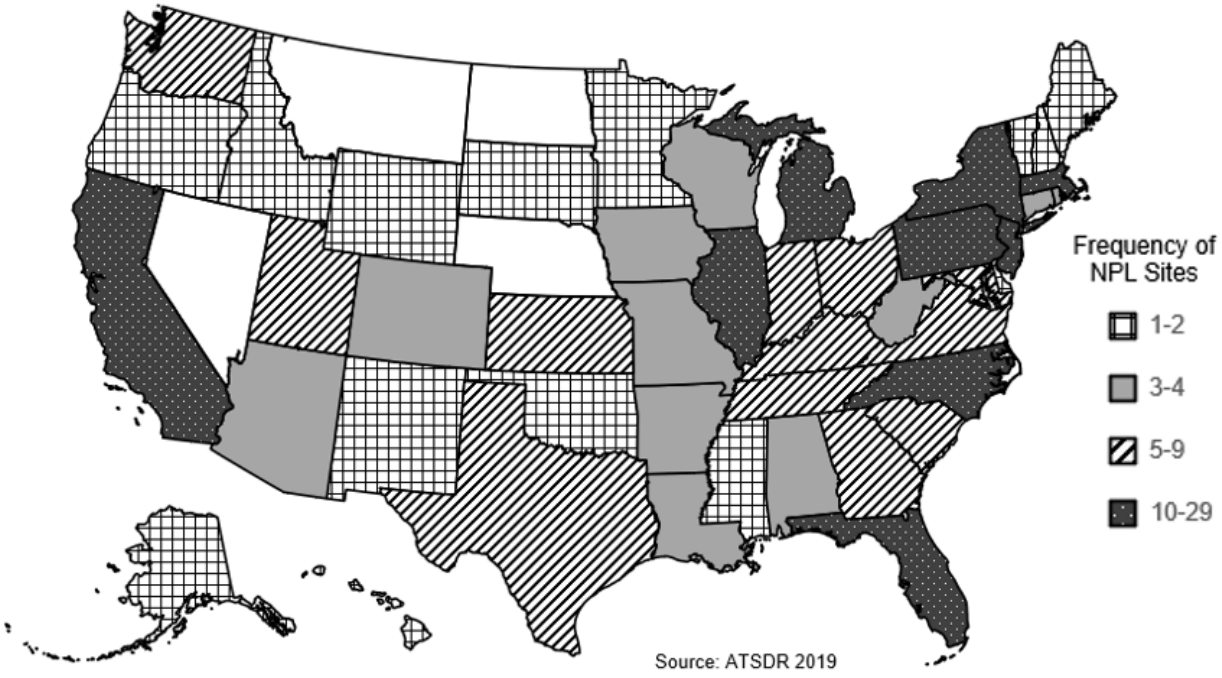
Aldrin has been identified in at least 221 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which aldrin has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 219 are located within the United States, 1 is located in the Virgin Islands, and 2 are located in Puerto Rico (not shown).

**Figure 5-1. Number of NPL Sites with Aldrin Contamination**




Dieldrin has been identified in at least 312 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which dieldrin has been evaluated is not known. The number of sites in each state is shown in Figure 5-2. Of these sites, 309 are located within the United States, 1 is located in the Guam, and 2 are located in Puerto Rico (not shown).

**Figure 5-2. Number of NPL Sites with Dieldrin Contamination**




- Since aldrin and dieldrin are no longer manufactured or used in the United States, exposure to aldrin and dieldrin is expected to be low.
- Low levels of aldrin and dieldrin have been infrequently detected in public water supplies; exposure could arise due to ingestion of drinking water.
- Dieldrin was detected in food items in the Food and Drug Administration (FDA) Total Diet Studies; thus, exposure can occur through ingestion of contaminated food items.
- Low levels of aldrin and dieldrin have been detected in soil, sediment, surface water, and groundwater. Wood homes previously treated for termites using aldrin and dieldrin have had measurable levels in air several years post application.
- Aldrin is converted to dieldrin by epoxidation. Both substances are moderately volatile and slow to biodegrade. The large soil adsorption coefficients suggest low mobility in soils and a tendency to partition to suspended solids and sediment in the water column.

Aldrin was first synthesized in the United States as a pesticide in 1948 (EPA 1986a) while dieldrin was first used by cotton growers in the 1950s (Clayton and Clayton 1994). By 1970, the USDA canceled all uses of aldrin and dieldrin (EPA 1980). Restrictions on their use as termiticides, for dipping of non-food plant roots and tops, and for moth-proofing were lifted by EPA in 1972. In 1974, however, the latter two uses were voluntarily canceled by the manufacturer, Shell Chemical Company (EPA 1986a). The final

registered use of aldrin and dieldrin as termiticides was voluntarily canceled by the Scallop Corporation (part of the Shell Chemical Company) on May 15, 1987 (EPA 1989a). The Chapman Chemical Company, however, continued to use aldrin in their termiticide formulation until it was ultimately canceled by the EPA on February 21, 1989.

Past agricultural uses of aldrin and dieldrin have resulted in persisting soil residues and uptake in a wide range of crops. Exposure of the general population to aldrin and dieldrin may occur through ingestion of contaminated water or food products and through inhalation of contaminated air.

## 5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

### 5.2.1 Production

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of aldrin in 2018; dieldrin is not on the Toxics Release Inventory (TRI) chemical list (TRI18 2019). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

| State[a] | Number of facilities | Minimum amount on site in pounds[b] | Maximum amount on site in pounds[b] | Activities and uses[c] |
|---|---|---|---|---|
| AR | 1 | 10,000 | 99,999 | 1, 5, 12 |
| IL | 1 | 1,000 | 9,999 | 12 |
| NE | 1 | 10,000 | 99,999 | 9, 12 |
| OH | 1 | 100 | 999 | 12 |
| OR | 1 | 1,000 | 9,999 | 12 |
| TX | 1 | 1,000 | 9,999 | 12 |
| UT | 1 | 10,000 | 99,999 | 9, 12 |

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI18 2019 (Data are from 2018)

Aldrin was first synthesized in the United States as a pesticide in 1948 (EPA 1986a). Aldrin and dieldrin have not been produced in the United States since 1974 (Sittig 1985). Jorgenson (2001) reported that trade literature and other data sources indicated that 11 companies reported some production of aldrin or dieldrin from 1989 to 1999; however, is not known if this was for exportation, use as chemical intermediates for other products, or only for scientific research. It is not known how much aldrin and dieldrin are presently stored in the United States; however, the TRI still shows facilities that are reporting some storage and disposal activities.

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

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

### 5.2.2 Import/Export

Before the 1974 near-total ban by EPA on aldrin and dieldrin use, aldrin and dieldrin were not imported into the United States. Aldrin was imported from Shell International (Holland) for formulation and limited use in the United States from 1974 to 1985, except when imports were temporarily ceased in 1979 and 1980. Between 1981 and 1985, an estimated 1–1.5 million pounds of aldrin were imported annually.

EPA reported that aldrin has not been imported since 1985 (EPA 1986a). No information could be found that explicitly provided information about dieldrin importation.

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

### 5.2.3 Use

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

In 1970, USDA canceled all uses of aldrin and dieldrin based on the concern that these chemicals could cause severe aquatic environmental change and are potentially carcinogenic (EPA 1980). Early in 1971, EPA initiated cancellation proceedings for aldrin and dieldrin, but did not order the suspension of aldrin and dieldrin use. In 1972, under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended by the Federal Pesticide Control Act of 1972, an EPA order lifted the cancellation of aldrin and dieldrin use in three cases: subsurface ground insertion for termite control; dipping of nonfood plant roots and tops; and moth-proofing in manufacturing processes using completely closed systems (EPA 1980, 1986a). In 1974, these last two registered uses were voluntarily abandoned by the registrant, Shell Chemical Company (EPA 1986a). The final registered use of aldrin and dieldrin as termiticides was voluntarily canceled by the Scallop Corporation (part of the Shell Chemical Company) on May 15, 1987 (EPA 1989a). Chapman Chemical Company, however, still used aldrin as the active ingredient in their termiticide formulation ALDREC. Chapman's failure to disclose the exact formulation of ALDREC to the EPA forced the EPA to cancel all use of the compound on February 21, 1989. Since this time, all uses of aldrin and dieldrin have been canceled (EPA 1990a).

### 5.2.4 Disposal

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

Substances like aldrin and dieldrin were recommended for disposal by incineration (EPA 1981). Incineration by rotary kiln (at 820–1,600°C), liquid injection (at 877–1,038°C), and fluidized bed (at 450–980°C), with residence times of seconds for gases and liquids and hours for solids, is recommended (EPA 1981).

Another recommended disposal method for aldrin and dieldrin is burying the chemicals in landfills. Finally, disposal of small amounts of aldrin and dieldrin can be accomplished through degradation by active metals (sodium or lithium) in liquid ammonia (Sittig 1985).

## 5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005a). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005a). Table 5-2 summarizes the releases of aldrin to the environment as reported to the TRI; dieldrin is not on the TRI chemical list.

**Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Aldrin[a]**

| | | Reported amounts released in pounds per year[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Total release | | |
| State[c] | RF[d] | Air[e] | Water[f] | UI[g] | Land[h] | Other[i] | On-site[j] | Off-site[k] | On- and off-site |
| AR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IL | 1 | 1 | 0 | 0 | 4 | 0 | 1 | 4 | 5 |
| NE | 1 | 0 | 0 | 0 | 14 | 0 | 0 | 14 | 14 |
| OH | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| OR | 1 | 0 | 0 | 0 | 7,453 | 0 | 7,453 | 0 | 7,453 |
| TX | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| UT | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 7 | 1 | 0 | 0 | 7,471 | 0 | 7,454 | 18 | 7,472 |

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI18 2019 (Data are from 2018)

Aldrin and dieldrin production and use in the United States has been canceled by the EPA for several decades (EPA 1990a). Because of the persistent nature of these compounds, however, these compounds are still present in the environment. Aldrin and dieldrin have been identified at several of the hazardous waste sites that have been proposed for inclusion on the EPA NPL (ATSDR 2019). The seven facilities reporting releases to the most recent TRI are chemical waste management or other services that remediate or incinerate chemical waste.

### 5.3.1 Air

Estimated releases of 1 pound of aldrin to the atmosphere from one of seven facilities reporting releases to TRI in 2018 accounted for about <1% of the estimated total environmental releases from facilities

required to report to the TRI (TRI18 2019). These releases of aldrin are summarized in Table 5-2; dieldrin is not on the TRI chemical list.

### 5.3.2 Water

There were no releases of aldrin to surface water from the seven domestic manufacturing and processing facilities in 2018; dieldrin is not on the TRI chemical list (TRI18 2019). As a result of secondary treatment processes in POTWs, only a small percentage of aldrin and dieldrin that enters POTWs is subsequently released to surface water. This information is available for some chemicals in the open literature.

Aldrin and dieldrin may be released to surface waters as a result of runoff from contaminated croplands and NPL sites. Although aldrin and dieldrin are no longer permitted for general use, dieldrin, in particular, has been detected in waterways and soils. Due to the persistence of these compounds, especially dieldrin, they have been detected in a wide variety of aquatic systems. Aldrin and dieldrin have been detected in seawater samples (Sauer et al. 1989), industrial effluents, and freshwater samples (Staples et al. 1985; USGS 2006). The high organic carbon partition coefficient ($K_{oc}$) values for aldrin and dieldrin suggest that movement through soil and contamination of groundwater will be minimal.

### 5.3.3 Soil

Estimated releases of 7,470 pounds (~3.4%) of aldrin to soil from domestic manufacturing and processing facilities in 2018 accounted for about 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). These releases of aldrin are summarized in Table 5-2; dieldrin is not on the TRI chemical list.

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

## 5.4 ENVIRONMENTAL FATE

### 5.4.1 Transport and Partitioning

**Air.** According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman 1988), aldrin, which has a vapor pressure of $7.5x10^{-5}$ mmHg at 25°C (Budavari 2001), and dieldrin with a vapor pressure of $3.1x10^{-6}$ mmHg (Budavari 2001), will exist in both the vapor and particulate phases in the ambient atmosphere. Particulate-phase aldrin and dieldrin may be transported through the atmosphere by wind and later removed from air by wet and dry deposition (Millet et al. 1997).

**Water.** Volatilization of aldrin from water surfaces is expected (Thomas 1990) based upon a Henry's law constant of $4.9x10^{-5}$ atm/$m^3$/mole (Guerin and Kennedy 1992). Volatilization from water surfaces, however, may be attenuated by adsorption to suspended solids and sediment in the water column. The volatile loss of aldrin from sterile, deionized water kept at 30°C was studied over a 30 day period (Guerin and Kennedy 1992); the volatilization half-life of aldrin from the open flask was 5.8 days. The volatile loss of dieldrin from sterile, deionized water kept at 30°C was studied over a 30-day period (Guerin and Kennedy 1992). The study found that the half-life for the volatilization of dieldrin from the open flask was 17 days. In one study, the desorption of aldrin from sediment into water was investigated (Ding and Wu 1993). Researchers simulated a riverbed by spiking a sediment sample with 287.6 ng aldrin/g sediment and passing 7,780 mL water/day over the sediment. The concentration of aldrin detected in the effluent water after 1 day was 0.135 ng/mL; by day 40, the concentration decreased to 0.06 ng/mL. The concentration of dieldrin was not measured in this study.

**Sediment and Soil.** Experimental log $K_{oc}$ values for aldrin range from 5.38 to 7.67 (Briggs 1981; Ding and Wu 1995). Dieldrin also has a strong affinity for organic matter and sorbs tightly to soil particulates based on its log $K_{oc}$ of 6.7 (Briggs 1981). Based on a classification scheme, these log $K_{oc}$ values indicate that aldrin and dieldrin are expected to be immobile in soil (Swann et al. 1983). The mobility of aldrin and dieldrin in the soil environment, however, can be enhanced at hazardous waste sites where organic solvents may be present. These organic solvents have the ability to increase the water solubility of nonpolar compounds, which in turn increases their mobility in soil (Sawhney 1989). The organic solvents, in a sense, act as a transport medium for chemicals that would normally bind strongly to soil. At waste disposal sites, where bioremediation techniques are proposed to reduce the mass of carbon-containing contaminants, there is the potential for augmenting the leaching properties of organochlorine

compounds such as aldrin and dieldrin. The lipid materials in bacterial cell membranes may lead to a repartitioning of aldrin and dieldrin sorbed to soil colloids. This can lead to a phenomenon called facilitated transport where the mobility of hydrophobic pollutants adsorbed to soils may be enhanced by biosorption on bacteria and move into aquifers along with the bioremedial bacterial cultures (Lindqvist and Enfield 1992). Except at NPL sites, however, this potential source of groundwater pollution would seem to be remote. This appears to be true in light of the small number of reports of aldrin and dieldrin groundwater contamination at locations other than NPL sites. Volatilization of aldrin from soil is more rapid when it is applied to the soil surface rather than incorporated into the soil. A loss of 50% from a surface application was estimated to occur within 1–2 weeks after application compared to 10–15 weeks for soil-incorporated aldrin (Caro and Taylor 1971; Elgar 1975). The relatively rapid loss of both aldrin and dieldrin from soil during the first few months after application has been attributed to loss by volatilization. The volatilization potential of field-applied dieldrin (10 ppm) was studied for 5 months using three different soil moisture regimes (Willis et al. 1972): (1) flooded to a depth of 10 cm; (2) moist; and (3) nonflooded with no water added except for natural rainfall. The results showed that the soil moisture had an effect on the volatilization rate. About 18% of the applied dieldrin volatilized from a moist plot in 5 months, but only 2 and 7% volatilized from the flooded and nonflooded plots, respectively. Flooding retarded the volatilization potential of surface-applied dieldrin. Volatilization of dieldrin from the non-flooded plot tended to increase with increasing precipitation (Willis et al. 1972).

**Other Media.** The logarithm of the n-octanol/water partition coefficient (log $K_{ow}$) is a useful preliminary indicator of potential bioaccumulation of a compound. The log $K_{ow}$ for aldrin ranges from 5.68 (McLean et al. 1988) to 7.4 (Briggs 1981), indicating a high potential for bioaccumulation, although its metabolism to dieldrin may attenuate its accumulation. Like aldrin, dieldrin has a high potential for bioaccumulation as indicated by a log $K_{ow}$ value that ranges from 4.32 (Geyer et al. 1987) to 6.2 (Briggs 1981). Bioconcentration factors (BCFs) for aldrin and dieldrin have been reported for several aquatic organisms. In many of the studies reviewed, it was unlikely that steady-state was ever achieved; often, the starting concentrations used in the experiments exceeded the solubility limits of the chemicals, which leads to uncertainty in the final reported value. All the studies, however, clearly indicate a high potential for bioconcentration and bioaccumulation in aquatic species.

In modeling ecosystem tests, BCFs for aldrin were 3,140 in fish and 44,600 in snails (Metcalf et al. 1973). Measured BCFs for dieldrin were reported as 2,700 in fish and 61,657 in snails (Metcalf et al. 1973). A second study using the same model ecosystem found BCFs for dieldrin to be 6,145 in fish, 7,480 in algae, 247 in crabs (*Uca minax*), 1,015 in clams (*Corbicula manilensis*), 1,280 in the water plant *Elodea*, and

114,935 in snails (Sanborn and Yu 1973). The BCF of aldrin in orange-red killifish was studied over an 8-week period in a semi-static system at 25°C (CITI 1992). At a concentration of 1 mg/L, aldrin had BCFs ranging from 3,490 to 20,000, while at 0.1 mg/L, aldrin had BCFs ranging from 1,550 to 9,450. Bioconcentration of dieldrin in orange-red killifish was also studied over an 8-week period using a semi-static system at 25°C (CITI 1992). At a concentration of 1 mg/L, dieldrin had BCFs ranging from 4,860 to 14,500, while at 0.1 mg/L, dieldrin had a BCF ranging from 5,390 to 12,500.

BCFs for aldrin and dieldrin were calculated in several tissues of two freshwater fish, *Puntius ticto* and *Cyprinus carpio*, following 15, 20, 25, and 30 days of exposure (Satyanarayan and Ramakant 2004; Satyanarayan et al. 2005); these data are presented in Table 5-3. The results indicate that partitioning was greatest in the liver as opposed to other tissues, and dieldrin had a greater potential to bioconcentrate compared to aldrin.

**Table 5-3. Bioconcentration Factors in Two Species of Freshwater Fish**

| | | Bioconcentration factor | | | | |
|---|---|---|---|---|---|---|
| | Exposure time, days | Gills | Muscle | Intestine | Kidney | Liver |
| *Puntius ticto*[a] | | | | | | |
| Aldrin | | | | | | |
| | 15 | 7.2 | 2 | 1.2 | — | 89 |
| | 20 | 48.8 | 5.6 | 3.8 | — | 151.4 |
| | 25 | 79.2 | 24.4 | 8.6 | 4.4 | 177.4 |
| | 30 | 83.4 | 58 | 17.6 | 16.6 | 246.6 |
| Dieldrin | | | | | | |
| | 15 | 98 | 12 | 8 | — | 60 |
| | 20 | 237 | 22 | 14 | — | 116 |
| | 25 | 282 | 192 | 32 | — | 9,862 |
| | 30 | 323 | 421 | 63 | — | 15,380 |
| *Cyprinus carpio*[b] | | | | | | |
| Aldrin | | | | | | |
| | 15 | 3.6 | 11.5 | 9.5 | — | — |
| | 20 | 4.42 | 20 | 15 | — | — |
| | 25 | 107.8 | 42.5 | 243 | 206.4 | 1,271.2 |
| | 30 | 147.2 | 64.5 | 478 | 604 | 2,824 |

**Table 5-3. Bioconcentration Factors in Two Species of Freshwater Fish**

| | Exposure time, days | Bioconcentration factor | | | | |
|---|---|---|---|---|---|---|
| | | Gills | Muscle | Intestine | Kidney | Liver |
| Dieldrin | | | | | | |
| | 15 | 6 | 11.5 | 9.5 | — | 44.5 |
| | 20 | 12.5 | 20 | 15 | 3 | 61.5 |
| | 25 | 29.45 | 42.5 | 243 | 198 | 24,743 |
| | 30 | 485.5 | 64.5 | 478 | 459.5 | 42,500 |

[a]Satyanarayan and Ramakant 2004.
[b]Satyanarayan et al. 2005.

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

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

Aldrin and dieldrin also bioconcentrate in terrestrial ecosystems. In a model ecosystem study, 2.09 ppm radiolabeled aldrin was applied to a vermiculite soil (Cole et al. 1976). After 20 days, researchers detected only 0.463 ppm aldrin and 0.159 ppm dieldrin. Corn that had been grown on the vermiculite soil for 14 days, contained 2.83 ppm radiolabeled carbon with 0.762 ppm being aldrin and 1.538 ppm dieldrin. Approximately 78% of the plant residue was in the roots and 22% in the shoots. On day 15, a prairie vole (*Microtus ochrogaster*) was introduced to the model ecosystem. After 5 days of exposure, the

concentrations of aldrin and dieldrin in the vole were 0.08 and 3.56 ppm, respectively. To study the uptake of pesticides in plants, radiolabeled aldrin and dieldrin were monitored over 1 week in a controlled laboratory setting (Kloskowski et al. 1981). After 1 week of exposure of barley plants to 2 ppm of both pesticides, the concentrations of aldrin and dieldrin in plant tissue were 9.7 and 4.0 ppm, respectively. Studies indicate that dieldrin is taken up by various crops (Beall and Nash 1969, 1971). To determine whether foliar contamination of soybean plants occurred via root sorption or vapor sorption, 20 ppm $^{14}$C-dieldrin was applied to surface or subsurface soil, and residue levels in soybean plants were determined (Beall and Nash 1971). The results indicated that foliar contamination by dieldrin occurred by both root sorption (10.8 ppm) and vapor sorption (8.5 ppm) (Beall and Nash 1971). In a greenhouse experiment, various crop seedlings took up dieldrin from soils treated with 0.5 or 5.0 ppm dieldrin (Beall and Nash 1969). Mean concentrations of dieldrin found in soybeans, wheat, corn, alfalfa, brome grass, and cucumber treated with 0.5 ppm dieldrin were 0.017, 0.147, 0.017, 0.031, 0.075, and 0.070 ppm (dry weight), respectively. Mean concentrations of dieldrin found in soybeans, wheat, corn, alfalfa, brome grass, and cucumber treated with 5.0 ppm dieldrin were 0.194, 1.385, 0.171, 0.350, 0.808, and 0.185 ppm (dry weight), respectively (Beall and Nash 1969). One study, however, observed no uptake of either aldrin or dieldrin in maize and pearl millet over a 3-year period grown in a clay loam soil (Gupta et al. 1979). Aldrin was applied at a rate of 3, 9, and 15 kg active ingredient (ai) per hectare (ha) once per year before the sowing of crops and mixed up to a depth of 10 cm. No residues of either aldrin or dieldrin could be detected in plant tissues from any of the years of experimentation, even at the highest dosage of 15 kg ai/ha.

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

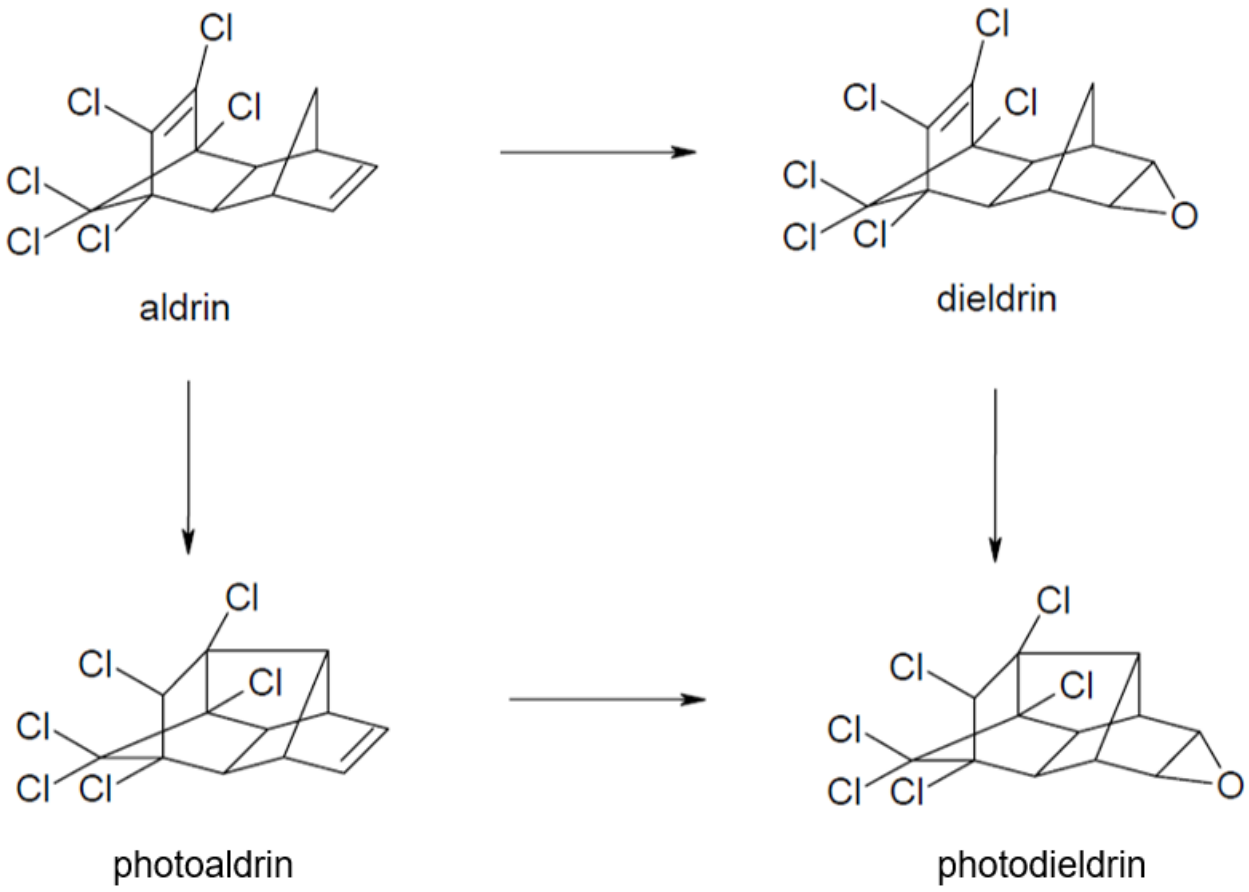
Biotransfer factors (BTFs) for beef and cow's milk have been determined for aldrin and dieldrin. BTFs for beef and milk are defined as the concentration of a compound in beef or milk (mg/kg) divided by the daily intake of the compound by the animal (mg/day). The biotransfer values of aldrin for beef and milk were estimated to be 0.085 and 0.023, respectively (Travis and Arms 1988). The biotransfer values for

dieldrin in beef and milk were estimated to be 0.008 and 0.011, respectively (Travis and Arms 1988). In addition, a BCF for aldrin and dieldrin in vegetables was also determined. The BCF was defined as the ratio of the concentration in aboveground parts (mg of compound/kg of dry plant) to the concentration in soil (mg of compound/kg of dry soil); BCFs were estimated to be 0.021 for aldrin and 0.098 for dieldrin (Travis and Arms 1988).

### 5.4.2 Transformation and Degradation

**Air.** While the evidence supports the view that a considerable proportion of the aldrin and dieldrin that was previously used in agriculture reaches the atmosphere, it seems probable that atmospheric degradation and wet and dry deposition prevents accumulation. In laboratory studies, vapor-phase aldrin is photochemically isomerized and epoxidated by sunlight to photoaldrin, dieldrin, or photodieldrin (see Figure 5-3) (Glotfelty 1978). In order to determine the potential for photodegradation to occur in the ambient atmosphere, the degradation of aldrin and dieldrin was studied on thin film plates and exposed to environmental ultraviolet (UV) radiation (>290 nm) (Chen et al. 1984). Aldrin and dieldrin had photodegradative half-lives of 113 and 153 hours, respectively. Researchers also reported that aldrin and dieldrin have UV absorbance maximums of 227 and 229 nm, respectively. Irradiation of aldrin (5 mg) vapor with ultraviolet light for 45 hours resulted in the formation of photoaldrin (20–30 µg) and dieldrin (50–60 µg). Irradiation of either photoaldrin (2 mg) or dieldrin (0.5 mg) vapor for 65 hours and 91 minutes, respectively, resulted in a single photoproduct, photodieldrin (20–30 µg), which was resistant to further photolysis (Crosby and Moilanen 1974). Since photodieldrin no longer contains a chromophore, it is believed to be a stable photoproduct of aldrin (dieldrin) (Glotfelty 1978). Results of a laboratory study, however, revealed that photolysis of photoaldrin and photodieldrin in the presence of triethylamine gave photometabolites arising from the loss of chlorine atoms (Dureja et al. 1986). Information regarding the persistence of photodieldrin in the atmosphere was not located; however, air samples taken in 1973 in Ireland contained dieldrin, but neither aldrin nor the photoproducts of aldrin or dieldrin were detected (Baldwin et al. 1977).

**Figure 5-3. Aldrin and Dieldrin Degradation**




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

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

Aldrin, irradiated with UV light in an oxygenated aqueous solution, underwent little change except in the presence of amino acids and humic acids present in natural waters (Ross and Crosby 1975, 1985). In filtered natural field water, aldrin was photooxidized by 75% to dieldrin after 48 hours of irradiation at 238 nm (Ross and Crosby 1985). More than 80% of the initial dieldrin added to natural water (from a drainage canal in an agricultural area) was present after 15 weeks of incubation in the dark (Sharom et al. 1980). Dieldrin exposed to sunlight is converted to photodieldrin, a stereoisomer of dieldrin. It is unlikely, however, that photodieldrin occurs widely in the environment. Microorganisms isolated from lake water and lake-bottom sediments may convert dieldrin to photodieldrin under anaerobic conditions (Fries 1972). The stability of dieldrin and aldrin was determined in distilled (pH 6.8) and roof water (pH 7.4) (McDougall et al. 1994). The samples were kept in the dark, at 23°C over a 36-week period. The study found that after 36 weeks, dieldrin remained stable while aldrin degraded in both roof water and distilled water. The half-lives of aldrin in distilled water and roof water were 4.9 and 5.1 weeks, respectively. The study did not find dieldrin as a breakdown product of aldrin degradation. An extrapolated hydrolysis rate constant of $3.8 \times 10^{-5}$ $hour^{-1}$ at pH 7 and 25°C has been determined for aldrin based on a measured value at 75°C (EPA 1989b). The half-life for this reaction is 760 days.

Aldrin was degraded under anaerobic conditions in biologically active waste water sludge (pH 7–8, 35°C), with a half-life of <1 week (Hill and McCarty 1967). Under aerobic conditions, however, only 1.5% of aldrin degraded when exposed to an activated sewage sludge (Freitag et al. 1985). Aldrin has a reported biodegradation half-life of 24 days in surface waters based on a non-acclimated river die-away test (Eichelberger and Lichtenberg 1971). Dieldrin does not undergo any significant degradation in biologically active waste water sludge or by sewage sludge microorganisms under anaerobic conditions (Battersby and Wilson 1988; Hill and McCarty 1967). After 48 hours of continuous anaerobic digestion with primary sludge, dieldrin was degraded by only 11% (Buisson et al. 1990). Likewise, when incubated for 32 days with anaerobic sludge, only 24% of the dieldrin was removed (Kirk and Lester 1988). In contrast, aerobic incubation with activated sludge removed 55% of the dieldrin in 9 days (Kirk and Lester 1988). A mixed, anaerobic microbial enrichment culture was able to degrade 10 µg/mL dieldrin by 50% in 30 days. Syn-monodechlorodieldrin and anti-monodechlorodieldrin, both of which are

resistant to microbial degradation, were identified as the initial degradation products (Maule et al. 1987). In another study, dieldrin was degraded by 30–60% using activated sludge treatment, with the most effective removal by activated sludge aged 4 days as opposed to sludge aged 6 and 9 days (Buisson et al. 1988). Both aldrin and dieldrin, present at 100 mg/L, reached 0% of their theoretical biological oxygen demand (BOD) in 2.5 weeks using an activated sludge inoculum at 30 mg/L and the Japanese Ministry of International Trade and Industry (MITI) test which is equivalent to the Organisation for Economic Cooperation and Development (OECD) 301C ready biodegradability test (CITI 1992).

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

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

The change in aldrin concentration and its conversion to dieldrin was also studied over a 3-year period in a clay loam soil in India (Gupta et al. 1979). Aldrin was applied at a rate of 3, 9, and 15 kg active ai/ha once per year before the sowing of crops and mixed up to a depth of 10 cm. After the first year of application at 3, 9, and 15 kg ai/ha, the concentrations of aldrin in soil were 1.801, 3.665, and 8.797 ppm, respectively. By the end of the third year, the concentrations of aldrin was 1.824, 3.453, and 9.736 ppm

for the three application rates of 3, 9, and 15 kg ai/ha, respectively. Dieldrin was detected as a breakdown product of aldrin by the third year at a concentration of 0.055, 0.245, and 0.695 ppm for the three application rates, respectively. Maize and pearl millet grown on the treated soil were also analyzed for aldrin and dieldrin concentrations. No residues of either aldrin or dieldrin could be detected in plant samples from any of the years of experimentation, even at the highest application rate of 15 kg ai/ha.

