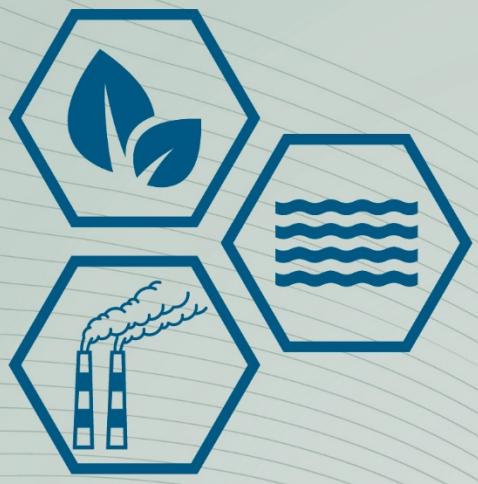

Toxicological Profile for Endrin

March 2021

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

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

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.

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 due to associated acute, intermediate, and chronic exposures;

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

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed 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.

VERSION HISTORY

Date	Description
March 2021	Final toxicological profile released
May 2019	Draft for public comment toxicological profile released
August 1996	Final toxicological profile released

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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.

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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.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Endrin [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-(1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-, CAS No. 72-20-8] was used as a pesticide until the voluntary cancellation of its registration in 1991. It has not been produced or used in the United States since 1991 (EPA 1984a, 1985a, 1986a, 1993; USDA 1993), which greatly reduces the potential for human exposure. This profile also covers endrin aldehyde and endrin ketone, which were never commercial products, but occurred as impurities of endrin or as degradation products (EPA 1985b; IARC 1974; SRI 1987). Because the United States no longer produces or uses endrin, future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low. The most significant route of exposure is most likely ingestion of imported foods contaminated with endrin; however, there may also be some localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin.

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

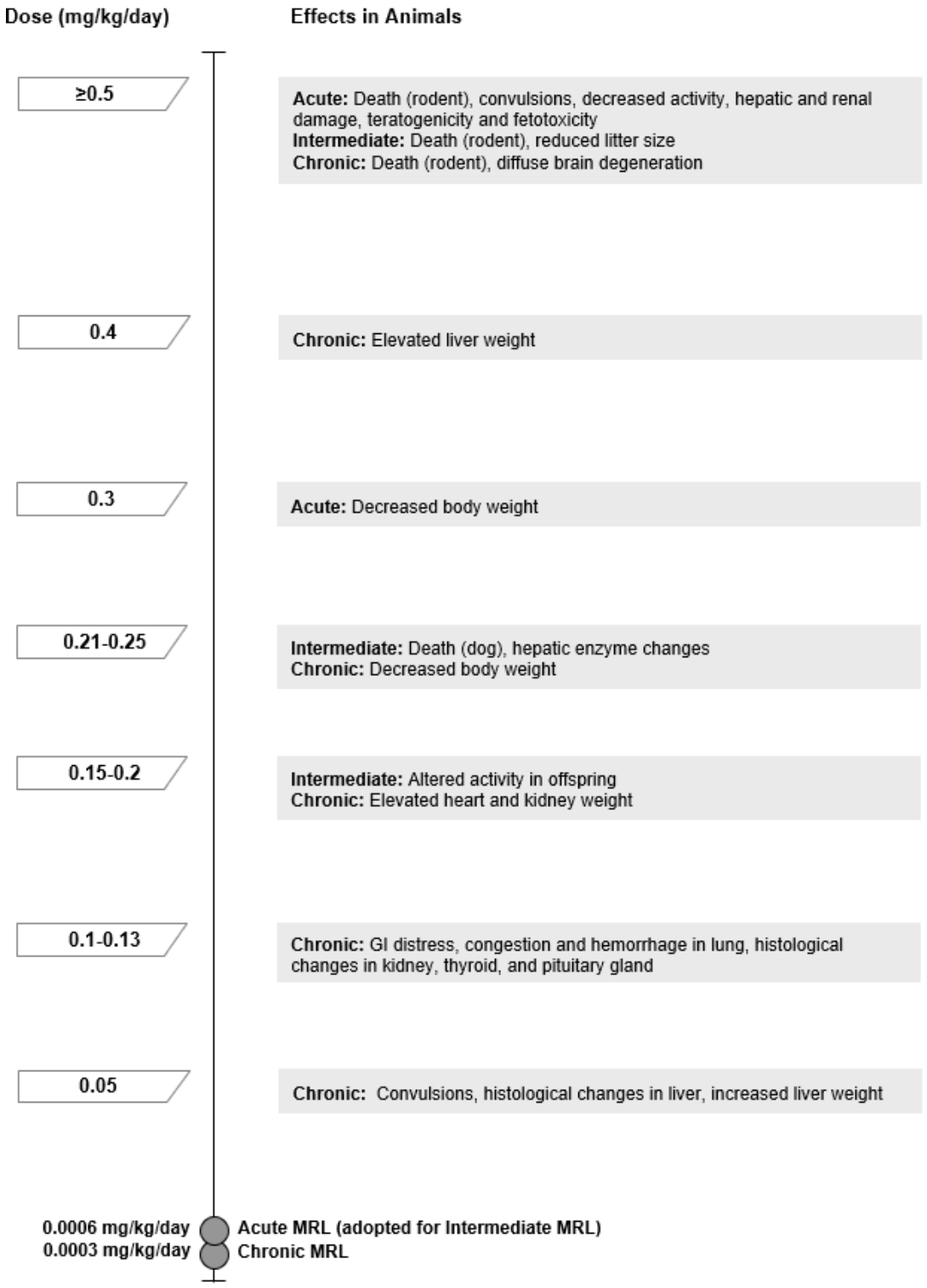
1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of endrin comes primarily from oral studies in animals; however, several occupational surveys and case reports in exposed humans contribute to the identification of primary toxicity targets. Sixty-three laboratory animal toxicity studies with health effects data have been identified: 2 inhalation, 57 oral, and 4 dermal.

As illustrated in Figure 1-1, the most sensitive effects in laboratory animals appear to be neurological effects (e.g., altered activity, convulsions) and hepatic toxicity. Other noncancer toxicity effects are generally only observed at doses associated with lethality, including diffuse organ damage (lungs, heart, kidney, endocrine glands) and body weight effects. With the exception of altered locomotor activity in offspring, developmental effects were only observed at doses that caused significant maternal mortality and/or toxicity. Data regarding these effects are discussed briefly below. Available data following exposure to endrin in humans and animals are inadequate to determine the potential for adverse effects in

the gastrointestinal, hematological, musculoskeletal, ocular, dermal, immunological, or reproductive systems.

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



Neurological Effects. Based on human reports, the central nervous system is the primary target system of endrin. Acute human poisonings by endrin were characterized by symptoms of central nervous system toxicity such as jerking of arms and legs, twitching facial muscles, tonic and clonic contractions, convulsions and sudden collapse, and death (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Rowley et al. 1987; Runhaar et al. 1985; Waller et al. 1992; Weeks 1967). Numerous case reports of convulsions following acute, high-level exposure have been reported in workers that manufacture endrin; changes in electroencephalogram (EEG) patterns were usually observed in these cases (Hoogendam et al. 1962, 1965).

Neurological effects occurred consistently in animals exposed to endrin via inhalation, oral, and dermal exposure. Reported findings included behavioral effects (e.g., altered activity) and frank neurotoxic effects (e.g., tremors and convulsions) (Chernoff et al. 1979; Deichmann et al. 1970; Gaines 1960; Kavlock et al. 1981; Kettering 1969, 1971; Lawrence et al. 1968; Mehrotra et al. 1989; NCI 1979; Pandy 1978; Speck and Maaske 1958; Treon et al. 1955), with altered EEG and diffuse brain lesions observed at lethal levels (Ressang et al. 1959; Speck and Maaske 1958; Treon et al. 1955). Altered activity levels have also been reported in rat and hamster offspring following maternal exposure to endrin (Gray et al. 1981).

Hepatic Effects. Human data on endrin-related hepatic effects are limited. The available human data consist of an occupational survey of endrin workers reporting a few cases of increased serum levels of liver enzymes (Hoogendam et al. 1965). However, only limited conclusions should be drawn from these results, as the levels were within normal limits at subsequent evaluations (1 week–3 months later), despite continued occupational exposure. Moreover, the study did not control for concurrent exposure to other chemicals or alcohol. Studies involving several species of laboratory animals have consistently reported hepatic effects following inhalation, oral, or dermal exposure at or near lethal levels. Effects included increased liver weight, altered liver serum enzymes, diffuse degenerative lesions, necrosis, vacuolation, fatty degeneration, and lipid peroxidation (Ali and Shakoori 1993; Bagchi et al. 1992a, 1992b, 1992c; Hassan et al. 1991; Hassoun et al. 1993; Kavlock et al. 1981; Lawrence et al. 1968, Treon et al. 1955; Young and Mehendale 1986). Chronic-duration oral studies in rats and dogs reported hepatic effects at sublethal doses, including increased liver weight and/or cloudy swelling of centrilobular cells (Deichmann et al. 1970; Kettering 1969; Treon et al. 1955).

Renal Effects. No human studies that assessed renal effects following endrin exposure were found. Inhalation, oral, and dermal exposure to lethal levels of endrin caused diffuse degenerative lesions in the

kidneys of various species (Treon et al. 1955). Available laboratory animal studies have reported inconsistent renal effects at sublethal exposure levels. A single study involving acute exposure to a high dose reported renal histopathologic effects in rats, mice, and hamsters, including moderate tubular necrosis and congestion, inflammation, and interstitial edema (Hassan et al. 1991). One chronic-duration oral study in rats reported renal effects (cloudy swelling of tubule epithelial cells) at sublethal levels (Deichmann et al. 1970). However, a 2-year bioassay did not observe any pathological renal effects in rats or mice (NCI 1979) or dogs (Kettering 1969) following sublethal chronic doses.

Endocrine Effects. Several epidemiological studies have examined the potential relationship between environmental endrin exposure and thyroid hormone levels in highly contaminated regions. In general, only weak (if any) relationships were observed, and findings are inconsistent between studies, sexes, and age groups (Freire et al. 2011, 2012, 2013; Piccoli et al. 2016). A potential increase in risk for Type I diabetes was observed in children with high serum endrin levels; however, the study did not adjust for any confounders, including other detectible pesticides (El Morsi et al. 2012). In laboratory animals, thyroid hyperplasia and pituitary cysts were observed in rats, but not in mice or dogs, in chronic bioassay studies with endrin administered in the feed (Kettering 1969; NCI 1979).

Respiratory Effects. Limited human and animal data showed respiratory effects following endrin exposure. Increased deaths due to pneumonia and other nonmalignant respiratory diseases were observed in workers at one of two plants that manufactured endrin (Ditraglia et al. 1981). However, simultaneous exposure to other chemicals occurred, and increased respiratory disease was not observed in the second endrin manufacturing facility. Pulmonary edema was observed in a patient poisoned with endrin, but was thought to be due to chemical pneumonitis from aspiration of aromatic hydrocarbons contained in the formulation (Runhaar et al. 1985). Some rats chronically exposed to low dietary doses exhibited focal hemorrhage and congestion of the lungs (Deichmann et al. 1970). Other histopathologic effects were only observed in animals at lethal doses and were attributed to widespread systemic failure at lethal exposure levels.

Cardiovascular Effects. Only limited reports of cardiovascular toxicity of endrin in animals were located. Diffuse degenerative lesions of the heart were observed in some dogs administered lethal doses of endrin, and enlarged hearts were observed at sublethal doses (Lawrence et al. 1968; Treon et al. 1955). The health significance of these finding is unclear, as the effects were not observed in other animal species.

1. RELEVANCE TO PUBLIC HEALTH

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

Developmental Effects. Available evidence in humans is inadequate to determine if endrin is associated with adverse birth outcomes or male reproductive development (Fernandez et al. 2007; Samra and Selim 2009); however, one study reported an association between endrin exposure and cord blood thyroid hormone levels (Freire et al. 2011). Prenatal exposure of animals to concentrations of endrin sufficient to cause maternal toxicity has resulted in a statistically significant increase in the incidence of fused ribs, cleft palate, exencephaly, meningoencephaloceles, and open eyes in hamsters and mice (Chernoff et al. 1979; Kavlock et al. 1981, 1985; Ottolenghi et al. 1974). Effects were not necessarily reproducible between studies (Goldenthal 1978b), and were not observed in rats (Goldenthal 1978a). Increased motor activity has been observed in hamster offspring after gestational exposure to maternally toxic doses (Gray et al. 1981). Adverse developmental effects generally have not been observed in rats (Kavlock et al. 1981), except for a transient increase in locomotor activity of pups at low doses that were not toxic to the dam (Gray et al. 1981) and delayed ossification at doses that resulted in maternal toxicity (Goldenthal 1978a).

Cancer. Studies of endrin-exposed workers have not detected significant increases in mortality due to cancer (Ribbens 1985). In two industries manufacturing endrin, small excesses of certain cancers were reported, including malignant neoplasms of the esophagus, rectum, liver, and lymphatic and hematopoietic systems (Ditraglia et al. 1981). However, these findings were not statistically significant, and the studies were limited by concurrent exposure to other chemicals. Endrin was reported to be noncarcinogenic in animal studies (Deichmann et al. 1970; NCI 1979; Treon et al. 1955). Reuber (1979) reported that endrin is carcinogenic; however, multiple reporting inconsistencies were identified, observed tumors did not show a dose-related response, and Reuber's criteria for classifying tissues as tumorigenic were not consistent with those of other investigators (IRIS 2002).

The U.S. Environmental Protection Agency (EPA) has classified endrin in Group D, not classifiable as to carcinogenicity in humans (IRIS 2002). The International Agency for Research on Cancer (IARC) has classified endrin in Group 3, not classifiable as to its carcinogenicity in humans (IARC 1987). The Department of Health and Human Services (HHS) has not classified the potential for endrin to cause cancer in humans (NTP 2016).

1.3 MINIMAL RISK LEVELS (MRLs)

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

The oral database was considered adequate for deriving an acute-duration MRL and a chronic-duration MRL. An MRL was not derived for intermediate-duration oral exposure because the MRL derived from the available data in the limited database would be higher than the acute-duration MRL. The acute-duration MRL is expected to be protective of intermediate-duration exposures; therefore, the acute oral MRL is adopted as the intermediate oral MRL. As presented in Figure 1-2, the available oral data for endrin suggest that the central nervous system and liver effects are the most sensitive targets of toxicity in laboratory animals; other potential sensitive targets include body weight, respiratory, renal, and endocrine effects.