Dieldrin is much more resistant to biodegradation than aldrin (Castro and Yoshida 1971; Gannon and Bigger 1958; Jagnow and Haider 1972; Willis et al. 1972). Of 20 soil microbes that were able to degrade dieldrin, only 13 of them could also degrade aldrin to dieldrin (Patil et al. 1970). The bacteria, *Aerobacter aerogenes*, aerobically degraded approximately 12% of dieldrin to aldrin diol within 5 days, but no further degradation was detected with increased incubation periods (Wedemeyer 1968). At a soil application rate of 1.1–3.4 kg/hectare, dieldrin was estimated to have a half-life of 2.5 years and a 95% disappearance from soil in 8 years (Freedman 1989), although other studies indicate that dieldrin loses between 75 and 100% of its biological activity in 3 years (Jury et al. 1987). After 6 months, dieldrin persisted in moist, flooded, and nonflooded soils, indicating that these three soil moisture conditions had no effect on the degradation of soil-incorporated dieldrin (Willis et al. 1972). The roots of grass grown on the plots contained 11.6 ppm dieldrin, while the aerial grass parts contained only 0.05 ppm (Voerman and Besemer 1975). Twenty-one years after the application of dieldrin to the foundation of a house at an application rate commonly used for termite control, 10% of the original dieldrin remained, primarily in the upper 6 inches of soil (Bennett et al. 1974). Aldrin and dieldrin applied to soil may also undergo degradation by ultraviolet light to form photodieldrin; this reaction may occur as a result of microbial action as well (Matsumura et al. 1970; Suzuki et al. 1974). After ultraviolet irradiation for 168 hours, dieldrin applied to various environmental media was found to be photodecomposed by 9.6% on loam soil, 1.2% on clay soil, and 44% on activated charcoal; the degradation products were photodieldrin and an unknown compound (Elbeit et al. 1983). Residues in soil samples found after application of dieldrin to soil (0.83 kg/hectare in soil that already contained 0.521 ppm dieldrin) consisted largely of unchanged dieldrin (2.581 ppm) and photodieldrin (0.029 ppm).

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

## 5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to aldrin and dieldrin depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of aldrin and dieldrin in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on aldrin and dieldrin levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are typically achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected for both aldrin and dieldrin in environmental media is presented in Table 5-5.

**Table 5-4. Lowest Limit of Detection Based on Standards[a]**

| Media | Detection limit | Reference |
|---|---|---|
| Air (ppbv) | ~$6.5 \times 10^{-8}$[b] | Nerin et al. 1996 |
| Drinking water (ppb) | 0.004 (aldrin); 0.002 (dieldrin) | EPA 1994 |
| Surface water and groundwater (ppb) | 0.004 (aldrin); 0.002 (dieldrin) | EPA 1994 |
| Soil (ppb) | 0.0006 (aldrin); 0.0005 (dieldrin) | EPA 2007b |
| Sediment (ppb) | 0.0006 (aldrin); 0.0005 (dieldrin) | EPA 2007b |
| Whole blood (ng/mL) | 1 (dieldrin) | MacCuaig 1976 |

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Detection limits for atmospheric monitoring depend on the length of the sampling period and collection volume.

**Table 5-5. Example of Environmental Levels of Aldrin/Dieldrin at Non-NPL Locations**

| Media | Low | High | For more information |
|---|---|---|---|
| Outdoor air (ppbv) | <LOD | $1 \times 10^{-4}$ | Section 5.5 |
| Indoor air (ppbv) | <LOD | 0.3 | Section 5.5.1 |
| Surface water (ppb) | <LOD | 0.395 | Section 5.5.2 |
| Ground water (ppb) | <LOD | 6.7 | Section 5.5.2 |
| Drinking water (ppb) | <LOD | 0.01 | Section 5.5.2 |
| Food (ppb) | <LOD | 5 | Table 5-8 |
| Soil (ppb) | <LOD | $4.9 \times 10^{6}$ | Section 5.5.3 |

Detections of aldrin and dieldrin in air, water, and soil at NPL sites are summarized in Table 5-6.

**Table 5-6. Aldrin and Dieldrin Levels in Water, Soil, and Air of National Priorities List (NPL) Sites**

| Medium | Median[a] | Geometric mean[a] | Geometric standard deviation[a] | Number of quantitative measurements | NPL sites |
|---|---|---|---|---|---|
| Aldrin | | | | | |
| Water (ppb) | 0.07 | 0.265 | 38.0 | 37 | 29 |
| Soil (ppb) | 440 | 925 | 51.1 | 89 | 64 |
| Air (ppbv) | 0.0898 | 0.0389 | 6.01 | 5 | 4 |
| Dieldrin | | | | | |
| Water (ppb) | 0.11 | 0.149 | 11.6 | 72 | 50 |
| Soil (ppb) | 500 | 868 | 23.4 | 174 | 109 |
| Air (ppbv) | 0.0308 | 0.00880 | 26.5 | 12 | 8 |

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

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

### 5.5.1 Air

In the past, aldrin and dieldrin entered the atmosphere through various mechanisms such as spray drift during application of the compounds as insecticides, water evaporation, and suspension of particulates to which the compounds are absorbed. The analysis of 2,479 air samples from 16 states from 1970 to 1972 revealed the following ambient concentrations: aldrin, mean 0.4 ng/m$^3$ (3x10$^{-5}$ ppbv), 13.5% of samples positive; and dieldrin, mean 1.6 ng/m$^3$ (1.0x10$^{-4}$ ppbv), 94% of samples positive (Kutz et al. 1976).

In ambient air samples collected by the EPA Great Lakes National Program in 2018, aldrin was not detected in 205 samples and dieldrin was detected in 133 of 240 samples (concentration range of 0.035–54.831 pg/m$^3$) (WQP 2020); dieldrin was also detected in 27 dry fall material samples (concentration range of 0.299–18.787 pg/m$^3$). The annual atmospheric deposition of dieldrin to the five Great Lakes was estimated based on measurements taken in the late 1970s (Eisenreich et al. 1981). The results indicated

that 0.54, 0.38, 0.55, 0.17, and 0.13 metric tons/year were deposited into Lake Superior, Lake Michigan, Lake Huron, Lake Erie, and Lake Ontario, respectively. The annual mean gas-phase, particulate-phase, and precipitation concentrations of dieldrin were studied over the U.S. Great Lakes from 1990 to 1992 (Hoff et al. 1996). The annual mean gas-phase concentrations of dieldrin over Lakes Superior, Michigan, Erie, and Ontario were 14, 34, 30, and 23 pg/m$^3$ (9.0x10$^{-7}$, 2.2x10$^{-6}$, 1.9x10$^{-6}$, and 1.5x10$^{-6}$ ppbv), respectively. The particulate-phase concentrations of dieldrin over Lakes Superior, Michigan, Erie, and Ontario were 1.5, 1.9, 3.2, and 1.6 pg/m$^3$ (9.6x10$^{-8}$, 1.2x10$^{-7}$, 2.0x10$^{-7}$, and 1.0x10$^{-7}$ ppbv), respectively. Finally, the concentrations of dieldrin in precipitation falling over Lakes Superior, Michigan, Erie, and Ontario were 0.4, 0.99, 0.8, and 0.6 ng/L, respectively. The total wet deposition mass of dieldrin in 1992 for Lakes Superior, Michigan, Erie, and Ontario was 21, 58, 28, and 11 kg, respectively. Shunthirasinham et al. (2016), measured the levels of 26 legacy pesticides including aldrin and dieldrin at three Canadian Great Lakes sites from 1992 to 2012. Annual mean levels of aldrin were 0.12–1.5 pg/m$^3$ (8.0x10$^{-9}$–1.0x10$^{-7}$ ppbv) at the Burnt Island location, 0.65–1.7 pg/m$^3$ (4.3x10$^{-8}$–1.1x10$^{-7}$ ppbv) at the Egbert location, and 0.11–1.5 pg/m$^3$ (7.3x10$^{-9}$–1.0x10$^{-7}$ ppbv) at the Point Petre location. Dieldrin concentrations tended to be an order of magnitude greater as compared to aldrin. The annual mean levels for dieldrin were 3.1–14 pg/m$^3$ (2.0x10$^{-7}$–9.0x10$^{-7}$ ppbv) at the Burnt Island location, 12–28 pg/m$^3$ (7.7x10$^{-7}$–1.8x10$^{-6}$ ppbv) at the Egbert location, and 4.4–24 pg/m$^3$ (2.8x10$^{-7}$–1.5x10$^{-6}$ ppbv) at the Point Petre location. The atmospheric concentration of both aldrin and dieldrin were studied in the National Park of Ordesa, Spain from April to August 1995 (Nerin et al. 1996). The study found that on April 10 and August 23, the concentration of aldrin was below detection limit (1.0 pg/m$^3$) (6.5x10$^{-8}$ ppbv), while on June 23, the concentration of aldrin was 12 pg/m$^3$ (8.0x10$^{-7}$ ppbv). The concentration of dieldrin on April 10 was also below the detection limit, but dieldrin was detected at a concentrations of 6 and 3 pg/m$^3$ (4x10$^{-7}$ and 2x10$^{-7}$ ppbv) on June 23 and August 23, respectively.

Data on the atmospheric concentrations of aldrin and dieldrin that were gathered in 1986, approximately 10 years after the use of aldrin and dieldrin was restricted in the Great Lakes Basin, still showed their presence in atmospheric precipitation (Chan and Perkins 1989). It was found that aldrin was present in 5 of 75 wet precipitation samples at three of four sampling sites located around the basin. Two of the three sites had a mean concentration of 0.01 ng/L (1.0x10$^{-5}$ ppb), while the third site had a mean concentration of 0.24 ng/L (2.4x10$^{-4}$ ppb). Dieldrin was detected at all four sites and in >60% of the samples at mean concentrations ranging from 0.41 to 1.81 ng/L (4.1x10$^{-4}$–1.8x10$^{-3}$ ppb). The highest concentrations of both aldrin and dieldrin were found in samples collected at Pelee Island at the western end of Lake Erie (maximum concentrations of 3.4 ng/L [3.4x10$^{-3}$ ppb] and 5.9 ng/L [5.9x10$^{-3}$ ppb], respectively). In 1979–1980, dieldrin was detected in the ambient air and rainfall over College Station,

Texas, at average concentrations of 0.08 ng/$m^3$ ($5.1x10^{-6}$ ppbv) and 0.80 ng/L ($8x10^{-4}$ ppb), respectively (Atlas and Giam 1988). The washout ratio (concentration in rain/concentration in air) for dieldrin was calculated to be 8.9. Dieldrin was present in rainfall measured at three points in Canada during 1984, at mean concentrations of 0.78 ng/L ($7.8x10^{-4}$ ppb) over Lake Superior, 0.27 ng/L in New Brunswick, and 0.38 ng/L ($3.8x10^{-4}$ ppb) over northern Saskatchewan (Strachan 1988).

Between 1991 and 1993, 18 fogwater samples, 31 rainwater samples, and 17 atmosphere (gas and particles) samples were analyzed for aldrin and dieldrin from a rural area in Colmar, east of France (Millet et al. 1997). The mean concentrations of aldrin and dieldrin in fogwater collected from 1991 to 1993 were 3.5 and 5 ng/mL, respectively. The mean concentrations of particle bound aldrin and dieldrin in fogwater collected from 1991 to 1993 were 15 and 17 ng/mL, respectively. The mean concentrations of aldrin and dieldrin in rainwater collected in 1992 were 0.05 and 0.5 ng/mL, respectively. The mean concentration for both aldrin and dieldrin in the vapor-phase collected in 1992 was the same at 0.7 ng/$cm^3$. Finally, the mean concentrations of aldrin and dieldrin in the particulate phase collected in 1992 were 0.6 and 0.7 ng/mL, respectively.

No recent studies of the indoor air concentrations of aldrin and dieldrin were located; however, high levels were observed in homes that were treated with aldrin or dieldrin for termite control and measurable levels persisted several years post application (Wallace et al. 1996). Aldrin and dieldrin levels in the living area of a two-story home treated for termites were 300 and 7 ng/$m^3$ (0.02 and 0.0004 ppbv), respectively; however, levels were 5,000 and 28 ng/$m^3$ (0.3 and 0.0018 ppbv), respectively, in the basement area where treatment had occurred. Two years later, the concentrations of aldrin and dieldrin were 125 and 13 ng/$m^3$ (0.0084 and 0.00083 ppbv), respectively, in the living area and 1,400 and 30 ng/$m^3$ (0.093 and 0.002 ppbv), respectively, in the basement. After 91 months, there were still measurable levels detected in the living area (2 ng/$m^3$ aldrin; 3 ng/$m^3$ dieldrin) and basement (12 ng/$m^3$ aldrin; 20 ng/$m^3$ dieldrin). Measurements of air concentrations in homes 1–10 years after termiticide treatment showed dieldrin levels ranging from 0.0006 to 0.03 ppbv in living rooms and bedrooms and all interior areas (Dobbs and Williams 1983). Air samples were also collected and analyzed for aldrin over the course of 6 months from 29 dwellings treated with aldrin for prevention of termite infestation (Gun et al. 1992). The concentration of atmospheric aldrin was recorded for the first 6 months of the study. The median concentrations of aldrin were 44 ng/$m^3$ (0.0029 ppbv) prior to treatment; 2,600 ng/$m^3$ (0.17 ppbv) 1 week post-treatment; 720 ng/$m^3$(0.048 ppbv) 6 weeks post-treatment; and 570 ng/$m^3$ (0.038 ppbv) 6 months post-treatment.

### 5.5.2 Water

A comprehensive study of U.S. drinking water samples in 1975 revealed that <17% of the samples contained dieldrin, with 78% of the positive samples containing concentrations between 4 and 10 ng dieldrin/L of water (0.004–0.01 µg/L) (EPA 1980). The concentration of various pesticides were measured six times from September 1995 to September 1996 in drinking water samples from 80 randomly selected residences of Maryland (MacIntosh et al. 1999). Dieldrin was not detected in any of the samples taken during this test. Between November 1, 1983 and July 1, 1992, the California EPA tested various wells for pesticide residues throughout the state of California (CalEPA 1995). Aldrin and dieldrin were not detected in any of the 1,304 wells (covering 33 counties) sampled during this study. In another study, dieldrin residues were analyzed for in 208 well water samples collected from nine urban areas from across the United States (Kolpin et al. 1997). Dieldrin was detected in 2.4% of wells samples (detection limit=0.005 µg/L) at a maximum concentration of 0.045 µg/L. EPA performed an assessment of unregulated contaminants in public water systems from 1993 to 1997 across 20 states (EPA 2001). Dieldrin was tested for in 11,788 public water systems and was detected above its minimum reporting level of 0.002 µg/L in just 0.09% of the public water systems tested.

Dieldrin was reported above the lower quantification limit in 0.3% of approximately 4,900 ambient surface water data points compiled for 2016–2020 from EPA STORage and RETrieval (STORET) and National Water Information System (NWIS) databases at a concentration range of 1.9–87 ng/L (ppt) (WQP 2020). In earlier studies, dieldrin was found more often than any other pesticide in water samples collected from all major river basins (mean concentration, 7.5 ng/L [0.0075 µg/L]) in the United States (Weaver et al. 1965). In 1976, dieldrin was reported in many fresh surface waters of the United States, with mean concentrations ranging from 5 to 395 ng/L (0.005–0.395 µg/L) (EPA 1980). A comprehensive study of pesticides in streams and groundwater from 51 major river basins in the United states from 1992 to 2001 indicated that dieldrin was detected in <5% of surface water samples collected from agricultural and urban areas (USGS 2006). There were practically no detections in undeveloped areas. Aldrin was not reported above the lower quantification limit in approximately 4,200 ambient surface water data points compiled for 2016–2020 from EPA STORET and NWIS databases (WQP 2020).

In groundwater, dieldrin was detected in 0.6% of over 1,870 groundwater data points compiled for 2016–2020 from EPA STORET and NWIS databases (WQP 2020); the concentrations ranged from 0.0000676 to 1.78 µg/L. In 918 groundwater data points, aldrin was not reported at or above the lower quantification limit (WQP 2020).

Influent and effluent samples from New York City's 14 water pollution control plants were collected and analyzed 6 times during the course of 5 years (1989–1993) to determine the concentration of chemical contaminants (Stubin et al. 1996). Of the 168 samples collected, aldrin was detected in 12 influent water samples in 1990, once in 1992 and 9 times in 1993. The concentration of aldrin in influent samples ranged from 0.024 to 1.1 µg/L. Aldrin was also detected in effluent samples 11 times in 1990, twice in 1992, and 6 times in 1993. The concentration of aldrin in effluent samples ranged from 0.008 to 0.44 µg/L. Dieldrin, however, was not detected in any influent samples, and was only detected in two effluent samples taken in 1993. The concentration of dieldrin in the effluent samples ranged from 0.012 to 0.028 µg/L.

In 1980, aldrin and dieldrin were detected in water samples taken from the Inner Harbor Navigation Canal of Lake Pontchartrain (New Orleans, Louisiana) on the ebb and flood tides at a depth of 1.5 m; respective concentrations were 0.3 ng/L (0.0003 µg/L) and 5.6 ng/L (0.0056 µg/L) for aldrin and 0.6 ng/L (0.0006 µg/L) and 5.9 ng/L (0.0059 µg/L) for dieldrin (McFall et al. 1985). In 1987, dieldrin was detected in seawater samples taken from the Gulf of Mexico at concentrations ranging from 0.009 to 0.02 ng/L ($9x10^{-6}$–$2x10^{-5}$ ppb) and from seawater off the southeastern United States at 0.007–0.01 ng/L ($7x10^{-6}$–$1x10^{-5}$ ppb); aldrin was also detected in the southeastern U.S. coastal waters at concentrations of 0.31–1.5 ng/L (0.0003–0.001 ppb) (Sauer et al. 1989). Aldrin and dieldrin were detected in water and sediment samples taken between 1975 and 1980 at 160–180 stations on major rivers of the United States as part of the National Pesticide Monitoring Program. Aldrin and dieldrin were both detected in 0.2% of the 2,946 water samples and in 0.6 and 12% of the approximately 1,016 sediment samples, respectively (USGS 1985). In 1988, dieldrin was detected in 9% of 422 groundwater samples taken from a sandy, alluvial aquifer in Illinois at a median concentration of 0.01 µg/L, and in 4% of groundwater well samples taken in the vicinity of an agrichemical dealer facility, at a mean concentration of 0.03 µg/L (Hallberg 1989). Out of 2,459 sites from the largest river basins and aquifers in the United States tested between 1992 and 1996, dieldrin had a frequency of detection of 1.63% and a maximum concentration of 0.068 µg/L (Kolpin et al. 2000).

Analysis of urban storm water runoff collected between 1979 and 1983 in the Canadian Great Lakes Basin found dieldrin to be present in approximately 32 of 124 water samples at a mean concentration of $5.1x10^{-4}$ µg/L) and in approximately 17 of 110 runoff sediment samples at a mean concentration of $4.4x10^{-3}$ mg/kg (4.4 ppb). Aldrin was found in approximately 13 of 129 runoff sediment samples at a mean concentration of $1.2x10^{-3}$ mg/kg (1.2 ppb) but was not detected in any water samples (Marsalek and

Schroeter 1988). These concentrations resulted in mean annual loadings to the Canadian Great Lakes Basin of 0.2 kg/year for aldrin and 0.6 kg/year for dieldrin. In 1982, water samples taken from 19 U.S. cities for the National Urban Runoff Program, found aldrin to be present only in samples taken from Washington, DC, at a concentration of 0.1 µg/L (6% of samples), and dieldrin was detected only in water from Bellevue, Washington, at 0.008–0.1 µg/L (2% of samples) (Cole et al. 1984). Water sampling conducted during the 1986 spring isothermal period in the Great Lakes did not detect aldrin in any samples. Dieldrin, however, was present in all samples at mean concentrations ranging from 0.300 ng/L (0.0003 µg/L) in Lake Superior to 0.402 ng/L ($4.2x10^{-4}$ µg/L) in Lake Erie (Stevens and Neilson 1989). The average concentration of dieldrin measured in Lake Huron water samples collected in 2007 (n=6) was reported as 0.069 ng/L ($6.9x10^{-5}$ µg/L) and the average concentration in Lake Ontario (n=7) samples collected in 2006 was 0.10 ng/L ($1.0x10^{-4}$ µg/L) (Shunthirasinham et al. 2016).

Aldrin was identified in leachate from the Love Canal industrial landfill in Niagara Falls, New York, at a concentration of 0.023 mg/L (23 µg/L) (data were gathered prior to 1982) (Brown and Donnelly 1988). In 1986, a waste site was identified in Clark County, Washington, that contained buried drums believed to have originally held chemicals used at a plywood manufacturing plant. Analysis of the soil and water contamination found aldrin to be present in groundwater samples taken from shallow wells on site at a maximum concentration of 2.12 µg/L and in groundwater samples from nearby private wells at 0.79 µg/L (EPA 1986b). At a hazardous waste site in Gallaway, Tennessee, drums and bottles containing chemicals from a pesticide blending operation had been emptied or discarded into a number of small ponds on the site. Dieldrin was present in on-site surface waters at 0.40–1.4 µg/L, but was not detected in any off-site water samples (EPA 1987c). Aldrin and dieldrin were detected in groundwater at a location in Clearwater, Florida, which previously housed a pesticide control company from 1969 to 1978 (ATSDR 2012). Maximum levels of aldrin were 0.33 µg/L and the maximum concentration of dieldrin was 6.7 µg/L.

### 5.5.3 Sediment and Soil

As a result of the rapid conversion of aldrin to dieldrin, soil residues of dieldrin are found in higher concentration and with greater frequency than residues of aldrin, even though aldrin was applied more frequently to the soil. The amount of dieldrin and aldrin residues in soils was monitored from 12 separate farmlands located in the Fraser Valley of British Columbia, Canada in 1989 (Szeto and Price 1991). Each farm had a known history of at least 25 years of vegetable growing and use of various pesticides. Aldrin was detected on one farmland with muck soil at a mean concentration of 78 ppb dry weight, while

dieldrin was detected on two farmlands containing muck soils at a mean concentration of 692 ppb dry weight (range from 104 to 1,280 ppb). In a separate study, the concentration ranges of dieldrin in agricultural soil samples taken in 1995 and 1996 from Alabama, Ohio, Indiana, and Illinois were not detected to 23 ng/g (ppb) dry weight, not detected to 4,250 ng/g (ppb) dry weight, not detected to 69 ng/g (ppb) dry weight, and not detected to 13 ng/g (ppb) dry weight, respectively (Bidleman 1999). In data compiled for 2018 from the EPA STORET database (WQP 2020), aldrin was detected above the lower quantification limit in 4 of 119 soil data points (concentrations ranging from 21.9 to 40.7 µg/kg [ppb]) and dieldrin was detected above the lower quantification limit at in 6 of 119 soil data points (concentrations of 25.2–34.8 µg/kg [ppb]).

An apartment complex near Memphis, Tennessee that had a history of used disposal of sanitary sewage and manufacturing wastewater was monitored for aldrin and dieldrin for a Health Consultation (ATSDR 2007). A total of 183 soil samples were collected from a depth of 0–72 inches, with most samples from the upper 24 inches. The mean and median concentrations were 60.4 and 0.9 ppm, respectively, for aldrin and 62.1 and 1.0 ppm, respectively, for dieldrin. Maximum concentrations observed were 4,540 ppm for aldrin and 4,990 ppm for dieldrin. Another Health Consultation, which monitored for aldrin and dieldrin levels in contaminated soils, was performed in 2012 at a location in Clearwater, Florida, which previously housed a pesticide control company from 1969 to 1978 (ATSDR 2012). The maximum concentration of aldrin in soils (0–1 foot depth) at commercial locations was 27 ppm and the maximum concentration of dieldrin was 45 ppm. In nearby residential soils, the maximum concentrations of aldrin and dieldrin were 0.0094 and 0.3 ppm, respectively. The National Soils Monitoring Program (Kutz et al. 1976) detected dieldrin in soils at varying concentrations and areas throughout 24 states; the mean concentration ranged from 1 to 49 ppb.

Aldrin was detected above the lower quantification limit at in 2.4% of 1,100 sediment data points (concentrations of 0.0249–12.34 µg/kg [ppb]) compiled for 2016–2020 from the EPA STORET database (WQP 2020). Dieldrin levels were above the lower quantification limit in 0.9% of 806 sediment data points (concentrations of 0.64–1.53 µg/kg [ppb]) (WQP 2020). An analysis of sediment samples taken from Lake Ontario in 1981 showed that dieldrin levels had increased from approximately 26 ng/g (26 ppb) in 1970 to 48 ng/g (48 ppb) in 1980, although the use of dieldrin was banned in much of the Great Lakes Basin in the early 1970s (Eisenreich et al. 1989). At a hazardous waste site in Gallaway, Tennessee, drums and bottles containing chemicals from a pesticide blending operation had been emptied or discarded into a number of small ponds on the site. Dieldrin was present in sediment samples from onsite ponds at 1,400 ppb and in one offsite sediment sample (concentration not specified) (EPA 1987c).

Sediment samples taken from two lakes near the U.S. Army Rocky Mountain Arsenal, Colorado in 1983 indicated that aldrin and dieldrin persisted in the sediments long after deposition ceased. Concentrations up to 2,050 ppb for aldrin and 100 ppb for dieldrin at a core depth of approximately 21 cm were found in one lake. A second lake also had elevated levels of aldrin and dieldrin contamination, but at lower concentrations (approximately 250 ppb for aldrin and 40 ppb for dieldrin) and at a lower core depth, indicating that most of the deposition had occurred at an earlier date (Bergersen 1987). The concentration of dieldrin and aldrin was also studied in sediment samples from three coastal lagoons in the southeast of the Gulf of Mexico (Botello et al. 1994). The average concentrations of aldrin in sediment samples taken from the Carmen, Machona, and Alvarado lagoons were 0.70, 1.15, and 2.11 ng/g dry weight, respectively. The average concentrations of dieldrin in sediment samples taken from the Carmen, Machona, and Alvarado lagoons were 6.84, 0.59, and 2.05 ng/g dry weight, respectively. A monitoring survey of 17 wetland areas in the north central United States, found dieldrin to be present in only one Iowa sediment sample at 170 ng/g (170 ppb) dry weight (Martin and Hartman 1985).

### 5.5.4 Other Media

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

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

samples), and Schrader Lake (five samples) were below the minimum detectable limit, 0.0, and 0.5 µg/g wet weight, respectively.

Blood samples were collected and analyzed for dieldrin concentrations from nestling bald eagles at active nests in the Canadian portion of the Great Lakes Basin from 1990 to 1994 (Donaldson et al. 1999). Mean dieldrin concentrations in eagle blood samples taken from Lake Erie, Huron, Nipigon, Superior, and Woods were 0.003 (30 samples), 0.007 (1 sample), 0.0031 (7 samples), 0.0051 (11 samples), and 0.0031 mg/kg wet weight (2 samples), respectively. Residue levels of dieldrin in unhatched bald eagle eggs collected along Lake Erie from 1974 to 1980 (six samples) and from 1989 to 1994 (six samples) were 1.28 and 0.49 mg/kg wet weight, respectively. Seven bald eagle eggs from the Tanana River, Alaska collected in 1990 and 1991 contained dieldrin with a mean concentration of 0.028 ppm (Ritchie and Ambrose 1996). Peregrine falcon eggs from Rankin Inlet collected from 1991 to 1994 (20 samples) and from 1982 and 1986 (36 samples) contained dieldrin at mean concentrations of 0.361 (range of 0.13–1.66) and 0.41 (range of 0.045–1.80) µg/g wet weight, respectively (Braune et al. 1999). Osprey eggs collected at five locations on the Fraser River from 1991 to 1997 contained dieldrin; the highest concentrations were reported at the Fraser River site below Quesnel with a mean value of 5.2 µg/kg wet weight (Elliott et al. 2000). Lower concentrations were reported for eggs collected at the other locations, with mean values generally <2 µg/kg wet weight. Dieldrin was detected with a mean concentration of 0.25 µg/g in 75 out of 312 double-crested cormorant eggs and embryos collected from Cat Island, Green Bay, Wisconsin in 1994 and 1995 (Custer et al. 1999). The mean concentration of dieldrin in tree swallow eggs and tree swallow nestlings collected in 1998 at Pigeon Creek, Iowa (three samples); Duck Creek, Iowa (three samples); and Lindsey Harbor, Iowa (seven samples) along the Upper Mississippi River was 0.03 µg/g wet weight (Custer et al. 2000).

Waterfowl from Northern Canada were collected from 1988 to 1995 and divided into browsers, grazers, omnivores, molluscivores, and piscivores (Braune et al. 1999). The highest concentrations of dieldrin were found in tissues of waterfowl feeding at the upper trophic levels. Concentrations of dieldrin ranged from not detected to 5.0 ng/g wet weight, not detected to 3.2 ng/g wet weight, not detected to 15.9 ng/g wet weight, not detected to 120 ng/g wet weight, and not detected to 54.7 ng/g wet weight, respectively.

Mean concentrations of dieldrin in snapping turtle eggs collected at four sites along the St. Lawrence River in the Mohawk territory of Akwesasne during June, 1998 ranged from 4 to 280 ng/g wet weight, with an overall mean concentration of 38.13 ng/g wet weight (de Solla et al. 2001). Aldrin and dieldrin were detected in the plasma of juvenile alligators from three lakes in central Florida (Guillette et al.

1999). The mean concentrations of dieldrin in males from Lake Woodruff, Lake Apopka, and Orange Lake were 0.24, 1.68, and 0.75 ng/mL plasma, respectively. The mean concentrations of dieldrin in females from these lakes were 0.31, 2.87, and 0.39 ng/mL plasma, respectively. The mean concentration of aldrin for juvenile alligators in all three lakes was 0.34 ng/mL plasma.

In 1985, fish samples taken from the lower Savannah River in Georgia and South Carolina were found to occasionally contain dieldrin, but at concentrations of <0.01 µg/g (10 ppb) (Winger et al. 1990); common carp and white bass samples from a lake in Kansas located in an agricultural area had mean concentrations of 0.069 and 0.058 ppb, respectively (Arruda et al. 1988). Fish samples taken from tributary rivers around the Great Lakes in 1980–1981 had dieldrin levels up to 0.15 mg/kg (150 ppb) (average concentration=0.03 mg/kg [30 ppb]) (DeVault 1985). Fish taken from Lake Huron between 1970 and 1980 had mean dieldrin concentrations ranging from 0.01 to 0.50 mg/kg (10–500 ppb) (EPA 1985); however, by 1984, mean concentrations of dieldrin in Lake Michigan Coho salmon had dropped to 0.01 µg/g (10 ppb) from 0.06 µg/g (60 ppb) in 1980 (DeVault et al. 1988). An analysis of 315 composite samples of whole fish collected from 107 sites nationwide in 1980–1981 as part of the National Pesticide Monitoring Program found that the mean concentrations of dieldrin were essentially unchanged since 1978–1979. In 1978, dieldrin was detected in 81% of the samples, and in 1980, in 75% of the samples at mean concentrations of 0.05 µg/g (50 ppb) wet weight and 0.04 µg/g (40 ppb), respectively (Schmitt et al. 1985). Three of eight samples of bluegill (*Lepomis macrochrius*) collected from the San Joaquin Valley in July 1981 contained dieldrin at concentrations ranging from 0.005 to 0.008 mg/kg (5–8 ppb) wet weight; four of the eight common carp (*Cyprinus carpio*) obtained from the same sites contained dieldrin at concentrations ranging from 0.015 to 0.067 mg/kg (15–67 ppb) wet weight (Saiki and Schmitt 1986). Dieldrin was also detected in a variety of fish taken from a section of Lake Oconee in Georgia that received storm runoff from insecticide-treated areas between 1981 and 1982. Dieldrin concentrations ranged from <10 to 200 µg/kg (10–200 ppb). Dieldrin was not detected in fish taken from the lake after 1982 (Bush et al. 1986). A survey of 17 wetland areas in the north central United States found dieldrin in two fish samples taken from Kansas and Iowa at concentrations of 6 ng/g (6 ppb) and 9 ng/g (9 ppb), respectively (Martin and Hartman 1985). Dieldrin was found in 5 of 20 raw bluefish fillets collected in Massachusetts waters in 1986, at concentrations of 0.02–0.04 ppm (20–40 ppb); after cooking, dieldrin was still detected in the fillets, indicating that heating does not degrade the pesticide in foods (Trotter et al. 1989). Aldrin and dieldrin were detected in shrimp (*Penaeus setiferus* and *Penaeus aztecus*) collected from the Calcasieu River Basin in an industrial area of Louisiana in 1985–1986. Aldrin was present in shrimp taken from 7 of 30 stations at concentrations ranging from 0.01 to 0.12 µg/g (10–120 ppb), and dieldrin was present in 21 of 30 samples at concentrations of 0.05–9.47 µg/g (50–9,470 ppb) (average

concentration 1.57 µg/g [1,570 ppb]) (Murray and Beck 1990). Between October 1981 and September 1986, over 12,044 imported and 6,391 domestic commodities were sampled for pesticide residues. Dieldrin was detected in 420 imported and 44 domestic products; however, the tolerance (the maximum amount of a residue expected in a food when a pesticide is used according to label directions, provided that the level does not present an unacceptable health risk) for dieldrin was exceeded in only eight imported products and one domestic product, indicating that most agricultural products do not contain harmful levels of dieldrin (Hundley et al. 1988).