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

Figure 1-2. Summary of Sensitive Targets of Endrin – Oral

The central nervous system and liver are the most sensitive targets of endrin oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

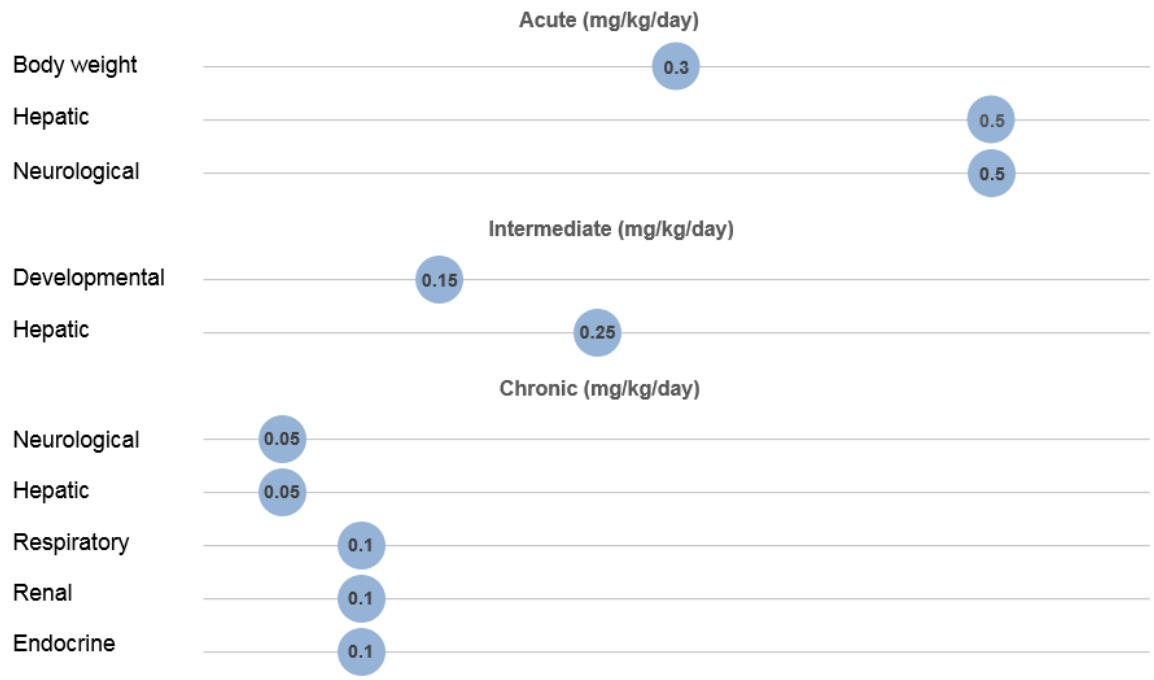


Table 1-1. Minimal Risk Levels (MRLs) for Endrin[a]

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	**0.0006**	Decreased locomotor activity	$BMDL_{1SD}$: 0.057	100	Kavlock et al. 1981
Intermediate	**0.0006**	Acute MRL is adopted as the intermediate MRL			
Chronic	**0.0003**	Convulsions, hepatic vacuolation	NOAEL: 0.025	100	Kettering 1969

[a]See Appendix A for additional information.

BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., 1SD = exposure concentration associated with 1 standard deviation change in outcome); 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 endrin. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

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 provides an overview 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 endrin, but may not be inclusive of the entire body of literature.

Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, animal oral studies are presented in Table 2-3 and Figure 2-3, and animal dermal studies are presented in Table 2-4. For the inhalation and dermal tables (Table 2-2 and Table 2-4, respectively), all studies evaluated endrin. For the oral table (Table 2-3), the experimental compound (endrin, endrin ketone, or endrin aldehyde) is indicated for each study.

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.

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

The health effects of endrin have been evaluated in 32 human studies and 63 animal studies. As illustrated in Figure 2-1, most of the health effects data come from oral exposure studies in animals. For the purposes of Figure 2-1, all occupational studies were classified as inhalation studies and all population-based studies were classified as oral studies; however, it is acknowledged that humans were likely exposed via multiple exposure routes in both occupational and environmental settings. For animal data, oral studies are available for the majority of health effect categories and all exposure duration categories. The inhalation and dermal animal databases are limited to three studies each, evaluating limited endpoints. The most examined endpoints were neurological, death, hepatic, renal, and body weight effects. Unless otherwise noted, the administered compound in animal studies was endrin; endrin aldehyde or endrin ketone were only administered in three acute oral studies. The available human studies were predominantly focused on neurological effects and cancer, with more recent studies focusing on potential endocrine, reproductive, and developmental effects.

The human and animal studies suggest that the neurological and hepatic systems are the most sensitive targets of endrin toxicity; other potential targets include the endocrine system, kidney, heart, and developing organism.

- **Neurological effects:** Numerous case reports of convulsions following acute, high-level exposure have been reported in workers who manufacture endrin and in cases of human oral poisoning. Convulsions and other signs of overt neurotoxicity have also been observed in numerous animal studies at or just below lethal exposure levels.

- **Hepatic effects:** An occupational survey of workers who manufacture endrin (and other organochlorine pesticides) reported occasional, transient changes in serum hepatic enzymes in workers. Hepatic damage has also been observed in numerous animal studies at oral doses associated with neurological effects.

- **Endocrine effects:** Data for this endpoint are limited. Human cross-sectional studies have reported mixed and conflicting findings regarding potential associations between endrin exposure and thyroid hormone levels. One chronic study in mice reported thyroid hyperplasia.

- **Renal effects:** No human data are available. Several oral studies in animals reported renal effects; however, observed effects were generally nonspecific (e.g., diffuse degeneration) and were attributed to widespread systemic effects at lethal exposure levels. A few studies reported effects at nonlethal doses, including increased kidney weight, cloudy swelling, and moderate tubular necrosis.

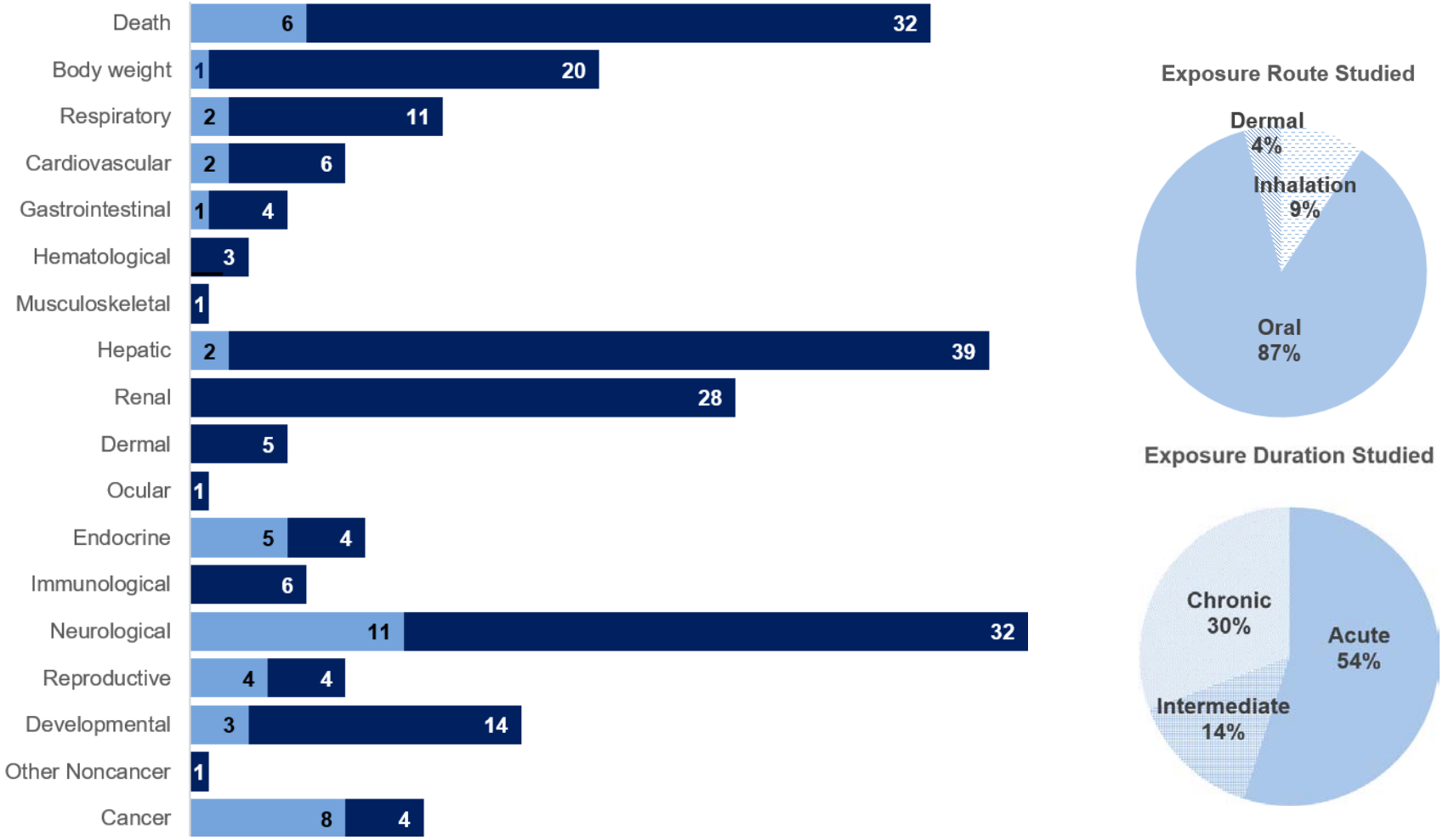
- **Cardiac and respiratory effects:** Limited data from human studies do not indicate that the cardiac and respiratory systems are sensitive targets of endrin toxicity. A few oral animal studies reported cardiac and respiratory effects; however, these effects were generally nonspecific (e.g., increased weight, hemorrhage) and were attributed to widespread systemic effects at or near lethal exposure levels.

- **Developmental effects:** Available human data are inadequate to determine if endrin exposure is associated with birth outcomes or male reproductive development; however, one study reported an association between endrin exposure and cord blood thyroid hormone levels. Teratogenic and fetotoxic effects have been reported in gestational oral exposure studies in laboratory animals at doses associated with maternal toxicity and death. These developmental effects are assumed to be secondary to maternal toxicity. One study reported altered locomotor activity in rat and hamster offspring following maternal exposure; effects in hamsters were only observed at maternally toxic doses.

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

Most studies examined the potential hepatic and neurological effects of endrin

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



*Includes studies discussed in Chapter 2. A total of 95 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints. All occupational studies were classified as inhalation studies and all population-based studies were classified as oral studies to avoid double counting these studies; however, it is acknowledged that humans were likely exposed via multiple exposure routes in both occupational and environmental settings.

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Occupational studies		
Ditraglia et al. 1981 Cohort study United States Exposure group: Plant 2: 305 workers from heptachlor/endrin manufacturing plant Plant 3: 1,155 workers from aldrin/dieldrin/endrin manufacturing plant Referent group: None (SMRs calculated using general population statistics)	Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal and oral exposure All workers had been employed for ≥6 months	Observed death (SMR; 95% CI) All causes: Plant 2: 24/305 (66; 42–98) Plant 3: 173/1155 (84; 72–98) Systems with significant increases in nonmalignant disease: Nonmalignant respiratory system disease Plant 2: 0/305 Plant 3: 22/1155 (212; 133–320)* All malignant neoplasms: Plant 2: 6/305 (91; 33–198) Plant 3: 31/1155 (82; 56–116) Specific cancers with nonsignificant increases: Esophageal cancer Plant 2: 0/305 Plant 3: 2/1155 (235; 26–850) Rectal cancer Plant 2: 0/305 Plant 3: 3/1155 (242; 49–707) Liver cancer Plant 2: 0/305 Plant 3: 3/1155 (242; 49–707) Lymphatic and hematopoietic system cancer Plant 2: 0/305 Plant 3: 6/1155 (147; 54–319)

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Hoogendam et al. 1962, 1965 Occupational health survey Netherlands Exposure group: 592 workers employed in an aldrin/dieldrin/ endrin manufacturing plants between 1956 and 1965 Referent group: None	Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal and oral exposure Neurological cases had been employed for 3 days – 4.5 years and liver cases had been employed for 1–9 years; all observed symptoms expected to be due to acute, high exposures (potentially without protective equipment)	Health effects noted during 9-year monitoring period: 17 cases of convulsions with recovery within 1–3 days; confirmed with abnormal EEGs (predominantly bilateral synchronous theta waves, and synchronous spike and wave complexes), which generally returned to normal within 0.5–1 month after removal from exposure 7 cases of abnormal liver function: 3 workers with increased thymol turbidity, 1 worker with increased AST, and 4 workers with increased ALT; all test values returned to normal at subsequent evaluations
Piccoli et al. 2016 Cross-sectional study Brazil Study population: 120 male and 155 female agricultural workers	Exposure expected to be primarily via inhalation, with potential for dermal and oral exposure Serum endrin levels detected >LOQ in 30.6% of workers Median: <LOQ 95%: 179.7 ng/g >50% had been agricultural workers for >25 years, >40% had handled pesticides for >20 years	Adjusted[a] regression coefficients between serum endrin levels and serum thyroid hormone levels Total T3: 0.97 (0.94–0.99)* Free T4: 0.98 (0.94–1.02) TSH: 0.99 (0.86–1.14)

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Ribbens 1985 Cohort study Netherlands Exposure group: 232 previously exposed workers in aldrin/dieldrin/ endrin/telodrin manufacturing plant Referent group: None (expected mortality calculated using general population statistics)	Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal and oral exposure Mean years exposed (range): 11 (4–27) Mean years since exposed (range): 24 (4–29)	Observed total mortality: 25 Expected total mortality: 38 Observed cancer mortality: 9 Expected cancer mortality: 12 Cancer SMR (95% CI): 0.75 (0.25–1.25)
Versteeg and Jager 1973 Cohort study Netherlands Exposure group: 52 former workers in aldrin/dieldrin/endrin/telodrin manufacturing plant Referent group: None	Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal and oral exposure Mean years exposed (range): 6.6 (4.0–12.3) Mean years since exposed (range): 7.4 (4.5–16)	Mortality was limited to one accidental death (automobile accident); there were no cases of malignant disease, hepatic disease, or epileptiform convulsions
General population studies		
Bapayeva et al. 2016 Cohort study South Kazakhstan Exposure group: 48 adolescent females (age 10–17 years) living in cotton-growing rural regions Referent group: 40 adolescent females (age 10–17 years) living in non-cotton-growing rural regions	Route(s) of exposure unknown, but most likely primarily oral via diet Mean serum endrin levels±SD Exposure group: 37.57±0.9 mg/L Referent group: 4.85±0.69 mg/L	Endrin levels were significantly elevated in exposure group compared with referents; lindane, dieldrin, and DDT levels were also significantly elevated Regression coefficient (R^2) between reproductive hormone levels and serum endrin (exposure and referent groups combined) FSH: -0.82705 Estradiol: -0.82705 Significant changes in several parameters indicated delayed physical and sexual development in female

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		adolescents exposed to endrin, lindane, dieldrin, and DDT (endrin-specific analysis not conducted for these parameters) Altered parameters included decreased height, body weight, chest circumference, external pelvic measurement, and delayed development of secondary sexual characteristics
Chen et al. 2018 Cross-sectional study Taiwan Study population: 68 pregnant women	Route(s) of exposure unknown, but most likely primarily oral via diet Breast milk geometric mean ± SD (range) (ng/g lipid) Total endrin: 0.381±0.701 (<MDL–4.61) Endrin: 0.176±0.435 (<MDL–3.04) Endrin aldehyde: 0.0618±0.261 (<MDL–1.56) Endrin ketone: 0.0594±0.180 (<MDL–0.867)	OR (95%) of average menstrual period >5 days for endrin ketone; Adjusted: 7.06 (1.58,31.6), p=0.011* No associations for total endrin, endrin, or endrin aldehyde No associations between total endrin or endrin compound and risk of infertility
El Morsi et al. 2012 Case-control study Egypt Cases: 36 boys and 39 girls with type 1 diabetes (mean age 6.01 years) Controls: 16 healthy boys and 19 healthy girls (mean age 6.1 years)	Route(s) of exposure unknown, may have occurred in utero, via diet, or via contact with contaminated house dust, carpets, chemically treated gardens, or pets treated with insecticides Serum endrin levels were detected >LOQ in 10.7% of cases and 0% of controls Median (minimum–maximum) endrin values: Cases: 0.90 (0.88–0.96) ng/mL Controls: <LOQ	Serum endrin levels were significantly elevated in cases versus controls Odds ratio (95%) of having type 1 diabetes if endrin was detected >LOQ in serum Unadjusted: 1.52 (1.32,1.75)*