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

One study examined persistent organochlorines concentrations in blubber samples from 16 dead beluga whales collected during 1993–1994 in the St. Lawrence River estuary (Muir et al. 1996). The mean concentrations of dieldrin in seven female and nine male beluga whales were 1,360 ng/g lipid weight (range=326–2,360 ng/g lipid weight) and 2,020 ng/g lw (range=1,440–2,620 ng/g lipid weight), respectively. The study found a temporal upward trend in dieldrin concentration in female beluga whales and slightly augmented levels of dieldrin in males. The average dieldrin concentration in female beluga whales in 1987 was 450 ng/g lipid weight, while in males, the average concentration of dieldrin measured from 1986 to 1988 was 1,650 ng/g lipid weight. In a separate study, biopsies were collected from Right whales in the Bay of Fundy in 1994 (30 samples), 1995 (17 samples), and 1996 (15 samples) and at sites in Georgia and Cape Cod Bay in 1997 (Weisbrod et al. 2000). For each collection period, mean concentrations were 513 and 93 ng/g sample lipid content and not detected, respectively, for aldrin and 1,141, 1,349, and 4,244 ng/g sample lipid content, respectively, for dieldrin. Zooplankton samples collected in 1995 and 1996 from Georges Bank, Bay of Fundy, and Cape Cod Bay contained aldrin at concentrations that were undetectable to 8.9 ng/g sample lipid content and dieldrin at concentrations that were undetectable to 23 ng/g sample lipid content.

Dieldrin concentrations were determined in archived samples of whole lake trout collected yearly from eastern Lake Ontario between 1977 and 1993 (Huestis et al. 1996). The mean concentrations of dieldrin in trout collected in 1977, 1980, 1983, 1986, 1989, 1990, 1992, and 1993 were 313, 218, 135, 103, 97.3, 99.0, 73.1, and 78.4 ng/g, respectively. An investigation of the temporal trends of pesticide residues in fish from Lake Michigan indicated a decrease in dieldrin concentrations from 1982 to 1990 (Miller et al. 1992). Total dieldrin concentrations in lake trout decreased 68% from 410±50 µg/kg in 1982 to 130±30 µg/kg in 1990. In Lake Superior, dieldrin concentrations in fish did not appear to change as much over a 3-year period. The total dieldrin concentration in lake trout in 1982 was 50±10 µg/kg, while in 1985, the concentration was 40±10 µg/kg. In a separate study (Zabik et al. 1996), concentrations of dieldrin in skin-off lake trout collected from both Lake Huron and Lake Michigan, and siscowets from Lake Superior were reported as 0.029, 0.076, and 0.027 ppm, respectively.

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

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

## 5.6 GENERAL POPULATION EXPOSURE

In the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2019), aldrin levels in blood were below the level of detection for all age groups for survey years 2001–2002 and 2003–2004. Dieldrin levels in serum (lipid adjusted) are presented in Table 5-7. Geometric mean levels were not calculated because the proportion of results below the limit of detection were too high to provide a valid result.

**Table 5-7. Selected Percentiles of Lipid Adjusted Serum Concentrations in ng/mL (ppb) of Dieldrin for the U.S. Population Aged 12 Years and Older[a]**

| Category | Survey year | 50th CI | 75th CI | 90th CI | 95th CI | Sample size |
|---|---|---|---|---|---|---|
| Total | 01–02 | <LOD | <LOD | 15.3 (14.5–17.4) | 20.3 (18.7–22.4) | 2,159 |
| | 03–04 | <LOD | 9.00 (8.30– 9.90) | 14.4 (12.1–16.4 | 19.0 (15.8–24.2) | 1,952 |
| 12–19 years | 01–02 | <LOD | <LOD | <LOD | <LOD | 716 |
| | 03–04 | <LOD | <LOD | <LOD | 9.10 (<LOD–16.4) | 587 |
| ≥20 years | 01–02 | <LOD | 10.5 (<LOD–11.6) | 6.6 (15.1–18.2) | 21.3 (19.1–24.0) | 1,443 |
| | 03–04 | <LOD | 9.50 (8.80–10.4) | 14.9 (12.8–17.0) | 19.5 (16.0–25.7) | 1,365 |
| Males | 01–02 | <LOD | <LOD | 15.7 (14.4–18.7) | 20.3 (18.6–24.0) | 1,007 |
| | 03–04 | <LOD | 9.30 (8.40–10.8) | 15.1 (13.1–19.1) | 21.9 (14.9–38.5) | 954 |
| Females | 01–02 | <LOD | <LOD | 15.3 (13.4–17.2) | 19.8 (18.0–21.6) | 1,152 |
| | 03–04 | <LOD | 8.70 (7.80–9.50) | 12.8 (11.2–15.4) | 16.9 (13.9–22.4) | 998 |
| Mexican-Americans | 01–02 | <LOD | <LOD | 11.7 (<LOD–15.1) | 15.4 (12.7–19.1) | 539 |
| | 03–04 | <LOD | <LOD | 10.8 (9.00–14.1) | 14.0 (10.6–24.1) | 456 |
| Non-Hispanic blacks | 01–02 | <LOD | <LOD | 15.0 (11.8–19.1) | 20.6 (15.8–25.2) | 484 |
| | 03–04 | <LOD | 8.80 (<LOD–10.1) | 13.0 (10.5–15.8) | 15.9 (13.3–21.5) | 487 |
| Non-Hispanic whites | 01–02 | <LOD | <LOD | 15.6 (14.8–17.8) | 21.1 (18.9–23.6) | 980 |
| | 03–04 | <LOD | 9.30 (8.60–10.2) | 14.9 (12.5–17.5) | 19.7 (15.6–33.4) | 885 |

[a]Data are from weighted pooled serum samples

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Use of aldrin and dieldrin for pest control on crops such as cotton, corn, and citrus products was canceled by the EPA in 1974 (EPA 1974), while use for extermination of termites was voluntarily canceled by the manufacturer in 1987 (EPA 1990a). However, during the period of widespread use and production of aldrin and dieldrin, intake by workers who manufactured these compounds was estimated to range from 0.72 to 1.10 mg/person/day with a good correlation between levels in tissue (fat, serum, and urine) and total length of exposure or intensity of exposure (Hayes and Curley 1968). One pest control operator was found to have 0.5 and 0.3 µg dieldrin on his left and right hands, respectively, >2 years after his last exposure to aldrin; serum blood levels taken at the same time showed 10 ppb dieldrin. A further analysis of individuals exposed to dieldrin found no correlation between the pesticide levels on their hands and in their sera (Kazen et al. 1974). A 1981 survey of Florida citrus field workers found dieldrin to be present

in >3% of the 567 serum samples, at a mean concentration of 1.8 ppm (1,800 ppb) (Griffith and Duncan 1985). Workers cleaning up hazardous waste sites may also be exposed, but no information on monitored levels of exposure was found.

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

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

have found wet weight BCFs ranging from 38 to 77 (mean, 48.7) and lipid basis BCFs ranging from 55 to 115 (mean, 70.9) (Geyer et al. 1986, 1987). Blood samples taken from residents of El Paso, Texas, during 1982–1983, showed aldrin to be present in 39 of 112 samples (34%) at a mean concentration of 4.6 ppb (Mossing et al. 1985).

Individuals living in homes contaminated by past termiticide treatment constitute a significant group exposed to aldrin and dieldrin in indoor air. Air samples were taken and analyzed for aldrin over the course of 6 months from 29 dwellings treated with aldrin for prevention of termite infestation (Gun et al. 1992). Blood samples were also analyzed for dieldrin levels of one occupant from each dwelling. The concentration of atmospheric aldrin was recorded for the first 6 months of the study. The median concentrations of aldrin were 0.044 µg/$m^3$ prior to treatment; 2.6 µg/$m^3$ 1 week post-treatment; 0.72 µg/$m^3$ 6 weeks post-treatment; and 0.57 µg/$m^3$ 6 months post-treatment. Prior to treatment, the median concentration of dieldrin in blood was 0.75 ng/mL, while 3 months post-treatment, the median concentration was 1.2 ng/mL.

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

A pilot study of non-occupational general population exposure to pesticides in ambient air inside and outside the home was conducted in nine homes in Florida in August 1985. Air was monitored for 24 hours outside the house and inside the house, and personal air monitors were worn by one occupant of each house. Aldrin and dieldrin were detected in indoor air at six and five of the nine households, respectively; outdoors at four of the nine households each; and by personal monitors for three and five of the nine individuals, respectively. In one designated high-pesticide-use household, aldrin and dieldrin were detected in the indoor air at average concentrations of 0.058 µg/$m^3$ (0.004 ppb) and 0.038 µg/$m^3$ (0.002 ppb), respectively. Neither compound was detected in the outdoor air immediately adjacent to the home, and concentrations detected with personal air monitors were half (aldrin) to one-third (dieldrin) the concentrations for ambient indoor air (Lewis et al. 1988). A composite sample of the dust from four Seattle homes collected in 1988–1989 showed dieldrin to be present at 1.1 ppm, although none of the homeowners could remember using the pesticide. It was suggested that the source of the dieldrin was soil

surrounding the homes; however, since the use of dieldrin is restricted to termite control, and Seattle has few termites, the source of the contaminated soil is unknown (Roberts and Camann 1989).

Atmospheric sampling of aldrin and dieldrin conducted from 1970 to 1972 indicated that aldrin and dieldrin were present at mean concentrations of 0.4 ng/$m^3$ ($3x10^{-5}$ ppbv) and 1.6 ng/$m^3$ ($1.0x10^{-4}$ ppbv), respectively (Kutz et al. 1976). Combining these figures and assuming that 20 $m^3$ of air are inspired each day, the average daily intake of aldrin plus dieldrin from the atmosphere would be 0.57 ng/kg body weight in 1972. However, the cancellation of the use of these compounds suggests that current inhalation intake will be much less. Guicherit and Schulting (1985) used data on air samples collected in the western part of the Netherlands in 1979–1981 and calculated the average daily intake by inhalation to be 0.02 ng dieldrin/kg body weight and 0.01 ng aldrin/kg body weight.

A significant source of general population exposure to dieldrin is through diet. In the absence of occupational or domestic use as a pesticide, food is probably the primary source of dieldrin residues in human adipose tissues (Ackerman 1980). Because of the rapid epoxidation of aldrin in the environment, it is not considered to be an important human dietary contaminant, with an average intake of <0.001 µg/kg/day. Dieldrin, however, may be ingested as a result of eating contaminated fish, milk, and other foods with a high fat content including meat. EPA established tolerances for aldrin and dieldrin in or on raw agricultural commodities at maximums of 0.0–0.1 ppm, depending on the crop (Sittig 1980). Table 5-8 shows a summary of dieldrin residues in adult dietary components analyzed in 1981–1982 (Gartrell et al. 1986a). A 1985 Canadian survey of foods found that although aldrin was not detected in any of the food samples analyzed, dieldrin was detected in all food composites at 0.00011 µg/g in fruit; 0.0019 µg/g in milk; 0.0031 µg/g in leafy vegetables, eggs, and meat; and 0.023 µg/g in root vegetables (Davies 1988). Dieldrin residues may persist in foods such as milk butterfat and subcutaneous fat in cattle with an estimated half-life in butterfat of 9 weeks (Dingle et al. 1989). Samples of ultra-pasteurized heavy cream and cow's milk purchased in Binghamton, New York, in 1986 had dieldrin levels of 0.006 and 0.003 ppm, respectively (Schecter et al. 1989b).

**Table 5-8. Dieldrin Residues in Adult Components (1980–1982)[a]**

| Food group | Residue range (ppm) | Average concentration (µg/day) |
|---|---|---|
| Dairy | Trace to 0.003 | 0.0006 |
| Fish, poultry, meat | Trace to 0.004 | 0.0012 |
| Potatoes | Trace to 0.002 | 0.0004 |
| Root vegetables | Trace to 0.005 | 0.0004 |

**Table 5-8. Dieldrin Residues in Adult Components (1980–1982)[a]**

| Food group | Residue range (ppm) | Average concentration (µg/day) |
|---|---|---|
| Leaf vegetables | Trace to 0.002 | 0.0002 |
| Legumes | Not detected | Not detected |
| Garden fruits | Trace to 0.011 | 0.0021 |
| Fruits | 0.001 | 0.0001 |
| Cereals and grains | 0.004 | 0.0001 |
| Oils and fats | Trace to 0.002 | 0.0003 |
| Sugar | Not detected | Not detected |
| Beverages | Not detected | Not detected |

Source: Gartrell et al. 1986a

During the period of 1965–1970, total U.S. dietary intakes were reported to be 0.05–0.08 µg dieldrin/kg/day and 0.0001–0.04 µg aldrin/kg/day (IARC 1974b). Since 1970, the use of aldrin and dieldrin on food has been cancelled, and dietary intake has decreased. An FDA Total Diet Study, conducted between 1982 and 1984, found that aldrin intake was <0.001 µg/kg/day for all age and sex groups (Gunderson 1988; Lombardo 1986). Adults had a dieldrin intake of 0.007 µg/kg/day (25–30-year-old males). Dieldrin was found in 15% of the food samples analyzed. These values represent a decrease from the 1980 Total Diet Study. Between 1980 and 1982–1984, daily intakes of dieldrin decreased from 22 to 8 ng/kg/day for adults (Gunderson 1988). A Total Diet Study conducted by FDA found dieldrin in only 6% of the food items analyzed in 1990 (FDA 1991). A daily intake of 0.0016 µg/kg body weight was estimated for 60–65-year-old females (FDA 1991). The average daily dietary intake of chemical contaminants in food were estimated for 116,957 U.S. adults in 1990 based on annual diet as part of the annual FDA Total Diet Study (MacIntosh et al. 1996). The estimated mean dietary exposure of dieldrin for 78,882 adult females and 38,075 adult males studied ranged from 0.08 to 0.43 µg/day (mean=0.5 µg/day) and from 0.02 to 4.0 µg/day (mean=0.5 µg/day), respectively. High levels of dietary exposures to dieldrin were estimated to be primarily due to frequent consumption of summer and winter squash, while those with low exposure were dominated by foods that contained residue levels below the limits of detection. During the Total Diet Study conducted by the FDA from November 1993 to June 1994, dieldrin was detected 58 times (concentrations and estimated daily intakes not specified) out of a total of 783 foods sampled (FDA 1995). Analysis of the FDA Total Diet Study market baskets 1991–1993 through 2003–2004 collected between September 1991 and October 2003 showed that dieldrin was detected above the limit of quantification in 215 out of 5,594 food samples tested (FDA 2006). Geyer et al. (1986) used historic levels of dieldrin in drinking water to estimate that intake of dieldrin from ingestion of drinking water may range from 0.1 to 0.29 ng/kg/day for a 70-kg adult. These levels are well

below the Acceptable Daily Intake (ADI) of 0.1 µg/kg/day recommended by the World Health Organization (WHO) for dieldrin (Geyer et al. 1986). Organohalogen residue levels were monitored from May 1990 to July 1991 in 806 composite milk samples collected from 63 cities within the United States (Trotter and Dickerson 1993). Dieldrin was detected in 172 milk samples ranging from trace amounts to 2 µg/L (detection limit=0.5 µg/L).

The widespread use of agricultural pesticides in California has raised concerns about exposures in nearby residential communities, particularly to children (Bradman et al. 1997). To determine the potential exposure to dieldrin, house dust and handwipe samples from children were collected and analyzed from 11 homes, 5 of which had at least 1 farmworker resident. Dieldrin was detected in house dust from one home of a farmworker at a concentration of 0.10 µg/g. Dust loading (the fraction dislodgeable by vacuum) of dieldrin was 0.45 $\mu g/m^2$. These data indicate that the highest chronic daily intake for children would be $1.0x10^{-3}$ µg/kg/day. Nine middle-income households located in the Raleigh-Durham-Chapel Hill area of North Carolina were evaluated for children's pesticide exposure (Lewis et al. 1994). Each house had at least one child in the 6-month to 5-year range. Aldrin was detected in five of the houses, while dieldrin was detected in all nine houses in various matrices (soil samples, dust samples, air samples, etc.). Since dieldrin was detected so often and at higher concentrations, it was studied more intently. The researchers found that the mean concentrations of dieldrin were 0.12 µg/g in house dust samples, <0.01 µg/g in child hand rinse samples, 0.01 $\mu g/m^3$ in air samples taken from the living room, and 0.03 µg/g in play area soil. The estimated exposures of children by respiration and ingestion of house dust ranged from not detectable to 0.13 µg/day and from not detectable to 0.04 µg/day, respectively. Based on these results, it appears that inhalation of indoor air from houses contaminated with aldrin and dieldrin is a major route of child exposure. Due to the greater persistence of dieldrin in the environment, children are expected to have greater exposure to dieldrin than aldrin.

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

in the atmosphere, especially closer to the ground since both compounds are heavier than air. This situation, however, is not expected to occur since aldrin and dieldrin are no longer produced or used commercially.

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

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

Several factors may influence the levels of dieldrin found in breast milk. For example, a highly significant ($p<0.001$) association was reported in women with low levels of dieldrin in breast milk and a history of breastfeeding several children (Ackerman 1980). In addition, women who consume foods

lower on the food chain (i.e., vegetarians) had dieldrin levels in their breast milk that were only 1–2% as high as the average levels in the United States (Hergenrather et al. 1981). Also, a mother's total body weight may influence the concentration of dieldrin found in breast milk. In a study of Israeli women conducted in 1975, those weighing over 72 kg had significantly lower levels of dieldrin in their breast milk (6 ppb) than those weighing under 63 kg (8.7 ppb) (Polishuk et al. 1977b). This difference was observed despite similar plasma levels of dieldrin in the two groups. A Swedish study found that dieldrin levels in mother's milk decreased from 0.076 µg/g (44 ppb) to 0.010 µg/g (10 ppb) between 1967 and 1984–1985; the use of dieldrin in Sweden was prohibited in 1970 (Norén and Meironyte 2000). A survey of 14 human milk donors whose homes in western Australia had been treated yearly with various pesticides for termite control found dieldrin residues in the milk ranging from 2 to 35 ng/g (2–35 ppb) (mean of 13 ng/g [13 ppb]) (Stacey and Tatum 1985). Milk levels of dieldrin peaked at 7–8 months after house treatment. Three of the 14 houses had recently been treated with aldrin, and the houses of the 11 other donors had been treated with aldrin previously. Dietary intake may have contributed partially to the milk levels since there was not a good correlation between dieldrin and the most recent use of aldrin.

A total of 412 breast milk samples from women in all provinces of Canada were analyzed for organochlorine residues in 1986 (Mes et al. 1993). Dieldrin was detected in 94% of all samples (detection limit=0.009 ng/g) at a mean concentration of 0.46 ng/g (maximum=4.42 ng/g). The study also examined dieldrin concentrations from earlier years. In both 1967 and 1970, the mean concentration of dieldrin in Canadian breast milk samples was 5 ng/g; in 1975, it was 2 ng/g, while in 1982, the concentration dropped to 1 ng/g. Breast milk samples were collected from 23 primiparous mothers and analyzed for their total amount of organochlorine residues from January to November 1992 (Quinsey et al. 1996). The results indicated that the mean daily intake of dieldrin from breast milk would be 0.32 µg/kg body weight/day with a range of 0.06–2.24 µg/kg body weight/day. The difference in organochlorine pesticide concentrations in human milk and infant formulas was examined in 1993 (Pico et al. 1995). Human milk samples were obtained from 15 women aged 29–40 years living along the Spanish Mediterranean coastal area. The infant formulas analyzed included 11 starting formulas, 11 follow-up formulas, 4 adapted infant formulas, and 17 specialized formulas. Aldrin and dieldrin were not detected in either human milk or formula samples (detection limit for aldrin=5.1 µg/L, detection limit for dieldrin=6.0 µg/L).

Dieldrin was detected in 38% of breast milk samples from 87 women living in Tunisia (Ennaceur et al. 2008). The mean concentration was 0.059 mg/kg fat weight with a range of not detected to 0.529 mg/kg fat weight. When the subjects were divided into groups based on the number of pregnancies, the dieldrin

levels were 0.062 (0.002–0.529), 0.045 (0.034–0.218), 0.043 (0.020–0.344), and 0.043 (0.009–0.295) mg/kg fat weight for 1, 2, 3, and ≥4 pregnancies, respectively; the levels were not significantly different from each other.

Studies show that transplacental transfer of aldrin and dieldrin occurs. A study of organochlorine compounds in mothers and fetuses during labor found that dieldrin concentrations in extracted lipids of fetal blood (1.22 ppm) and placenta (0.80 ppm) greatly exceeded those in maternal blood (0.53 ppm) and uterine muscle (0.54 ppm) (Polishuk et al. 1977a). In a study measuring contaminant levels in the cord blood of newborn aboriginals and non-aboriginals of the Northwest Territories and Southern Quebec, Canada, mean concentrations of aldrin were found to be 0.01 µg/L in all populations (Van Oostdam et al. 1999). A study of four Iraqi women with no known exposure to organochlorine pesticides found dieldrin levels in the placenta to range from 0.006 to 0.020 mg/kg total tissue weight and average dieldrin levels in their milk to range from 0.007 to 0.023 mg/kg whole milk. However, there was no correlation between the level of dieldrin in the placenta and the level in milk for each individual (Al-Omar et al. 1986).

An FDA Total Diet Study, conducted between 1982 and 1984, found that aldrin intake was <0.001 µg/kg/day for all age and sex groups and that toddlers (2 years old) had the highest intake levels for dieldrin at 0.016 µg/kg/day, followed by infants at 0.010 µg/kg/day (Gunderson 1988; Lombardo 1986). In 1980 and from 1982 to 1984, daily intakes of dieldrin decreased from 33 to 10 µg/kg/day for infants and from 46 to 16 ng/kg/day for toddlers (Gunderson 1988). The average daily dietary intake for adolescent males (14–16 years old) was 0.08 µg/kg/day in 1984. A Total Diet Study conducted by the FDA found dieldrin residues in only 6% of the food items analyzed from 1990 (FDA 1991). Daily intakes of 0.0014 and 0.0016 µg/kg body weight were estimated for infants 6–11 months old and for 14–16-year-old adolescents in 1990 (FDA 1991). During the Total Diet Study conducted by the FDA from November 1993 to June 1994, dieldrin was detected 58 times (concentrations and estimated daily intakes not specified) out of a total of 783 foods sampled (FDA 1995). Total Diet Study market baskets for food items collected between September 1991 and October 2003 showed that dieldrin was detected above its limit of quantification in 215 out of 5,594 food samples tested (FDA 2006). The Total Diet Study food list includes many foods eaten by infants and children.

Infants and toddlers were possibly exposed to higher levels of aldrin or dieldrin in the diet than were adults. Table 5-9 provides a list of calculated daily dietary intakes of dieldrin for adults, toddlers, and infants. Infant and toddler dietary intakes decreased significantly from 1978 to 1982. Current estimates

of daily dietary intakes are expected to be much lower than these previous values since aldrin and dieldrin have not been used in the United States for over 30 years.

**Table 5-9. Calculated Dietary Intakes (µg/kg of Body Weight/Day) of Dieldrin for Three Population Groups[a]**

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

Source: Gartrell et al. 1986a, 1986b

## 5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

No recent studies of the indoor air concentration of aldrin and dieldrin were located; however, high exposure rates were expected for large segments of the population residing in homes treated with aldrin or dieldrin for termite control (Section 5.5.1).

An assessment of the environmental contamination of a residential community built on a thick layer of harbor sludge in the Netherlands, found that the maximal combined daily intake of aldrin, dieldrin, isodrin, and telodrin by soil ingestion, inhalation of contaminated indoor air, and diet exceeded the ADI by a factor of 3 (Van Wijnen and Stijkel 1988). The concentrations of these compounds were highest in soil samples taken from the top 40 cm. The total indoor air concentrations of the compounds in the living rooms of homes built on contaminated soil were 10 times higher than outdoor air levels (9.9 ng/$m^3$ versus 0.8 ng/$m^3$); levels in the crawl spaces of these homes were 100 times higher (88.7 ng/$m^3$) than outdoor levels, although no explanation was given for these elevated levels. Dieldrin concentrations were also elevated in vegetables grown in the soil (up to 40 mg/kg fresh weight) and resulted in a recommendation against the consumption of home-grown vegetables. Dieldrin concentrations were not elevated in drinking water samples in any of the homes tested.

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

of surface runoff of contaminated soil. Only limited information in available regarding the extent of contamination at hazardous waste sites and the levels to which individuals may be exposed.

In a study examining potential pesticide exposure in children living on farms in California, dieldrin was detected in 10% of toddler's solid food samples (concentration of <1.5–4.8 ng/g); in leftover handled food samples (used to assess residues transferred to foods from children's hands or contaminated dusts in the home), dieldrin was detected in 6.7% of the samples at concentrations of 1.5–6.1 ng/g (Bradman et al. 2007).

# CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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.

## 6.1 INFORMATION ON HEALTH EFFECTS

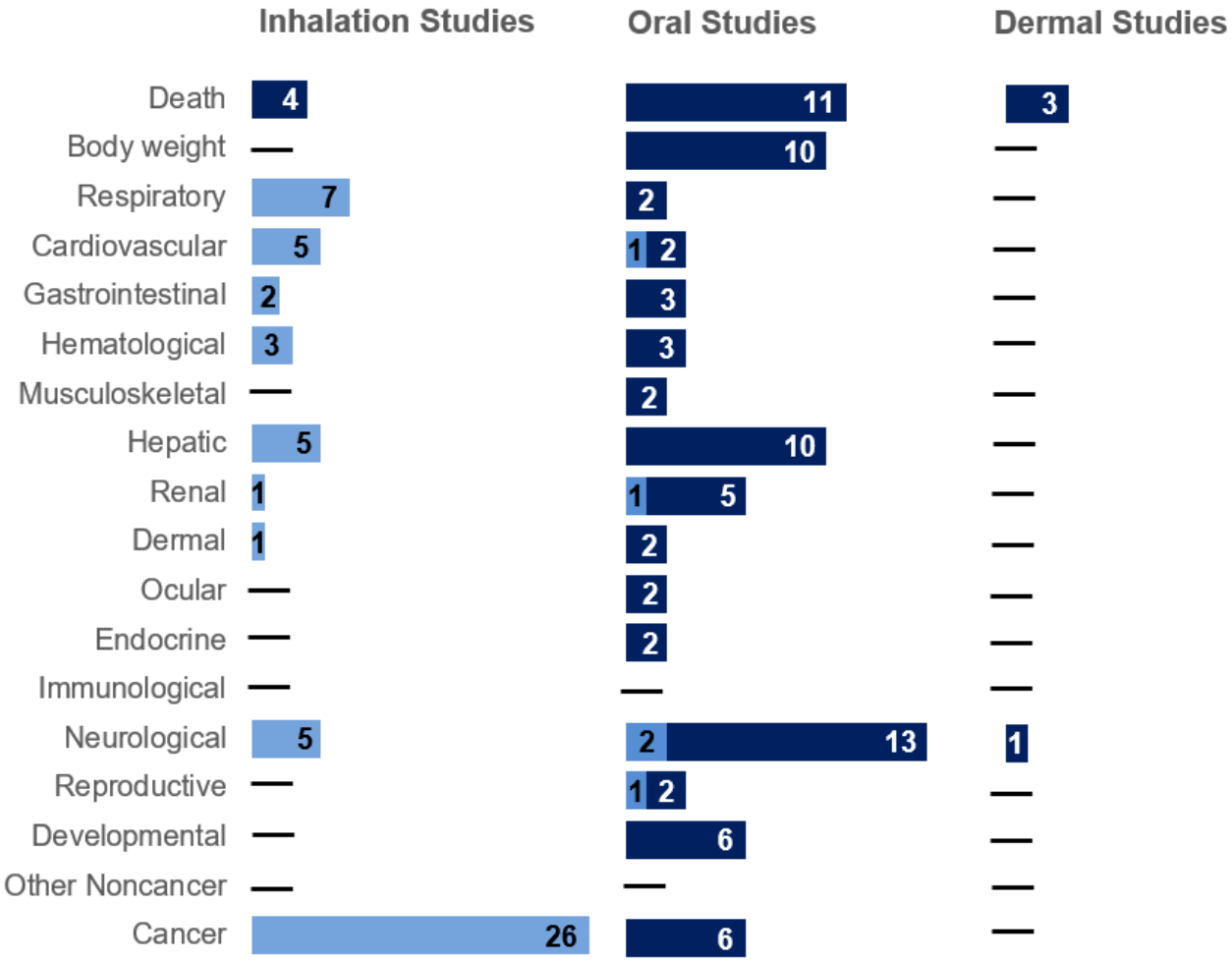
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to aldrin or dieldrin that are discussed in Chapter 2 are summarized in Figures 6-1 and 6-2, respectively. The purpose of these figures is to illustrate the information concerning the health effects of aldrin and dieldrin. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

## 6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 and/or Figure 6-2 should not 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.

## Figure 6-1. Summary of Existing Health Effects Studies on Aldrin By Route and Endpoint*

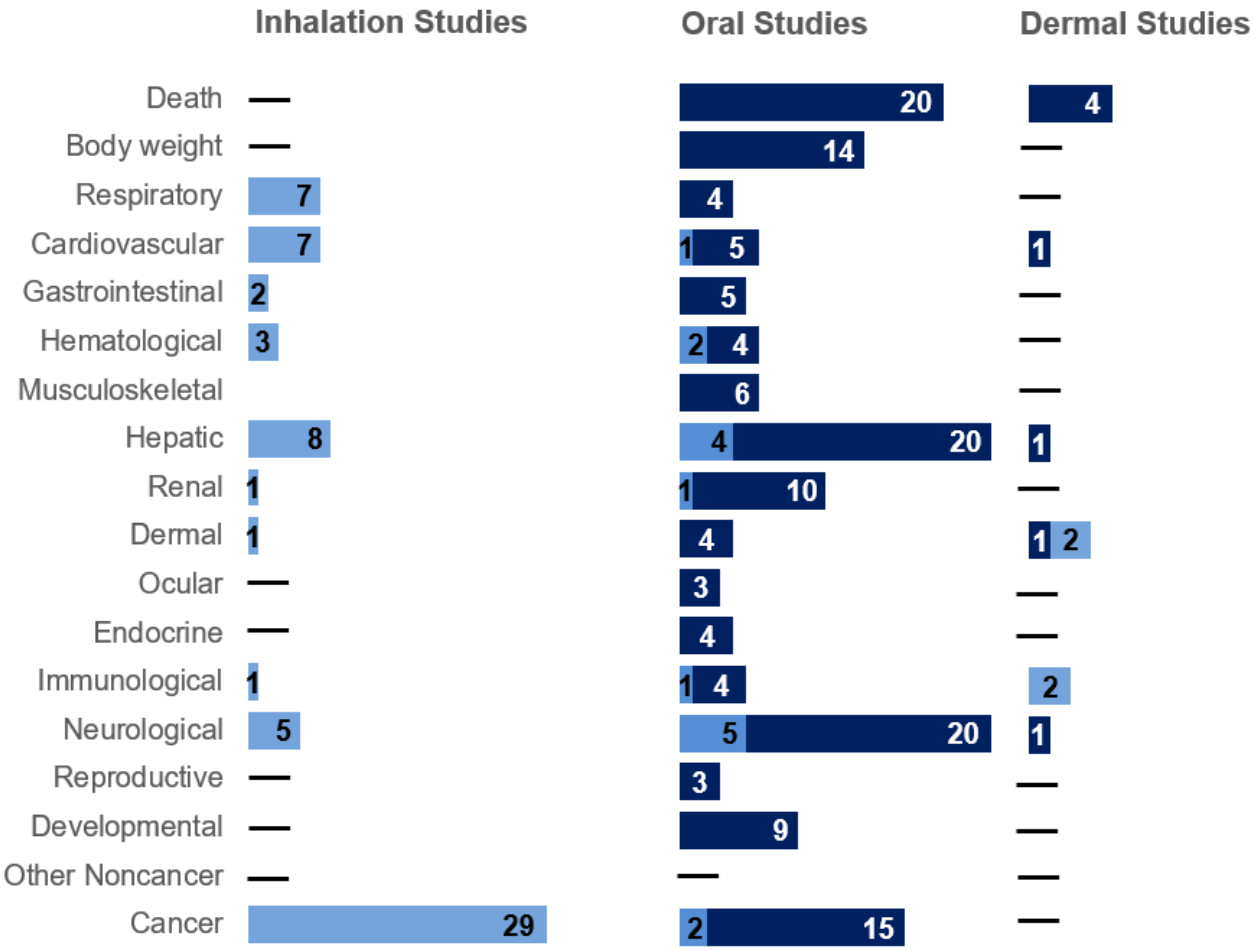
**Potential body weight, hepatic, and neurological effects were the most studied endpoints**
The majority of the studies examined oral exposure in animals (versus humans)




*Includes studies discussed in Chapter 2; the number of studies include those finding no effect; more than one endpoint may have been evaluated in a study. Occupational studies likely involved multiple exposure routes, but are presented as inhalation studies (the most likely major route of exposure).