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Fernandez et al. 2007 Case-control study Granada Cases: 48 mother-son pairs, diagnosed with cryptorchidism and/or hypospadias at birth Controls: 114 mother-son pairs, no malformations	Route(s) of exposure unknown, but most likely primarily oral via diet Placental endrin levels were detected >LOQ in 22 cases (46%) and 48 controls (42%) Mean±SD (range) placental endrin levels (ng/g lipid) Cases: 5.0±4.8 (3.0–19.47) Controls: 7.4±11.9 (3.0–67.0)	Placental endrin levels were not elevated in cases compared with controls
Freire et al. 2011 Cross-sectional study Granada Study population: 220 mother-son pairs (from a larger cohort of 700 mother-son pairs in the INMA-Granada male birth cohort, born between 2000 and 2002)	Route(s) of exposure unknown, but most likely primarily oral via diet Placental endrin levels detected >LOQ in 75 placental samples GM (95% CI): 2.53 (2.12, 3.01) ng/g placenta	Odds ratio (95% CI) of having elevated TSH[b] in cord blood (≥5 mU/L) if endrin was detected >LOQ in placenta Unadjusted: 2.32 (1.18, 4.55)* Adjusted[c]: 2.05 (1.01, 4.18)* Association (β, 95% CI) between ln-transformed placental endrin levels and ln-transformed cord thyroid hormones Unadjusted: 0.08 (-0.10, 0.25) Adjusted[c]: 0.03 (-0.15, 0.20)
Freire et al. 2012 Cross-sectional study Brazil Study population: 193 children (<15 years old) from a rural area (Cidade dos Meninos) with heavy pesticide contaminations; mean age 6.5 years (range 5 months–14 years)	Primarily exposed via dermal contact and ingestion of contaminated soil, water, and locally produced food Serum endrin levels detected >LOQ in 88.1% of children Median (20^{th}–80^{th} %): 1.49 (0.28, 3.56) ng/mL	Adjusted[d] regression coefficients (95% CI) between serum endrin levels and serum thyroid hormone levels by quintile Total T3 Q1: referent Q2: -0.80 (-13.3, 11.7) Q3: -2.08 (-14.2, 10.0) Q4: 2.28 (-10.0, 14.6) Q5 13.3 (1.15, 25.4) p-trend: 0.03 Free T4

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Q1: referent Q2: -0.02 (-0.11, 0.07) Q3: 0.03 (-0.06, 0.11) Q4: 0.02 (-0.06,0.11) Q5 0.02 (-0.07, 0.10) p-trend: 0.42 TSH Q1: referent Q2: 0.33 (-0.10, 0.75) Q3: 0.05 (-0.37, 0.46) Q4: 0.17 (-0.25, 0.59) Q5 0.38 (-0.03, 0.79) p-trend: 0.19
Freire et al. 2013 Cross-sectional study Brazil Study population: 303 men and 305 women from a rural area (Cidade dos Meninos) with heavy pesticide contaminations; mean age 39 years	Primarily exposed via dermal contact and ingestion of contaminated soil, water, and locally produced food Exposure duration: Since birth: 82 men, 89 women Since childhood (<14 years old): 75 men, 57 women Since adulthood (≥15 years old): 147 men, 159 women Serum endrin levels detected >LOQ in 87.4% of men and 87.1% of women Median (25^{th}–75^{th} %) serum endrin levels: Men: 0.63 (0.24, 1.48) ng/mL Women: 0.58 (0.25,1.51) ng/mL	Adjusted[e] association (β, 95% CI) between serum endrin levels and serum thyroid hormone levels Total T3 Men: -0.40 (-1.75, 0.95) Women: 0.62 (-1.39, 2.61) Free T4 Men: -0.002 (-0.01, 0.01) Women: 0.01 (-0.004, 0.03) TSH Men: -0.03 (-0.07, 0.02) Women: -0.02 (-0.09, 0.05) When stratified by exposure duration, the study authors reported that a positive relationship was observed between serum endrin levels and serum T4 and TSH in women who were born in Cidade dos

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Meninos; however, data were not provided and statistical significance of findings were not discussed
Freire et al. 2014 Cross-sectional study Brazil Study population: 304 men and 300 women from a rural area (Cidade dos Meninos) with heavy pesticide contaminations; mean age 39 years	Primarily exposed via dermal contact and ingestion of contaminated soil, water, and locally produced food Exposure duration: Since birth: 82 men, 88 women Since childhood (<14 years old): 75 men, 57 women Since adulthood (≥15 years old): 147 men, 155 women Serum endrin levels detected >LOQ in 87.4% of men, 87.9% of premenopausal women, and 87.0% of peri-/postmenopausal women Median (25^{th}-75^{th}%) serum endrin levels: Men: 0.63 (0.24, 1.48) ng/mL Premenopausal women: 0.59 (0.27,1.57) ng/mL Postmenopausal women: 0.54 (0.23, 1.38) ng/mL	Adjusted[f] association (β, 95% CI) between serum endrin levels and serum reproductive hormone levels Men Testosterone: -0.01 (-0.03,0.007) Premenopausal women Estradiol: 0.007 (-0.08, 0.09) Progesterone: -0.05 (-0.19,0.08) Prolactin: 0.00 (-0.07, 0.07) LH: -0.04 (-0.13, 0.06) FSH: -0.04 (-0.13, 0.06) Peri-/postmenopausal women Estradiol: 0.008 (-0.05, 0.07) Progesterone: 0.007 (-0.05, 0.07) Prolactin: 0.02 (-0.10, 0.14) LH: -0.09 (-0.19, 0.01) FSH: -0.05 (-0.13, 0.03)
Henríquez-Hernández et al. 2014 Cross-sectional study Canary Islands Study population: 191 males, 237 females; aged 18.1–77.3 years	Route(s) of exposure unknown, but most likely primarily oral via diet Serum endrin levels detected >LOQ in 291 samples Median (25^{th}–75^{th}%): 0.23 (0.00–0.49) µg/L	Odds ratio (95% CI) of having hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or antihypertensive medication) if endrin was detected >LOQ in blood Unadjusted: 1.077 (0.980–1.184); p=0.124

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Henríquez-Hernández et al. 2017 Cross-sectional study Canary Islands Study population: 187 males, 242 females; mean age 47.0 years	Route(s) of exposure unknown, but most likely primarily oral via diet Serum endrin levels detected >LOQ in 293 samples (68.3%) Median (5^{th}–95^{th}%): 0.2 (<LOQ–6.1) µg/L	Serum endrin levels were not significantly higher in subjects with diabetes, blood glucose levels ≥126 mg/dL, or BMI ≥25.
Samra and Selim 2009 Cross-sectional study Egypt 123 mother-child pairs (including 43 women with preterm deliveries and 80 women with full-term deliveries)	Route(s) of exposure unknown, but most likely primarily oral via diet Mean±SD maternal serum endrin levels Preterm: 0.223±0.516 mic/L Full-term: 0.003±0.014 mic/L Mean±SD cord blood serum endrin levels Preterm: 0.208±0.497mic/L Full-term: 0.002±0.010 mic/L	Mean maternal and cord serum endrin levels were significantly elevated (p<0.001) in preterm deliveries, compared with full term (note that several other organochlorine pesticides were also significantly elevated; e.g., heptachlor, dieldrin, DDT); no significant differences in maternal serum endrin levels between pre-term births with gestation length of ≤32 weeks and pre-term births with gestation length >32 weeks Correlation coefficients between maternal serum endrin levels and birth outcomes (preterm and full-term births combined) Gestational age: -0.332 (p=0.000) Weight: -0.345 (p=0.000) Length: -0.298 (p=0.001) Head circumference: -0.322 (p=0.000) Correlation coefficients between cord serum endrin levels and birth outcomes (preterm and full-term births combined) Gestational age: -0.332 (p=0.000) Weight: -0.345 (p=0.001) Length: -0.298 (p=0.001) Head circumference: -0.322 (p=0.000)

Table 2-1. Health Effects in Humans Exposed to Endrin—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Note: Despite p-values indicating significance, the study authors did not conclude that correlations between endrin and birth outcomes were significant; the rationale for this discrepancy is unclear
Rowley et al. 1987 Case-series report Pakistan Study population:194 cases of acute poisoning	Cause for outbreak unverified, but expected to be food contamination	Patients presented with CNS symptoms; 19/194 died
Curley et al. 1970; Weeks 1967 Case series report Saudi Arabia Study population: 874 people hospitalized after acute exposure to endrin-contaminated flour	Dietary exposure estimates ranged from 48 to 1,807 ppm (contaminated flour contained 2,153–3,367 ppm endrin)	Patients presented with convulsions, loss of consciousness, headache, nausea, and vomiting; 26/874 patients died within 12 hours Recovery was rapid in survivors

[a]Adjusted for sex, age, BMI, current smoking status, and alcohol intake.
[b]Defined as “moderately elevated neonatal concentration” by the World Health Organization.
[c]Adjusted for maternal age, gestational age, alcohol consumption and cigarette smoking during pregnancy, parity, birth weight, maternal education, and placental lipid concentration.
[d]Adjusted for age (continuous), sex, triglycerides, and cholesterol.
[e]Adjusted for age, ethnicity, and years of residence in Cidade dos Meninos.
[f]Adjusted for age, ethnicity, years of residence in Cidade dos Meninos, BMI, and smoking.

* = statistically significant ($p<0.05$), as reported by the study authors; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CNS = central nervous system; CI = confidence interval; EEG = electroencephalogram; FSH = follicle-stimulating hormone; GM = geometric mean; INMA = Infancia y Medio Ambiente; LH = luteinizing hormone; LOQ = level of quantitation; MDL = method detection limit; Q = quintile; SD = standard deviation; SMR = standardized mortality ratio; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

Table 2-2. Levels of Significant Exposure to Endrin – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
INTERMEDIATE EXPOSURE									
1	Mouse (NS) 3 NS	150 days 5 days/week 7 hours/day	0.36	LE	Death			0.36	1/3 died
Treon et al. 1955									
2	Rabbit (NS) 4 NS	165 days 5 days/week 7 hours/day	0.36	LE	Death			0.36	2/4 died
Treon et al. 1955									

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

LE = lethality; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

Figure 2-2. Levels of Significant Exposure to Endrin – Inhalation
Intermediate (15–364 days)