## Figure 6-2. Summary of Existing Health Effects Studies on Dieldrin By Route and Endpoint*

**Potential hepatic and neurological effects were the most studied endpoints**
The majority of the studies examined oral exposure in **animals** (versus **humans**)




*Includes studies discussed in Chapter 2; the number of studies include those finding no effect; more than one endpoint may have been evaluated in a study. Occupational studies likely involved multiple exposure routes, but are presented as inhalation studies (the most likely major route of exposure).

**Acute-Duration MRLs.** No quantitative exposure-response human data are available regarding acute-duration inhalation, oral, or dermal exposure to aldrin or dieldrin.

Available acute-duration inhalation data from experimental animals are limited to findings of death and respiratory effects (mucous membrane irritation) among rats, mice, rabbits, and cats acutely exposed to aldrin vapor generated by sublimating aldrin at 200°C (Treon et al. 1957). Inhalation exposure to aldrin or dieldrin is not likely because both substances were banned for pesticidal usage between 1974 and 1987. Although lack of data for the inhalation exposure route represents a data gap, additional studies regarding the effects of inhaled aldrin or dieldrin do not appear necessary.

The database was considered adequate for derivation of a provisional acute-duration oral MRL for aldrin. Additional animal studies do not appear necessary.

An acute duration oral MRL was not derived for dieldrin; the provisional intermediate-duration oral MRL was considered protective of acute-duration oral exposure to dieldrin. Additional animal studies do not appear necessary.

**Intermediate-Duration MRLs.** No quantitative exposure-response human data are available regarding intermediate-duration inhalation, oral, or dermal exposure to aldrin or dieldrin.

No intermediate-duration inhalation data were available for experimental animals. Although lack of data for the inhalation exposure route represents a data gap, additional studies regarding the effects of inhaled aldrin or dieldrin do not appear necessary.

An intermediate-duration oral MRL was not derived for aldrin due to lack of appropriate effect levels. A 3-generation study identified the lowest LOAEL (a serious LOAEL of 0.26 mg/kg/day) for 3.2-fold increased mortality of F1a pups in the absence of an identified NOAEL (Treon et al. 1954a). It is not appropriate to derive an intermediate-duration oral MRL for aldrin because the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL in the absence of an identified NOAEL. Given that aldrin is no longer used and is readily converted to dieldrin in the environment, the general public is not likely to be exposed to aldrin by the oral route. It does not appear necessary to conduct additional intermediate-duration oral studies of aldrin in experimental animals.

The intermediate-duration database was considered adequate for derivation of a provisional intermediate-duration oral MRL. Additional animal studies do not appear necessary.

**Chronic-Duration MRLs.** No quantitative exposure-response human data are available regarding chronic-duration inhalation, oral, or dermal exposure to aldrin or dieldrin.

No chronic-duration inhalation data were available for experimental animals. Although lack of data for the inhalation exposure route represents a data gap, additional studies regarding the effects of inhaled aldrin or dieldrin do not appear necessary.

A provisional chronic-duration oral MRL has been derived for aldrin. Additional animal studies do not appear necessary.

A provisional chronic-duration oral has been derived for dieldrin. Additional animal studies do not appear necessary.

**Health Effects.**

***Hepatic.*** Available human data mainly concern evaluation of serum liver enzyme levels in workers exposed to aldrin and/or dieldrin during manufacture and/or use of these pesticides. Slightly increased serum ALT and AST levels were reported in one study of pesticide-exposed workers (Morgan and Lin 1978). However, there was no evidence of exposure-related hepatic effects in other studies (de Jong 1991; Hoogendam et al. 1965; Hunter et al. 1972; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987; Warnick and Carter 1972). No adverse hepatic effects were observed in a study of healthy male subjects who consumed dieldrin at up to 0.0003 mg/kg/day for 18 months in a study designed to evaluate dieldrin kinetics (Hunter and Robinson 1967). Liver dysfunction has been reported in cases of inadvertent or intentional ingestion of relatively large amounts of dieldrin (Black 1974; Garrettson and Curley 1969). All pesticide uses for aldrin and dieldrin were banned in the United States since prior to 1988. In the environment, aldrin is readily converted to dieldrin and dieldrin has persisted and entered some food products. Populations with detectable blood dieldrin levels should be monitored, although it is not likely that the general population would be exposed to dieldrin at levels high enough to cause adverse hepatic effects.

The hepatotoxicity of orally-administered aldrin or dieldrin has been reported in a number of experimental animal species (Ahmed et al. 1986a; Fitzhugh et al. 1964; Goel et al. 1988; Harr et al. 1970; Kitselman 1953; Kohli et al. 1977; Shakoori et al. 1982; Thorpe and Walker 1973; Treon et al. 1951a, 1955; Walker et al. 1969; Wright et al. 1972, 1978). Additional animal studies do not appear necessary.

***Renal.*** The only available report of aldrin- or dieldrin-related renal effects was clinical chemistry evidence of renal damage in a case of intentional ingestion of an estimated 25.6 mg aldrin/kg (Spiotta 1951). Populations with detectable blood dieldrin levels should be monitored, although it is not likely that the general population would be exposed to dieldrin at levels high enough to cause adverse renal effects.

Adverse renal effects have been reported in studies of rats and dogs administered aldrin or dieldrin orally (Ahmed et al. 1986a; Bandyopadhyay et al. 1982b; Deichmann et al. 1967; Fitzhugh et al. 1964; Harr et al. 1970; Kitselman 1953; Reuber 1980; Treon et al. 1955). There were no signs of adverse renal effects in chronic-duration oral studies of rats, mice, or dogs administered aldrin or dieldrin orally at doses in the range of 0.05–4.2 mg/kg/day (NCI 1978a; Treon et al. 1951a; Walker et al. 1969). Additional animal studies do not appear necessary.

***Neurological.*** Excitation of the central nervous system is the principal effect reported in occupational studies of workers employed in either the application or manufacture of aldrin or dieldrin (Avar and Czegledi-Janko 1970; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Kazantzis et al. 1964; Patel and Rao 1958). Other central nervous system symptoms reported by workers involved in the manufacture or application of aldrin and/or dieldrin included headaches, dizziness, hyperirritability, general malaise, nausea and vomiting, anorexia, muscle twitching, and myoclonic jerking (Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). Inadvertent or intentional ingestion of relatively large amounts of aldrin or dieldrin have resulted in a variety of central nervous system symptoms (Black 1074; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951). Populations with detectable blood dieldrin levels should be monitored, although it is not likely that the general population would be exposed to dieldrin at levels high enough to cause adverse neurological effects.

Neurological endpoints have been assessed in multiple experimental animal species following acute- intermediate- or chronic-duration oral exposure of experimental animals to aldrin or

dieldrin (Burt 1975; et al. 1989; Carlson and Rosellini 1987; Kitselman 1953; NCI 1978a, 1978b; Smith et al. 1976; Treon et al. 1951b; Wagner and Greene 1978; Walker et al. 1969; Woolley et al. 1985). Additional animals studies do not appear necessary.

***Reproductive.*** Limited information was located regarding aldrin or dieldrin exposure-related reproductive effects in humans. Populations with detectable blood dieldrin levels should be monitored, although it is not likely that the general population would be exposed to dieldrin at levels high enough to cause adverse reproductive effects.

Several animal studies were designed to evaluate potential aldrin or dieldrin exposure-related reproductive effects (Dean et al. 1975; Deichmann et al. 1971; Epstein et al. 1972; Good and Ware 1969; Harr et al. 1970; Keplinger et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975). Decreased fertility was reported in some studies (Keplinger et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975). Delayed estrus, reduced libido, lack of mammary function and development, and an increased number of stillbirths were reported in dogs orally administered aldrin for 14 months prior to mating (Deichmann et al. 1971). Studies examining the mechanisms of action would be useful in evaluating the human relevance of the reproductive effects observed in laboratory animals.

***Developmental.*** No studies were located regarding aldrin or dieldrin treatment-related developmental effects in humans. Developmental effects such as increased postnatal mortality and external and skeletal malformations/anomalies have been observed in animal studies. Populations with detectable blood dieldrin levels should be monitored, although it is not likely that the general population would be exposed to dieldrin at levels high enough to cause adverse developmental effects.

**Epidemiology and Human Dosimetry Studies.** A variety of human studies are available. Several investigators reported cases of accidental or intentional poisonings (Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958; Spiotta 1951). Two cohorts of workers in the manufacture of aldrin and/or dieldrin have been followed (Amoateng-Adjepong et al. 1995; Brown 1992; de Jong 1991; Ditraglia et al. 1981; Swaen et al. 2002; van Amelsvoort et al. 2009). Other studies evaluated health effects in workers involved with application of aldrin and/or dieldrin (Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). A

number of studies evaluated possible associations between self-reported use of aldrin and/or dieldrin and selected health outcomes (Alavanja et al. 2014; Bonner et al. 2017; Brown et al. 1990; Cantor et al. 1992; Clary and Ritz 2003; Dennis et al. 2010; De Roos et al. 2003; Engel et al. 2005; Flower et al. 2004; Koutros et al. 2013a, 2013b; Lee et al. 2004a, 2004b; Louis et al. 2017; McDuffie et al. 2001; Pahwa et al. 2011; Schroeder et al. 2001).

Exposures in the case reports are virtually all oral, whereas exposures in the epidemiological studies are mainly inhalation and dermal, with very slight potential for accidental oral intake. Additional follow-up of cohorts from previously conducted epidemiological studies would be the best approach for obtaining additional human data. Locating new populations for future epidemiological studies is likely to be difficult because aldrin and dieldrin have not been manufactured in the United States since 1974 and the all uses were banned by 1987.

**Biomarkers of Exposure and Effect.** Exposure to aldrin and dieldrin is currently measured almost exclusively by determining the level of dieldrin in the blood (Jager 1970). This measure is specific for both aldrin and dieldrin. However, because aldrin is rapidly converted to dieldrin in the body (Wong and Terriere 1965), it is impossible to determine which of the two substances caused the blood levels of dieldrin to rise. Because dieldrin has a long half-life of elimination in humans (Hunter and Robinson 1967; Hunter et al. 1969; Jager 1970), measurement of dieldrin levels in the blood does not give any information about whether an acute-, intermediate-, or chronic-term exposure has occurred, whether such exposures have occurred recently, or whether a substantial period of time has elapsed since exposure occurred. The sensitivity of this biomarker of exposure appears to be sufficient to measure even background levels in the population; thus, no new biomarkers of exposure appear to be needed at this time.

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

fundamental mechanism by which aldrin and dieldrin cause central nervous system excitation develops, tests may be developed to specifically monitor underlying neurological changes caused by aldrin and dieldrin. No tests specific for aldrin- or dieldrin-induced toxic effects on the liver or kidney exist; however, standard liver and kidney function tests should be able to identify the hepatic or renal toxicity that is produced. Microsomal enzyme induction may be measured by determining parameters such as urinary levels of D-glucaric acid and the ratio of urinary 6-β-hydroxycortisol to 17-hydroxy-corticosteroids. However, these tests are not specific for aldrin or dieldrin. Immune suppression of the type produced by aldrin or dieldrin may be detected by challenge with a T-lymphocyte-dependent antigen; however, this test also is not specific for aldrin or dieldrin.

**Absorption, Distribution, Metabolism, and Excretion.** Human and animal data demonstrate that aldrin and dieldrin are absorbed after inhalation, oral, or dermal exposure (Feldmann and Maibach 1974; Graham et al. 1987; Hayes 1974; Heath and Vandekar 1964; Hunter and Robinson 1967; Hunter et al. 1969; Mehendale and El-Bassiouni 1975; Stacey and Tatum 1985). Quantitative data on the absorption of aldrin and dieldrin in humans and animals following exposure via all routes are limited. Animal studies indicate that aldrin and dieldrin are absorbed rather quickly and that the amount absorbed is proportional to the dose applied for the oral and dermal routes (Graham et al. 1987; Heath and Vandekar 1964; Iatropoulos et al. 1975). Because of the limited number of absorption studies for all three routes in general, it would be helpful to have additional quantitative data in animals that might serve as a basis for estimates of absorption in humans.

Data exist regarding distribution after oral administration of aldrin or dieldrin (Adeshina and Todd 1990; Ahmad et al. 1988; Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974; Holt et al. 1986; Hunter and Robinson 1967, 1968; Hunter et al. 1969; Iatropoulos et al. 1975). These studies indicate that dieldrin is distributed in the blood to adipose tissue, brain, and liver tissues, and is then redistributed primarily to fat. Concentrations of dieldrin have been shown to increase in a dose-related manner in blood and adipose tissues of humans and eventually reach a steady state (Hunter and Robinson 1967; Hunter et al. 1969). Kinetic studies in rats and dogs support these findings and provide further information on steady-state kinetics following repeated dosing (Baron and Walton 1971; Davison 1973; Ludwig et al. 1964; Walker et al. 1969). Because data are sufficient regarding distribution following oral exposure to aldrin or dieldrin, no more studies are needed.

**Comparative Toxicokinetics.** Numerous studies using a variety of animal species indicate that the kinetics of aldrin and dieldrin differ across species (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968;

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

**Children's Susceptibility.** Limited reports of adverse effects in aldrin- or dieldrin-exposed children (Garrettson and Curley 1969; Gupta 1975) indicate similar signs and symptoms to those in adults. Limited animal data indicate that young animals may respond to aldrin or dieldrin differently than adult animals (Buck and Van Note 1968; Lu et al. 1965), but there is no conclusive evidence to suggest that young animals are more susceptible than older ones. Further studies that evaluate a number of different endpoints in young as well as older organisms would provide valuable information.

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

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

There are no biomarkers of exposure or effect that have been validated in children. There are no data on interactions of aldrin or dieldrin with other chemicals in children, and extremely limited data in adults which are inadequate to determine whether the same effects will be observed in children. There are no

pediatric-specific methods to reduce peak absorption of aldrin or dieldrin following exposure, or to reduce body burden, or to interfere with mechanisms of action for aldrin or dieldrin.

**Physical and Chemical Properties.** The physical and chemical properties of aldrin and dieldrin are sufficiently well defined to allow assessments of the environmental fate of the compounds to be made (Budavari 2001; Clayton and Clayton 1994; Guerin and Kennedy 1992; Hayes 1982; NLM 2020a, 2020b; NIOSH 1997; Verschueren 2001). No additional information is needed.

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

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

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

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. TRI, which contains this information for 2018, became available in 2019. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Incineration and activated-carbon adsorption have >99% efficiencies as methods for disposing of aldrin or dieldrin (EPA 1981). However, no information is available regarding the amounts of aldrin or dieldrin disposed of by each method. Additional information on current disposal patterns would prove useful.

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

Dieldrin sorbs to soils and sediments (Briggs 1981; Cliath and Spencer 1971). The compound also partitions to biota and slowly volatilizes from soils to the atmosphere (Nash 1983). Dieldrin is transported in the particulate phase in surface water runoff (Caro and Taylor 1971; Eye 1968; Hardee et al. 1964) and in the atmosphere (Baldwin et al. 1977). In deep subsurface soils, dieldrin is sorbed to particulates and does not leach to groundwater (Dobbs et al. 1989). The compound is persistent in environmental media, being resistant to biodegradation and abiotic transformation (Gannon and Bigger 1958; Jagnow and Haider 1972). Based on dieldrin's vapor pressure, it will exist in both the vapor and particulate phase in the atmosphere (Grayson and Fosbraey 1982). Vapor-phase dieldrin is expected to react with hydroxyl radicals, while particulate phase dieldrin will be removed from the atmosphere by wet and dry deposition. Information concerning the relative percentage of dieldrin that will exist in the particulate and vapor-phase in the environment would prove useful in predicting its atmospheric fate.

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

**Food Chain Bioaccumulation.** Aldrin and dieldrin are bioconcentrated by plants, animals, and aquatic organisms and biomagnified in aquatic and terrestrial food chains (Bhatnagar et al. 1988; Cole et al. 1976; Connell 1989; Donaldson et al. 1999; Metcalf et al. 1973; Sanborn and Yu 1973; Shannon 1977;

Travis and Arms 1988). Food chain bioaccumulation appears to be a more important fate process for dieldrin, which is very persistent in nature, than for aldrin, which is rapidly converted to dieldrin (EPA 1980; Metcalf et al. 1973). No additional information is necessary.

**Exposure Levels in Environmental Media.** Aldrin and dieldrin have historically been detected in ambient air (Hoff et al. 1996), surface water (EPA 1980; Stubin et al. 1996), drinking water (EPA 1980, 2001), soils (ATSDR 2007; Eisenreich et al. 1989; Kutz et al. 1976), sediments (Bergersen 1987; Staples et al. 1985), and foods (EPA 1985; FDA 2006; Hundley et al. 1988). Studies suggest that the concentrations of both aldrin and dieldrin in environmental matrices are decreasing (CalEPA 1995; MacIntosh et al. 1999; Miller et al. 1992). Aldrin and dieldrin have been identified at several of the hazardous waste sites that have been proposed for inclusion on the EPA NPL (ATSDR 2019). Estimates of dietary intake, which is believed to be the most important source of exposure for most members of the general population, are also available (FDA 1991, 1995). More recent monitoring data would be useful in more accurately predicting human exposure.

**Exposure Levels in Humans.** The presence of dieldrin in human blood and adipose tissue has been used as an indicator of exposure to aldrin and dieldrin (Brock et al. 1998; CDC 2018). The compounds have also been widely detected in human breast milk (Davies and Mes 1987; Quinsey et al. 1996; Savage et al. 1981; Takei et al. 1983). Additional information on the concentration of these compounds in the biological tissue and fluids of populations living in the vicinity of NPL sites would be helpful in assessing the extent to which these populations have been exposed to these compounds.

**Exposures of Children.** With the detection of dieldrin in drinking water (EPA 2001; Kolpin et al. 1997), studies that detail the exposure of infants fed formula prepared from tap water would prove helpful. More data are needed to properly assess aldrin and dieldrin exposure to children who live, play, or attend school near NPL sites and farmlands that have been treated with these pesticides. Information regarding the number of houses in the United States that have been treated with aldrin and dieldrin formulations in the past would be useful in determining the number of children that would be potentially exposed today. The stability of these compounds, especially dieldrin, suggests the possibility that they may be brought home by farm workers who work on farmlands previously treated with these compounds. More exposure studies that monitor aldrin and dieldrin exposure to children of farm workers would be useful for evaluating potential exposure.

## 6.3 ONGOING STUDIES

No ongoing research pertaining to aldrin was identified. The following ongoing research pertaining to dieldrin (Table 6-1) was identified in the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (RePORTER 2019).

**Table 6-1. Ongoing Studies on Dieldrin**

| Investigator | Affiliation | Research description | Sponsor |
|---|---|---|---|
| Alison Bernstein | Neurosciences, Schools of Medicine, Michigan State University | Dieldrin exposure and synucleinopathy | NIEHS |
| Alison Bernstein | Neurosciences, Schools of Medicine, Michigan State University | Epigenetic effects of adult and developmental exposure to Parkinsonian toxicants | NIEHS |
| Jonathan A. Doorn | Pharmacology, Schools of Pharmacy, University of Iowa | Pesticide-mediated generation of a toxic neurotransmitter metabolite | NIEHS |
| Anumantha Gounder Kanthasamy | Veterinary Sciences, Schools of Veterinary Medicine, Iowa State University | Novel mechanisms of pesticide-induced neurotoxicity | NIEHS |
| Mark N. Wu | Neurology, School of Medicine, Johns Hopkins University | Molecular and cellular mechanisms underlying the circadian timing of sleep (dieldrin included in the list of project terms) | NINDS |

NIEHS = National Institute of Environmental Health Sciences; NINDS = National Institute of Neurological Disorders and Stroke

Source: RePORTER 2019

# CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding aldrin or dieldrin in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for aldrin and dieldrin.

**Table 7-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin**

| Agency | Description | Information | Reference |
|---|---|---|---|
| | **Air** | | |
| EPA | RfC | Not evaluated | IRIS 1987, 1988 |
| WHO | Air quality guidelines | Not listed | WHO 2010 |
| | **Water & Food** | | |
| EPA | Drinking water standards and health advisories | | EPA 2018a |
| | 1-Day health advisory (10-kg child) | | |
| | Aldrin | 0.0003 mg/L | |
| | Dieldrin | 0.0005 mg/L | |
| | 10-Day health advisory (10-kg child) | | |
| | Aldrin | 0.0003 mg/L | |
| | Dieldrin | 0.0005 mg/L | |
| | DWEL | | |
| | Aldrin | 0.001 mg/L | |
| | Dieldrin | 0.002 mg/L | |
| | Lifetime health advisory | No data | |
| | $10^{-4}$ Cancer risk | | |
| | Aldrin | 0.0002 mg/L | |
| | Dieldrin | 0.0002 mg/L | |
| | National primary drinking water regulations | No data | EPA 2009 |

## Table 7-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin

| Agency | Description | Information | Reference |
|---|---|---|---|
| | RfD | | |
| | Aldrin | $3x10^{-5}$ mg/kg/day[a] | IRIS 1987 |
| | Dieldrin | $5x10^{-5}$ mg/kg/day[b] | IRIS 1988 |
| | Subchronic provisional RfD | | |
| | Aldrin | $4x10^{-5}$ mg/kg/day[c] | EPA 2005b |
| WHO | Drinking water quality guidelines | | WHO 2017 |
| | Guideline value, aldrin and dieldrin combined | 0.00003 mg/L | |
| | Provisional tolerable daily intake, aldrin and dieldrin combined | 0.1 µg/kg body weight | |
| FDA | Substances Added to Food | Not listed[d] | FDA 2019 |
| | **Cancer** | | |
| HHS | Carcinogenicity classification | No data | NTP 2016a |
| EPA | Carcinogenicity classification | | IRIS 1987, 1988 |
| | Aldrin and dieldrin | B2[e] | |
| IARC | Carcinogenicity classification | | IARC 2019 |
| | Dieldrin, and aldrin metabolized to dieldrin | Group 2A[f] | |
| | **Occupational** | | |
| OSHA | PEL (8-hour TWA) for general industry, shipyards and construction | | OSHA 2019a, 2019b, 2019c |
| | Aldrin and dieldrin | 0.25 $mg/m^3$ [g] | |
| NIOSH | REL (up to 10-hour TWA) | | NIOSH 2019a, 2019b |
| | Aldrin and dieldrin | 0.25 $mg/m^3$ [g, h] | |
| | IDLH | | |
| | Aldrin | 25 $mg/m^3$ [h] | NIOSH 2019a |
| | Dieldrin | 50 $mg/m^3$ [h] | NIOSH 2019b |
| | **Emergency Criteria** | | |
| EPA | AEGLs-air | No data | EPA 2018b |
| DOE | PACs-air | | DOE 2018a |
| | Aldrin | | |
| | PAC-1[i] | 0.91 $mg/m^3$ | |
| | PAC-2[i] | 10 $mg/m^3$ | |
| | PAC-3[i] | 100 $mg/m^3$ | |

## Table 7-1. Regulations and Guidelines Applicable to Aldrin/Dieldrin

| Agency | Description | Information | Reference |
|---|---|---|---|
| | Dieldrin | | |
| | PAC-1[i] | 0.3 mg/m$^3$ | |
| | PAC-2[i] | 6.8 mg/m$^3$ | |
| | PAC-3[i] | 450 mg/m$^3$ | |

[a]Aldrin RfD is based on a LOAEL of 2.5x10$^{-2}$ mg/kg/day for liver toxicity in a rat chronic feeding study.
[b]Dieldrin RfD is based on a NOAEL of 0.1 ppm for liver lesions in a rat 2-year feeding study.
[c]Aldrin subchronic p-RfD is based on a LOAEL of 0.043 mg/kg/day for renal lesions in a dog chronic feeding study.
[d]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[e]B2: probable human carcinogen.
[f]Group 2A: probably carcinogenic to humans.
[g]Skin designation.
[h]Potential occupational carcinogen.
[i]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LOAEL = lowest-observed-adverse-effect level; NIOSH = National Institute for Occupational Safety and Health; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

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# APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
***CAS Numbers:*** 309-00-2
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** The acute-duration inhalation data were not considered adequate for derivation of an acute-duration inhalation MRL for aldrin.

***Rationale for Not Deriving an MRL:*** No exposure concentration-response data are available for humans. Available data from experimental animals are restricted to findings of death and respiratory effects (mucous membrane irritation) among rats, mice, rabbits, and cats acutely exposed to aldrin vapor generated by sublimating aldrin at 200°C (Treon et al. 1957). The Treon et al. (1957) study was not considered an adequate basis for an MRL for aldrin because the study examined a limited number of endpoints and lacked exposure concentration-response data. Given the limitations of the only available acute inhalation study, the database was not considered adequate for derivation of an acute-duration inhalation MRL for aldrin.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
***CAS Numbers:*** 309-00-2
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** The intermediate-duration inhalation data were not considered adequate for derivation of an intermediate-duration inhalation MRL for aldrin.

***Rationale for Not Deriving an MRL:*** No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
***CAS Numbers:*** 309-00-2
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** The chronic-duration inhalation data were not considered adequate for derivation of a chronic-duration inhalation MRL for aldrin.

***Rationale for Not Deriving an MRL:*** No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
***CAS Numbers:*** 309-00-2
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Oral
***Duration:*** Acute
***MRL:*** 0.002 mg/kg/day (provisional)
***Critical Effect:*** Neurodevelopmental toxicity in offspring
***Reference:*** Al-Hachim 1971
***Point of Departure:*** 2 mg/kg/day (LOAEL)
***Uncertainty Factor:*** 1,000
***LSE Graph Key:*** 7
***Species:*** Mouse

***MRL Summary:*** A provisional acute-duration oral MRL of 0.002 mg/kg/day has been derived for aldrin. The MRL is based on a LOAEL of 2 mg/kg/day for neurodevelopmental effects (increased electroconvulsive shock threshold) in offspring of maternal mice administered aldrin by gavage during the third trimester of pregnancy (Al-Hachim 1971). The study did not identify a NOAEL. The LOAEL of 2 mg/kg/day was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

***Selection of the Critical Effect:*** No adequate exposure-response data were available for humans. Table A-1 summarizes results from candidate acute-duration oral studies in experimental animals.

**Table A-1. Summary of Selected NOAELs and LOAELs from Candidate Acute-Duration Studies in Experimental Animals Orally Exposed to Aldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Neurological effects | | | | | |
| Charles Foster rat | Once (GO) | ND | 2 | Increased locomotor activity; peak effect at 2 hours postdosing | Jamaluddin and Poddar 2001a |
| Charles Foster rat | Up to 30 days 1 time/day (GO) | ND | 2 | Increased locomotor activity; peak effect at day 12 | Jamaluddin and Poddar 2001b |
| Charles Foster rat | Up to 30 days 1 time/day (GO) | ND | 2 | Increased locomotor activity; peak effect at day 12 | Jamaluddin and Poddar 2003 |
| Sprague-Dawley rat | 3 days 1 time/day (GO) | ND | 10 | Tremors, convulsions | Mehrotra et al. 1989 |

**Table A-1. Summary of Selected NOAELs and LOAELs from Candidate Acute-Duration Studies in Experimental Animals Orally Exposed to Aldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Developmental effects | | | | | |
| ICR/Ha Swiss mouse | Third trimester of pregnancy (GO) | ND | 2[a] | Depressed pup body weight, increased seizure threshold | Al-Hachim 1971 |

[a]Used to derive a provisional acute-duration oral MRL for aldrin.

(GO) = gavage in oil vehicle; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Four studies identified the lowest LOAEL (2 mg/kg for single dose or 2 mg/kg/day for repeated dosing) and were considered potential candidate principal studies for deriving an intermediate-duration oral MRL for aldrin. Jamaluddin and Poddar (2001a, 2001b) observed increased locomotor activity in rats dosed at 2 mg aldrin/kg; the effect peaked at 2 hours following single gavage dosing of aldrin. In two other gavage studies of rats administered aldrin at 2 mg/kg/day for up to 30 days, increased locomotor activity was observed as well; the peak effect occurred at treatment day 12 (Jamaluddin and Poddar 2001b, 2003). Al-Hachim (1971) observed depressed pup body weight and increased electroshock seizure threshold in pups from maternal mice gavaged with aldrin during the third trimester of pregnancy.

***Selection of the Principal Study:*** Jamaluddin and Poddar presented mean locomotor activity ± standard error of the mean numerically (Jamaluddin and Poddar 2001a) or graphically (Jamaluddin and Poddar 2001b, 2003) using 6–8 separate observations per group. Benchmark dose (BMD) analysis is precluded because the actual numbers of animals contributing to the reported levels of locomotor activity were not available. The studies of Al-Hachim (1971) and Jamaluddin and Poddar (2001a, 2001b, 2003) identified a common LOAEL (2 mg/kg/day). The study of Al-Hachim (1971) was selected as a representative principal study for deriving an acute-duration oral MRL for aldrin. A NOAEL/LOAEL approach to deriving an acute-duration oral MRL for aldrin based on results from either Jamaluddin and Poddar (2001a, 2001b, 2003) or Al-Hachim (1971) would result in the same MRL value.

***Summary of the Principal Study:***

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

Groups of pregnant ICR/Ha Swiss mice (7/group) were treated with aldrin (grade and purity not specified) by gavage (in corn oil vehicle) at 0, 2, or 4 mg/kg/day during the 3rd trimester of pregnancy. The study report stated that the dams were treated daily for 7 consecutive days, but also stated that each pregnant animal received 5-7 doses. Offspring were weaned at 30 days of age and culled to 10 mice/exposure group. Beginning at 30 days of age, each pup was weighed daily for 7 days and tested daily for conditioned avoidance responses (number of responses out of 16 trials of daily training for 7 days). At 38 days of age, each pup was tested for electroshock seizure threshold.

Mean body weights of the low- and high-dose offspring were 18 and 8% less, respectively, than controls. Aldrin had no effect on the acquisition of a conditioned avoidance response but did significantly raise the electroshock seizure threshold in low- and high-dose groups (38 and 34% higher, respectively, than controls). Table A-2 presents summary data for body weight and electroshock seizure threshold.

**Table A-2. Body Weight and Electroshock Seizure Threshold Data for Mouse Pups Following Maternal Gavage Administration of Aldrin During the Third Trimester of Pregnancy**

| Test | Dose (mg/kg/day) | | | p-value (%) |
|---|---|---|---|---|
| | 0 | 2 | 4 | |
| Body weight (g) | 19.1±0.58[a] | 15.7±0.47 | 17.6±0.7 | 0.5 |
| Electroshock seizure threshold (volts) | 79.9±5.4 | 109.1±10.88 | 106.0±4.0 | 0.5 |

[a]Mean ± SEM for 10 pups/group.

Source: Al-Hachim 1971

***Selection of the Point of Departure for the MRL:*** Initially, a BMD approach to deriving an acute-duration oral MRL for aldrin was considered. The body weight data are not amenable to BMD analysis because, although the 2 mg/kg/day dose level resulted in 18% depressed mean pup body weight, the higher dose level (4 mg/kg/day) only resulted in 8% depressed mean pup body weight. Although the electroshock seizure threshold was higher in the 2 mg/kg/day dose group compared to the 4 mg/kg/day dose group (indicating lack of adequate fit of BMD models to the dataset), all continuous models in EPA's Benchmark Dose Software (BMDS; version 3.1.2) were applied to the dataset using a benchmark response (BMR) of 1 standard deviation from the control mean in the absence of information to suggest an alternative BMR. None of the models provided adequate fit to the data. Therefore, a NOAEL/LOAEL approach was implemented to derive an acute-duration oral MRL for aldrin. The LOAEL of 2 mg/kg/day for increased seizure threshold was selected as the representative critical effect level for deriving an acute-duration oral MRL for aldrin.

***Uncertainty Factor:*** The LOAEL of 2 mg/kg/day was divided by an uncertainty factor of 1,000:

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

Provisional MRL = LOAEL ÷ uncertainty factor
2 mg/kg/day ÷ 1,000 = 0.002 mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Administration of aldrin by gavage caused an increased incidence of webbed feet in mice following gavage administration of aldrin to pregnant dams on GD 9 at 25 mg/kg; increased fetal mortality was noted in hamsters following gavage administration of aldrin to pregnant hamsters on GD 7, 8, or 9 at 50 mg/kg/day (Ottolenghi et al. 1974). These results support the developmental toxicity of aldrin. The neurodevelopmental effect is consistent with evidence showing that the central nervous system is a target of aldrin toxicity in adult animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
***CAS Numbers:*** 309-00-2
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** The intermediate-duration oral data were not considered adequate for derivation of an intermediate-duration oral MRL for aldrin.