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
ACUTE EXPOSURE									
1	Monkey (NS) 2 B	Once (GO)	Not reported	LE	Death			3	LD_{50}
Endrin									
Treon et al. 1955									
2	Rat (Sprague-Dawley) 4 F	1–2 days (F)	0, 8.2	BC, BI, BW, HP, OF, OW	Bd wt	8.2			
					Hepatic		8.2		48–82% increase in hepatic serum enzymes (ALP, AST, ALT, serum isocitrate dehydrogenase) and 27–35% increase in cholesterol); vacuolization; fatty infiltration
					Other noncancer		8.2		41–51% decrease in serum glucose
Endrin									
Ali and Shakoori 1993									
3	Rat (Sprague-Dawley) 4 F	Once (GO)	0, 3, 4.5, 6	OW, BI	Hepatic		3		Increased relative liver weight
Endrin									
Bagchi et al. 1992a									
4	Rat (Sprague-Dawley) 4 F	Once (GO)	0, 1.5, 3, 4.5, 6	OW, BI	Hepatic		3		11% increase in relative liver weight relative to low-dose group (control values not reported)
Endrin									
Bagchi et al. 1992b									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
5	Rat (Sprague-Dawley) 4 F	Once (GO)	0, 3, 4.5, 6	OW, BI	Hepatic		3		9% increase in relative liver weight
Endrin									
Bagchi et al. 1992c									
6	Rat (Carworth Farm E) 4–8 M, 4–8 F	Once (G)	Not reported	LE, CS	Death			5.6 M 5.3 F	LD_{50}
Endrin									
Bedford et al. 1975a									
7	Rat (Holtzman albino) 10 M	8 days, every 2–3 days (GO)	0, 1 (TWA)	BC, BI, OW, UR	Cardio Hepatic Renal Neuro	1 1 1 1			
Endrin									
Coleman et al. 1968 [TWA dose = 1 mg/kg/day]									
8	Rat (Sherman) 90 M, 50 F	Once (GO)	Not reported	LE	Death			17.8 M 7.5 F	LD_{50}
Endrin									
Gaines 1960, 1969									
9	Rat (Sherman) 25 F	9 d GDs 6–15 (G)	0, 0.1, 0.5, 2.0	MX, DX, FX, TG, CS, BW, LE	Death			2	2/25 died on GDs 13 and 14
					Bd wt	0.5	2		Decreased maternal weight gain (12% of control)
					Develop	0.5	2		Delayed ossification
Endrin									
Goldenthal 1978a [Note: vehicle was methocel]									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
10	Rat (Sprague-Dawley) 4 F	Once (GO)	0, 4	HP, BI	Hepatic		4		Moderate focal necrosis, fatty degeneration, inflammation, and cell regeneration; 1.9-fold increase in lipid peroxidation
					Renal		4		Moderate tubular necrosis, hyaline and red cell casts; 3.3-fold increase in lipid peroxidation
Endrin									
Hassan et al. 1991									
11	Rat (Sprague-Dawley) 4 F	Once (GO)	0, 4.5	BI, EA	Hepatic		4.5		14.5% increase in mitochondrial lipid peroxidation at 6 hours; 28% increase at 12 hours
Endrin									
Hassoun et al. 1993									
12	Rat (CD) 15–32 F	14 days GDs 7–20 (GO)	0, 0.075, 0.15, 0.3, 0.45	LE, OW, BW, CS, OF, DX, TG	Bd wt	0.15		0.3	38% decrease in maternal body weight gain
					Hepatic	0.45			
					Develop	0.45			
Endrin									
Kavlock et al. 1981									
13	Rat (CD) 5–9 F	14 days (GO)	0, 0.5, 1, 2, 4	LE, BW, BH, CS	Death			0.5	3/5 died; 100% mortality at higher doses
					Bd wt			0.5	94% decrease in body weight gain in survivors
					Neuro		0.5[b]	4	Depressed locomotor activity at ≥0.5 mg/kg; convulsions in 2/6 rats at 4 mg/kg ($BMDL_{1SD}$ = 0.057 mg/kg)
Endrin									
Kavlock et al. 1981 [Range-finding study; neurological assessment conducted 2–4 hours after initial dose]									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
14	Rat (Hotlzman albino) 10–12 M	Once (GO)	0, 25	BC, BI, OW	Cardio		25		15% increase in heart weight
					Hepatic		25		27% increase in liver weight
					Renal		25		9% increase in kidney weight
					Neuro			25	Convulsions
Endrin									
Lawrence et al. 1968									
15	Rat (Sprague-Dawley) 4 M	3 days (GO)	0, 0.5, 1, 5	CS, BI	Neuro	1		5	Tremors and convulsions
Endrin									
Mehrotra et al. 1989									
16	Rat (Sprague-Dawley) 4 F	Once (GO)	0, 0.5, 1, 2, 4	BI, BW, OW	Bd wt	4			
					Hepatic	4			No change in liver weight
					Renal	4			No change in kidney weight
Endrin									
Numan et al. 1990a									
17	Rat (Sprague-Dawley) 10 F	Once (GO)	0, 8	LE	Death			8	100% mortality
Endrin									
Numan et al. 1990b									
18	Rat (Sprague-Dawley)	Once (GO)	20–80	LE	Death			40	LD_{50}
Endrin									
Speck and Maaske 1958									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
19	Rat (Carworth) 10 M, 10 F	Once (GO)	Not reported	LE	Death			7.3 F 43.4 M	LD_{50}
Endrin									
Treon et al. 1955 [Rats exposed at 6 months of age]									
20	Rat (Carworth) 10 M, 10 F	Once (GO)	Not reported	LE	Death			16.8 F 28.8 M	LD_{50}
Endrin									
Treon et al. 1955 [Rats exposed at PND 29, 30, or 31]									
21	Mouse (Swiss Webster) 4 F	Once (GO)	0, 4	HP, BI	Hepatic		4		Moderate focal necrosis and inflammation; 1.8-fold increase in lipid peroxidation
					Renal		4		Moderate tubular necrosis; 1.7-fold increase in lipid peroxidation
Endrin									
Hassan et al. 1991									
22	Mouse (C57BL/6J) 5–8 F	Once GD 12 (GO)	0, 4.5, 6	BW, FX, LE, MX, TG	Death			6	25% maternal death
					Bd wt	6			
					Develop		4.5	6	10% decrease in fetal weight, 13% decrease in fetal thymus weight, and 14% decrease in placental weight at 4.5 mg/kg; 28.9% fetal death/resorption, 28% decrease in fetal weight, 17% decrease in fetal thymus weight, and increased percent of fetuses/litter with hydronephrosis at 6 mg/kg
Endrin									
Hassoun and Stohs 1996a									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
23	Mouse (DBA/2J) 5–8 F	Once GD 12 (GO)	0, 4.5, 6	BW, FX, LE, MX, TG	Death			6	25% maternal death
					Bd wt	6			
					Develop		4.5		6–13% decrease in fetal weight at ≥4.5 mg/kg; 20% decrease in placental weight at 6 mg/kg
Endrin									
Hassoun and Stohs 1996a									
24	Mouse (CD-1) 20–40 F	11 days GDs 7–17 (GO)	0, 0.5, 1.0, 1.5, 2.0	LE, OW, BW, CS, OF, DX, TG	Death			1.5	4/20 died at 1.5 mg/kg/day; 18/20 died at 2.0 mg/kg/day
					Bd wt	0.5		1	24% decrease in maternal body weight gain
					Hepatic	0.5	1		10% increase in relative liver weight
					Develop	0.5	1		Delayed ossification, decrease in number of caudal vertebrae, altered development of renal pelvis, decreased fetal body weight
Endrin									
Kavlock et al. 1981									
25	Mouse (CD-1) 7–8 F	11 days (GO)	0, 0.5, 1.5, 4.5	LE, BW, BH, CS	Death			4.5	100% mortality
					Bd wt	0.5		1.5	43% decrease in body weight gain
					Neuro	0.5	1.5		38–46% decrease in locomotor activity on days 1 and 3
Endrin									
Kavlock et al. 1981 [Range-finding study; neurological assessment conducted 2–4 hours after 1st, 3rd, and 10th doses]									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
26	Mouse (CD-1) 21–40 F	Once GD 8 (GO)	0, 7, 9	LE, BW, CS, HP, GN	Death			7	3/21 died
					Develop		7		Increased incidence of exencephaly, fused ribs, and supernumerary ribs
Endrin									
Kavlock et al. 1985									
27	Mouse (CD-1) 10 F	Once GD 9 (GO)	0, 2.5	FX, MX, DX, TG	Develop			2.5	2.7% increase in open eye; 2.2% increase in cleft palate
Endrin									
Ottolenghi et al. 1974									
28	Guinea pig (NS) 4 F	Once (GO)	0, 4	HP, BI	Hepatic		4		Moderate focal necrosis and inflammation; 1.3-fold increase in lipid peroxidation
					Renal		4		Cloudy swelling and narrowing of tubular lumen
Endrin									
Hassan et al. 1991									
29	Guinea pig (NS) 2 M, 2 F	Once (GO)	Not reported	LE	Death			16 F 36 M	LD_{50}
Endrin									
Treon et al. 1955									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
30	Hamster (Golden Syrian) 20–63 F	10 days GDs 5–14 (GO)	0, 0.75, 1.5, 2.5, 3.5	LE, OW, BW, CS, FX, MX, TG, DX	Death			1.5	37% of dams died
					Bd wt	0.75		1.5	19 times more weight loss than controls
					Hepatic	3.5			
					Develop	0.75		1.5	2-fold increase in fetal death; 30% decrease in fetal weight, skeletal and visceral abnormalities
Endrin									
Chernoff et al. 1979									
31	Hamster (Golden Syrian) 18–87 F	Once GD 8 (GO)	0, 0.5, 1.5, 5, 7.5, 10	LE, OW, BW, CS, FX, MX, TG, DX	Neuro	7.5		10	1/30 animals displayed convulsions
					Develop	1.5		5.0	Increased incidence (5/7) of meningoencephaloceles
Endrin									
Chernoff et al. 1979									
32	Hamster (Golden Syrian) NS F	Once (GO)	Not reported	LE, OW, BW, CS, FX, MX, TG, DX	Death			18.6	LD_{50}
Endrin									
Chernoff et al. 1979									
33	Hamster (Golden Syrian) 28 F	10 days GDs 4–13 (G)	0, 0.1, 0.75, 2.5	MX, DX, FX, TG, CS, BW, LE	Develop	2.5			
Endrin									
Goldenthal 1978b [Vehicle was methocel]									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
34	Hamster (Golden Syrian) 10–63 F	10 days GDs 5–14 (GO)	0, 0.75, 1.5	LE, BX, FX, OF, DX, CS	Death			1.5	57% of dams died
					Neuro		0.75		Hypoactivity
					Develop	0.75	1.5		Altered habituation in locomotor testing on PNDs 15–125
Endrin									
Gray et al. 1981									
35	Hamster (NS) 4 F	Once (GO)	0, 4	HP, BI	Hepatic		4		Moderate necrosis and inflammation, 1.3-fold increase in lipid peroxidation
					Renal		4		Moderate tubular necrosis, hyaline and calcium containing casts, lipid peroxidation
Endrin									
Hassan et al. 1991									
36	Hamster (Golden Syrian) 8 F	Once GD 7, 8, or 9 (GO)	0, 5	FX, DX, TG	Develop			5	Increased incidence of dead and resorbed fetuses, increased incidence of cleft palate and fused ribs, decreased fetal weight; increased incidence of open eyes and webbed feet after exposure on GD 8 only
Endrin									
Ottolenghi et al. 1974									
37	Rabbit (NS) 4 F	Once (GO)	Not reported	LE, CS, GN, HP, BW, OW BC,	Death			7–10	LD_{50}
Endrin									
Treon et al. 1955									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
INTERMEDIATE EXPOSURE									
38	Rat (Long-Evans) 10 M/10 F (F0)	79 days (F)	0, 0.005, 0.05, 0.1	BW, DX, FX, GN, HP, OW	Repro Develop	0.1 0.1			
Endrin									
Eisenlord et al. 1968 [3-generation study]									
39	Rat (CD) 5–21 F	28 days GD 7–PND 15 (GO)	0, 0.075, 0.15, 0.3	LE, BX, FX, OF, DX, CS	Develop	0.075	0.15		Altered habituation in locomotor testing in offspring on PND 16 and 20
Endrin									
Gray et al. 1981									
40	Rat (Carworth) 3 M, 3 F	10 weeks 5 day/week (GO)	Males: 2, 5 Females: 1, 2	LE, BW, CS, GN	Death			5 M 2 F	3/3 males died 1/3 females died
Endrin									
Treon et al. 1955 [Rats 6 months of age at start of exposure]									
41	Rat (Carworth) 3 M, 2–3 F	10 weeks 5 days/week (GO)	1, 2	LE, BW, CS, GN	Death			2 F	1/2 females died
Endrin									
Treon et al. 1955 [Rats PND 29 at start of exposure]									
42	Rat (Sprague-Dawley) 6 M, 6 F	15 days (F)	0, 0.25, 0.5	BC, OF	Hepatic		0.25		Altered hepatobiliary function; no change in serum ALT or AST
Endrin									
Young and Mehendale 1986									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
43	Rat (Sprague-Dawley) 6 M	15 days (F)	0, 0.5	BC, OF	Hepatic		0.5		10-fold increase in serum ALT and 5-fold increase in serum AST; no change in hepatobiliary function
Endrin aldehyde									
Young and Mehendale 1986									
44	Rat (Sprague-Dawley) 6 M	15 days (F)	0, 0.25	BC, OF	Hepatic		0.25		8-fold increase in serum ALT, no change in hepatobiliary function
Endrin ketone									
Young and Mehendale 1986									
45	Mouse (CFW Swiss) 101 M, 101 F	120 days (F)	0, 0.65	LE, OF	Death			0.65	Deaths in 33/101 breeding pairs
					Repro		0.65		5% reduction in litter size
Endrin									
Good and Ware 1969 [1-generation study]									
46	Dog (Beagle) 1–4 B	Up to 9.9 months 6 days/week (F)	0.18, 0.24, 0.38, 0.46, 0.62, 0.65, 1.71, 3.25	LE, CS, GN, HP, BW, OW, BC	Death			0.24 M	Death in 1/1 after 47 days; 1/2 died at 0.38 and 0.46 mg/kg/day; 100% mortality at higher doses
Endrin									
Treon et al. 1955 [Doses above represent the midpoint of the reported range for each dose group]									
47	Rabbit (NS) 5 F	10 weeks 5 days/week (GO)	1	LE	Death			1	4/5 rabbits died
Endrin									
Treon et al. 1955									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
CHRONIC EXPOSURE									
48	Rat (Osborne Mendel) 50–100 M, 50–100 F	17.6–20.8 months (F)	0, 0.1, 0.29, 0.56	GN, HP, LE, BW	Bd wt	0.56			
					Resp		0.1		Congestion, focal hemorrhage in lungs
					Hepatic		0.1		Cloudy swelling of centrilobular cells
					Renal		0.1		Cloudy swelling of tubule epithelial cells
					Neuro			0.1	Convulsions and tremors
					Cancer				No neoplastic lesions in liver, kidney, or lungs
Endrin									
Deichmann et al. 1970									
49	Rat (Osborne-Mendel) 10–50 M, 10–50 F	80 weeks (F)	Males: 0, 0.13, 0.25 Females: 0, 0.15, 0.3	LE, CS, HP, GN, UR, BW	Bd wt	0.25			
					Resp		0.13		Shortness of breath, epistaxis
					Cardio	0.25			
					Gastro		0.13		Diarrhea
					Hepatic	0.25			
					Renal		0.13		Discolored urine
					Dermal		0.13		Dermatitis, alopecia
					Endocr		0.13		Thyroid hyperplasia and pituitary cysts
					Neuro	0.25			
					Cancer				No exposure-related neoplasms
Endrin									
NCI 1979									
50	Rat (Carworth) 20 M, 20 F	2 years (F)	0, 0.08, 0.42, 2.1, 4.2, 8.4	LE, CS, GN, HP, BW, OW, BC	Death			2.1 F 4.2 M	Increased mortality
					Bd wt	0.42 M	2.1 M		>10% reduction in weight gain

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
					Hepatic	0.08 M 0.42 F	0.42 M 2.1 F		>10% increase in relative liver weight in males at ≥0.42 mg/kg/day and in females at ≥2.1 mg/kg/day; diffuse degeneration of the liver in animals that died
					Renal	0.42	2.1		Diffuse degeneration of kidneys in animals that died
					Endocr	0.42	2.1		Diffuse degeneration of adrenals in animals that died
					Neuro	0.42	2.1	4.2	Diffuse degeneration of the brain in animals that died; convulsions and hypersensitivity at ≥4.2 mg/kg/day
Endrin									
Treon et al. 1955									
51	Mouse (B6C3F1) 10–60 M, 10–60 F	80 weeks (F)	Males: 0, 0.21, 0.42 Females: 0, 0.33, 0.65	LE, CS, HP, GN, UR, BW	Bd wt	0.42			
					Resp	0.42			
					Cardio	0.42			
					Gastro		0.21		Abdominal distension
					Hepatic	0.42			
					Renal	0.42			
					Dermal		0.21		Hair loss
					Endocr	0.42			
					Neuro		0.21 M 0.33 F		Hyperexcitability
					Cancer				No exposure-related neoplasms
Endrin									
NCI 1979									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
52	Dog (Beagle) 3 M, 3 F	2 years (F)	0, 0.0025, 0.0125, 0.025, 0.05, 0.1	BW, FI, BC, HE, HP, OW, CS	Bd wt	0.1			
					Resp	0.1			
					Cardio	0.1			
					Gastro	0.1			
					Hemato	0.1			
					Musc/skel	0.1			
					Hepatic	0.025[c] F 0.05 M	0.05 F 0.1 M		Hepatic cell vacuolation
					Renal	0.1			
					Dermal	0.1			
					Ocular	0.1			
					Endocr	0.1			
					Immuno	0.1			
					Neuro	0.025[c] F 0.05 M		0.05 F 0.1 M	Convulsions
Endrin **Kettering 1969**									
53	Dog (Beagle) 3 F	64–156 weeks (F)	0, 0.003, 0.014, 0.027, 0.059	BW, FI, CS, OW, HP, GN, BC, MX, UR	Hemato	0.059			
					Hepatic	0.059			
					Renal	0.059			
					Neuro			0.059	Seizures
Endrin **Kettering 1971**									

Table 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – 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)	Effect
54	Dog (Beagle) 2–4 B	16.4–18.7 months 6 days/week (F)	0, 0.08, 0.19	LE, CS, GN, HP, BW, OW, BC	Bd wt	0.19			
					Resp	0.19			
					Cardio	0.08	0.19		25% increase in relative heart weight
					Hemato	0.19			
					Hepatic	0.19			
					Renal	0.08	0.19		24% increase in relative kidney weight
					Immuno	0.19			
					Neuro	0.19			

Endrin

Treon et al. 1955 [Doses above represent the midpoint dose of the reported range for each dose group]

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute oral minimal risk level (MRL) of 0.0006 mg/kg/day; $BMDL_{1SD}$ of 0.057 mg/kg divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The acute oral MRL was adopted as the intermediate oral MRL.
[c]Used to derive a chronic oral MRL of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Highlighted rows indicate MRL principal study.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both male(s) and female(s); BC = serum (blood) chemistry; Bd Wt or BW = body weight; BH = behavioral; BI = biochemical changes; BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = exposure concentration associated with 1 standard deviation change in outcome); Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; (F) = food; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LD50 = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; TG = teratogenicity; TWA = time-weighted average; UR = urinalysis

Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Acute (≤14 days)

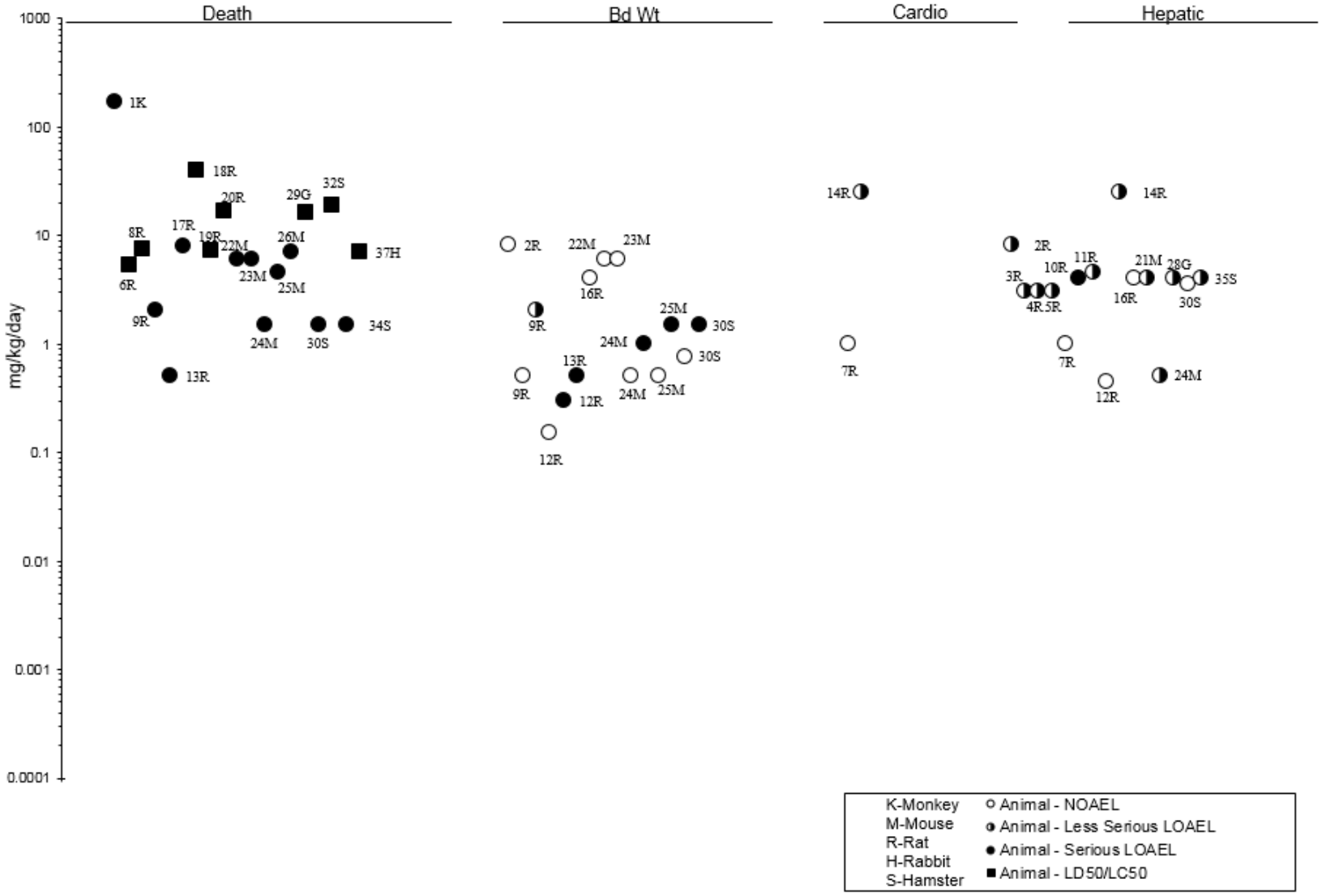


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Acute (≤14 days)

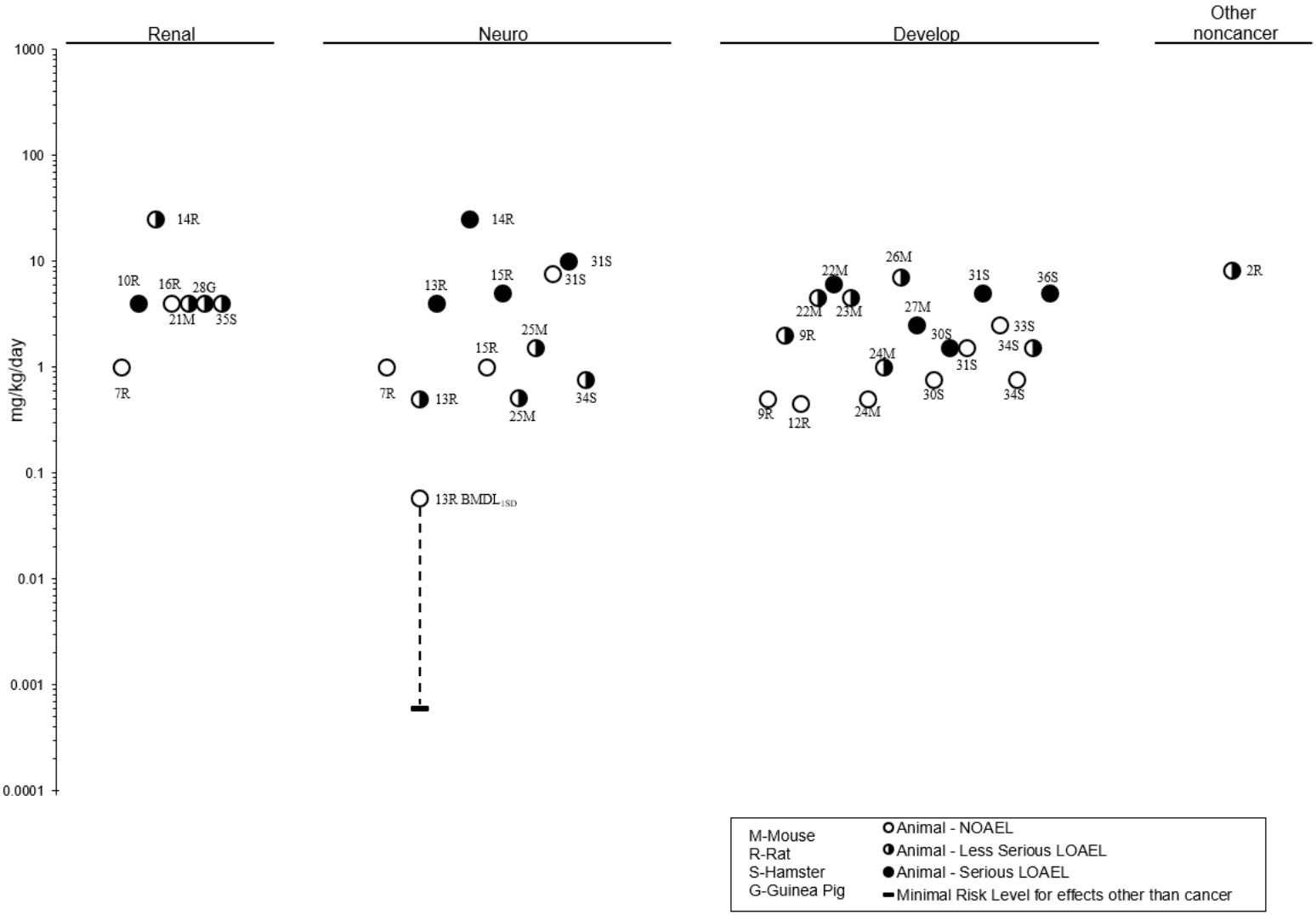


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Intermediate (15-364 days)

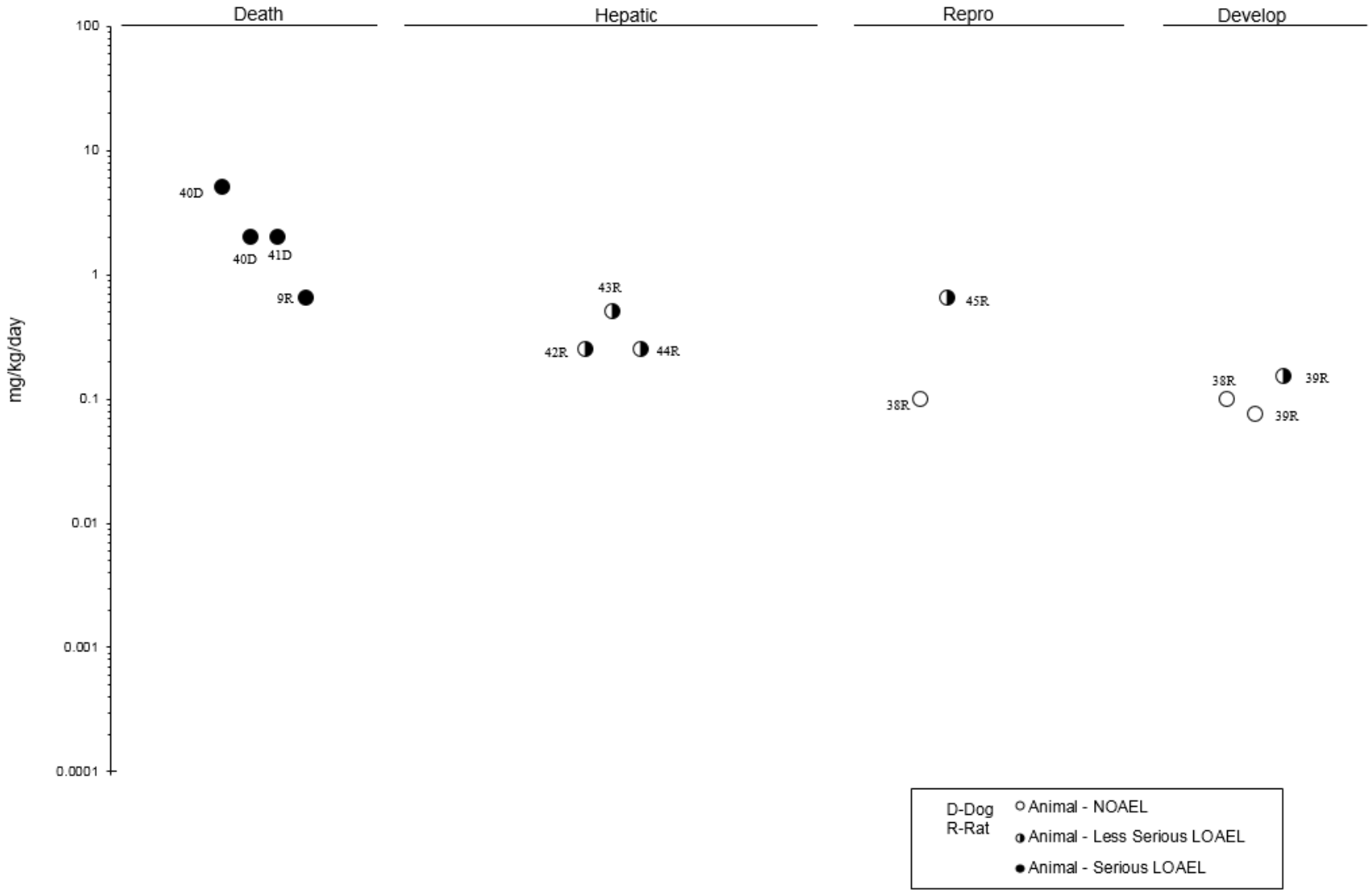


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Chronic (≥365 days)

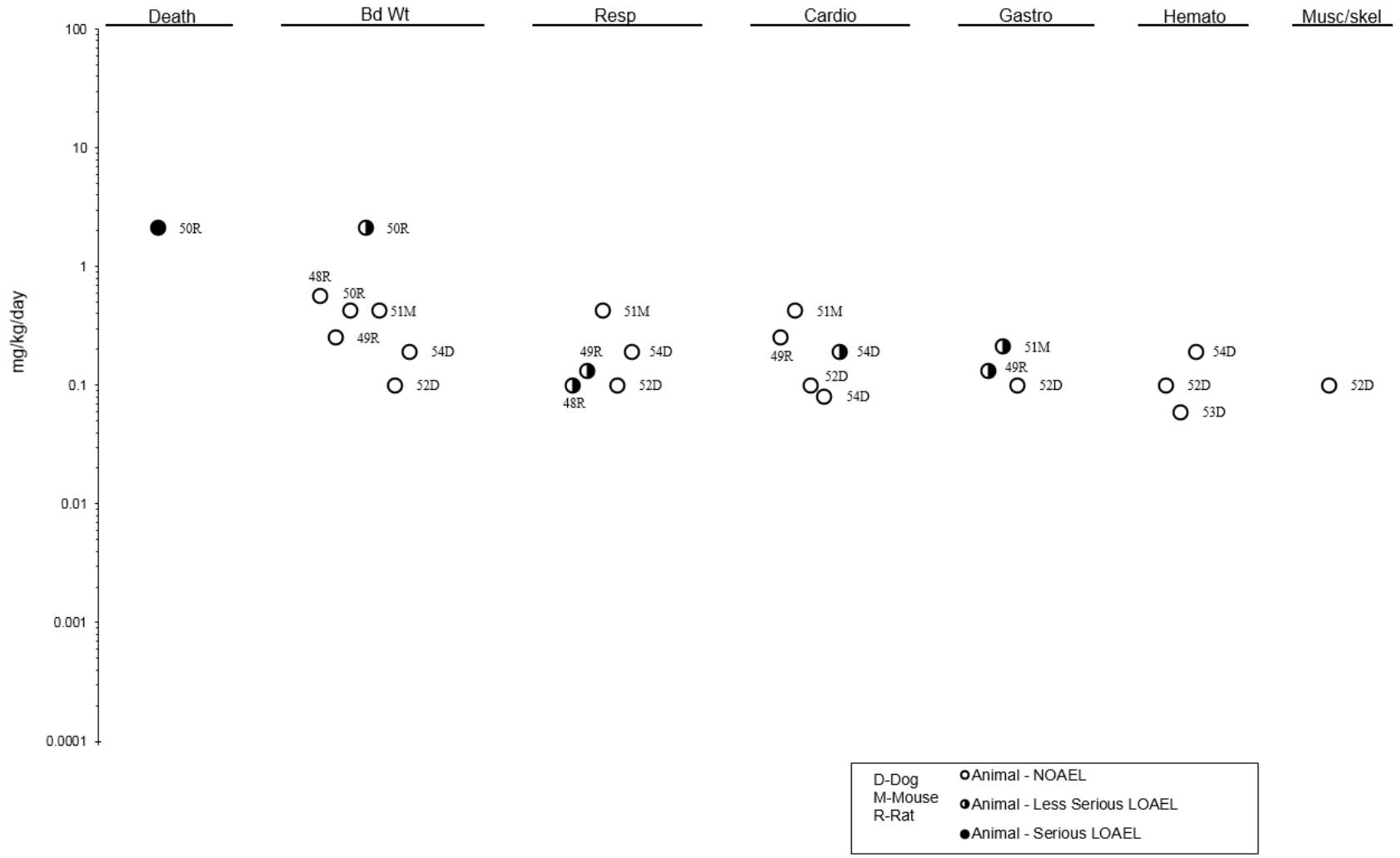


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Chronic (≥365 days)