***Rationale for Not Deriving an MRL:*** No dose-response data are available for humans. Table A-3 summarizes results from candidate intermediate-duration oral studies in experimental animals.

**Table A-3. Summary of Selected NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Experimental Animals Orally Exposed to Aldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Body weight effects | | | | | |
| Dog | Up to 37 days<br>5 days/week<br>1 x/day<br>(C) | ND | 1.5 | Depressed body weight gain at lethal dose level | Treon et al. 1951b |
| Gastrointestinal effects | | | | | |
| Dog | Up to 9 months<br>(F) | ND | 0.89 | Vomiting | Treon et al. 1951b |
| Hepatic effects | | | | | |
| Carworth rat | 6 months<br>(F) | 0.53 | 2.6 | Increased liver weight; liver lesions | Treon et al. 1951a |
| Dog | Up to 9 months<br>(F) | ND | 1.25 | Degenerative liver lesions | Treon et al. 1951b |
| Neurological effects | | | | | |
| Dog | Up to 9 months<br>(F) | ND | 0.89 | Hypersensitivity, tremors, twitching, convulsions, neuronal degeneration in brain | Treon et al. 1951b |
| Dog | Up to 37 days<br>5 days/week<br>1 x/day<br>(C) | ND | 1.5 | Lethargy, intoxication | Treon et al. 1951b |
| Reproductive effects | | | | | |
| Carworth rat | 3 generations<br>(F) | 0.26 | 1.3 | 40% decreased number of litters from first parental mating | Treon et al. 1954a |
| Swiss mouse | 6 generations | ND | 0.56 | Decreased number of pregnant dams | Keplinger et al. 1970 |

**Table A-3. Summary of Selected NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Experimental Animals Orally Exposed to Aldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Developmental effects | | | | | |
| Carworth rat | 3 generations (F) | | 0.26 | 3.2-fold increased mortality of F1a pups | Treon et al. 1954a |
| Swiss mouse | 6 generations | ND | 0.56 | Decreased pup survival to PPD 4 | Keplinger et al. 1970 |

(C) = capsule; (F) = food; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PPD = postpartum day

An intermediate-duration oral MRL was not derived for aldrin due to lack of appropriate effect levels. In intermediate-duration oral studies, the lowest NOAEL of 0.26 mg/kg/day was associated with a serious LOAEL of 1.3 mg/kg/day for 40% decreased number of litters from first parental mating in a 3-generation reproductive/developmental toxicity study (Treon et al. 1954a). However, the 3-generation study also identified a serious LOAEL of 0.26 mg/kg/day (the lowest dose level tested) for 3.2-fold increased mortality of F1a pups. Keplinger et al. (1970) identified a serious LOAEL of 0.56 mg/kg/day for decreased number of pregnant mice and decreased survival of pups to postpartum day 4 in a 6-generation reproductive/developmental toxicity study. An intermediate-duration oral MRL for aldrin was not derived because the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL, and it is ATSDR practice to not base MRLs on serious LOAELs.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
***CAS Numbers:*** 309-00-2
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Oral
***Duration:*** Chronic
***MRL:*** 0.00004 mg/kg/day (provisional)
***Critical Effect:*** Increased liver weight and histological alterations in liver
***Reference:*** Fitzhugh et al. 1964
***Point of Departure:*** 0.037 mg/kg/day (LOAEL)
***Uncertainty Factor:*** 1,000
***LSE Graph Key:*** 23
***Species:*** Rat

***MRL Summary:*** A provisional chronic-duration oral MRL of 0.00004 mg/kg/day has been derived for aldrin. The MRL is based on a LOAEL of 0.037 mg/kg/day for increased liver weight and hepatic histological alterations (enlarged centrilobular hepatocytes with cytoplasmic oxyphilia, and peripheral migration of basophilic granules) in rats receiving aldrin from the food for 2 years (Fitzhugh et al. 1964). The study did not identify a NOAEL. The LOAEL of 0.037 mg/kg/day was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

***Selection of the Critical Effect:*** No adequate exposure-response data were available for humans. Table A-4 summarizes results from candidate chronic-duration oral studies in experimental animals that identified the lowest NOAELs and/or LOAELs.

**Table A-4. Summary of Selected NOAELs and LOAELs from Candidate Chronic-Duration Studies in Experimental Animals Orally Exposed to Aldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Body weight effects | | | | | |
| Dog | Up to 25 months<br>6 days/week<br>1 time/day<br>(C) | 0.2 | 0.5 | Body weight loss | Fitzhugh et al. 1964 |
| Hematological effects | | | | | |
| Dog | Up to 25 months<br>6 days/week<br>1 time/day<br>(C) | 0.5 | 1 | Reduced bone marrow cellularity | Fitzhugh et al. 1964 |

**Table A-4. Summary of Selected NOAELs and LOAELs from Candidate Chronic-Duration Studies in Experimental Animals Orally Exposed to Aldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Hepatic effects | | | | | |
| Osborne-Mendel rat | 2 years (F) | ND | 0.037[a] | 23–31% increased liver weight; liver histopathology (enlarged centrilobular hepatocytes with cytoplasmic oxyphilia, and peripheral migration of basophilic granules) | Fitzhugh et al. 1964 |
| Dog | Up to 25 months 6 days/week 1 time/day (C) | 0.5 | 1 | Fatty degenerative hepatic changes | Fitzhugh et al. 1964 |
| Osborne-Mendel rat | 31 months (F) | 1.4 | 2.1 | Increased liver weight in males | Deichmann et al. 1970 |
| Renal effects | | | | | |
| Dog | Up to 25 months 6 days/week 1 time/day (C) | 0.5 | 1 | Fatty degenerative renal changes | Fitzhugh et al. 1964 |
| Neurological effects | | | | | |
| B6C3F1 mouse | 80 weeks (F) | ND | 0.5 | Hyperexcitability | NCI 1978a |
| Osborne-Mendel rat | 74 weeks (F) | ND | 2.1 | Hyperexcitability | NCI 1978a |

[a]Used to derive a provisional chronic-duration oral MRL for aldrin.

(C) = capsule; (F) = food; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

The 2-year oral rat study of Fitzhugh et al. (1964) identified the lowest LOAEL (0.037 mg/kg/day for increased liver weight and histopathology). Dose-related increasing incidence and severity of histopathologic liver lesions were reported at doses ≥0.15 mg/kg/day. The lesions were described as "enlarged centrilobular hepatic cells, with cytoplasmic oxyphilia somewhat increased, and peripheral migration of the basophilic granules." NOAELs and/or LOAELs identified in the other studies summarized in Table A-4 range from 0.2 to 2.1 mg/kg/day. Therefore, hepatotoxicity was selected as the critical effect for deriving a chronic-duration oral MRL for aldrin.

***Selection of the Principal Study:*** As shown in Table A-4, the 2-year oral rat study of Fitzhugh et al. (1964) identified the lowest LOAEL (0.037 mg/kg/day for increased liver weight and histopathologic liver lesions) among candidate principal studies. Therefore, the 2-year oral rat study of Fitzhugh et al. (1964) was selected as the principal study.

***Summary of the Principal Study:***

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

Groups of weanling Osborne-Mendel rats (12/sex/group) were administered aldrin (recrystallized and ≥99% purity; in 1% corn oil vehicle) in the diet at 0, 0.5, 2, 10, 50, 100, or 150 ppm for up to 2 years (Fitzhugh et al. 1964). Rats were monitored for survival, clinical signs, and body weight. Rats that survived to terminal sacrifice at week 104 were processed for gross examination and organ weights (heart, liver, spleen, kidney, testis). Rats that died prior to terminal sacrifice were subjected to gross examination only. Histopathologic examinations were performed on most rats. Only liver, kidney, and testes (and tumors and gross abnormalities) were examined for most rats; a selected few rats were subjected to more comprehensive histopathologic examination.

Estimated aldrin doses in the 0.5, 2, 10, 50, 100, and 150 ppm groups of Osborne-Mendel rats were 0.037, 0.15, 0.73, 3.65, 7.3, and 11 mg/kg/day, respectively, for combined sexes (calculations performed using EPA [1988] chronic reference values for food intake [0.033 kg] and body weight [0.452 kg]). Significantly decreased survival was noted at the two highest dose levels (7.3 and 11 mg/kg/day). There were no significant treatment-related effects on body weight. Male and female rats exhibited significantly increased relative liver weight at all aldrin exposure concentrations except 2 ppm (generally dose-related and ranged from 23 to >50% higher than that of controls), as shown in Table A-5. Histopathologic liver lesions (described as enlarged centrilobular hepatocytes with cytoplasmic oxyphilia somewhat increased, and peripheral migration of basophilic granules) were noted with increasing severity in a dose-related manner, as shown in Table A-6. Occasional increased relative spleen and kidney weights were observed among aldrin-treated female rats, but these changes did not exhibit dose-response characteristics. The study authors noted "exaggeration" of the usual type of kidney lesion, but did not provide quantitative data, thus precluding assignment of NOAEL or LOAEL values.

**Table A-5. Mean Relative Liver Weight in Osborne-Mendel Rats Administered Aldrin in the Food for up to 2 Years**

| Concentration in food (ppm) | Dose[a] (mg/kg/day) | Number of animals | | Liver weight (g/kg body weight) | |
|---|---|---|---|---|---|
| | | Males | Females | Males | Females |
| 0 | 0 | 10 | 7 | 22.94 | 24.55 |
| 0.5 | 0.037 | 9 | 10 | 28.28[b] | 32.27[c] |
| 2 | 0.15 | 9 | 10 | 23.59 | 30.17[b] |
| 10 | 0.73 | 11 | 8 | 26.12[b] | 33.20[b] |
| 50 | 3.65 | 9 | 4 | 28.86[c] | 38.14[b] |
| 100 | 7.3 | 8 | 0 | 34.61[c] | – |
| 150 | 11.0 | 3 | 2 | 34.49[d] | 59.49[c] |

[a]Doses estimated using EPA (1988b) chronic reference values for food intake (0.033 kg) and body weight (0.452 kg) for the Osborne-Mendel rat (combined sexes).
[b]Significantly different from controls at 95% confidence limit.
[c]Significantly different from controls at 99% confidence limit.
[d]Statistical significance not stated in study report, presumably due to the low number of high-dose rats evaluated.

Source: Reprinted from Fitzhugh et al. (1964) with permission from Elsevier.

**Table A-6. Incidences of Nonneoplastic Liver Lesions in Osborne-Mendel Rats Administered Aldrin in the Food for up to 2 Years**

| Concentration in food (ppm) | Dose[a] (mg/kg/day) | Severity of liver lesion | | | | | |
|---|---|---|---|---|---|---|---|
| | | None | Trace | Very slight | Slight | Slight-to-moderate and moderate | Greater than moderate |
| 0 | 0 | 16 | 1 | 0 | 0 | 0 | 0 |
| 0.5 | 0.037 | 15 | 4 | 0 | 0 | 0 | 0 |
| 2 | 0.15 | 10 | 8 | 0 | 1 | 0 | 0 |
| 10 | 0.73 | 11 | 3 | 7 | 1 | 0 | 0 |
| 50 | 3.65 | 0 | 0 | 0 | 6 | 10 | 2 |
| 100 | 7.3 | 0 | 0 | 0 | 0 | 5 | 6 |
| 150 | 11.0 | 0 | 0 | 0 | 0 | 2 | 7 |

[a]Doses estimated using EPA (1988b) chronic reference values for food intake (0.033 kg) and body weight (0.452 kg) for the Osborne-Mendel rat (combined sexes)

Source: Reprinted from Fitzhugh et al. (1964) with permission from Elsevier.

***Selection of the Point of Departure for the MRL:*** A BMD approach was initially considered to derive a chronic-duration oral MRL for aldrin. However, BMD analysis is precluded by the lack of reported variance in the liver weight data and uncertainty in the degree of severity associated with an adverse effect for the reported liver lesion data. Therefore, a NOAEL/LOAEL approach was taken to derive a

chronic-duration oral MRL for aldrin based on the LOAEL of 0.037 mg/kg/day for increased mean relative liver weight. For the Fitzhugh et al. (1964) study, the dietary concentrations were converted to estimated doses using EPA (1988b) chronic reference values for food intake (0.033 kg) and body weight (0.452 kg) for the rat:

Dose (mg/kg/day) = (concentration of aldrin in food x food intake) ÷ body weight
(0.5 mg/kg food [0.5 ppm] x 0.033 kg food/day) ÷ 0.452 kg = 0.037 mg/kg/day

***Uncertainty Factor:*** The LOAEL of 0.037 mg/kg/day was divided by an uncertainty factor of 1,000:

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

Provisional MRL = LOAEL ÷ uncertainty factor
0.037 mg/kg/day ÷ 1,000 = 0.00004 mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Two other chronic-duration oral toxicity studies identified the liver as a target of aldrin toxicity. Increased liver weight was observed in male rats receiving aldrin from the food for 31 months at an estimated dose of 2.1 mg/kg/day; the NOAEL was 1.4 mg/kg/day (Deichmann et al. 1970). Fatty degenerative hepatic changes were reported in dogs administered aldrin in capsule for up to 25 months at 1 mg/kg/day; the NOAEL was 0.5 mg/kg/day (Fitzhugh et al. 1964).

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
***CAS Numbers:*** 60-57-1
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** The acute-duration inhalation data were not considered adequate for derivation of an acute-duration inhalation MRL for dieldrin.

***Rationale for Not Deriving an MRL:*** No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
***CAS Numbers:*** 60-57-1
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** The intermediate-duration inhalation data were not considered adequate for derivation of an intermediate-duration inhalation MRL for dieldrin.

***Rationale for Not Deriving an MRL:*** No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
***CAS Numbers:*** 60-57-1
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** The chronic-duration inhalation data were not considered adequate for derivation of a chronic-duration inhalation MRL for dieldrin.

***Rationale for Not Deriving an MRL:*** No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
***CAS Numbers:*** 60-57-1
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** The acute-duration oral data were not considered adequate for derivation of an acute-duration oral MRL for dieldrin.

***Rationale for Not Deriving an MRL:*** No adequate dose-response data are available for humans. Severe signs of neurotoxicity were reported in humans inadvertently or intentionally ingesting relatively large doses of dieldrin (Black 1974; Garrettson and Curley 1969). Table A-7 summarizes results from potential candidate acute-duration oral studies in experimental animals that identified the lowest NOAELs and/or LOAELs.

**Table A-7. Summary of Selected NOAELs and LOAELs from Potential Candidate Acute-Duration Studies in Experimental Animals Orally Exposed to Dieldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Body weight effects | | | | | |
| CD rat | GDs 7–16 1 time/day (GO) | 3 | 6 | 32% depressed maternal body weight gain | Chernoff et al. 1975 |
| CD-1 mouse | GDs 7–16 1 time/day (GO) | 3 | 6 | Essentially no maternal body weight gain | Chernoff et al. 1975 |
| Hepatic effects | | | | | |
| CD-1 mouse | GDs 7–16 1 time/day (GO) | 1.5 | 3 | 25% increased mean maternal liver weight | Chernoff et al. 1975 |
| Immunological effects | | | | | |
| BALB/c mouse | 2 weeks (F) | ND | 0.09 | Impaired antigen processing by macrophages | Loose et al. 1981 |
| Neurological effects | | | | | |
| Sprague-Dawley rat | Once (GO) | ND | 0.5 | Impaired escape behavior | Carlson and Rosellini 1987 |
| Wistar rat | Once (GO) | ND | 2.5 | Disrupted operant behavior | Burt 1975 |

**Table A-7. Summary of Selected NOAELs and LOAELs from Potential Candidate Acute-Duration Studies in Experimental Animals Orally Exposed to Dieldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Developmental effects | | | | | |
| CD-1 mouse | GDs 7–16 1 time/day (GO) | 1.5 | 3 | Supernumerary ribs | Chernoff et al. 1975 |

(F) = food; GD = gestation days; (GO) = gavage in oil vehicle; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Depressed maternal body weight gain or no gain were observed in studies of rats and mice administered dieldrin by gavage at 6 mg/kg/day during GDs 7–16; the NOAEL was 3 mg/kg/day for each species (Chernoff et al. 1975). Other effects in the mice treated at 3 mg/kg/day included increased maternal liver weight and increased incidences of supernumerary ribs in fetuses. Disruption of operant behavior at 2.5 mg dieldrin/kg/day (Burt 1975), and impaired responses in an inescapable foot shock stress paradigm at 0.5 mg dieldrin/kg/day (Carlson and Rosellini 1987) were reported in rats administered dieldrin once by gavage. Loose et al. (1981) reported impaired antigen processing by macrophages from mice that had been administered dieldrin in the food for 2 weeks at 1 ppm (estimated dose of 0.09 mg/kg/day based on EPA [1988b] reference values for food intake and body weight); the study did not identify a NOAEL. However, no additional data were located to provide support to an adverse effect level as low as 0.09 mg/kg/day for immunotoxicity and the immune system has not been identified as a sensitive target of dieldrin toxicity in humans. Thus, the lowest LOAEL was 0.5 mg/kg/day for neurological effects identified in the Carlson and Rosellini (1987) study; the study did not identify a NOAEL. The database was not considered suitable for derivation of an acute-duration oral MRL because the lowest LOAEL was considered a serious LOAEL, and it is ATSDR practice to not use a serious LOAEL as a point of departure for an MRL.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
***CAS Numbers:*** 60-57-1
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Oral
***Duration:*** Intermediate
***MRL:*** 0.0001 mg/kg/day (provisional)
***Critical Effect:*** Neurotoxicity
***Reference:*** Smith et al. 1976
***Point of Departure:*** 0.01 mg/kg/day (NOAEL)
***Uncertainty Factor:*** 100
***LSE Graph Key:*** 31
***Species:*** Monkey

***MRL Summary:*** A provisional intermediate-duration oral MRL of 0.0001 mg/kg/day has been derived for dieldrin. The MRL is based on a NOAEL of 0.01 mg/kg/day and a LOAEL of 0.1 mg/kg/day for impaired task learning in monkeys administered dieldrin orally for 55 days (Smith et al. 1976). The NOAEL of 0.01 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect:*** No adequate exposure-response data were available for humans. Table A-8 summarizes results from candidate intermediate-duration oral studies in experimental animals that identified the lowest NOAELs and/or LOAELs.

**Table A-8. Summary of Selected NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Experimental Animals Orally Exposed to Dieldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Hepatic effects | | | | | |
| Dog | Up to 9 months (F) | ND | 0.73 | Degenerative liver lesions | Treon et al. 1951b |
| Immunological effects | | | | | |
| BALB/c mouse | 3, 6, or 18 weeks (F) | ND | 0.18 | Increased lethality following tumor implantation | Loose et al. 1981 |
| Neurological effects | | | | | |
| Squirrel monkey | 55 days 1 time/day (F) | 0.01[a] | 0.1 | Learning deficit | Smith et al. 1976 |
| Wistar rat | 60–120 days (F) | 0.046 | 0.46 | Disrupted operant behavior | Burt 1975 |

**Table A-8. Summary of Selected NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Experimental Animals Orally Exposed to Dieldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Dog | Up to 9 months (F) | ND | 0.73 | Hypersensitivity, tremors, twitching convulsions prior to death; neuronal degeneration in brain | Treon et al. 1951b |
| Reproductive effects | | | | | |
| Swiss-Vancouver mouse | 4 weeks premating through PPD 28 (F) | 1 | 2 | 18% of bred females did not become pregnant | Virgo and Bellward 1975 |
| Carworth rat | 3 generations (F) | ND | 0.26 | 34% decreased number of litters from first parental mating | Treon et al. 1954a |
| Developmental effects | | | | | |
| Swiss-Vancouver Mouse | 4 weeks premating through PPD 28 (F) | 0.5 | 1 | Increased pup mortality | Virgo and Bellward 1975 |
| Carworth rat | 3 generations (F) | 0.26 | 1.3 | 1.9-fold increased 5-day mortality of F3a pups | Treon et al. 1954a |

[a]Used to derive a provisional intermediate-duration oral MRL for dieldrin.

(F) = food; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PPD = postpartum day

Degenerative liver lesions and neurological effects (hypersensitivity, tremors, twitching convulsions prior to death; neuronal degeneration in brain) were reported in dogs receiving dieldrin from the food for up to 9 months at an estimated dose of 0.73 mg/kg/day, the lowest exposure level tested (Treon et al. 1951b). Decreased fertility and increased pup mortality were observed in a study in which mouse dams received dieldrin from the diet at estimated doses of 2 and 1 mg/kg/day, respectively for 4 weeks prior to mating, during gestation, and up to postpartum day 28; respective NOAELs were 1 and 0.5 mg/kg/day (Virgo and Bellward 1975). In a 3-generation study, decreased numbers of litters were reported at an estimated dieldrin dose of 0.26 mg/kg/day, the lowest exposure level tested; increased pup mortality occurred at 1.3 mg/kg/day with a NOAEL of 0.26 mg/kg/day (Treon et al. 1954a). Increased mortality following tumor implantation (an indication of a compromised immune system) was reported in mice receiving dieldrin from the diet for up to 18 weeks at an estimated dose of 0.18 mg/kg/day (the lowest exposure level tested) (Loose et al. 1981). Among candidate critical effects for deriving an intermediate-duration oral MRL for dieldrin, the lowest LOAEL was 0.1 mg/kg/day for learning deficit in monkeys administered dieldrin in marshmallows for 55 days; the NOAEL was 0.01 mg/kg/day (Smith et al. 1976). Therefore, dieldrin treatment-related neurotoxicity was selected as the critical effect.

***Selection of the Principal Study:*** The intermediate-duration oral study in monkeys (Smith et al. 1976) was selected as the principal study for deriving an intermediate-duration oral MRL for dieldrin because it identified the lowest LOAEL (0.1 mg/kg/day) among candidate principal studies.

***Summary of the Principal Study:***

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

Dieldrin (technical grade, purity not specified) dissolved in ethanol was injected into marshmallows fed to squirrel monkeys at doses of 0, 0.01, or 0.1 mg dieldrin/kg/day for 55 days. Monkeys were evaluated for performance in a visual nonspatial successive discrimination reversal task. After 55 days, the group receiving the low dose was switched to the high dose, and the group receiving the high dose was switched to the control diet for 54 days to test effects in task maintenance. The high-dose group (0.1 mg/kg/day) exhibited impaired learning of the task (acquisition). There was no evidence of impaired learning in the low-dose group (0.01 mg/kg/day).

***Selection of the Point of Departure for the MRL:*** A BMD approach to deriving an intermediate-duration oral MRL for dieldrin based on neurological effects in the monkey study of Smith et al. (1976) was initially considered. However, although mean number of reversals (the index for evaluating the visual nonspatial successive discrimination reversal task) were reported for each monkey (two controls, two low-dose, and three high-dose animals), the small numbers of animals preclude quantitative evaluation of the data. Therefore, a NOAEL/LOAEL approach was implemented. The NOAEL of 0.01 mg/kg/day served as the point of departure for deriving an intermediate-duration oral MRL for dieldrin

***Calculations***

***Intermittent Exposure:*** Not applicable.

***Uncertainty Factor:*** The NOAEL of 0.01 mg/kg/day was divided by an uncertainty factor of 100:

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

Provisional MRL = NOAEL ÷ uncertainty factor
0.01 mg/kg/day ÷ 100 = 0.0001 mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Neurological effects (hypersensitivity, tremors, twitching convulsions, and neuronal degeneration in brain tissue) were observed in dogs administered dieldrin orally for up to 9 months at 0.73–1.85 mg/kg/day, the lowest dose range tested (Treon et al. 1951b). Dieldrin is a known neurotoxicant to humans and animals.

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
***CAS Numbers:*** 60-57-1
***Date:*** July 2021
***Profile Status:*** Draft for Public Comment
***Route:*** Oral
***Duration:*** Chronic
***MRL:*** 0.00005 mg/kg/day (provisional)
***Critical Effect:*** Hepatotoxicity
***Reference:*** Walker et al. 1969
***Point of Departure:*** 0.005 mg/kg/day (NOAEL)
***Uncertainty Factor:*** 100
***LSE Graph Key:*** 52
***Species:*** Rat

***MRL Summary:*** A provisional chronic-duration oral MRL of 0.00005 mg/kg/day has been derived for dieldrin. The MRL is based on a NOAEL of 0.005 mg/kg/day and LOAEL of 0.05 mg/kg/day for increased liver weight in female rats administered dieldrin orally for 2 years (Walker et al. 1969). The NOAEL of 0.005 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect:*** No adequate exposure-response data were available for humans. Table A-9 summarizes results from candidate chronic-duration oral studies in experimental animals that identified the lowest NOAELs and/or LOAELs.

**Table A-9. Summary of Selected NOAELs and LOAELs from Candidate Chronic-Duration Studies in Experimental Animals Orally Exposed to Dieldrin**

| Species | Exposure scenario | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Hepatic effects | | | | | |
| Osborne-Mendel rat | 2 years (F) | ND | 0.037 | 34% increased relative liver weight in females; dose-related increasing incidence and severity of liver lesions | Fitzhugh et al. 1964 |
| Carworth Farm E rat | 2 years (F) | 0.005[a] F | 0.05 F | 13% increased relative liver weight in females; parenchymal cell changes at 0.5 mg/kg/day | Walker et al. 1969 |
| Neurological effects | | | | | |
| Carworth Farm E rat | 2 years (F) | 0.05 | 0.5 | Tremors, occasional convulsions | Walker et al. 1969 |
| B6C3F1 mouse | 80 weeks (F) | ND | 0.43 | Hyperexcitability, tremors | NCI 1978a |

[a]Used to derive a provisional chronic-duration oral MRL for dieldrin.

(F) = food; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

The liver represents the most sensitive target of dieldrin toxicity. Therefore, liver toxicity was selected as the critical effect for deriving a chronic-duration oral MRL for dieldrin.

***Selection of the Principal Study:*** LOAELs for increased relative liver weight were relatively similar in two chronic-duration rat studies (0.037 mg/kg/day in the study of Fitzhugh et al. 1964 and 0.05 mg/kg/day in the study of Walker et al. 1969). The study of Walker et al. (1969) was selected as the principal study for deriving a chronic-duration oral MRL for dieldrin because the study also identified a NOAEL of 0.005 mg/kg/day.

***Summary of the Principal Study:***

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

Groups of Carworth Farms E (CFE) rats (25/sex/group) were administered dieldrin (>99% purity) in the diet at 0.1, 1.0, or 10 ppm for 2 years. The study authors stated that intake of 1 ppm at 7 months of age was equivalent to 0.0475 mg dieldrin/kg/day in males and 0.0582 mg dieldrin/kg/day in females. On this basis, estimated average doses to the 0.1, 1.0, and 10 ppm groups (sexes combined) were 0.005, 0.05, and 0.5 mg/kg/day, respectively. Controls consisted of 45 rats/sex. Additional groups of 15 rats/sex were similarly treated and 5/sex/group were sacrificed after 26, 52, and 78 weeks on treatment. Rats were monitored for survival, clinical signs, body weight, and food intake. At death or sacrifice, blood samples were collected for hematology and clinical chemistry. Major organ weights were recorded, and gross and histopathologic examinations were performed.

Effects in the rats included increased absolute and relative liver weights in females at 0.05 and 0.5 mg/kg/day. Liver parenchymal cell changes, "considered to be characteristic of exposure to organochlorine insecticide" but not otherwise specified, were increased in high-dose females; total incidences during 2 years of exposure were 0/23, 0/23, 0/23, and 6/23 females at dose levels of 0, 0.005, 0.05, and 0.5 mg/kg/day, respectively. In males, these liver parenchymal changes were only observed in one high-dose animal. Two of the 0.5 mg/kg/day females and one control female also showed focal hyperplasia of the hepatic parenchymal cells, forming microscopic nodules. Other types of hepatic lesions (focal parenchymal necrosis, proliferated ductules, focal fibrosis and/or cystic hyperplasia of intrahepatic bile ducts) were seen in a few rats of both sexes but were dispersed among the test and control groups (5/23, 0/23, 2/23, and 5/23 in females and 4/43, 0/23, 1/23, and 2/23 in males at 0, 0.1, 1, and 10 ppm, respectively) and not considered treatment-related. There were no indications of dieldrin-related changes in serum AP or ALT. Irritability, tremors, and occasional convulsions (characteristic signs of dieldrin neurotoxicity) occurred at 0.5 mg/kg/day. These behavioral changes usually occurred during handling, did not progress after 3 months of exposure, and did not affect well-being. Males receiving 0.05 mg/kg/day (but not 0.5 mg/kg/day) exhibited decreases in hemoglobin, packed cell volume, and red blood cells. Thus, the biological significance is unknown.

Relative liver weight data from the 2-year rat study of Walker et al. (1969) are summarized in Table A-10.

**Table A-10. Mean Relative Liver Weight in Osborne-Mendel Rats Administered Dieldrin in the Food for up to 2 Years**

| Concentration in food (ppm) | Dose (mg/kg/day) | Number of animals | | Mean relative liver weight (g/100 g body weight) | |
|---|---|---|---|---|---|
| | | Males | Females | Males | Females |
| 0 | 0 | 18 | 18 | 3.66±0.126[a] | 4.08±0.147 |
| 0.1 | 0.005 | 15 | 13 | 3.72±0.138 | 4.33±0.173 |
| 1.0 | 0.05 | 14 | 10 | 3.70±0.143 | 4.61±0.198[b] |
| 10 | 0.5 | 10 | 9 | 3.77±0.119 | 4.84±0.208[c] |

[a]The study report did not define the measure of variance to the mean values.
[b]Significantly different from controls at 95% confidence limit.
[c]Significantly different from controls at 99% confidence limit.

Source: Walker et al. 1969

The critical effect was increased liver weight in the female rats (Walker et al. 1969); the study identified a NOAEL of 0.005 mg/kg/day and a LOAEL of 0.05 mg/kg/day for increased relative liver weight.

***Selection of the Point of Departure for the MRL:*** A BMD approach to deriving a chronic-duration oral MRL for dieldrin was initially considered. However, although the study report included mean relative liver weight for each group of rats, the measure of variance associated with the mean was not defined. The absence of a defined measure of variance (e.g., standard deviation, standard error of the mean, etc.) precludes a BMD approach. Therefore, a NOAEL/LOAEL approach was implemented to derive a chronic-duration oral MRL for dieldrin; the NOAEL of 0.005 mg/kg/day served as the point of departure.

***Uncertainty Factor:*** The NOAEL of 0.005 mg/kg/day was divided by an uncertainty factor of 100:

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

Provisional MRL = NOAEL ÷ uncertainty factor
0.005 mg/kg/day ÷ 100 = 0.00005 mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Fitzhugh et al. (1964) observed increased liver weight in rats receiving dieldrin from the food for 2 years at an estimated LOAEL of 0.037 mg/kg/day, the lowest dose level tested. Acute-and intermediate-duration oral studies in experimental animals have also reported dieldrin treatment-related liver effects at relatively low oral doses (Chernoff et al. 1975; Treon et al. 1951b).

***Agency Contacts (Chemical Managers):*** Carolyn Harper

# APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ALDRIN/DIELDRIN

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to aldrin or dieldrin.

## B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for aldrin/dieldrin. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of aldrin/dieldrin have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of aldrin/dieldrin are presented in Table B-1.

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

| | |
|---|---|
| | Other noncancer effects |
| | Cancer |
| Toxicokinetics | |
| | Absorption |
| | Distribution |
| | Metabolism |
| | Excretion |
| | PBPK models |
| Biomarkers | |
| | Biomarkers of exposure |
| | Biomarkers of effect |
| Interactions with other chemicals | |
| Potential for human exposure | |
| | Releases to the environment |
| | Air |
| | Water |
| | Soil |
| | Environmental fate |
| | Transport and partitioning |
| | Transformation and degradation |
| | Environmental monitoring |
| | Air |
| | Water |
| | Sediment and soil |
| | Other media |
| | Biomonitoring |
| | General populations |
| | Occupation populations |

### B.1.1 Literature Search

The current literature search was intended to update the 2002 toxicological profile for aldrin/dieldrin; thus, the literature search was restricted to studies published between October 2000 and April 2019. The following main databases were searched in April 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for aldrin/dieldrin. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to aldrin/dieldrin were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

**Table B-2. Database Query Strings**

| Database search date | Query string |
|---|---|
| **PubMed** | |
| 04/2019 | (("Aldrin"[mh] OR 309-00-2[rn] OR "Dieldrin"[mh] OR 60-57-1[rn]) AND (2000/01/01 : 3000[dp] OR 2000/10/01 : 3000[edat] OR 2000/10/01 : 3000[crdt] OR 2000/10/01 : 3000[mhda])) OR ((((("(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | hexahydro-, endo, exo-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "Aldocit"[tw] OR "Aldrex"[tw] OR "Aldrin"[tw] OR "Aldrite"[tw] OR "Aldron"[tw] OR "Aldrosol"[tw] OR "Algran"[tw] OR "Altox"[tw] OR "Andrex"[tw] OR "Complex Hydrocarbon Adrex 30"[tw] OR "Compound 118"[tw] OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene"[tw] OR "HHDN"[tw] OR "Isodrin"[tw] OR "Kortofin"[tw] OR "NA 2761"[tw] OR "NA 2762"[tw] OR "Octalene"[tw] OR "SD 2794"[tw] OR "Seedrin"[tw] OR "Soilgrin"[tw] OR "Tatuzinho"[tw] OR "Tipula"[tw] OR ("dimethanonaphthalene"[tw] AND "hexachloro"[tw] AND "hexahydro"[tw])) OR ("(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-Dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-, endo, exo-"[tw] OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6.2.1.1 3,6.0 2,7)dodec-9-ene"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "Alvit"[tw] OR "Compound 497"[tw] OR "Dieldren"[tw] OR "Dieldrex"[tw] OR "Dieldrin"[tw] OR "Dieldrite"[tw] OR "Dielmoth"[tw] OR "Dildrin"[tw] OR "Dorytox"[tw] OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "endo, exo-3,4,5,6,9,9-Hexachloro- |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | 1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethenapth(2,3-b)oxirene"[tw] OR "HEOD"[tw] OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene"[tw] OR "Illoxol"[tw] OR "Insecticide No. 497"[tw] OR "Insectlack"[tw] OR "Kombi-Albertan"[tw] OR "Moth Snub D"[tw] OR "NA 2761"[tw] OR "Octalox"[tw] OR "Panoram D-31"[tw] OR "Red Shield"[tw] OR "SD 3417"[tw] OR "Shelltox"[tw] OR "Termitox"[tw] OR ("dimethanonaphth"[tw] AND "oxirene"[tw] AND "hexachloro"[tw] AND "octahydro"[tw]) OR ("dimethanonaphthalene"[tw] AND "hexachloro"[tw] AND "octahydro"[tw] AND "epoxy"[tw])) AND (2000/01/01 : 3000[dp] OR 2000/10/01 : 3000[edat] OR 2000/10/01 : 3000[crdt] OR 2000/10/01 : 3000[mhda])) NOT medline[sb]) |
| | (((("(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-, endo, exo-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "Aldocit"[tw] OR "Aldrex"[tw] OR "Aldrin"[tw] OR "Aldrite"[tw] OR "Aldron"[tw] OR "Aldrosol"[tw] OR "Algran"[tw] OR "Altox"[tw] OR "Andrex"[tw] OR "Complex Hydrocarbon Adrex 30"[tw] OR "Compound 118"[tw] OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene"[tw] OR |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | "HHDN"[tw] OR "Isodrin"[tw] OR "Kortofin"[tw] OR "NA 2761"[tw] OR "NA 2762"[tw] OR "Octalene"[tw] OR "SD 2794"[tw] OR "Seedrin"[tw] OR "Soilgrin"[tw] OR "Tatuzinho"[tw] OR "Tipula"[tw] OR ("dimethanonaphthalene"[tw] AND "hexachloro"[tw] AND "hexahydro"[tw])) OR ("(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-Dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-, endo, exo-"[tw] OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6.2.1.1 3,6.0 2,7)dodec-9-ene"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "Alvit"[tw] OR "Compound 497"[tw] OR "Dieldren"[tw] OR "Dieldrex"[tw] OR "Dieldrin"[tw] OR "Dieldrite"[tw] OR "Dielmoth"[tw] OR "Dildrin"[tw] OR "Dorytox"[tw] OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "endo, exo-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethenapth(2,3-b)oxirene"[tw] OR "HEOD"[tw] OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene"[tw] OR "Illoxol"[tw] OR "Insecticide No. 497"[tw] OR "Insectlack"[tw] OR "Kombi-Albertan"[tw] OR "Moth Snub D"[tw] OR "NA 2761"[tw] OR "Octalox"[tw] OR "Panoram D-31"[tw] OR "Red Shield"[tw] OR "SD 3417"[tw] OR "Shelltox"[tw] OR "Termitox"[tw] OR |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | ("dimethanonaphth"[tw] AND "oxirene"[tw] AND "hexachloro"[tw] AND "octahydro"[tw]) OR ("dimethanonaphthalene"[tw] AND "hexachloro"[tw] AND "octahydro"[tw] AND "epoxy"[tw])) AND (2000/01/01 : 3000[dp] OR 2000/10/01 : 3000[edat] OR 2000/10/01 : 3000[crdt] OR 2000/10/01 : 3000[mhda])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR "pharmacology"[sh:noexp] OR toxicokinetics[mh:noexp]) |
| **Toxline** | |
| 04/2019 | **Date limit 2000 to present:**<br>("1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene" OR "Aldrex" OR "Aldrin" OR "Aldron" OR "Altox" OR "Compound 118" OR "HHDN" OR "Isodrin" OR "Octalene" OR "Tipula" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "Alvit" OR "Dieldren" OR "Dieldrex" OR "Dieldrin" OR "HEOD" OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene" OR "Shelltox" OR 309-00-2[rn] OR 60-57-1[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org]<br>((“dimethanonaphthalene" AND "hexachloro" AND "hexahydro") OR ("dimethanonaphth" AND "oxirene" AND "hexachloro" AND "octahydro") OR ("dimethanonaphthalene" AND "hexachloro" AND "octahydro" AND "epoxy")) AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org]<br>"(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene" |
| | "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-" |
| | "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "Aldocit" OR "Aldrite" OR "Aldrosol" OR "Algran" OR "Andrex" OR "Complex Hydrocarbon Adrex 30" OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene" OR "Kortofin" OR "NA 2761" OR "NA 2762" OR "SD 2794" OR "Seedrin" OR "Soilgrin" OR "Tatuzinho" |
| | "(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" |
| | "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a- |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | octahydro-, endo, exo-" OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6.2.1.1 3,6.0 2,7)dodec-9-ene" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"<br>"2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"<br>"3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "Compound 497" OR "Dieldrite" OR "Dielmoth" OR "Dildrin" OR "Dorytox" OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4 5,8-dimethanonaphthalene" OR "endo, exo-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethenapth(2,3-b)oxirene" OR "Illoxol" OR "Insecticide No. 497" OR "Insectlack" OR "Kombi-Albertan" OR "Moth Snub D" OR "NA 2761" OR "Octalox" OR "Panoram D-31" OR "Red Shield" OR "SD 3417" OR "Termitox" |
| **Toxcenter** | |
| 04/2019 | FILE 'TOXCENTER' ENTERED AT 13:12:18 ON 12 APR 2019<br>L1 9933 SEA FILE=TOXCENTER 309-00-2<br>L2 17723 SEA FILE=TOXCENTER 60-57-1<br>L3 20660 SEA FILE=TOXCENTER L1 OR L2<br>L4 20360 SEA FILE=TOXCENTER L3 NOT (PATENT/DT)<br>L5 20328 SEA FILE=TOXCENTER L4 NOT TSCATS/FS<br>L6 20328 SEA FILE=TOXCENTER L5 AND ED>=20001001<br>L7 6268 SEA FILE=TOXCENTER L5 AND PY>1999<br>ACT TOXQUERY/Q<br>---------<br>L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)<br>L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)<br>L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)<br>L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT<br>L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)<br>L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)<br>L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)<br>L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))<br>L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)<br>L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)<br>L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) |
| | L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) |
| | L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) |
| | L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) |
| | L23 QUE (ENDOCRIN? AND DISRUPT?) |
| | L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) |
| | L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) |
| | L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) |
| | L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) |
| | L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) |
| | L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) |
| | L30 QUE (NEPHROTOX? OR HEPATOTOX?) |
| | L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) |
| | L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) |
| | L33 QUE L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 |
| | L34 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) |
| | L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) |
| | L36 QUE L33 OR L34 OR L35 |
| | L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) |
| | L38 QUE L36 OR L37 |
| | --- |
| | L39 3357 SEA FILE=TOXCENTER L7 AND L38 |
| | L40 3179 SEA FILE=TOXCENTER L39 AND PY>2000 |
| | L41 251 SEA FILE=TOXCENTER L39 AND MEDLINE/FS |
| | L42 702 SEA FILE=TOXCENTER L39 AND BIOSIS/FS |
| | L43 2394 SEA FILE=TOXCENTER L39 AND CAPLUS/FS |
| | L44 10 SEA FILE=TOXCENTER L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L45 2801 DUP REM L41 L42 L44 L43 (556 DUPLICATES REMOVED) ANSWERS '1-2801' FROM FILE TOXCENTER |
| | L*** DEL 251 S L39 AND MEDLINE/FS |
| | L*** DEL 251 S L39 AND MEDLINE/FS |
| | L46 251 SEA FILE=TOXCENTER L45 |
| | L*** DEL 702 S L39 AND BIOSIS/FS |
| | L*** DEL 702 S L39 AND BIOSIS/FS |
| | L47 578 SEA FILE=TOXCENTER L45 |
| | L*** DEL 2394 S L39 AND CAPLUS/FS |
| | L*** DEL 2394 S L39 AND CAPLUS/FS |
| | L48 1964 SEA FILE=TOXCENTER L45 |
| | L*** DEL 10 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L*** DEL 10 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L49 8 SEA FILE=TOXCENTER L45 |
| | L50 2550 SEA FILE=TOXCENTER (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS D SCAN L50 |

## Table B-3. Strategies to Augment the Literature Search

| Source | Query and number screened when available |
|---|---|
| **TSCATS via ChemView** | |
| 04/2019 | Compounds searched: 309-00-2; 60-57-1 |
| **NTP** | |
| 04/2019 | **NTP Site Search (http://ntpsearch.niehs.nih.gov/home):**<br>"309-00-2" "Aldrin" "60-57-1" "Dieldrin"<br>"Isodrin"<br>"Aldrex" "Aldron" "Altox"<br>"1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"<br>"Compound 118" "HHDN" "Octalene" "Tipula"<br>"1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene"<br>"Alvit" "Dieldren"<br>"Dieldrex" "HEOD" "Shelltox" "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene"<br>"1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene |
| **Regulations.gov** | |
| 04/2019 | **Notices or rules:**<br>309-00-2; 60-57-1; "aldrin"; "dieldrin" |
| **NIH RePORTER** | |
| 12/2019 | (**Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects Text search:**<br>"1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "Aldrex" OR "Aldrin" OR "Aldron" OR "Altox" OR "Compound 118" OR "HHDN" OR "Isodrin" OR "Octalene" OR "Tipula" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "Alvit" OR "Dieldren" OR "Dieldrex" OR "Dieldrin" OR "HEOD" OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene" OR "Shelltox"<br>"(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta )-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 |

## Table B-3. Strategies to Augment the Literature Search

| Source | Query and number screened when available |
|---|---|
| | alpha ,8 alpha ,8a beta )-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-" |
| | "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta )-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta )-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "Aldocit" OR "Aldrite" OR "Aldrosol" OR "Algran" OR "Andrex" OR "Complex Hydrocarbon Adrex 30" OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene" OR "Kortofin" OR "NA 2761" OR "NA 2762" OR "SD 2794" OR "Seedrin" OR "Soilgrin" OR "Tatuzinho" |
| | "(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha )-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha )Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-, endo, exo-" OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6 2 1 1 3,6 0 2,7)dodec-9-ene" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha )-" |
| | "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha )-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a- |

**Table B-3. Strategies to Augment the Literature Search**

| Source | Query and number screened when available |
|---|---|
| | octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "Compound 497" OR "Dieldrite" OR "Dielmoth" OR "Dildrin" OR "Dorytox" OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4 5,8-dimethanonaphthalene" OR "endo, exo-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethenapth(2,3-b)oxirene" OR "Illoxol" OR "Insecticide No 497" OR "Insectlack" OR "Kombi-Albertan" OR "Moth Snub D" OR "NA 2761" OR "Octalox" OR "Panoram D-31" OR "Red Shield" OR "SD 3417" OR "Termitox" |
| **Other** | Identified throughout the assessment process |

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 3,610
- Number of records identified from other strategies: 69
- Total number of records to undergo literature screening: 3,679

### B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on aldrin/dieldrin:

- Title and abstract screen
- Full text screen

***Title and Abstract Screen.*** Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

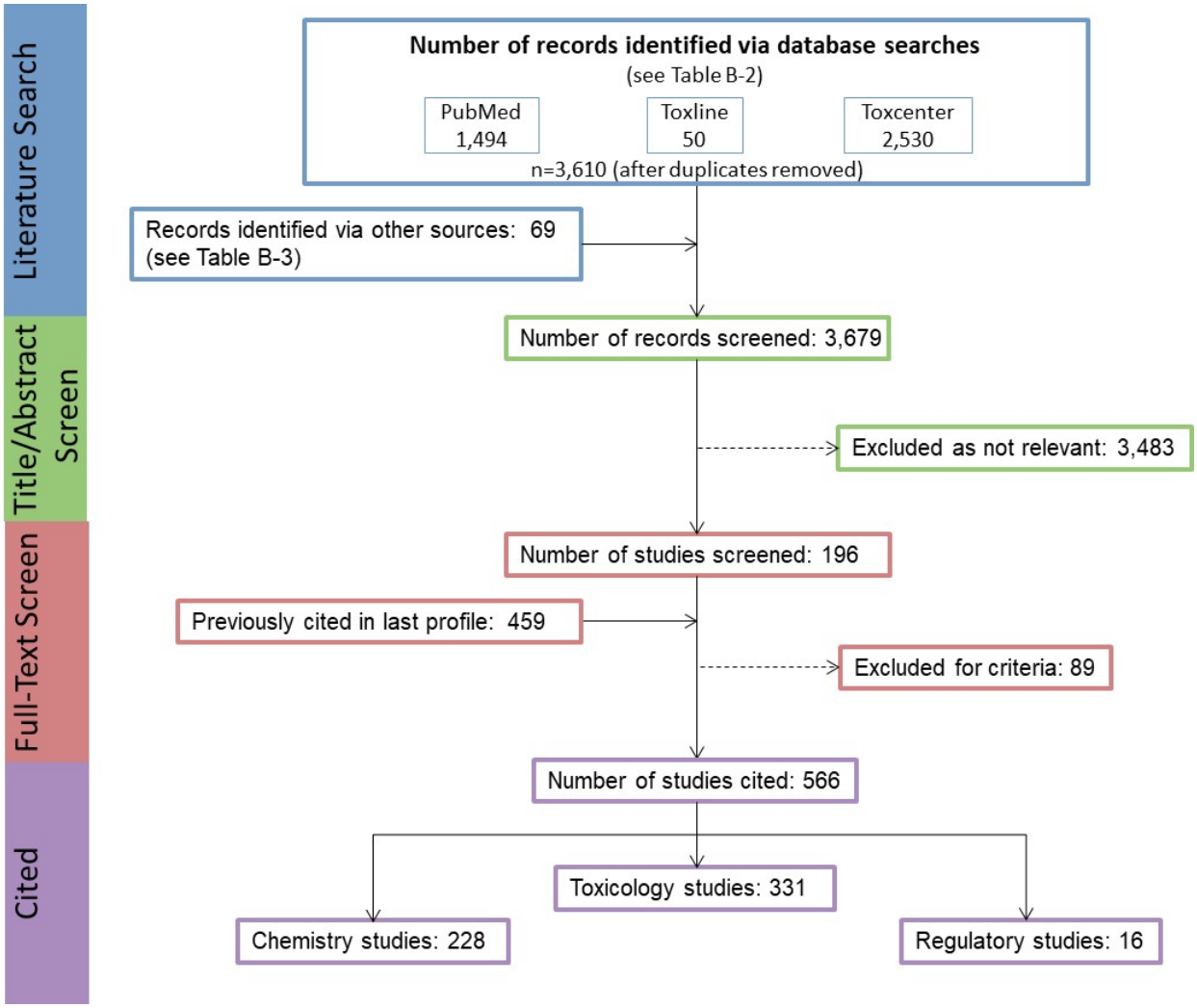
- Number of titles and abstracts screened: 3,679
- Number of studies considered relevant and moved to the next step: 196

***Full Text Screen.*** The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 196
- Number of studies cited in the pre-public draft of the toxicological profile: 459
- Total number of studies cited in the profile: 566

A summary of the results of the literature search and screening is presented in Figure B-1.

## Figure B-1. April 2019 Literature Search Results and Screen for Aldrin/Dieldrin



# APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ALDRIN AND DIELDRIN

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to aldrin/dieldrin, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to aldrin and dieldrin:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

The systematic review for this profile is divided into three sections:

1. Steps 1, 2, and 3 for aldrin and dieldrin (Sections C.1, C.2, and C.3)
2. Steps 4, 5, 6, 7, and 8 for aldrin (Sections C.4, C.5, C.6, C.7, and C.8)
3. Steps 4, 5, 6, 7, and 8 for dieldrin (Sections C.9, C.10, C.11, C.12, and C.13)

## C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to aldrin and dieldrin. The inclusion criteria used to identify relevant studies examining the health effects of aldrin/dieldrin are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

**Table C-1. Inclusion Criteria for Identifying Health Effects Studies**

| |
|---|
| Species |
| Human |
| Laboratory mammals |
| Route of exposure |
| Inhalation |
| Oral |
| Dermal (or ocular) |
| Parenteral (these studies will be considered supporting data) |

**Table C-1. Inclusion Criteria for Identifying Health Effects Studies**

| |
|---|
| Health outcome |
| Death |
| Systemic effects |
| Body weight effects |
| Respiratory effects |
| Cardiovascular effects |
| Gastrointestinal effects |
| Hematological effects |
| Musculoskeletal effects |
| Hepatic effects |
| Renal effects |
| Dermal effects |
| Ocular effects |
| Endocrine effects |
| Immunological effects |
| Neurological effects |
| Reproductive effects |
| Developmental effects |
| Other noncancer effects |
| Cancer |

## C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of aldrin/dieldrin. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

### C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 2002 toxicological profile for aldrin/dieldrin; thus, the literature search was restricted to studies published between October 2000 and April 2019. See Appendix B for the databases searched and the search strategy.

A total of 3,679 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

### C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of aldrin/dieldrin.

***Title and Abstract Screen.*** In the Title and Abstract Screen step, 3,679 records were reviewed; 101 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

***Full Text Screen.*** In the second step in the literature screening process for the systematic review, a full text review of 132 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 132 documents, 204 studies were included in the qualitative review.

## C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

**Table C-2. Data Extracted From Individual Studies**

| |
|---|
| Citation |
| Chemical form |
| Route of exposure (e.g., inhalation, oral, dermal) |
| Specific route (e.g., gavage in oil, drinking water) |
| Species |
| Strain |
| Exposure duration category (e.g., acute, intermediate, chronic) |
| Exposure duration |
| Frequency of exposure (e.g., 6 hours/day, 5 days/week) |
| Exposure length |
| Number of animals or subjects per sex per group |
| Dose/exposure levels |
| Parameters monitored |
| Description of the study design and method |
| Summary of calculations used to estimate doses (if applicable) |
| Summary of the study results |
| Reviewer's comments on the study |
| Outcome summary (one entry for each examined outcome) |
| No-observed-adverse-effect level (NOAEL) value |
| Lowest-observed-adverse-effect level (LOAEL) value |
| Effect observed at the LOAEL value |

A summary of the extracted data for each study is presented in the Supplemental Document for Aldrin/Dieldrin and overviews of the results are presented in Sections 2.2–2.18 of the profile. Results from oral exposure studies are summarized in the Table 2-1 (Levels of Significant Exposure to Aldrin) and Table 2-2 (Levels of Significant Exposure to Dieldrin). Limited information regarding the effects of inhalation or dermal exposure to aldrin or dieldrin mainly involves evaluation of acute lethality. Results from animal studies that employed inhalation or dermal exposure routes are summarized in the appropriate sections of Chapter 2 but are not presented in tables summarizing levels of significant exposure.

## C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—ALDRIN

Overviews of the potential health effect outcomes for aldrin identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Multiple occupational cohorts were evaluated for possible associations between aldrin and/or dieldrin exposure and risk of death from selected noncancer or cancer endpoints. Cohorts with potential exposure to both aldrin and dieldrin are included in sections C.4–C-8 for aldrin and Sections C.9–C.13 for dieldrin. Studies in which the reported exposure was to aldrin during its production or use are assumed to have primarily involved the inhalation exposure route and exposure duration was considered to be chronic unless otherwise indicated. Other human studies involving aldrin include case-control studies, self-reported use, and individual case reports. Data from human studies evaluating possible associations between serum dieldrin levels and selected health outcomes are presented in sections C.9–C.13 under the assumption that exposures were to dieldrin, although some exposures may have been to aldrin because dieldrin is readily formed from aldrin in biological systems. Animal studies of aldrin predominantly employed the oral exposure route. Collectively, the animal studies examined a number of endpoints. The most sensitive endpoints (outcomes) were body weight, hepatic, neurological, reproductive, and developmental. Animal studies evaluating these potential outcomes were carried through Steps 4–8 of the systematic review. Human studies evaluating potential hepatic, neurological, and reproductive outcomes were also carried through Steps 4–8 of the systematic review. No human studies evaluated body weight or developmental outcomes.

APPENDIX C

## Table C-3. Overview of the Health Outcomes for Aldrin Evaluated in Human Studies

| | Body weight | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Dermal | Ocular | Endocrine | Immunological | Neurological | Reproductive | Developmental | Other Noncancer | Caner |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhalation studies | | | | | | | | | | | | | | | | | |
| Cohort | | 6<br>2 | 5 | 1 | 1 | | 4 | 1 | 1 | | | | 3<br>2 | | | | 14<br>4 |
| Case control | | | | | | | | | | | | | | | | | 2 |
| Population | | | | | | | | | | | | | | | | | 6<br>1 |
| Case series | | | | | 1<br>1 | | | | | | | | 2<br>2 | | | | |
| Oral studies | | | | | | | | | | | | | | | | | |
| Cohort | | | | | | | | | | | | | | | | | |
| Case control | | | | | | | | | | | | | | | | | |
| Population | | | | | | | | | | | | | | | | | |
| Case series | | | | | | | | 1<br>1 | | | | | 2<br>2 | 1<br>1 | | | |
| Dermal studies | | | | | | | | | | | | | | | | | |
| Cohort | | | | | | | | | | | | | | | | | |
| Case control | | | | | | | | | | | | | | | | | |
| Population | | | | | | | | | | | | | | | | | |
| Case series | | | | | | | | | | | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Number of studies examining endpoint | 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10 |
| Number of studies reporting outcome | 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10 |

APPENDIX C

## Table C-4. Overview of the Health Outcomes for Aldrin Evaluated in Experimental Animal Studies

| | Body weight | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Dermal | Ocular | Endocrine | Immunological[a] | Neurological[a] | Reproductive[a] | Developmental | Other Noncancer | Caner |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhalation studies | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | | | | | | | | | | | | | |
| Intermediate-duration | | | | | | | | | | | | | | | | | |
| Chronic-duration | | | | | | | | | | | | | | | | | |
| Oral studies | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | | | 1<br>1 | | | | | | 8<br>8 | | 3<br>3 | | |
| Intermediate-duration | 3<br>1 | | | 1<br>1 | | | 3<br>2 | 1<br>0 | | | | | 2<br>2 | 2<br>2 | 2<br>2 | | |
| Chronic-duration | 7<br>2 | 2<br>0 | 2<br>0 | 2<br>0 | 3<br>1 | 2<br>0 | 6<br>4 | 4<br>2 | 2<br>0 | 2<br>0 | 2<br>0 | | 3<br>3 | | 1<br>1 | | 2<br>2 |
| Dermal studies | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | | | | | | | | | 1<br>1 | | | | |
| Intermediate-duration | | | | | | | | | | | | | | | | | |
| Chronic-duration | | | | | | | | | | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of studies examining endpoint | 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10 | |
| Number of studies reporting outcome | 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10 | |

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

## C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—ALDRIN

### C.5.1 Risk of Bias Assessment—Aldrin

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

**Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies**

| |
|---|
| **Selection bias** |
| Were the comparison groups appropriate? |
| **Confounding bias** |
| Did the study design or analysis account for important confounding and modifying variables? |
| **Attrition/exclusion bias** |
| Were outcome data complete without attrition or exclusion from analysis? |
| **Detection bias** |
| Is there confidence in the exposure characterization? |
| Is there confidence in outcome assessment? |
| **Selective reporting bias** |
| Were all measured outcomes reported? |

## Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

| |
|---|
| **Selection bias** |
| Was administered dose or exposure level adequately randomized? |
| Was the allocation to study groups adequately concealed? |
| **Performance bias** |
| Were the research personnel and human subjects blinded to the study group during the study? |
| **Attrition/exclusion bias** |
| Were outcome data complete without attrition or exclusion from analysis? |
| **Detection bias** |
| Is there confidence in the exposure characterization? |
| Is there confidence in outcome assessment? |
| **Selective reporting bias** |
| Were all measured outcomes reported? |

## Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

| |
|---|
| **Selection bias** |
| Was administered dose or exposure level adequately randomized? |
| Was the allocation to study groups adequately concealed? |
| **Performance bias** |
| Were experimental conditions identical across study groups? |
| Were the research personnel blinded to the study group during the study? |
| **Attrition/exclusion bias** |
| Were outcome data complete without attrition or exclusion from analysis? |
| **Detection bias** |
| Is there confidence in the exposure characterization? |
| Is there confidence in outcome assessment? |
| **Selective reporting bias** |
| Were all measured outcomes reported? |

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

***First Tier.*** Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

***Second Tier.*** A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

***Third Tier.*** Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of aldrin health effects studies (observational epidemiology studies and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

## Table C-8. Summary of Risk of Bias Assessment for Aldrin—Observational Epidemiology Studies

| Reference | Risk of bias criteria and ratings | | | | | | Risk of bias tier |
|---|---|---|---|---|---|---|---|
| | Selection bias | Confounding bias | Attrition / exclusion bias | Detection bias | | Selective reporting bias | |
| | Comparison groups appropriate? | **Study design or analysis account for important confounding and modifying variables?*** | Outcome data complete without attrition or exclusion from analysis? | **Confidence in the exposure characterization?*** | **Confidence in the outcome assessment?*** | All measured outcomes reported? | |
| ***Outcome: Hepatic effects*** | | | | | | | |
| *Cohort* | | | | | | | |
| De Jong 1991 | + | - | + | - | + | + | Second |
| Hoogendam et al. 1965 | + | - | + | - | + | + | Second |
| Hunter et al. 1972 | + | - | + | - | + | + | Second |
| Jager 1970 | + | - | + | - | + | + | Second |
| Van Sittert and de Jong 1987 | + | - | + | - | + | + | Second |
| ***Outcome: Neurological effects*** | | | | | | | |
| *Cohort* | | | | | | | |
| De Jong 1991 | + | - | + | - | + | + | Second |
| Hoogendam et al. 1962 | NA | - | + | - | + | + | Second |
| Hoogendam et al. 1965 | NA | - | + | - | + | + | Second |
| *Case reports* | | | | | | | |
| Avar and Czegledi-Janko 1970 | NA | - | + | - | + | + | Second |
| Gupta 1975 | NA | - | + | - | + | + | Second |
| Kazantzis et al. 1964 | NA | - | + | - | + | + | Second |
| Spiotta 1951 | NA | + | + | - | + | + | Second |

## Table C-8. Summary of Risk of Bias Assessment for Aldrin—Observational Epidemiology Studies

| Reference | Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate? | Confounding bias — **Study design or analysis account for important confounding and modifying variables?*** | Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis? | Detection bias — **Confidence in the exposure characterization?*** | Detection bias — **Confidence in the outcome assessment?*** | Selective reporting bias — All measured outcomes reported? | Risk of bias tier |
|---|---|---|---|---|---|---|---|
| ***Outcome: Reproductive effects*** | | | | | | | |
| *Population-based case-control* | | | | | | | |
| Saxena et al. 1980 | + | - | + | - | + | + | Second |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

## Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings | | | | | | | | | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| | Selection bias | | Performance bias | | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | Other bias | |
| | Administered dose or exposure level adequately randomized? | Allocation to study groups adequately concealed? | Experimental conditions identical across study groups? | Research personnel blinded to the study group during the study? | Outcome data complete without attrition or exclusion from analysis? | Confidence in the exposure characterization? | **Confidence in the outcome assessment?*** | All measured outcomes reported? | Study design or analysis account for important confounding and modifying variables? | |
| ***Outcome: Body weight*** | | | | | | | | | | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Treon et al. 1951a rat | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1953a rat | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1955 dog | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Deichmann et al. 1967 rat | + | + | + | + | + | + | + | + | + | First |
| Deichmann et al. 1970 rat | + | + | + | + | + | + | + | + | + | First |
| Fitzhugh et al. 1964 rat | + | + | + | + | + | + | + | + | + | First |
| Fitzhugh et al. 1964 dog | + | + | + | + | + | + | + | + | + | First |
| NCI 1978a rat | ++ | + | + | + | + | + | + | + | + | First |
| NCI 1978a mouse | ++ | + | + | + | + | + | + | + | + | First |
| Treon et al. 1955 dog | + | + | + | + | + | + | + | + | + | First |
| ***Outcome: Hepatic effects*** | | | | | | | | | | |
| *Oral acute exposure* | | | | | | | | | | |
| Treon et al. 1951a rat | + | + | + | + | + | + | + | + | + | First |
| *Oral intermediate exposure* | | | | | | | | | | |
| Treon et al. 1951a rat | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1951b dog | + | + | + | + | + | + | + | + | + | First |

## Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized? | Selection bias: Allocation to study groups adequately concealed? | Performance bias: Experimental conditions identical across study groups? | Performance bias: Research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis? | Detection bias: Confidence in the exposure characterization? | Detection bias: **Confidence in the outcome assessment?*** | Selective reporting bias: All measured outcomes reported? | Other bias: Study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| Treon et al. 1953a rat | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Deichmann et al. 1970 rat | + | + | + | + | + | + | + | + | + | First |
| Fitzhugh et al. 1964 rat | + | + | + | + | + | + | + | + | + | First |
| Fitzhugh et al. 1964 dog | + | + | + | + | + | + | + | + | + | First |
| Kitselman 1953 dog | + | + | + | + | + | + | + | + | + | First |
| NCI 1978a rat | ++ | + | + | + | + | + | + | + | + | First |
| NCI 1978a mouse | ++ | + | + | + | + | + | + | + | + | First |
| ***Outcome: Neurological effects*** | | | | | | | | | | |
| *Oral acute exposure* | | | | | | | | | | |
| Jamaluddin and Poddar 2001a rat | + | + | + | + | + | + | + | + | + | First |
| Jamaluddin and Poddar 2001b rat | + | + | + | + | + | + | + | + | + | First |
| Jamaluddin and Poddar 2003 rat | + | + | + | + | + | + | + | + | + | First |
| Mehrotra et al. 1989 rat | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1951a rat | + | + | + | + | + | + | + | + | + | First |

## Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings | | | | | | | | | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| | Selection bias | | Performance bias | | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | Other bias | |
| | Administered dose or exposure level adequately randomized? | Allocation to study groups adequately concealed? | Experimental conditions identical across study groups? | Research personnel blinded to the study group during the study? | Outcome data complete without attrition or exclusion from analysis? | Confidence in the exposure characterization? | **Confidence in the outcome assessment?*** | All measured outcomes reported? | Study design or analysis account for important confounding and modifying variables? | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Treon et al. 1951b dog | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1955 dog | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Kitselman 1953 dog | + | + | + | + | + | + | + | + | + | First |
| NCI 1978a rat | ++ | + | + | + | + | + | + | + | + | First |
| NCI 1978a mouse | ++ | + | + | + | + | + | + | + | + | First |
| *Dermal acute exposure* | | | | | | | | | | |
| Treon et al. 1953b rabbit | + | + | + | + | + | + | + | + | + | First |
| ***Outcome: Reproductive effects*** | | | | | | | | | | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Keplinger et al. 1970 mouse | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1954a rat | + | + | + | + | + | + | + | + | + | First |
| ***Outcome: Developmental effects*** | | | | | | | | | | |
| *Oral acute exposure* | | | | | | | | | | |
| Al-Hachim 1971 mouse | + | + | + | + | + | + | + | + | + | First |
| Ottolenghi et al. 1974 mouse | + | + | + | + | + | + | + | + | + | First |
| Ottolenghi et al. 1974 hamster | + | + | + | + | + | + | + | + | + | First |

## Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized? | Selection bias: Allocation to study groups adequately concealed? | Performance bias: Experimental conditions identical across study groups? | Performance bias: Research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis? | Detection bias: Confidence in the exposure characterization? | Detection bias: **Confidence in the outcome assessment?*** | Selective reporting bias: All measured outcomes reported? | Other bias: Study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| *Oral intermediate exposure* | | | | | | | | | | |
| Keplinger et al. 1970 mouse | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1954a rat | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Kitselman 1953 dog | + | + | + | + | + | + | + | + | + | First |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

## C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—ALDRIN

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to aldrin and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

### C.6.1 Initial Confidence Rating—Aldrin

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to aldrin and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

## Table C-10. Key Features of Study Design for Observational Epidemiology Studies

| |
|---|
| Exposure was experimentally controlled |
| Exposure occurred prior to the outcome |
| Outcome was assessed on individual level rather than at the population level |
| A comparison group was used |

## Table C-11. Key Features of Study Design for Human Controlled Exposure Studies

| |
|---|
| A comparison group was used or the subjects served as their own control |
| A sufficient number of subjects were tested |
| Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported) |
| Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis |

## Table C-12. Key Features of Study Design for Experimental Animal Studies

| |
|---|
| A concurrent control group was used |
| A sufficient number of animals per group were tested |
| Appropriate parameters were used to assess a potential adverse effect |
| Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis |

The presence or absence of the key features and the initial confidence levels for studies examining hepatic, neurological, and reproductive outcomes in the observational epidemiology studies; and body weight, hepatic, neurological, reproductive, and developmental outcomes in animal experimental studies are presented in Tables C-13 and C-14, respectively.