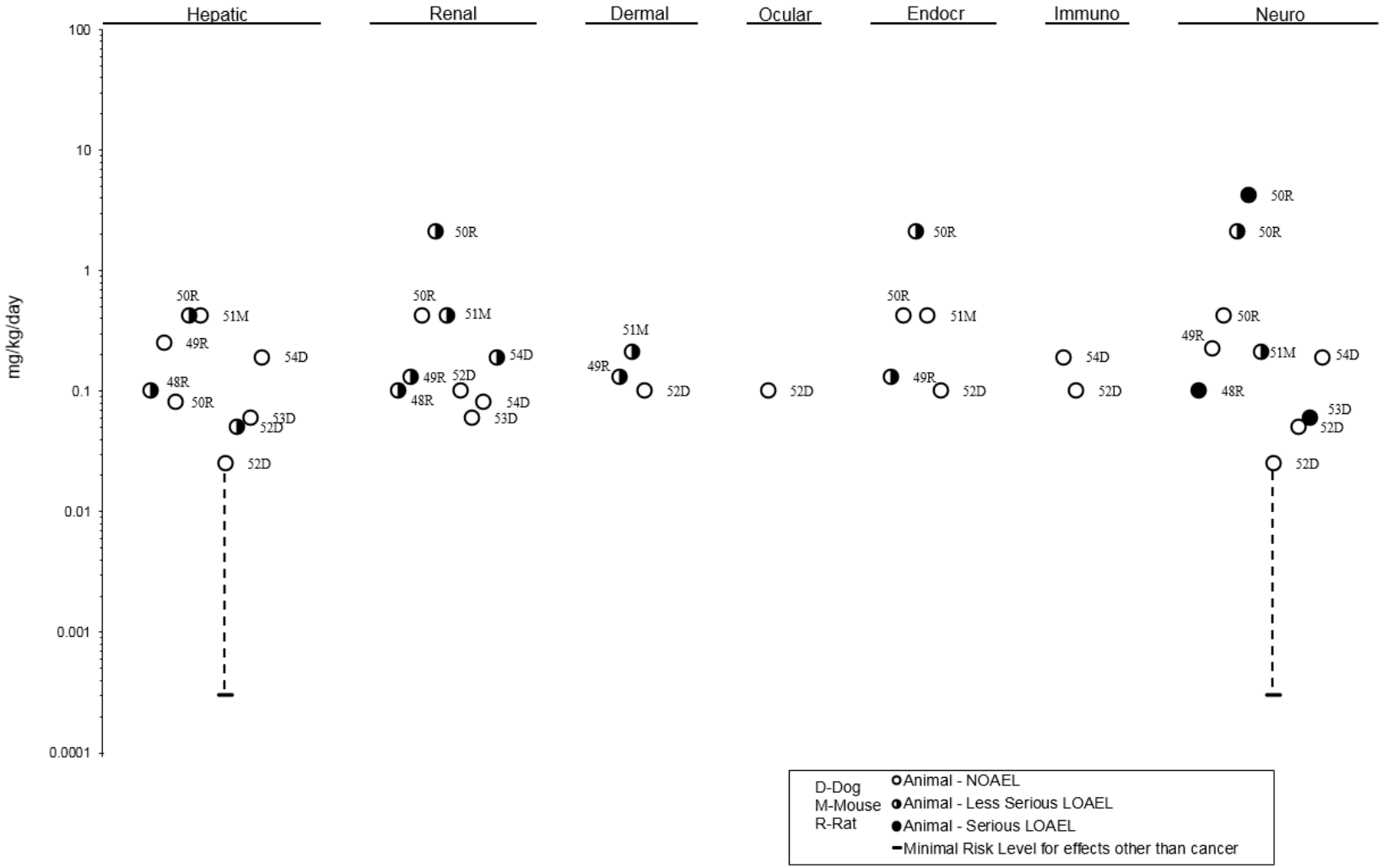


Table 2-4. Levels of Significant Exposure to Endrin – Dermal

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)	Effect
ACUTE EXPOSURE								
Rat (Sherman) NS F	Once	Not reported	LE	Death			15	LD_{50}
Gaines 1960 [A total of 50 rats were used in study, number per group not reported]								
Rat (Sherman) NS M	Once	Not reported	LE	Death			18	LD_{50}
Gaines 1969 [A total of 40 rats were used in study, number per group not reported]								
Rabbit (NS) 3–8 F	24 hours	60, 94, 125, 160, 250–3,600	LE, GN, HP	Death			94	1/3 died
				Dermal	3,600			
Treon et al. 1955								
INTERMEDIATE EXPOSURE								
Rabbit (NS) 4 F	25–45 exposures 5 days/week 2 hours/day	27–44	LE, GN, HP	Death			27–44	1/4 died
				Dermal	27–44			
Treon et al. 1955 [Abraded skin]								
Rabbit (NS) 3 F	19–70 exposures 5 days/week 2 hours/day	20–42, 67–91	LE, GN, HP	Death			20–42	1/3 died at low dose; 3/3 died at high dose
				Dermal	67–91			
Treon et al. 1955 [Intact skin]								

F = female(s); LD_{50} = lethal dose, 50% kill; GN = gross necropsy; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

Deaths have rarely been associated with occupational exposure to endrin. Retrospective cohort studies have reported lower than expected overall mortality in workers manufacturing endrin (along with related chemicals) compared to the general population, likely due to the healthy worker effect (Ditraglia et al. 1981; Ribbens 1985). One facility that manufactured aldrin, endrin, and dieldrin reported a significant excess of death due to nonmalignant respiratory system disease, but similar effects were not observed in another facility that manufactured heptachlor and endrin (Ditraglia et al. 1981; see Table 2-1). These studies are limited by small cohort size and/or multiple chemical exposures. Human reports of high occupational exposure have not reported deaths, even at exposure levels high enough to cause tonic-clonic contractions and seizures (Hoogendam et al. 1962, 1965).

Human deaths have occurred following community-wide poisoning events involving acute exposure to endrin via ingestion. In 1967, 26/ 874 hospitalized people died in Saudi Arabia following exposure to endrin-contaminated flour containing 2,153–3,367 ppm endrin (Weeks 1967). Estimated concentrations of endrin in bread eaten by victims ranged from 48 to 1,807 ppm (Curley et al. 1970). A similar outbreak of endrin poisoning in 1984 resulted in 19/194 patient deaths in Pakistan; however, the source of the contamination was not identified (assumed to be a contaminated food item) (Rowley et al. 1987). In both cases, severe central nervous system toxicity preceded death.

Case studies also report death following acute ingestion of endrin. A 49-year old man died 11 days after intentional ingestion of 12 g of endrin dissolved in aromatic hydrocarbons (~171 mg/kg); death was preceded by convulsions (Runhaar et al. 1985). Eleven other cases of endrin ingestion resulted in death within 1–6 hours after exposure (Tewari and Sharma 1978). In cases where endrin ingestion occurred with milk or alcohol, death occurred more rapidly (within 1–2 hours), presumably as the result of enhanced absorption that increased toxicity. An elderly senile woman died 7 hours after ingesting an unknown quantity of liquid pesticide containing endrin; tissue concentrations ranged from 0.467 to 13.3 mg/kg, and the amount of endrin adsorbed onto activated charcoal (administered as a treatment) was 66 mg (Moriya and Hashimoto 1999).

Studies involving laboratory animals have reported death following inhalation exposure. A cat exposed twice for 1 hour to 417 ppm endrin as a spray of 1.5% aqueous solution died within 24 hours (Ressang et al. 1959). In another inhalation study, six species of animals were exposed to endrin vapor at 0.36 ppm for 7 hours/day, 5 days/week for 150–185 days (Treon et al. 1955). Two of four rabbits died after 26 and

90 exposures, and one of three mice died after 22 exposures. The cat, two guinea pigs, two hamsters, and three rats survived. Additional groups of one to two mice survived 18–64 exposures over 3–13 weeks (5 days/week; 7 hours/day), and additional three rabbits survived 12 exposures over 16 days (7 hours/day) (Treon et al. 1955). Diffuse degenerative changes were observed in kidneys, livers, and brains in all animals that died, except in the mouse where effects on the brain were not observed.

Endrin is also lethal to animals when sufficiently high doses are administered by gavage or in the diet. Reported oral LD_{50} values (the dose that has been calculated to cause death in 50% of the experimental animal population) ranged from 3 mg/kg in monkeys (Treon et al. 1955), 5.3–43.4 mg/kg in adult rats (Bedford et al. 1975a; Gaines 1960, 1969; Speck and Maaske 1958; Treon et al. 1955), 16.8–28.8 mg/kg in young rats approximately 4–5 weeks old (Treon et al. 1955), 16–36 mg/kg in guinea pigs (Treon et al. 1955), 18.6 mg/kg in hamsters (Chernoff et al. 1979), and 7–10 mg/kg in rabbits (Treon et al. 1955). Phillips et al. (1962) reported an acute oral LD_{50} of >500 mg/kg for endrin aldehyde in male mice, but did not provide experimental details. Other single-exposure studies observed mortality in 100% of rats at 8 mg/kg dose (Numan et al. 1990b), a cat that was exposed to 3 mg/kg/day for 3 days (Ressang et al. 1959), a cat that was exposed once to 6 mg/kg (Ressang et al. 1959), and 7/8 hunting dogs that accidently ingested an unknown quantity in endrin-containing bait (Quick et al. 1989). Single or repeated doses of endrin to pregnant dams during gestation also resulted in maternal lethality at doses as low as 0.5 mg/kg/day in rats (Goldenthal 1978a; Kavlock et al. 1981), 1.5 mg/kg/day in mice (Hassoun and Stohs 1996a; Kavlock et al. 1981, 1985), or 1.5 mg/kg/day in hamsters (Chernoff et al. 1979; Gray et al. 1981). Longer-duration studies have reported increased mortality in rats at chronic dietary doses ≥2.1 mg/kg/day (Treon et al. 1955), in mice administered 0.42 mg/kg of endrin in feed for 120 days (Good and Ware 1969), and in dogs exposed to doses ≥0.24 mg/kg/day for ≥47 days (Treon et al. 1955).

Dermal studies reported LD_{50} values of 18 mg/kg in male rats and 15 mg/kg in female rats for endrin in xylene (Gaines 1960, 1969). In cats (one cat/group), topical application of 75 mg/kg in a 0.5% formulation resulted in death 22 days later and topical application of 150 mg/kg in a 2.5% formulation resulted in the death within 48 hours; however, application of 75 mg/kg in a 2.5% formulation did not result in death or toxic signs in another cat (Ressang et al. 1959). In rabbits, dermal exposure to 94 mg/kg for 24 hours resulted in death in 1/3 animals; 2/3 died at 60 mg/kg, and mortality was 100% at ≥250 mg/kg (Treon et al. 1955). When rabbits were exposed for longer durations, 1/4 rabbits died following 25 applications of endrin at doses ranging from 27 to 44 mg/kg/day on abraded skin (the remaining three rabbits survived 45 exposures), 1/3 rabbits died following 40 applications of endrin at doses ranging from 20 to 42 mg/kg/day on intact skin (the remaining two rabbits survived

70 applications), and 3/3 rabbits died following 19–25 applications of endrin at doses ranging from 67 to 91 mg/kg on intact skin (Treon et al. 1955). Regardless of exposure duration, convulsions preceded death and animals that died showed diffuse degenerative lesions of the liver, kidney, and brain.

2.3 BODY WEIGHT

Information on potential body weight effects in humans following exposure to endrin is limited to a cross-sectional study that reported that serum endrin levels were not elevated in subjects with a body mass index (BMI) of ≥25 (Henríquez-Hernández et al. 2017).

Laboratory studies have observed body weight effects in multiple species following oral endrin exposure. Studies involving pregnant animals reported significant decreases in body weight gain in maternal rats at ≥0.3 mg/kg/day, mice at ≥1 mg/kg/day, and hamsters at ≥1.5 mg/kg/day for 9–11 days during gestation (Chernoff et al. 1979; Goldenthal 1978a; Kavlock et al. 1981). Nonpregnant animals did not experience body weight effects following single oral exposures up to 8.2 mg/kg in rats (Ali and Shakoori 1993; Numan et al. 1900a) or 6 mg/kg in mice (Hassoun and Stohs 1996b). In an older study, dogs became emaciated prior to death following exposure to dietary doses ≥0.24 mg/kg/day for up to 9.9 months; according to the authors, the dogs "did not grow normally" at the nonlethal dose of approximately 0.18 mg/kg/day (Treon et al. 1955). However, the inadequate data reporting did not clearly define an effect level in this study. Chronic studies in dogs did not observe body weight effects following dietary doses up to 0.19 mg/kg/day (Kettering 1969; Treon et al. 1955). Chronic rodent dietary studies reported significant decreases in body weight gain in male rats exposed to doses ≥2.1 mg/kg/day, but not ≤0.56 mg/kg/day; female rats showed no body weight effects at doses up to 5 mg/kg/day, and doses up to 0.42 mg/kg/day did not affect body weights of male or female mice (Deichmann et al. 1970; NCI 1979; Treon et al. 1955).

2.4 RESPIRATORY

Information regarding potential respiratory effects in humans following endrin exposure is extremely limited. In a retrospective cohort study (see Table 2-1 for details), the number of deaths due to nonmalignant respiratory diseases (e.g., pneumonia) was increased in workers employed at a plant that manufactured aldrin, dieldrin, and endrin, compared with the rate in the general population (Ditraglia et al. 1981). However, Ditraglia et al. (1981) did not observe an excess of death from nonmalignant respiratory disease in another plant that manufactured endrin and heptachlor. The only additional information on endrin's potential to cause respiratory disease or dysfunction in humans comes from a

case report of pulmonary edema in a patient that attempted suicide by drinking an endrin formulation (Runhaar et al. 1985). However, the study authors attributed pulmonary edema to chemical pneumonitis resulting from aspiration of aromatic hydrocarbons contained in the ingested formulation, since hydrocarbon-induced chemical pneumonitis is a well-established clinical entity.

Information regarding potential respiratory effects in laboratory animals following inhalation exposure is limited to a single, inadequately designed lethality study in multiple species. The authors reported granulomatous pneumonitis in two rabbits that survived intermittent exposure to 0.36 ppm of endrin vapors over 165 days (7 hours/day, 5 days/week); however, the study did not include control animals, so it is unclear if this finding is exposure-related (Treon et al. 1955). The study authors did not report pneumonitis in one cat, two guinea pigs, two hamsters, three rats, or two mice that survived similar exposure for up to 185 days, but the limited data reporting, small animal number, and lack of controls limits the usefulness of this study. Therefore, no NOAEL/LOAEL determinations for respiratory effects were included in the LSE for this study.

There are also limited data regarding respiratory effects in animals following oral exposure to endrin. Severe congestion and serofibrinous exudate were observed in the lungs of five hunting dogs that died after acute exposure via ingestion of an unknown quantity of endrin-containing bait (Quick et al. 1989). In an intermediate-duration study in dogs, the study authors noted respiratory distress, pulmonary hyperplasia and edema in all dogs that died following exposure to dietary doses ≥0.24 mg/kg/day for up to 9.9 months (Treon et al. 1955). However, the study did not provide a clearly defined effect level due to inadequate data reporting. Moreover, the dogs were observed regurgitating their food and may have aspirated endrin-contaminated material. In chronic oral studies, rats exposed to dietary doses ≥0.1 mg/kg/day exhibited shortness of breath and focal hemorrhage and congestion of the lungs at necropsy (Deichmann et al. 1970; NCI 1979). No adverse respiratory effects were observed in similarly exposed mice at dietary doses up to 0.42 mg/kg/day (NCI 1979) or dogs at dietary doses up to 0.1 mg/kg/day (Kettering 1969).

2.5 CARDIOVASCULAR

Two human studies contained limited information on the potential effects of endrin exposure on cardiovascular function and health (see Table 2-1 for details). A population-based study in the Canary Islands found no association between hypertension and serum endrin levels (Henríquez-Hernández et al. 2014). In a retrospective cohort study, workers employed at plants that manufactured endrin (and other

chemicals) for at least 6 months did not have an increased risk of death due to circulatory system disease compared with the general population (Ditraglia et al. 1981). One plant reported a significantly decreased risk of death due to circulatory system disease, likely due to the healthy worker effect.

Limited reports of cardiovascular toxicity of orally administered endrin in animals were located. An acute rat study reported a 15% increase in heart weight following a single gavage exposure to 25 mg/kg (Lawrence et al. 1968); however, this finding is difficult to interpret in the absence of histological examination. No change in heart weight was observed in rats exposed to 1 mg/kg/day for 8 days via gavage (Coleman et al. 1968). At intermediate durations, diffuse degeneration changes occurred in the hearts of dogs who died following exposure to dietary doses ≥0.24 mg/kg/day for up to 9.9 months (Treon et al. 1955). However, data reporting was inadequate to clearly define an effect level for this finding. Chronic rodent studies did not observe cardiovascular lesions in rats at doses up to 0.25 mg/kg/day or in mice at doses up to 0.42 mg/kg/day (NCI 1979). A chronic dog study noted a 25% increase in relative heart weight without cardiac lesions following exposure to an approximate dietary dose of 0.19 mg/kg/day for up to 18.7 months (Treon et al. 1955). A second chronic dog study did not observe any exposure-related changes in heart weight or histology at dietary doses up to 0.1 mg/kg/day for 2 years (Kettering 1969).

2.6 GASTROINTESTINAL

A report of nausea and vomiting in people who consumed endrin-contaminated taquitos provides the only available human data on potential gastrointestinal effects (Waller et al. 1992).

In chronic dietary studies, rats exhibited diarrhea at doses ≥0.13 mg/kg/day and mice had abdominal distension at ≥0.21 mg/kg/day; however, rats did not develop gastrointestinal lesions at doses up to 0.25 mg/kg/day or mice at doses up to 0.42 mg/kg/day (NCI 1979). Treon et al. (1955) noted that dogs regurgitated food containing endrin at dietary levels of ≥0.24 mg/kg/day (Treon et al. 1955). No gastrointestinal lesions were observed in dogs exposed to dietary levels up to 0.1 mg/kg/day for 2 years (Kettering 1969).

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans following exposure to endrin.

The only available animal data on hematological effects are from three dog studies that found no hematological effects following chronic oral exposure. The peripheral blood of male and female dogs given endrin in their diet at doses up to 0.19 mg/kg/day for periods of 16.4–18.7 months did not show changes in the relative numbers or types of formed elements (Treon et al. 1955). Similarly, no hematological changes were observed in dogs administered doses up to 0.059 mg/kg/day for 64–156 weeks or 0.1 mg/kg/day for 2 years (Kettering 1969, 1971).

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans following exposure to endrin. The only animal study evaluating musculoskeletal effects reported a lack of exposure-related histological changes in skeletal muscle or bone in dogs given endrin in their diet at doses up to 0.1 mg/kg/day for 2 years (Kettering 1969).

2.9 HEPATIC

Two occupational reports assessed hepatic effects in humans exposed to chemical mixtures that included endrin. Seven of 592 workers manufacturing aldrin/dieldrin/endrin had abnormal liver function tests, as shown by three cases of increased thymol turbidity, increased serum aspartate aminotransferase (AST) in one worker, and increased serum alanine aminotransferase (ALT) in four workers (Hoogendam et al. 1965). Exposure to other compounds was not controlled, and serum values returned to normal during continued exposure. No cases of hepatic disease were reported in 52 former workers from an aldrin/dieldrin/endrin/telodrin manufacturing plant (Versteeg and Jager 1973).

In the only available inhalation study evaluating hepatic effects in animals, diffuse degenerative changes were observed in the livers of rabbits and mice exposed over 6 months at a lethal endrin concentration of 0.36 ppm (Treon et al. 1955). The authors did not provide details of the liver pathology.

Oral studies in animals consistently report histopathological changes in the liver (e.g., degeneration, necrosis, vacuolization, hypertrophy, lipid peroxidation) following single- or repeat-dose exposure to endrin. There is inconsistent evidence for elevated liver weight and changes in hepatic serum chemistry parameters.

Three studies have reported histopathological changes in the liver following acute oral exposures in multiple species. An LD_{50} study reported diffuse hepatic degeneration in multiple species at lethal doses

(Treon et al. 1955). Rats, mice, and guinea pigs administered 4 mg/kg endrin and sacrificed 24 hours later showed moderate hepatic necrosis, fatty degeneration (rats only), and inflammation; histological examination found lipofuscin deposits in hepatocytes and Kupffer cells (Hassan et al. 1991). Similar changes were observed in control and endrin-treated hamsters; however, the hepatic effects were more severe in the treated animals, and only livers from treated animals had lipofuscin pigment deposits associated with lipid peroxidation (Hassan et al. 1991). Hepatic cell hypertrophy, dilation of sinusoidal spaces, zonal disorganization/degeneration, vacuolization, and fatty infiltration were also observed in the livers of rats exposed to dietary endrin at doses of 8.2 mg/kg/day for 2 days (Ali and Shakoori 1993). Congestion and serofibrinous exudate were observed in the livers of dogs that died apparently following ingestion of endrin-containing bait (Quick et al. 1989).

Two intermediate-duration oral studies in dogs and rats also observed histopathological changes in the liver; however, inadequate data reporting in both studies precluded identification of a clearly defined effect level. Speck and Maaske (1958) reported spotty livers with zones of basophilic cells around the central and portal veins in rats exposed to endrin for 3–7 months; however, the report does not clearly identify the dose at which these effects occurred (administered doses were 0.8, 1.7, and 3.5 mg/kg/day). Treon et al. (1955) reported diffuse degeneration changes in the livers of dogs that died following exposure to dietary doses ≥0.24 mg/kg/day for up to 9.9 months; in some cases, fatty vacuolation occurred (number not specified).

In chronic-duration studies, histopathological findings in the liver have been inconsistent between studies and species. The livers of Osborne-Mendel rats exposed to dietary levels ≥0.1 mg/kg/day for 17.6–20.8 months showed minor histologic changes (cloudy swelling of centrilobular cells) (Deichmann et al. 1970); however, NCI (1979) did not report any exposure-related nonneoplastic hepatic lesions in Osborne-Mendel rats exposed to dietary levels up to 0.25 mg/kg/day for 80 weeks. In another chronic study, diffuse degeneration occurred in the livers of Carworth rats that died following dietary exposure to doses as low as 2.1 mg/kg/day for up to 2 years; lesions were not observed at nonlethal doses ≤0.42 mg/kg/day (Treon et al. 1955). No significant increase in nonneoplastic hepatic lesions was observed in B6C3F1 mice exposed to dietary endrin levels up to 0.42 mg/kg/day for 80 weeks (NCI 1979). In chronic dog studies, Kettering (1969) reported slight vacuolization of hepatic cells in dogs following exposure to dietary doses ≥0.05 mg/kg/day for 2 years (Kettering 1969), but Treon et al. (1955) did not observe hepatic lesions in dogs following exposure to dietary doses up to 0.19 mg/kg/day for 16.4–18.7 months. Additionally, a 1-generation study found no hepatic lesions in female dogs exposed to doses up to 0.059 mg/kg/day for 64–156 weeks in (Kettering 1971).

A series of acute studies reported time- and dose-related increases in relative liver weights (9–30%) in rats administered a single oral dose of 3–6 mg/kg and sacrificed at intervals over 3 days, compared with the lowest dose of 1.5 mg/kg; organ weight data were not reported for concurrent control groups in these studies (Bagchi et al. 1992a, 1992b, 1992c). A significant 27% increase in absolute liver weight occurred in rats exposed once to 25 mg/kg (Lawrence et al. 1968); body and relative liver weights were not reported. In contrast, no significant changes in liver weight were noted for rats 24 hours after a single oral administration of 4 mg/kg (Numan et al. 1990a), dietary exposure to 8.2 mg/kg/day for 1–2 days (Ali and Shakoori 1993), or gavage administration of 1–3 mg/kg every 2–3 days for 8 days (total dose 8 mg/kg) (Coleman et al. 1968). Studies in pregnant animals reported increases in maternal relative liver weight ≥10% in mice administered ≥1 mg/kg/day of endrin for 11 days during gestation (Kavlock et al. 1981), but not in hamsters and rats at doses up to 3.5 or 0.45 mg/kg/day, respectively (Chernoff et al. 1979; Kavlock et al. 1981).

In chronic-duration studies, relative liver weights increased by >10% in male rats exposed to doses ≥0.42 mg/kg/day and female rats exposed to doses ≥2.1 mg/kg/day for up to 2 years (Treon et al. 1955). In dogs, no significant or biologically relevant liver weight changes were observed at doses up to approximately 3.25 mg/kg/day for up to 9.9 months (Treon et al. 1955), 0.19 mg/kg/day for up to 18.7 months (Treon et al. 1955), 0.059 mg/kg/day for 64–156 weeks (Kettering 1971), or 0.1 mg/kg/day for 2 years (Kettering 1969).

Significant alterations in liver serum enzymes occurred in Sprague-Dawley rats following dietary exposure to approximately 8.2 mg/kg/day for 1–2 days (Ali and Shakoori 1993). After 24 and 48 hours, endrin exposure caused a significant 48–69% increase in alkaline phosphatase, a 82–97% increase in AST, a 55–71% increase in ALT, and a 65% increase in isocitrate dehydrogenase, relative to controls. Serum cholesterol also significantly increased by 27 and 35% at 24 and 48 hours, respectively (Ali and Shakoori 1993). A 15-day dietary exposure experiment evaluating liver function in rats after exposure to endrin, endrin aldehyde, or endrin ketone reported 10- and 5-fold elevations in serum ALT and AST, respectively, following exposure to 0.5 mg/kg/day endrin aldehyde. Serum ALT also increased 8-fold following exposure to 0.25 mg/kg/day endrin ketone; neither serum ALT or AST significantly changed following exposure to endrin doses up to 0.5 mg/kg/day (Young and Mehendale 1986). However, endrin-treated animals experienced alterations in hepatobiliary function, as measured by phenolphthalein glucuronide or bile flow, (decreased in males, increased in females), but not animals treated with endrin aldehyde or endrin ketone (Young and Mehendale 1986).

Rabbits fatally poisoned by an acute dermal endrin dose ≥94 mg/kg body weight had centrilobular degeneration of the liver (Treon et al. 1955). The study did not provide details regarding the histopathology of the lesions and only tested a small number of animals. Rabbits surviving multiple skin applications exhibited severe fatty degeneration of the liver.

Mechanisms of Hepatotoxicity. Administration of endrin to animals has been associated with hepatic histopathology, including the presence of lipofuscin pigment (Hassan et al. 1991). One laboratory studied the ability of endrin to elicit hepatic lipid peroxidation and associated cell injury. Administration of single doses of endrin to rats was associated with increased lipid peroxidation, decreased membrane fluidity, and deoxyribonucleic acid (DNA) damage (single strand breaks) in hepatocytes (Bagchi et al. 1995a, 1995b, 1992a, 1993a, 1993b, 2000, 2002; Hassoun et al. 1993). The authors suggested that membrane alterations and DNA damage may result from the enhanced formation of free radical or reactive oxygen species. These reactive species could lead to altered cell proliferation and differentiation, potentially through activation of the protein kinase C (PKC) pathway (Bagchi et al. 1997). Endrin caused dose-related increases in lipid peroxidation in rats resulting in breakdown of polyunsaturated fatty acids as evidenced by the urinary excretion of the lipid metabolites formaldehyde, acetaldehyde, malondialdehyde, and acetone (Bagchi et al. 1992b). Induction of microsomal cytochrome P450 has also been observed following intraperitoneal injections of endrin (Khan et al. 1998). As discussed in Section 2.20 (Mechanisms of Toxicity), general mechanisms of toxicity that may contribute to observed hepatic toxicity include glutathione depletion and alterations in metal homeostasis. Pretreatment with various antioxidants (vitamin E succinate, ellagic acid, lazaroid U74389F) ameliorated endrin-related lethality, histopathologic damage, lipid peroxidation, DNA damage, glutathione depletion, alterations in iron homeostasis, and excretion of lipid metabolites (Bagchi et al. 1992c, 1993b, 1995b; Hassan et al. 1991; Numan et al. 1990a, 1990b).

In studies with dioxin-responsive and -nonresponsive strains of mice, there was no clear evidence for involvement of the Ah receptor in endrin-induced lipid peroxidative effects in liver (Bagchi et al. 1993c). Endrin is also not likely to exert hepatotoxicity via peroxisome proliferator-activated receptors (PPARs) because it was not an agonist for mouse PPARα or PPARγ in an *in vitro* reporter gene assay (Takeuchi et al. 2006). However, endrin was a human pregnane X receptor (hPXR) agonist in an *in vitro* reporter gene assay, resulting in induction of CYP3A4 and CYP2B6 in hepatocytes (Lemaire et al. 2004). Together, PXR and the constitutive androstane receptor (CAR) can mediate hepatotoxicity via alterations in

metabolism and hepatic proliferations (Hernandez et al. 2009). No information on whether or not endrin can induce CAR was available (Hernandez et al. 2009).

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

2.10 RENAL

No studies were located regarding renal effects in humans following exposure to endrin.

One inhalation study found diffuse degenerative changes in the kidneys of two rabbits and one mouse that died following exposure to 0.36 ppm of endrin (Treon et al. 1955). The study did not provide further details of the kidney pathology.

Kidney damage has been reported in multiple species following acute oral exposure. Consistent with inhalation data, diffuse degenerative changes were also observed in the kidneys of multiple species at lethal oral doses in LD_{50} studies; no further information was reported (Treon et al. 1955). In other acute oral studies, moderate tubular necrosis and congestion, inflammation, and interstitial edema were observed in rats and mice sacrificed 24 hours after a single oral exposure to 4 mg/kg (Hassan et al. 1991). These effects without inflammation were also observed in similarly exposed hamsters, and cloudy swelling of cells and narrowing of tubular lumina were observed in similarly exposed guinea pigs (Hassan et al. 1991). Severe congestion and serofibrinous exudate were observed in the kidneys of dogs that died following apparent ingestion of endrin-containing bait (Quick et al. 1989). Among acute studies that only evaluated kidney weight, one reported a 9% increase in rats following a single gavage exposure to 25 mg/kg (Lawrence et al. 1968), but another found no effect after a single exposure to 4 mg/kg (Numan et al. 1990a) or to 1–3 mg/kg/day for 8 days (dosed every 2–3 days; time-weighted average [TWA] dose = 1 mg/kg/day) (Coleman et al. 1968).

Kidney damage was also seen in longer-duration oral studies, but generally only at concentrations resulting in increased mortality. An older study observed diffuse degeneration changes in the kidneys of dogs that died following exposure to dietary doses ≥0.24 mg/kg/day for up to 9.9 months (Treon et al.

1955). However, data reporting was inadequate to clearly define an effect level. These lesions were not observed at nonlethal concentrations up to approximately 0.19 mg/kg/day for up to 2 years (Treon et al. 1955), but did cause a 24% increase in relative kidney weight (Treon et al. 1955). Exposure to 0.08 mg/kg/day had no effect on kidney weight. No changes in kidney weight or histology were observed in dogs exposed to dietary concentrations up to 0.1 mg/kg/day for 2 years (Kettering 1969). Diffuse degeneration of the kidney also occurred in rats that died following dietary exposure to doses as low as 2.1 mg/kg/day for 2 years; nonlethal doses ≤0.42 mg/kg/day did not result in kidney lesions (Treon et al. 1955). In addition, cloudy swelling of tubule epithelial cells occurred in rats chronically exposed to nonlethal doses ranging from 0.1 to 0.56 mg/kg/day (Deichmann et al. 1970). An NCI (1979) bioassay of rats and mice did not observe any pathological changes in the kidney at dietary doses up to 0.25 and 0.42 mg/kg/day, respectively; however, discolored urine occurred in rats administered >0.13 mg/kg/day.

Dermal exposure to lethal doses of endrin once or for an intermediate duration resulted in diffuse degenerative changes of the kidney in rabbits (Treon et al. 1955).

2.11 DERMAL

No studies were located regarding dermal effects in humans following exposure to endrin.

Chronic administration of endrin in feed resulted in alopecia in mice (0.21 mg/kg/day) and both dermatitis and alopecia in rats (0.13 mg/kg/day) at the lowest tested doses (NCI 1979). In dogs, no changes in skin histology were observed at dietary doses up to 0.1 mg/kg/day for 2 years (Kettering 1969). No damage to the skin at the site of application was observed in rabbits exposed to a single or repeated dermal application of dry endrin (Treon et al. 1955).

2.12 OCULAR

No studies were located regarding ocular effects in humans following exposure to endrin. The only animal study evaluating ocular effects reported a lack of exposure-related histological changes in the eyes of dogs given endrin in their diet at doses up to 0.1 mg/kg/day for 2 years (Kettering 1969).