## Table C-13. Presence of Key Features of Study Design for Aldrin—Observational Epidemiology Studies

| | Key features | | | | |
|---|---|---|---|---|---|
| Reference | Controlled exposure | Exposure prior to outcome | Outcomes assessed on an individual level | Comparison group | Initial study confidence |
| ***Outcome: Hepatic effects*** | | | | | |
| *Cohort* | | | | | |
| De Jong 1991 | No | Yes | Yes | Yes | Moderate |
| Hoogendam et al. 1965 | No | Yes | Yes | No | Low |

## Table C-13. Presence of Key Features of Study Design for Aldrin—Observational Epidemiology Studies

| Reference | Key features: Controlled exposure | Exposure prior to outcome | Outcomes assessed on an individual level | Comparison group | Initial study confidence |
|---|---|---|---|---|---|
| Hunter et al. 1972 | No | Yes | Yes | Yes | Moderate |
| Jager 1970 | No | Yes | Yes | Yes | Moderate |
| Van Sittert and de Jong 1987 | No | Yes | Yes | Yes | Moderate |
| ***Outcome: Neurological effects*** | | | | | |
| *Cohort* | | | | | |
| De Jong 1991 | No | Yes | Yes | Yes | Moderate |
| Hoogendam et al. 1962 | No | Yes | Yes | No | Low |
| Hoogendam et al. 1965 | No | Yes | Yes | No | Low |
| *Case reports* | | | | | |
| Avar and Czegledi-Janko 1970 | No | Yes | Yes | No | Low |
| Gupta 1975 | No | Yes | Yes | No | Low |
| Kazantzis et al. 1964 | No | Yes | Yes | No | Low |
| Spiotta 1951 | No | Yes | Yes | No | Low |
| ***Outcome: Reproductive effects*** | | | | | |
| *Population-based case-control* | | | | | |
| Saxena et al. 1980 | No | Yes | Yes | Yes | Moderate |

## Table C-14. Presence of Key Features of Study Design for Aldrin—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| ***Outcome: Body weight effects*** | | | | | |
| *Oral intermediate exposure* | | | | | |
| Treon et al. 1951a rat | Yes | Yes | Yes | Yes | High |
| Treon et al. 1953a rat | Yes | Yes | Yes | Yes | High |
| Treon et al. 1955 dog | Yes | No | Yes | No | Low |

## Table C-14. Presence of Key Features of Study Design for Aldrin—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Key feature: Sufficient number of animals per group | Key feature: Appropriate parameters to assess potential effect | Key feature: Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| *Oral chronic exposure* | | | | | |
| Deichmann et al. 1967 rat | Yes | Yes | Yes | Yes | High |
| Deichmann et al. 1970 rat | Yes | Yes | Yes | Yes | High |
| Fitzhugh et al. 1964 rat | Yes | Yes | Yes | Yes | High |
| Fitzhugh et al. 1964 dog | Yes | No | Yes | Yes | Moderate |
| NCI 1978a rat | Yes | Yes | Yes | Yes | High |
| NCI 1978a mouse | Yes | Yes | Yes | Yes | High |
| Treon et al. 1955 dog | Yes | No | Yes | No | Low |
| ***Outcome: Hepatic effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Treon et al. 1951a rat | Yes | Yes | Yes | No | Moderate |
| *Oral intermediate exposure* | | | | | |
| Treon et al. 1951a rat | Yes | Yes | Yes | Yes | High |
| Treon et al. 1951b dog | Yes | No | No | No | Very low |
| Treon et al. 1953a rat | Yes | Yes | Yes | Yes | High |
| *Oral chronic exposure* | | | | | |
| Deichmann et al. 1970 rat | Yes | Yes | Yes | Yes | High |
| Fitzhugh et al. 1964 rat | Yes | Yes | Yes | Yes | High |
| Fitzhugh et al. 1964 dog | Yes | No | Yes | Yes | Moderate |
| Kitselman 1953 dog | Yes | No | No | No | Very low |
| NCI 1978a rat | Yes | Yes | Yes | Yes | High |
| NCI 1978a mouse | Yes | Yes | Yes | Yes | High |
| ***Outcome: Neurological effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Jamaluddin and Poddar 2001a rat | Yes | No | Yes | Yes | Moderate |
| Jamaluddin and Poddar 2001b rat | Yes | No | Yes | Yes | Moderate |
| Jamaluddin and Poddar 2003 rat | Yes | No | Yes | Yes | Moderate |
| Mehrotra et al. 1989 rat | Yes | No | Yes | Yes | Moderate |
| Treon et al. 1951a rat | Yes | Yes | Yes | No | Moderate |
| *Oral intermediate exposure* | | | | | |
| Treon et al. 1951b dog | Yes | No | No | No | Very low |
| Treon et al. 1955 dog | Yes | No | Yes | No | Low |

**Table C-14. Presence of Key Features of Study Design for Aldrin—Experimental Animal Studies**

| Reference | Key feature: Concurrent control group | Key feature: Sufficient number of animals per group | Key feature: Appropriate parameters to assess potential effect | Key feature: Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| *Oral chronic exposure* | | | | | |
| Kitselman 1953 dog | Yes | No | No | No | Very low |
| NCI 1978a rat | Yes | Yes | Yes | No | Moderate |
| NCI 1978a mouse | Yes | Yes | Yes | No | Moderate |
| *Dermal acute exposure* | | | | | |
| Treon et al. 1953b rabbit | | | | | |
| ***Outcome: Reproductive effects*** | | | | | |
| *Oral intermediate exposure* | | | | | |
| Keplinger et al. 1970 mouse | Yes | Yes | Yes | Yes | High |
| Treon et al. 1954a rat | Yes | Yes | Yes | Yes | High |
| ***Outcome: Developmental effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Al-Hachim 1971 mouse | Yes | No | Yes | Yes | Moderate |
| Ottolenghi et al. 1974 mouse | Yes | No | Yes | Yes | Moderate |
| Ottolenghi et al. 1974 hamster | Yes | No | Yes | Yes | Moderate |
| *Oral intermediate exposure* | | | | | |
| Keplinger et al. 1970 mouse | Yes | Yes | Yes | Yes | High |
| Treon et al. 1954a rat | Yes | Yes | Yes | Yes | High |
| *Oral chronic exposure* | | | | | |
| Kitselman 1953 dog | Yes | No | No | No | Very low |

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

## Table C-15. Initial Confidence Rating for Aldrin Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| ***Outcome: Body weight effects*** | | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Treon et al. 1951a rat | High | High |
| Treon et al. 1953a rat | High | |
| Treon et al. 1955 dog | Low | |
| *Oral chronic exposure* | | |
| Animal studies | | |
| Deichmann et al. 1967 rat | High | High |
| Deichmann et al. 1970 rat | Moderate | |
| Fitzhugh et al. 1964 rat | Moderate | |
| Fitzhugh et al. 1964 dog | Very low | |
| NCI 1978a rat | High | |
| NCI 1978a mouse | High | |
| Treon et al. 1955 dog | High | |
| ***Outcome: Hepatic effects*** | | |
| *Inhalation chronic exposure* | | |
| Human studies | | |
| De Jong 1991 | Moderate | Moderate |
| Hoogendam et al. 1965 | Low | |
| Hunter et al. 1972 | Moderate | |
| Jager 1970 | Moderate | |
| Van Sittert and de Jong 1987 | Moderate | |
| *Oral acute exposure* | | |
| Animal studies | | |
| Treon et al. 1951a rat | Moderate | Moderate |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Treon et al. 1951a rat | High | High |
| Treon et al. 1951b dog | Very low | |
| Treon et al. 1953a rat | High | |
| *Oral chronic exposure* | | |
| Animal studies | | |
| Deichmann et al. 1970 rat | High | High |
| Fitzhugh et al. 1964 rat | Moderate | |
| Fitzhugh et al. 1964 dog | Moderate | |
| Kitselman 1953 dog | Very low | |
| NCI 1978a rat | High | |
| NCI 1978a mouse | High | |
| ***Outcome: Neurological effects*** | | |
| *Inhalation acute exposure* | | |
| Human studies | | |
| Kazantzis et al. 1964 | Low | Low |

## Table C-15. Initial Confidence Rating for Aldrin Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| *Inhalation chronic exposure* | | |
| Human studies | | |
| Avar and Czegledi-Janko 1970 | Low | Moderate |
| De Jong 1981 | Moderate | |
| Hoogendam et al. 1962 | Low | |
| Hoogendam et al. 1965 | Low | |
| *Oral acute exposure* | | |
| Human studies | | |
| Spiotta 1951 | Low | Low |
| Animal studies | | |
| Jamaluddin and Poddar 2001a rat | Moderate | Moderate |
| Jamaluddin and Poddar 2001b rat | Moderate | |
| Jamaluddin and Poddar 2003 rat | Moderate | |
| Mehrotra et al. 1989 rat | Moderate | |
| Treon et al. 1951a rat | Moderate | |
| *Oral intermediate exposure* | | |
| Human studies | | |
| Gupta 1975 | Low | Low |
| Animal studies | | |
| Treon et al. 1951b dog | Very low | Low |
| Treon et al. 1955 dog | Low | |
| *Oral chronic exposure* | | |
| Animal studies | | |
| Kitselman 1953 dog | Very low | Moderate |
| NCI 1978a rat | Moderate | |
| NCI 1978a mouse | Moderate | |
| *Dermal acute exposure* | | |
| Animal studies | | |
| Treon et al. 1953b rabbit | | |
| ***Outcome: Reproductive effects*** | | |
| *Oral intermediate exposure* | | |
| Human studies | | |
| Saxena et al. 1980 | Moderate | Moderate |
| Animal studies | | |
| Keplinger et al. 1970 mouse | High | High |
| Treon et al. 1954a rat | High | |
| *Oral chronic exposure* | | |
| Human studies | | |
| Saxena et al. 1980 | High | High |
| ***Outcome: Developmental effects*** | | |
| *Oral acute exposure* | | |
| Animal studies | | |
| Al-Hachim 1971 mouse | Moderate | Moderate |
| Ottolenghi et al. 1974 mouse | Moderate | |

**Table C-15. Initial Confidence Rating for Aldrin Health Effects Studies**

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| Ottolenghi et al. 1974 hamster | Moderate | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Keplinger et al. 1970 mouse | High | High |
| Treon et al. 1954a rat | High | |
| *Oral chronic exposure* | | |
| Animal studies | | |
| Kitselman 1953 dog | Very low | Very low |

## C.6.2 Adjustment of the Confidence Rating—Aldrin

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for body weight, hepatic, neurological, reproductive, and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with aldrin exposure is presented in Table C-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

## Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

| | Initial confidence | Adjustments to the initial confidence rating | Final confidence |
|---|---|---|---|
| **Body weight effects:** | | | |
| Animal studies | High | No adjustments | High |
| **Hepatic effects:** | | | |
| Human studies | Moderate | Downgrade one confidence level; all studies in risk of bias second tier | Low |
| Animal studies | High | No adjustments | High |
| **Neurological effects:** | | | |
| Human studies | Moderate | Downgrade one confidence level; all studies in risk of bias second tier | Low |
| Animal studies | Moderate | No adjustments | Moderate |
| **Reproductive effects:** | | | |
| Human studies | Moderate | Downgrade one confidence level; all studies in risk of bias second tier | Low |
| Animal studies | High | No adjustments | High |
| **Developmental effects:** | | | |
| Animal studies | High | No adjustments | High |

**Table C-17. Confidence in the Body of Evidence for Aldrin**

| | Confidence in body of evidence | |
|---|---|---|
| Outcome | Human studies | Animal studies |
| Body weight effects | | High |
| Hepatic effects | Low | High |
| Neurological effects | Low | Moderate |
| Reproductive effects | Low | High |
| Developmental effects | | High |

## C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—ALDRIN

In the seventh step of the systematic review of the health effects data for aldrin, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for aldrin is presented in Table C-18.

**Table C-18. Level of Evidence of Health Effects for Aldrin**

| Outcome | Confidence in body of evidence | Direction of health effect | Level of evidence for health effect |
|---|---|---|---|
| **Human studies** | | | |
| Hepatic effects | Low | Health effect | Moderate |
| Neurological effects | Low | Health effect | Moderate |
| Reproductive effects | Low | Health effect | Low |
| **Animal studies** | | | |
| Body weight effects | High | Health effect | High |
| Hepatic effects | High | Health effect | High |
| Neurological effects | Moderate | Health effect | Moderate |
| Reproductive effects | High | Health effect | High |
| Developmental effects | High | Health effect | High |

## C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—ALDRIN

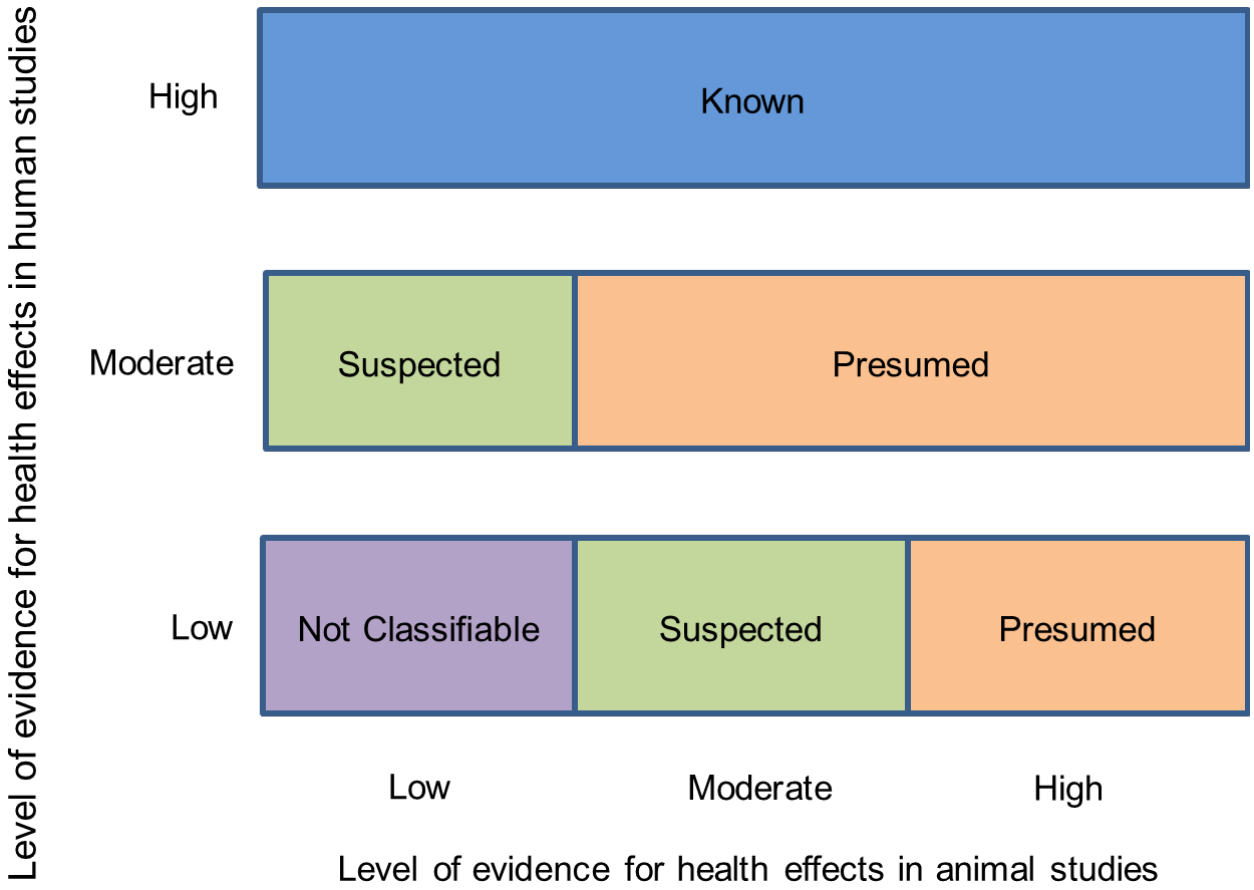
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

**Figure C-1. Hazard Identification Scheme**




Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for aldrin are listed below and summarized in Table C-19.

**Presumed Health Effects**

- Body weight effects
  - No human studies evaluated body weight effects.
  - Depressed body weight or actual body weight loss have been reported in intermediate- and chronic-duration oral studies in laboratory animals (Deichmann et al. 1970; Fitzhugh et al. 1964; Treon et al. 1955).

- Hepatic effects
  - Human studies evaluating hepatic endpoints have not provided convincing evidence of aldrin-induced liver effects.
  - Increased liver weight and histopathologic hepatic changes have been observed in laboratory animals following oral exposure to aldrin (Fitzhugh et al. 1964; Treon et al. 1951a, 1955).

- Neurological effects
  - Various clinical signs and abnormal EEGs have been observed among workers involved in the production of aldrin or its use as an insecticide (Avar and Czegledi-Janko 1970; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). Neurological effects were observed in individuals inadvertently ingesting wheat containing aldrin and lindane (Gupta 1975).
  - Increased locomotor activity was observed in rats following single or repeated oral exposure to aldrin (Jamaluddin and Poddar 2001a, 2001b, 2003). Repeated oral dosing of laboratory animals with aldrin has resulted in increased locomotor activity, convulsions, tremors, and neuronal degeneration (Jamaluddin and Poddar 2001a, 2001b, 2003; Kitselman 1953; NCI 1978a, 1978b; Treon et al. 1951b; Walker et al. 1969).

- Reproductive effects
  - A limited human study reported significantly higher aldrin blood levels in a group of women who had premature labor or spontaneous abortion when compared to a group of controls (Saxena et al. 1980).
  - A variety of adverse reproductive effects were reported in dogs administered aldrin orally for 14 months prior to mating (Deichmann et al. 1971).

- Developmental effects
  - No human studies evaluated developmental endpoints.
  - Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975). Aldrin or dieldrin exposure during gestation has resulted in some evidence of external malformations or skeletal anomalies in animals (Chernoff et al. 1975; Ottolenghi et al. 1974).

**Table C-19. Hazard Identification Conclusions for Aldrin**

| Outcome | Hazard identification |
|---|---|
| Body weight effects | Presumed health effect in humans |
| Hepatic effects | Presumed health effect in humans |
| Neurological effects | Presumed health effect in humans |
| Reproductive effects | Presumed health effect in humans |
| Developmental effects | Presumed health effect in humans |

## C.9 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—DIELDRIN

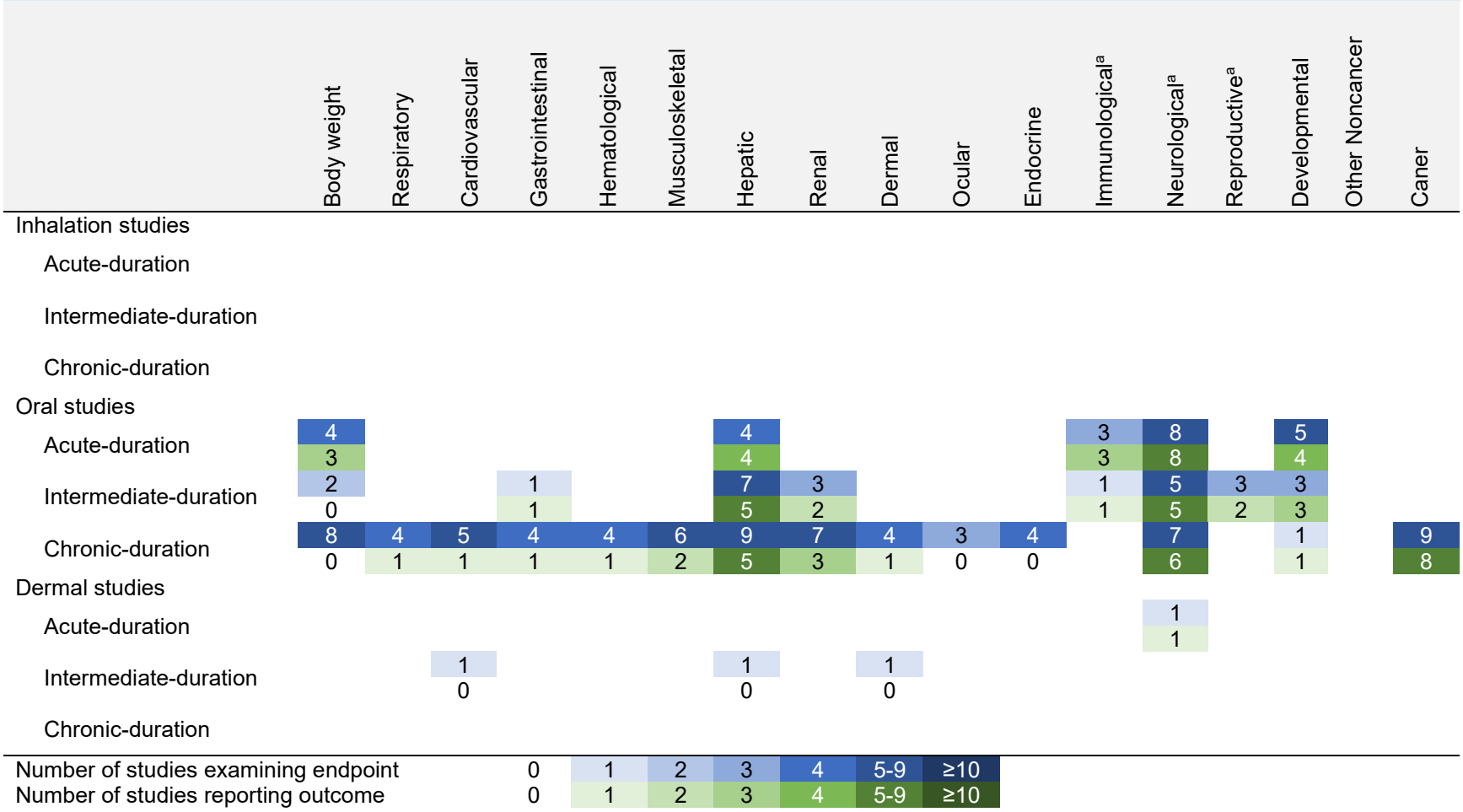
Overviews of the potential health effect outcomes for dieldrin identified in human and animal studies are presented in Tables C-20 and C-21, respectively. Multiple cohorts were evaluated for possible associations between aldrin and/or dieldrin exposure and risk of death from selected noncancer or cancer endpoints. Cohorts with potential exposure to both aldrin and dieldrin are included in sections C.4–C-8 for aldrin and Sections C.9–C.13 for dieldrin. Studies involving production or use are assumed to have primarily involved the inhalation exposure route; exposure duration was considered to be chronic unless otherwise indicated. Other human studies involving dieldrin include case-control studies, self-reported use, and individual case reports. Data from human studies evaluating possible associations between serum dieldrin levels and selected health outcomes are presented in Sections C.9–C.13 under the assumption that exposures were to dieldrin, although some exposures may have been to aldrin because dieldrin is readily formed from aldrin in biological systems. Animal studies of dieldrin predominantly employed the oral exposure route. Collectively, these studies examined a number of endpoints. The most sensitive endpoints (outcomes) were hepatic, neurological, reproductive, and developmental. Animal studies examining these potential outcomes were carried through Steps 4–8 of the systematic review. Human studies evaluating potential hepatic and neurological outcomes were also carried through Steps 4–8 of the systematic review. No human studies evaluated reproductive or developmental outcomes.

## Table C-20. Overview of the Health Outcomes for Dieldrin Evaluated In Human Studies

| | Body weight | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Dermal | Ocular | Endocrine | Immunological | Neurological | Reproductive | Developmental | Other Noncancer | Caner |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhalation studies | | | | | | | | | | | | | | | | | |
| Cohort | | 7 | 7 | 2 | 3 | | 8 | 1 | 1 | | | | 3 | | | | 15 |
| | | 2 | 0 | 0 | 0 | | 0 | 0 | 0 | | | | 2 | | | | 2 |
| Case control | | | | | | | | | | | | | 1 | | | | 9 |
| | | | | | | | | | | | | | 1 | | | | 5 |
| Population | | | | | | | | | | | | | | | | | 8 |
| Case series | | | | | | | | | | | | 1 | 1 | | | | |
| | | | | | | | | | | | | 1 | 1 | | | | |
| Oral studies | | | | | | | | | | | | | | | | | |
| Cohort | | | | | | | | | | | | | | | | | |
| Case control | | | | | | | | | | | | | 2 | | | | |
| | | | | | | | | | | | | | 2 | | | | |
| Population | | | | | | | | | | | | | | | | | 1 |
| Case series | | | 1 | | 1 | | 3 | 1 | | | | 1 | 2 | | | | 1 |
| | | | 1 | | | | 3 | | | | | 1 | 2 | | | | 1 |
| Dermal studies | | | | | | | | | | | | | | | | | |
| Cohort | | | | | | | | | | | | | | | | | |
| Case control | | | | | | | | | | | | | | | | | |
| Population | | | | | | | | | | | | 1 | | | | | |
| | | | | | | | | | | | | 1 | | | | | |
| Case series | | | | | | | | | 1 | | | | | | | | |
| | | | | | | | | | 1 | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of studies examining endpoint | 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10 | |
| Number of studies reporting outcome | 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10 | |

## Table C-21. Overview of the Health Outcomes for Dieldrin Evaluated in Experimental Animal Studies




[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

## C.10 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES— DIELDRIN

### C.10.1 Risk of Bias Assessment—Dieldrin

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies were presented above in Tables C-5, C-6, and C-7, respectively. As described in Section C.5.1, each risk of bias question was answered on a four-point scale and studies were assigned to one of three risk of bias tiers.

The results of the risk of bias assessment for the different types of dieldrin health effects studies (observational epidemiology, human controlled-exposure studies, and animal experimental studies) are presented in Tables C-22, C-23, and C-24, respectively.

## Table C-22. Summary of Risk of Bias Assessment for Dieldrin—Observational Epidemiology Studies

| Reference | Risk of bias criteria and ratings | | | | | | Risk of bias tier |
|---|---|---|---|---|---|---|---|
| | Selection bias | Confounding bias | Attrition / exclusion bias | Detection bias | | Selective reporting bias | |
| | Comparison groups appropriate? | **Study design or analysis account for important confounding and modifying variables?*** | Outcome data complete without attrition or exclusion from analysis? | **Confidence in the exposure characterization?*** | **Confidence in the outcome assessment?*** | All measured outcomes reported? | |
| ***Outcome: Hepatic effects*** | | | | | | | |
| *Cohort* | | | | | | | |
| de Jong 1991 | + | - | + | - | + | + | Second |
| Hoogendam et al. 1965 | + | - | + | - | + | + | Second |
| Hunter et al. 1972 | + | - | + | - | + | + | Second |
| Jager 1970 | + | - | + | - | + | + | Second |
| Morgan and Lin 1978 | - | - | + | - | + | + | Second |
| Morgan and Roan 1974 | + | - | + | - | + | + | Second |
| Van Sittert and de Jong 1987 | + | - | + | - | + | + | Second |
| Warnick and Carter 1972 | + | - | + | - | + | + | Second |
| *Case series* | | | | | | | |
| Black 1974 | NA | **NA** | + | - | + | + | Second |
| Garrettson and Curley 1969 | NA | **NA** | + | - | + | + | Second |
| Radomski et al. 1968 | + | **NA** | + | - | + | + | Second |
| ***Outcome: Neurological effects*** | | | | | | | |
| *Cohort* | | | | | | | |
| De Jong 1991 | + | - | + | - | + | + | Second |
| Hoogendam et al. 1962 | NA | - | + | - | + | + | Second |
| Hoogendam et al. 1965 | + | - | + | - | + | + | Second |

## Table C-22. Summary of Risk of Bias Assessment for Dieldrin—Observational Epidemiology Studies

| Reference | Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate? | Confounding bias — **Study design or analysis account for important confounding and modifying variables?*** | Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis? | Detection bias — **Confidence in the exposure characterization?*** | Detection bias — **Confidence in the outcome assessment?*** | Selective reporting bias — All measured outcomes reported? | Risk of bias tier |
|---|---|---|---|---|---|---|---|
| *Case-control* | | | | | | | |
| Sandifer et al. 1981 | + | - | + | - | + | + | Second |
| Weisskopf et al. 2010 | + | - | + | - | + | + | Second |
| *Case series* | | | | | | | |
| Black 1974 | NA | **NA** | + | - | + | + | Second |
| Garrettson and Curley 1969 | NA | **NA** | + | - | + | + | Second |
| Patel and Rao 1958 | NA | **NA** | + | - | + | + | Second |
| Pennell et al. 2006 | NA | - | + | - | + | + | Second |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

## Table C-23. Summary of Risk of Bias Assessment for Dieldrin—Human Controlled-Exposure Studies

| Reference | Risk of bias criteria and ratings | | | | | | | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|
| | Selection bias | | Performance bias | Attrition / exclusion bias | Detection bias | | Selective reporting bias | |
| | Administered dose or exposure level adequately randomized? | Allocation to study groups adequately randomized | **Researchers, human subjects blinded to study group?*** | Outcome data complete without attrition or exclusion? | **Confidence in the exposure characterization?*** | **Confidence in the outcome assessment?*** | All measured outcomes reported? | |
| ***Outcome: Hepatic effects*** | | | | | | | | |
| *Oral chronic exposure* | | | | | | | | |
| Hunter and Robinson 1967 | ++ | ++ | ++ | ++ | ++ | ++ | ++ | First |
| ***Outcome: Neurological effects*** | | | | | | | | |
| *Oral chronic exposure* | | | | | | | | |
| Hunter and Robinson 1967 | ++ | ++ | ++ | ++ | ++ | ++ | ++ | First |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

## Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias — Administered dose or exposure level adequately randomized? | Selection bias — Allocation to study groups adequately concealed? | Performance bias — Experimental conditions identical across study groups? | Performance bias — Research personnel blinded to the study group during the study? | Attrition/ exclusion bias — Outcome data complete without attrition or exclusion from analysis? | Detection bias — Confidence in the exposure characterization? | Detection bias — **Confidence in the outcome assessment?*** | Selective reporting bias — All measured outcomes reported? | Other bias — Study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Outcome: Hepatic effects*** | | | | | | | | | | |
| *Oral acute exposure* | | | | | | | | | | |
| Chernoff et al. 1975 mouse | + | + | + | + | + | + | + | + | + | First |
| Goel et al. 1988 rat | + | + | + | + | + | + | + | + | + | First |
| Kohli et al. 1977 rat | + | + | + | + | + | + | + | + | + | First |
| Wright et al. 1972 mouse | + | + | + | + | + | + | + | + | + | First |
| *Oral intermediate exposure* | | | | | | | | | | |
| Ahmed et al. 1986 rat | + | + | + | + | + | + | + | + | + | First |
| Bandyopadhyay et al. 1982b rat | + | + | + | + | + | + | + | + | + | First |
| Shakoori et al. 1982 rat | + | + | + | + | + | + | + | + | + | First |
| Stevenson et al. 1995 mouse | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1951 rat | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1951b dog | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1953a rat | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Deichmann et al. 1970 rat | + | + | + | + | + | + | + | + | + | First |
| Fitzhugh et al. 1964 rat | + | + | + | + | + | + | + | + | + | First |
| Fitzhugh et al. 1964 dog | + | + | + | + | + | + | + | + | + | First |

## Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized? | Selection bias: Allocation to study groups adequately concealed? | Performance bias: Experimental conditions identical across study groups? | Performance bias: Research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis? | Detection bias: Confidence in the exposure characterization? | Detection bias: **Confidence in the outcome assessment?*** | Selective reporting bias: All measured outcomes reported? | Other bias: Study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| Harr et al. 1970 rat | + | + | + | + | + | + | + | + | + | First |
| Kitselman 1953 dog | + | + | + | + | + | + | + | + | + | First |
| NCI 1978a rat | + | + | + | + | + | + | + | + | + | First |
| NCI 1978a mouse | + | + | + | + | + | + | + | + | + | First |
| Walker et al. 1973 rat | + | + | + | + | + | + | + | + | + | First |
| Walker et al. 1973 dog | + | + | + | + | + | + | + | + | + | First |
| ***Outcome: Neurological effects*** | | | | | | | | | | |
| *Oral acute exposure* | | | | | | | | | | |
| Burt 1975 rat (16.7 mg/kg) | + | + | + | + | + | + | + | + | + | First |
| Burt 1975 rat (2.5, 5 mg/kg) | + | + | + | + | + | + | + | + | + | First |
| Burt 1975 rat (8.4, 16.7 mg/kg) | + | + | + | + | + | + | + | + | + | First |
| Foster et al.2008 mouse | + | + | + | + | + | + | + | + | + | First |
| Foster et al.2008 mouse rep | + | + | + | + | + | + | + | + | + | First |
| Mehrotra et al. 1989 rat | + | + | + | + | + | + | + | + | + | First |
| Sandler et al. 1969 sheep | + | + | + | + | + | + | + | + | + | First |
| Woolley et al. 1985 rat | + | + | + | + | + | + | + | + | + | First |

## Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings | | | | | | | | | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| | Selection bias | | Performance bias | | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | Other bias | |
| | Administered dose or exposure level adequately randomized? | Allocation to study groups adequately concealed? | Experimental conditions identical across study groups? | Research personnel blinded to the study group during the study? | Outcome data complete without attrition or exclusion from analysis? | Confidence in the exposure characterization? | **Confidence in the outcome assessment?*** | All measured outcomes reported? | Study design or analysis account for important confounding and modifying variables? | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Burt 1975 rat | + | + | + | + | + | + | + | + | + | First |
| NCI 1978b rat | + | + | + | + | + | + | + | + | + | First |
| Smith et al. 1976 monkey | + | + | + | + | – | + | + | + | + | First |
| Treon et al. 1951b dog | + | + | + | + | + | + | + | + | + | First |
| Van Gelder 1975 sheep | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Khairy 1960 rat | + | + | + | + | + | + | + | + | + | First |
| Kitselman 1953 dog | + | + | + | + | + | + | + | + | + | First |
| NCI 1978a mouse | + | + | + | + | + | + | + | + | + | First |
| NCI 1987b rat | + | + | + | + | + | + | + | + | + | First |
| Walker et al. 1969 rat | ++ | + | + | + | + | + | + | + | + | First |
| Walker et al. 1969 dog | ++ | + | + | + | + | + | + | + | + | First |
| Walker et al. 1973 mouse 128 weeks | ++ | + | + | + | + | + | + | + | + | First |
| *Dermal acute exposure* | | | | | | | | | | |
| Treon et al. 1953b rabbit | + | + | + | + | + | + | + | + | + | First |

## Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized? | Selection bias: Allocation to study groups adequately concealed? | Performance bias: Experimental conditions identical across study groups? | Performance bias: Research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis? | Detection bias: Confidence in the exposure characterization? | Detection bias: **Confidence in the outcome assessment?*** | Selective reporting bias: All measured outcomes reported? | Other bias: Study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Outcome: Reproductive effects*** | | | | | | | | | | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Good and Ware 1969 mouse | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1954a rat | + | + | + | + | + | + | + | + | + | First |
| Virgo and Bellward 1975 mouse | + | + | + | + | + | + | + | + | + | First |
| ***Outcome: Developmental effects*** | | | | | | | | | | |
| *Oral acute exposure* | | | | | | | | | | |
| Carlson and Rosellini 1987 rat | + | + | + | + | + | + | + | + | + | First |
| Chernoff et al. 1975 mouse | + | + | + | + | + | + | + | + | + | First |
| Dix et al. 1977 mouse | + | + | + | + | + | + | + | + | + | First |
| Ottolenghi et al. 1974 mouse | + | + | + | + | + | + | + | + | + | First |
| Ottolenghi et al. 1974 hamster | + | + | + | + | + | + | + | + | + | First |

## Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized? | Selection bias: Allocation to study groups adequately concealed? | Performance bias: Experimental conditions identical across study groups? | Performance bias: Research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis? | Detection bias: Confidence in the exposure characterization? | Detection bias: **Confidence in the outcome assessment?*** | Selective reporting bias: All measured outcomes reported? | Other bias: Study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| *Oral intermediate exposure* | | | | | | | | | | |
| Harr et al. 1970 rat | + | + | + | + | + | + | + | + | + | First |
| Treon et al. 1954a rat | + | + | + | + | + | + | + | + | + | First |
| Virgo and Bellward 1975 mouse | + | + | + | + | + | + | + | + | + | First |
| *Oral chronic exposure* | | | | | | | | | | |
| Kitselman 1953 dog | + | + | + | + | + | + | + | + | + | First |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

## C.11 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME— DIELDRIN

As discussed in greater detail in Section C.6, confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

### C.11.1 Initial Confidence Rating—Dieldrin

As discussed in greater detail in Section C.6.1, the body of evidence for an association (or no association) between exposure to dieldrin and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. Refer to Tables C-10, C-11, and C-12, respectively, for the key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies.

The presence or absence of the key features and the initial confidence levels for studies examining hepatic and neurological outcomes observed in the observational epidemiology studies; human controlled-exposure studies; and hepatic, neurological, reproductive, and developmental outcomes in animal experimental studies are presented in Tables C-25, C-26, and C-27, respectively.

**Table C-25. Presence of Key Features of Study Design for Dieldrin—Observational Epidemiology Studies**

| Reference | Key features | | | | Initial study confidence |
|---|---|---|---|---|---|
| | Controlled exposure | Exposure prior to outcome | Outcomes assessed on an individual level | Comparison group | |
| ***Outcome: Hepatic effects*** | | | | | |
| *Cohort* | | | | | |
| de Jong 1991 | No | Yes | Yes | Yes | Moderate |
| Hoogendam et al. 1965 | No | Yes | Yes | No | Low |
| Hunter et al. 1972 | No | Yes | Yes | Yes | Moderate |
| Jager 1970 | No | Yes | Yes | Yes | Moderate |
| Morgan and Lin 1978 | No | Yes | Yes | No | Low |
| Morgan and Roan 1974 | No | Yes | Yes | Yes | Moderate |
| Van Sittert and de Jong 1987 | No | Yes | Yes | Yes | Moderate |
| Warnick and Carter 1972 | No | Yes | Yes | Yes | Moderate |
| *Case series* | | | | | |
| Black 1974 | No | Yes | Yes | NA | Low |
| Garrettson and Curley 1969 | No | Yes | Yes | NA | Low |
| Radomski et al. 1968 | No | Yes | Yes | Yes | Moderate |

## Table C-25. Presence of Key Features of Study Design for Dieldrin—Observational Epidemiology Studies

| Reference | Key features: Controlled exposure | Exposure prior to outcome | Outcomes assessed on an individual level | Comparison group | Initial study confidence |
|---|---|---|---|---|---|
| ***Outcome: Neurological effects*** | | | | | |
| Cohort | | | | | |
| De Jong 1991 | No | Yes | Yes | Yes | Moderate |
| Hoogendam et al. 1962 | No | Yes | Yes | No | Low |
| Hoogendam et al. 1965 | No | Yes | Yes | No | Low |
| Case-control | | | | | |
| Sandifer et al. 1981 | No | Yes | Yes | Yes | Moderate |
| Weisskopf et al. 2010 | No | Yes | Yes | Yes | Moderate |
| Case series | | | | | |
| Black 1974 | No | Yes | Yes | NA | Low |
| Garrettson and Curley 1969 | No | Yes | Yes | NA | Low |
| Patel and Rao 1958 | No | Yes | Yes | NA | Low |
| Pennell et al. 2006 | No | Yes | Yes | NA | Low |

## Table C-26. Presence of Key Features of Study Design for Dieldrin—Human Controlled-Exposure Studies

| Reference | Key features: Comparison group or subjects as own controls | Sufficient number of subjects | Appropriate methods to measure outcomes | Appropriate statistics or adequate data for independent statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| ***Outcome: Hepatic effects*** | | | | | |
| *Oral chronic exposure* | | | | | |
| Hunter and Robinson 1967 | Yes | No | No | No | Very low |
| ***Outcome: Neurological effects*** | | | | | |
| *Oral chronic exposure* | | | | | |
| Hunter and Robinson 1967 | Yes | No | No | No | Very low |

## Table C-27. Presence of Key Features of Study Design for Dieldrin—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Key feature: Sufficient number of animals per group | Key feature: Appropriate parameters to assess potential effect | Key feature: Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| ***Outcome: Hepatic effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Chernoff et al. 1975 rat | Yes | Yes | No | Yes | Moderate |
| Chernoff et al. 1975 mouse | Yes | Yes | No | Yes | Moderate |
| Goel et al. 1988 rat | Yes | No | No | Yes | Low |
| Kohli et al. 1977 rat | Yes | Yes | No | Yes | Moderate |
| Wright et al. 1972 mouse | Yes | Yes | Yes | No | Moderate |
| *Oral intermediate exposure* | | | | | |
| Ahmed et al. 1986 rat | Yes | Yes | No | Yes | Moderate |
| Bandyopadhyay et al. 1982b rat | Yes | Yes | No | Yes | Moderate |
| Shakoori et al. 1982 rat | Yes | Yes | No | Yes | Moderate |
| Stevenson et al. 1995 mouse | | | | | |
| Treon et al. 1951a rat | Yes | Yes | Yes | No | Moderate |
| Treon et al. 1951b dog | Yes | No | No | No | Very low |
| Treon et al. 1953a rat | Yes | Yes | Yes | Yes | High |
| *Oral chronic exposure* | | | | | |
| Deichmann et al. 1970 rat | Yes | Yes | Yes | Yes | High |
| Fitzhugh et al. 1964 rat | Yes | Yes | Yes | Yes | High |
| Fitzhugh et al. 1964 dog | Yes | No | Yes | Yes | Moderate |
| Harr et al. 1970 rat | Yes | No | Yes | Yes | Moderate |
| Kitselman 1953 dog | Yes | No | No | No | Very low |
| NCI 1978a rat | Yes | Yes | Yes | Yes | High |
| NCI 1978a mouse | Yes | Yes | Yes | Yes | High |
| Walker et al. 1969 rat | Yes | Yes | Yes | Yes | High |
| Walker et al. 1969 dog | Yes | Yes | Yes | Yes | High |
| ***Outcome: Neurological effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Burt 1975 rat (16.7 mg/kg) | Yes | Yes | No | Yes | Moderate |
| Burt 1975 rat (2.5, 5 mg/kg) | Yes | Yes | No | Yes | Moderate |
| Burt 1975 rat (8.4, 16.7 mg/kg) | Yes | Yes | No | Yes | Moderate |
| Foster et al.2008 mouse | Yes | Yes | No | No | Low |
| Foster et al.2008 mouse rep | Yes | Yes | No | No | Low |
| Mehrotra et al. 1989 rat | Yes | No | Yes | Yes | Moderate |

## Table C-27. Presence of Key Features of Study Design for Dieldrin—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| Sandler et al. 1969 sheep | No | No | No | No | Very low |
| Woolley et al. 1985 rat | No | No | No | No | Very low |
| *Oral intermediate exposure* | | | | | |
| Burt 1975 rat | Yes | Yes | No | Yes | Moderate |
| NCI 1978b rat | Yes | Yes | No | No | Low |
| Smith et al. 1976 monkey | Yes | No | Yes | No | Low |
| Treon et al. 1951b dog | Yes | No | No | No | Very low |
| Van Gelder 1975 sheep | | | | | |
| *Oral chronic exposure* | | | | | |
| Khairy 1960 rat | Yes | No | No | No | Very low |
| Kitselman 1953 dog | Yes | No | No | No | Very low |
| NCI 1978a rat | Yes | Yes | Yes | No | Moderate |
| NCI 1978a mouse | Yes | Yes | Yes | No | Moderate |
| NCI 1978b rat | Yes | Yes | Yes | No | Moderate |
| Walker et al. 1969 rat | Yes | Yes | Yes | No | Moderate |
| Walker et al. 1969 dog | Yes | Yes | Yes | No | Moderate |
| Walker et al. 1973 mouse 128 weeks | Yes | Yes | Yes | No | Moderate |
| *Dermal acute exposure* | | | | | |
| Treon et al. 1953b rabbit | | | | | |
| ***Outcome: Reproductive effects*** | | | | | |
| *Oral intermediate exposure* | | | | | |
| Good and Ware 1969 mouse | Yes | Yes | Yes | Yes | High |
| Treon et al. 1954a rat | Yes | Yes | Yes | Yes | High |
| Virgo and Bellward 1975 mouse | Yes | Yes | Yes | Yes | High |
| ***Outcome: Developmental effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Carlson and Rosellini 1987 rat | | | | | |
| Chernoff et al. 1975 rat | Yes | Yes | Yes | Yes | High |
| Chernoff et al. 1975 mouse | Yes | Yes | Yes | Yes | High |
| Dix et al. 1977 mouse | | | | | |
| Ottolenghi et al. 1974 mouse | Yes | No | Yes | Yes | Moderate |
| Ottolenghi et al. 1974 hamster | Yes | No | Yes | Yes | Moderate |

## Table C-27. Presence of Key Features of Study Design for Dieldrin—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Key feature: Sufficient number of animals per group | Key feature: Appropriate parameters to assess potential effect | Key feature: Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| *Oral intermediate exposure* | | | | | |
| Harr et al. 1970 rat | Yes | No | Yes | Yes | Moderate |
| Treon et al.1954a rat | Yes | Yes | Yes | Yes | High |
| Virgo and Bellward 1975 mouse | Yes | Yes | Yes | Yes | High |
| *Oral chronic exposure* | | | | | |
| Kitselman 1953 dog | Yes | No | No | No | Very low |

A summary of the initial confidence ratings for each outcome is presented in Table C-28. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-28.

## Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| ***Outcome: Hepatic effects*** | | |
| *Inhalation chronic exposure* | | |
| Human studies | | |
| De Jong 1991 | Moderate | Moderate |
| Hoogendam et al. 1965 | Low | |
| Hunter et al. 1972 | Moderate | |
| Jager 1970 | Moderate | |
| Morgan and Lin 1978 | Low | |
| Morgan and Roan 1974 | Moderate | |
| van Sittert and de Jong 1987 | Moderate | |
| Warnick and Carter 1972 | Moderate | |
| *Oral acute exposure* | | |
| Human studies | | |
| Black 1974 | Low | Low |
| Garrettson and Curley 1969 | Low | |
| Animal studies | | |
| Chernoff et al. 1975 rat | Moderate | Moderate |
| Chernoff et al. 1975 mouse | Moderate | |

## Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| Goel et al. 1988 rat | Low | |
| Kohli et al. 1977 rat | Moderate | |
| Wright et al. 1972 mouse | Moderate | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Ahmed et al. 1986 rat | Moderate | |
| Bandyopadhyay et al. 1982b rat | Moderate | |
| Shakoori et al. 1982 rat | Moderate | |
| Stevenson et al. 1995 mouse | | High |
| Treon et al. 1951a rat | Moderate | |
| Treon et al. 1951b dog | Very low | |
| Treon et al. 1953a rat | High | |
| *Oral chronic exposure* | | |
| Human studies | | |
| Radomski et al. 1968 | Moderate | Moderate |
| Animal studies | | |
| Deichmann et al. 1970 rat | High | |
| Fitzhugh et al. 1964 rat | Moderate | |
| Fitzhugh et al. 1964 dog | Moderate | |
| Harr et al. 1970 rat | Moderate | |
| Kitselman 1953 dog | Very low | High |
| NCI 1978a rat | High | |
| NCI 1978a mouse | High | |
| Walker et al. 1969 rat | High | |
| Walker et al. 1969 dog | High | |
| ***Outcome: Neurological effects*** | | |
| *Inhalation acute exposure* | | |
| Human studies | | |
| Patel and Rao 1958 | Low | Low |
| *Inhalation chronic exposure* | | |
| Human studies | | |
| De Jong 1991 | Moderate | |
| Hoogendam et al. 1962 | Low | Moderate |
| Hoogendam et al. 1965 | Low | |
| Sandifer et al. 1981 | Moderate | |
| *Oral acute exposure* | | |
| Human studies | | |
| Black 1974 | Low | Low |
| Garrettson and Curley 1969 | Low | |
| Animal studies | | |
| Burt 1975 rat (16.7 mg/kg) | Moderate | |
| Burt 1975 rat (2.5, 5 mg/kg) | Moderate | Moderate |
| Burt 1975 rat (8.4, 16.7 mg/kg) | Moderate | |
| Foster et al.2008 mouse | Low | |

## Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| Foster et al.2008 mouse rep | Low | |
| Mehrotra et al. 1989 rat | Moderate | |
| Sandler et al. 1969 sheep | Very low | |
| Woolley et al. 1985 rat | Very low | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Burt 1975 rat | Moderate | |
| NCI 1978b rat | Low | |
| Smith et al. 1976 monkey | Low | Moderate |
| Treon et al. 1951b dog | Very low | |
| Van Gelder 1975 sheep | | |
| *Oral chronic exposure* | | |
| Human studies | | |
| Pennell et al. 2006 | Low | Moderate |
| Weisskopf et al. 2010 | Moderate | |
| Animal studies | | |
| Khairy 1960 rat | Very low | |
| Kitselman 1953 dog | Very low | |
| NCI 1978a rat | Moderate | |
| NCI 1978a mouse | Moderate | Moderate |
| NCI 1978b rat | Moderate | |
| Walker et al. 1969 rat | Moderate | |
| Walker et al. 1969 dog | Moderate | |
| Walker et al. 1973 mouse 128 weeks | Moderate | |
| *Dermal acute exposure* | | |
| Animal studies | | |
| Treon et al. 1953b rabbit | | |
| ***Outcome: Reproductive effects*** | | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Good and Ware 1969 mouse | High | |
| Treon et al. 1954a rat | High | High |
| Virgo and Bellward 1975 mouse | High | |
| ***Outcome: Developmental effects*** | | |
| *Oral acute exposure* | | |
| Animal studies | | |
| Carlson and Rosellini 1987 rat | | |
| Chernoff et al. 1975 rat | High | |
| Chernoff et al. 1975 mouse | High | |
| Dix et al. 1977 mouse | | |
| Ottolenghi et al. 1974 mouse | Moderate | |
| Ottolenghi et al. 1974 hamster | Moderate | High |

**Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies**

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Harr et al. 1970 rat | Moderate | High |
| Treon et al. 1954a rat | High | |
| Virgo and Bellward 1975 mouse | High | |
| *Oral chronic exposure* | | |
| Animal studies | | |
| Kitselman 1953 dog | Very low | Very low |

## C.11.2 Adjustment of the Confidence Rating—Dieldrin

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The five properties of the body of evidence that were considered to determine whether the confidence rating should be downgraded and the four properties of the body of evidence that were considered to determine whether the confidence rating should be upgraded are described above in Section C.6.2. The summaries of the assessment of the confidence in the body of evidence for hepatic effects, neurological effects, reproductive effects, and developmental effects are presented in Table C-29. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with dieldrin exposure is presented in Table C-30.

## Table C-29. Adjustments to the Initial Confidence in the Body of Evidence

| | Initial confidence | Adjustments to the initial confidence rating | Final confidence |
|---|---|---|---|
| **Outcome: Hepatic effects** | | | |
| Human studies | Moderate | Downgrade one confidence level; most studies in risk of bias second tier | Low |
| Animal studies | High | No adjustments | High |
| **Outcome: Neurological effects** | | | |
| Human studies | Moderate | Downgrade one confidence level; most studies in risk of bias second tier | Low |
| Animal studies | Moderate | No adjustments | Moderate |
| **Outcome: Reproductive effects** | | | |
| Animal studies | High | No adjustments | High |
| **Outcome: Developmental effects** | | | |
| Animal studies | High | No adjustments | High |

**Table C-30. Confidence in the Body of Evidence for Dieldrin**

| | Confidence in body of evidence | |
|---|---|---|
| Outcome | Human studies | Animal studies |
| Hepatic effects | Low | High |
| Neurological effects | Low | Moderate |
| Reproductive effects | | High |
| Developmental effects | | High |

## C.12 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—DIELDRIN

As described in Section C.7, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted.

A summary of the level of evidence of health effects for dieldrin is presented in Table C-31.

**Table C-31. Level of Evidence of Health Effects for Dieldrin**

| Outcome | Confidence in body of evidence | Direction of health effect | Level of evidence for health effect |
|---|---|---|---|
| **Human studies** | | | |
| Hepatic effects | Low | Health effect | Moderate |
| Neurological effects | Low | Health effect | Moderate |
| **Animal studies** | | | |
| Hepatic effects | High | Health effect | High |
| Neurological effects | Moderate | Health effect | Moderate |
| Reproductive effects | High | Health effect | High |
| Developmental effects | High | Health effect | High |

## C.13 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—DIELDRIN

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. Refer to Section C.8 for the four hazard identification conclusion categories for health effects, the hazard characterization scheme (see Figure C-1), and the hazard identification conclusion categories.

The hazard identification conclusions for dieldrin are listed below and summarized in Table C-32.

**Presumed Health Effects**

- Hepatic effects
  - Human studies evaluating hepatic endpoints have not provided convincing evidence of aldrin-induced liver effects.

- Increased liver weight and histopathologic hepatic changes have been observed in laboratory animals following chronic-duration oral exposure to dieldrin (Ahmed et al. 1986a; Fitzhugh et al. 1964; Harr et al. 1970; Kitselman 1953; Shakoori et al. 1982; Thorpe and Walker 1973; Treon et al. 1951a; Walker et al. 1969).

- Neurological effects
  - Various clinical signs and abnormal EEGs have been observed among workers involved in the production of dieldrin or its use as an insecticide (Avar and Czegledi-Janko 1970; Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). Neurological effects were observed in individuals inadvertently or intentionally ingesting dieldrin-containing solutions (Black 1974; Garrettson and Curley 1969).
  - Oral dosing of laboratory animals with dieldrin has resulted in neurological effects such as increased locomotor activity, impaired operant behavior, impaired learning, convulsions, tremors, and neuronal degeneration (Burt 1975; Carlson and Rosellini 1987; Kitselman 1953; Mehrotra et al. 1989; NCI 1978a; Sandler et al. 1969; Smith et al. 1976; Van gelder 1975; Wagner and Greene 1978; Woolley et al. 1985).

- Reproductive effects
  - No human studies evaluated reproductive endpoints.
  - Decreased fertility was observed in studies of laboratory animals administered dieldrin orally (Keplinger et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975).

- Developmental effects
  - No human studies evaluated developmental endpoints.
  - Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975). Aldrin or dieldrin exposure during gestation has resulted in some evidence of external malformations or skeletal anomalies in animals (Chernoff et al. 1975; Ottolenghi et al. 1974).

**Table C-32. Hazard Identification Conclusions for Dieldrin**

| Outcome | Hazard identification |
|---|---|
| Hepatic effects | Presumed health effect in humans |
| Neurological effects | Presumed health effect in humans |
| Reproductive effects | Presumed health effect in humans |
| Developmental effects | Presumed health effect in humans |

# APPENDIX D. USER'S GUIDE

## Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

### Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

## Chapter 2. Health Effects

### Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**TABLE LEGEND**

**See Sample LSE Table (page D-5)**

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

**FIGURE LEGEND**

**See Sample LSE Figure (page D-6)**

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 chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints 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) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

**Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral** (1)

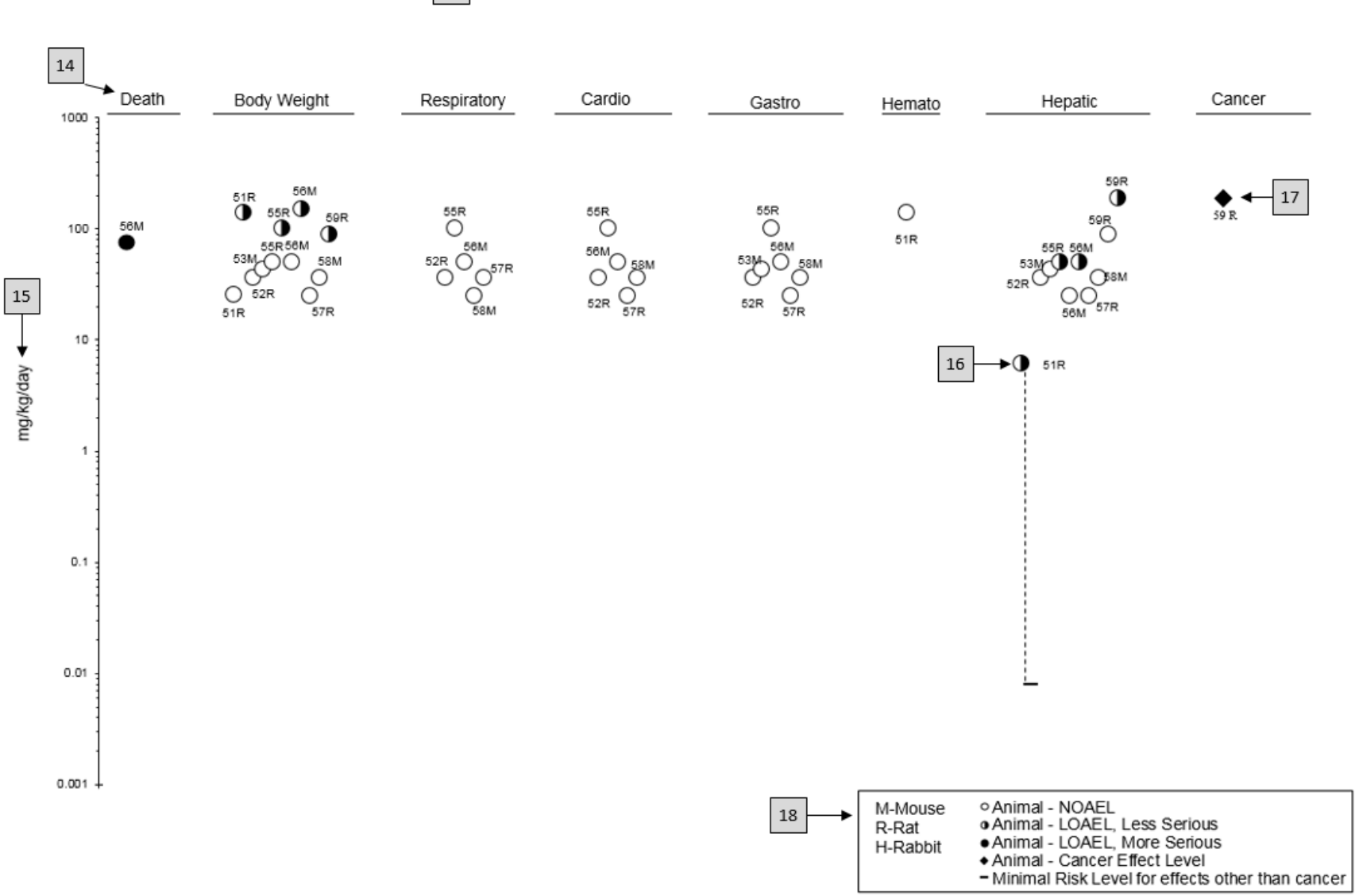
| Figure key[a] (3) | Species (strain) No./group (4) | Exposure parameters (5) | Doses (mg/kg/day) (5) | Parameters monitored (6) | Endpoint (7) | NOAEL (mg/kg/day) (8) | Less serious LOAEL (mg/kg/day) (9) | Serious LOAEL (mg/kg/day) (9) | Effect |
|---|---|---|---|---|---|---|---|---|---|
| **CHRONIC EXPOSURE** (2) | | | | | | | | | |
| 51 | Rat (Wistar) 40 M, 40 F | 2 years (F) | M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4 | CS, WI, BW, OW, HE, BC, HP | Bd wt | 25.5 | 138.0 | | Decreased body weight gain in males (23–25%) and females (31–39%) |
| | | | | | Hemato | 138.0 | | | |
| | | | | | Hepatic | | 6.1[c] | | Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure |
| **Aida et al. 1992** (10) | | | | | | | | | |
| 52 | Rat (F344) 78 M | 104 weeks (W) | 0, 3.9, 20.6, 36.3 | CS, BW, FI, BC, OW, HP | Hepatic | 36.3 | | | |
| | | | | | Renal | 20.6 | 36.3 | | Increased incidence of renal tubular cell hyperplasia |
| | | | | | Endocr | 36.3 | | | |
| **George et al. 2002** | | | | | | | | | |
| 59 | Rat (Wistar) 58M, 58F | Lifetime (W) | M: 0, 90 F: 0, 190 | BW, HP | Cancer | | 190 F | | Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided |
| **Tumasonis et al. 1985** | | | | | | | | | |

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

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

## Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



# APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

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***Primary Chapters/Sections of Interest***

**Chapter 1: Relevance to Public Health**: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

**Chapter 2: Health Effects**: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
***NOTE***: Not all health effects reported in this section are necessarily observed in the clinical setting.

**Pediatrics**:

**Section 3.2 Children and Other Populations that are Unusually Susceptible**
**Section 3.3 Biomarkers of Exposure and Effect**

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***ATSDR Information Center***

***Phone:*** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
***Internet***: http://www.atsdr.cdc.gov

The following additional materials are available online:

*Case Studies in Environmental Medicine* are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

*Managing Hazardous Materials Incidents* is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp).

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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***Other Agencies and Organizations***

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

*The National Institute for Occupational Safety and Health* (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

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***Clinical Resources (Publicly Available Information)***

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

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

*The American College of Medical Toxicology* (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

*The Pediatric Environmental Health Specialty Units* (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

*The American Association of Poison Control Centers* (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

# APPENDIX F. GLOSSARY

**Absorption—**The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

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

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

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

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

**Benchmark Dose (BMD) or Benchmark Concentration (BMC)—**is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a $BMD_{10}$ would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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

**Biomarkers—**Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

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

**Carcinogen—**A chemical capable of inducing cancer.

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

**Case Report—**A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

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

**Ceiling Value—**A concentration that must not be exceeded.

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

**Clastogen—**A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

**Cohort Study—**A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

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

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

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

**Dose-Response Relationship—**The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

**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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

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

**Excretion—**The process by which metabolic waste products are removed from the body.

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

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

**Health Advisory—**An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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)—**A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

**Immunotoxicity—**Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

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

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

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

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

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

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

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

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

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

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

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

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

**Metabolism—**Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

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

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

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

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

**Mutagen—**A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

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

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

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

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

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

**Permissible Exposure Limit (PEL)—**An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

**Pesticide—**General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

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

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

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

**Physiologically Based Pharmacokinetic (PBPK) Model—**A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

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

**Reference Dose (RfD)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

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

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

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

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

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

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

**Short-Term Exposure Limit (STEL)—**A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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

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

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

**Threshold Limit Value (TLV)—**An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)—**An average exposure within a given time period.

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

**Toxics Release Inventory (TRI)—**The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

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

**Xenobiotic—**Any substance that is foreign to the biological system.

# APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| AAPCC | American Association of Poison Control Centers |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ACMT | American College of Medical Toxicology |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AEGL | Acute Exposure Guideline Level |
| AIC | Akaike's information criterion |
| AIHA | American Industrial Hygiene Association |
| ALT | alanine aminotransferase |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BCF | bioconcentration factor |
| BMD/C | benchmark dose or benchmark concentration |
| $BMD_X$ | dose that produces a X% change in response rate of an adverse effect |
| $BMDL_X$ | 95% lower confidence limit on the $BMD_X$ |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| C | centigrade |
| CAA | Clean Air Act |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| cm | centimeter |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DWEL | drinking water exposure level |
| EAFUS | Everything Added to Food in the United States |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| ERPG | emergency response planning guidelines |
| F | Fahrenheit |
| F1 | first-filial generation |
| FDA | Food and Drug Administration |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FR | Federal Register |

| | |
|---|---|
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GGT | γ-glutamyl transferase |
| GRAS | generally recognized as safe |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| HHS | Department of Health and Human Services |
| HPLC | high-performance liquid chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Level of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| mCi | millicurie |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| MSHA | Mine Safety and Health Administration |
| Mt | metric ton |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NCEH | National Center for Environmental Health |
| ND | not detected |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |

| | |
|---|---|
| NIOSH | National Institute for Occupational Safety and Health |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NTP | National Toxicology Program |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| PAC | Protective Action Criteria |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PEHSU | Pediatric Environmental Health Specialty Unit |
| PEL | permissible exposure limit |
| PEL-C | permissible exposure limit-ceiling value |
| pg | picogram |
| PND | postnatal day |
| POD | point of departure |
| ppb | parts per billion |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure level/limit |
| REL-C | recommended exposure level-ceiling value |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SD | standard deviation |
| SE | standard error |
| SGOT | serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST) |
| SGPT | serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT) |
| SIC | standard industrial classification |
| SMR | standardized mortality ratio |
| sRBC | sheep red blood cell |
| STEL | short term exposure limit |
| TLV | threshold limit value |
| TLV-C | threshold limit value-ceiling value |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |
| USNRC | U.S. Nuclear Regulatory Commission |

| | |
|---|---|
| VOC | volatile organic compound |
| WBC | white blood cell |
| WHO | World Health Organization |
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| $q_1^*$ | cancer slope factor |
| – | negative |
| + | positive |
| (+) | weakly positive result |
| (–) | weakly negative result |