2.13 ENDOCRINE

Several epidemiological studies have examined the potential relationship between environmental endrin exposure and thyroid hormone levels. In general, the studies observed only weak (if any) relationships,

and reported inconsistent findings between studies, sexes, and age groups (see Table 2-1 for more details). In Brazilian agricultural workers, a weak, but statistically significant, association was observed between serum endrin levels and decreased serum total triiodothyronine (T3) levels; no association was observed between serum endrin levels and serum thyroid stimulating hormone (TSH) or free thyroxine (T4) levels (Piccoli et al. 2016). The predominant exposure route is expected to be inhalation; however, dermal and oral exposure may have also occurred. In the general population, no significant associations were observed between serum total T3, free T4, or TSH levels in adults living in a heavily contaminated rural area in Brazil (Freire et al. 2013). When stratified by exposure duration, Freire et al. (2013) reported that a positive relationship was observed between serum endrin levels and serum T4 and TSH in women who were born in the area; however, data are not provided and statistical significance of findings were not discussed. In contrast, children from the same area showed a significant increase in total T3 levels with increasing serum endrin levels, but no associations were observed between serum endrin levels and serum T4 or TSH (Freire et al. 2012). In infants, the risk of elevated cord blood TSH levels was increased 2-fold when endrin was detected in the placenta (Freire et al. 2011; see Section 2.17 Developmental for more details). Exposure in these studies is most likely via dermal contact and ingestion of contaminated soil, water, and locally produced food. A major limitation in all these studies is lack of adjustment for measured serum levels of other pesticides.

El Morsi et al. (2012) provides limited evidence of a potential risk of type 1 diabetes in children with endrin exposure. This case-control study in Egypt reported a significant increase in serum endrin levels in children diagnosed with type 1 diabetes compared with healthy controls (see Table 2-1 for more details). The risk of having type 1 diabetes was significantly increased by 1.5-fold with detectible serum endrin levels. However, the study did not adjust for any confounders, including other detectible pesticides. Exposure may have occurred *in utero*, via diet, or via contact with contaminated house dust, carpets, chemically treated gardens, or pets treated with insecticides. In a cross-sectional study of adults, serum endrin levels were not significantly elevated in subjects with diabetes or blood glucose levels of ≥126 mg/dL (Henríquez-Hernández et al. 2017).

Data regarding potential endocrine effects in laboratory animals exposed to endrin are limited. In a chronic dietary bioassay, thyroid hyperplasia and pituitary cysts were observed in rats at dietary doses ≥0.13 mg/kg/day, but not mice at doses up to 0.42 mg/kg/day (NCI 1979). In another chronic study in rats, diffuse degeneration of the adrenal glands was observed in rats that died following dietary exposure to doses as low as 2.1 mg/kg/day for 2 years; lesions were not observed at nonlethal doses ≤0.42 mg/kg/day (Treon et al. 1955). In dogs, no changes in thyroid, adrenal, pancreas, or pituitary

weight and/or histology were observed following dietary exposure to doses up to 0.1 mg/kg/day for 2 years (Kettering 1969).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to endrin. An *in vitro* study of endrin effects on human lymphocyte mitogenic responses to phytohemagglutinin and neutrophil chemotaxis was negative (Lee et al. 1979).

Immunological data in animals following exposure to endrin are limited to inconsistent alterations in immune organ weight following oral exposure. Time- and dose-related increases in spleen-to-body weight ratios were observed in rats administered a single oral dose of 1.5–6 mg/kg and sacrificed at intervals over 3 days, while relative thymus weights were decreased (Bagchi et al. 1992b, 1992c). Organ weight data were not reported for concurrent control groups in these studies. No changes in spleen weight were observed in rats sacrificed 2 hours following a single exposure to 25 mg/kg; thymus weights were not evaluated (Lawrence et al. 1968). In another acute rat study, increased absolute spleen weights were observed in rats exposed to a total of 8 mg/kg over 8 days (dosed every 2–3 days); however, interpretation of these data are difficult due to lack of body weight data despite reported “changes in eating habits” (Coleman et al. 1968). Thymus weights were not evaluated by Coleman et al. (1968). In dogs, there were no effects on spleen weight at dietary doses up to 0.19 mg/kg/day for 16.4–18.7 months (Treon et al. 1955) or dietary doses up to 0.1 mg/kg/day for 2 years (Kettering 1969). The adversity of the sporadic organ weight findings is unclear due to inconsistency and lack of concurrent histopathological evaluation; therefore, no NOAEL/LOAEL determinations were made for immune effects based on organ weight data. The only study evaluating immune organ histology was Kettering (1969), which reported a lack of exposure-related histopathological changes in spleen, thymus, mesenteric lymph nodes, and bone marrow in dogs exposed to dietary endrin at doses up to 0.1 mg/kg/day. No studies evaluating immune function were available.

Decreased thymic weight was reported in mouse fetuses following maternal exposure to ≥4.5 mg/kg/ on gestation day (GD) 12 (Hassoun and Stohs 1996a, 1996b); see Section 2.17 (Developmental) for more information.

2.15 NEUROLOGICAL

Studies in humans demonstrate that the nervous system is a primary target for acute endrin toxicity in the occupational setting. Exposure in this setting is primarily due to inhalation, with potential for dermal and oral exposure. An occupational health survey at a plant that manufactured aldrin, dieldrin, and endrin, reported 17 acute cases of convulsions over a 9-year period (Hoogendam et al. 1962, 1965). The authors stated that acute, high exposures, often without proper protective gear, accounted for all the cases; however, they did not report any exposure levels. After removal from exposure, seizures subsided, and the patients made a complete recovery within 1–3 days. Abnormal electroencephalograms (EEGs) were usually observed in endrin-poisoned workers, and sometimes occurred without any clinical symptoms. Predominantly bilateral synchronous theta waves, and synchronous spike and wave complexes were seen (Hoogendam et al. 1962). These are believed to be associated with brain stem injury. Abnormal EEGs generally returned to normal within a period of 0.5–1 month after removal of the worker from exposure (Hoogendam et al. 1965). Retrospective cohort studies evaluating long-term effects of occupational organochlorine exposure (including endrin) in former workers reported no incidences of epileptiform convulsions in the years following employment (Versteeg and Jager 1973), and did not observe excesses in death due to neurological diseases (Ditraglia et al. 1981).

Poisoning episodes in humans show that the central nervous system is the primary target system of orally administered endrin. Acute human poisonings by endrin-contaminated food caused symptoms of central nervous system toxicity such as jerking of arms and legs, tonic-clonic contractions, convulsions, and sudden collapse and death (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Rowley et al. 1987; Waller et al. 1992; Weeks 1967). Convulsions were also reported in a man who attempted suicide by drinking an endrin formulation (Runhaar et al. 1985).

In a severe case of poisoning in a 1-year-old child, severe convulsions, coma, decerebrate rigidity, and permanent brain injury occurred after the child played in his room following application of an endrin-containing pesticide (endrin content and other compounds present not available) (Jacobziner and Raybin 1959). The floors and walls of the boy's room had endrin residue; therefore, the exposure was likely a combination of dermal and oral (due to hand-to-mouth activities of young children).

Data regarding potential neurological effects in animals following inhalation exposure to endrin are limited to reports of diffuse lesions in acute lethality studies. Degenerative lesions of the brain were observed in two rabbits that died after exposure to 0.36 ppm for 165 days (5 days/week); these lesions

were not observed in a mouse that died after similar exposure (Treon et al. 1955). Seizures were not observed prior to death. Ressang et al. (1959) also reported slight degenerative lesions of ganglion cells in the brains of a cat exposed to a lethal concentration of endrin.

Neurological effects are commonly observed in animals following acute oral exposure to endrin. Diffuse degenerative changes were observed in the brains of multiple species at lethal doses in LD_{50} studies; no further information was reported (Treon et al. 1955). Beagle dogs that had apparently ingested endrin-containing bait exhibited tetanic convulsions (Quick et al. 1989). Death occurred within 45 minutes of the onset of convulsions in five of eight dogs (and later for an additional two of eight dogs). Tremors and convulsions were noted in rats administered acute doses ≥4 mg/kg (Gaines 1960; Kavlock et al. 1981; Lawrence et al. 1968; Mehrotra et al. 1989; Speck and Maaske 1958), but not ≤3 mg/kg (Coleman et al. 1968; Kavlock et al. 1981; Mehrotra et al. 1989). Decreased activity levels were observed in pregnant rats, mice, and hamsters administered endrin during gestation at doses as low as 0.5 mg/kg/day (Gray et al. 1981; Kavlock et al. 1981). Altered neurodevelopment was observed in some rat and hamster offspring (Gray et al. 1981); see Section 2.17 (Developmental) for more information.

Neurological effects were also observed in longer-duration oral studies. The most sensitive species appears to be the dog, with convulsions observed at chronic doses ≥0.05 mg/kg/day (Kettering 1969, 1971). An intermediate-duration study observed various neurological effects (lethargy, tremors, twitching, hyperirritability to stimuli, convulsions, tremors, and diffuse degenerative brain lesions) in animals that died following exposure to dietary doses of approximately ≥0.24 mg/kg/day for up to 9.9 months; however, data reporting in this study is inadequate to define an effect level (Treon et al. 1955). Petechial hemorrhages and cerebral edema were observed in the brain of one dog having convulsions at the time of death (Kettering 1969). In rats, Deichmann et al. (1970) reported convulsions and tremors following chronic dietary exposure to ≥0.1 mg/kg/day; however, no clinical signs of neurotoxicity or brain lesions were observed in rats in an NCI (1979) bioassay at dietary exposures up to 0.25 mg/kg/day. In another chronic study in rats, diffuse degeneration of the brain was observed in rats that died following dietary exposure to doses as low as 2.1 mg/kg/day and convulsions and hypersensitivity to stimuli were observed at lethal doses ≥4.2 mg/kg/day; these effects were not observed at nonlethal doses ≤0.42 mg/kg/day (Treon et al. 1955). Speck and Maaske (1958) reported altered EEGs and audiogenic convulsions (convulsions triggered by noise) in rats exposed to endrin for 3–7 months; however, the report does not clearly indicate the dose(s) at which these effects occurred (administered doses were 0.8, 1.7, and 3.5 mg/kg/day); due to inadequate reporting, this study was not included in the

LSE. Mice exhibited hyperexcitability following dietary doses of ≥0.21 mg/kg/day for up to 80 weeks; however, no histologic changes in the brain were found (NCI 1979).

Convulsions, tremors, and/or twitching of the facial muscles were the chief signs of endrin intoxication in rabbits and rats following dermal exposure (Gaines 1960; Treon et al. 1955). Diffuse degenerative lesions of the brain were observed in rabbits that died (Treon et al. 1955).

Mechanisms of Neurotoxicity. The mechanism by which endrin induces its neurotoxic effects has been the subject of a number of research investigations. Based on experimental and clinical findings of convulsions and seizures in humans and animals, and altered electrophysiologic activity in animals, endrin appears to exert its neurotoxic effects at the level of the central nervous system. The 12.5-fold greater toxicity of endrin when administered intracerebrally versus intraperitoneally to male mice supports the brain being the primary target site for endrin (Bloomquist 1992).

Central nervous system function may be altered via changes in neurotransmitter systems, particularly the inhibitory γ-aminobutyric acid (GABA) system. *In vitro* exposure of male rat brain preparations to endrin induced noncompetitive inhibition of GABA-regulated chloride transport (Wafford et al. 1989) and chloride current in patch clamp studies (Narahashi 1991). Other studies support the correlation between inhibition of GABA-dependent chloride uptake and the acute intracerebral toxicity of endrin (Bloomquist 1992). The results of these studies support the hypothesis that endrin disrupts the GABAergic system, which could explain observed hyperexcitability of the central nervous system and convulsions. No evidence of alterations in the serotonergic system were observed following *in vivo* exposure in mice (Miller and Fink 1973) or the dopaminergic system following *in vitro* exposure in PC6-3 cells (Allen et al. 2013).

Alterations in calcium homeostasis could also contribute to neurotoxicity of endrin. Mehrotra et al. (1989) observed that isolated fractions of brain and heart cells from rats orally administered 0.5–10 mg endrin/kg showed significant inhibition of Ca+2 pump activity and decreased levels of calmodulin, indicating disruption of membrane Ca+2 transport mechanisms; exogenous addition of calmodulin restored Ca+2-ATPase activity. *In vitro* exposure of rat brain synaptosomes and heart sarcoplasmic reticuli decreased total and calmodulin-stimulated calcium ATPase activity with greater inhibition in brain preparations (Mehrotra et al. 1989). However, endrin showed no inhibitory effects on the calmodulin-sensitive calcium ATPase activity when incubated with human erythrocyte membranes (Janik and Wolf 1992). *In vitro* exposure of rat brain synaptosomes to endrin had no effect on the activities of

adenylate cyclase or 3',5'-cyclic phosphodiesterase, two enzymes associated with synaptic cyclic AMP metabolism (Kodavanti et al. 1988).

Studies in one laboratory show that administration of single doses of endrin to rats was associated with increased lipid peroxidation and DNA damage (single strand breaks) in brain tissue (Bagchi et al. 1995a, 1995b, 2000, 2002). DNA damage associated with generation of reactive oxygen species was also observed in PC-12 neuroactive cells exposed to endrin *in vitro* (Bagchi et al. 1995a), and induction of protective heat shock (stress) proteins was observed (Bagchi et al. 1996). As discussed in Section 2.9 (Hepatic), these effects were also observed in hepatocytes. This pathway may represent a general mechanism by which endrin exerts toxicity in various tissues, including tissues of the nervous system.

2.16 REPRODUCTIVE

A number of epidemiological studies have examined reproductive outcomes in the context of endrin use in agricultural regions. However, the data are inadequate to determine the potential for endrin to cause adverse reproductive effects.

An Egyptian case-control study found significantly elevated maternal and cord serum organochlorine levels (including endrin) in 43 cases of premature delivery compared with 80 full-term deliveries (Samra and Selim 2009). However, when the authors combined cases and controls for analysis, they did not observe a significant association between serum endrin levels and gestational age (see Table 2-1 for additional details). Due to elevation of several other organochlorine pesticides in case subjects (e.g., heptachlor, dieldrin, DDT), no conclusion regarding a potential association between endrin exposure and preterm delivery can be made. A cross-sectional study conducted in Taiwan found an association between breast milk endrin ketone levels and average menstrual cycle lengths of >5 days (Chen et al. 2018); no association were found for endrin, endrin aldehyde, or total endrin. The study also found association between breast milk levels of endrin compounds and the risk of infertility.

A cohort study in Kazakhstan reported delayed physical and sexual development in adolescent females exposed to organochlorine pesticides (lindane, dieldrin, DDT, and endrin) in cotton-growing regions compared with age-matched controls living in non-cotton-growing regions (Bapayeva et al. 2016). The study specifically reported a decrease in serum follicle stimulating hormone and estradiol in the exposed females; however, a statistical analysis is not provided. No significant associations between serum male or female reproductive hormone levels and serum endrin levels were observed in a cross-sectional study

of a rural area in Brazil with heavy pesticide contaminations (Freire et al. 2014). *In vitro* screens showed that endrin does not have a high estrogenic potential (Lemaire et al. 2006; Mumtaz et al. 2002; Tully et al. 2000)

No exposure-related effects on fertility, gestation, viability, or lactation indices were observed in a three-generation reproduction study in rats fed diets containing endrin at doses up to 0.1 mg/kg/day (Eisenlord et al. 1968). Interpretation of the study results is confounded by the potential presence of viral pneumonitis in controls and, thus, possibly in all animals in the study. Similarly, no adverse effects on fertility or fecundity were observed in mice given diets containing endrin at doses up to 0.65 mg/kg/day for 120 days beginning 30 days before mating; however, this dose was associated with reduced litter size and 30% mortality in breeding pairs (Good and Ware 1969).

One animal study examined reproductive outcomes following oral exposure to endrin, but data quality is insufficient to characterize an effect level. In a single-generation reproduction study, groups of three female Beagle dogs were administered dietary doses of 0.0, 0.003, 0.014, 0.027, or 0.059 mg/kg/day and mated with endrin-treated males from a concurrent chronic toxicity study (Kettering 1971). Four treated females (one each at 0.014 and 0.027 mg/kg/day and two at 0.059 mg/kg/day) never accepted a male and, despite artificial insemination, did not become pregnant. The failure to conceive in the high-dose groups could suggest an endrin-mediated effect on fertility; however, exploratory laparotomies and necropsies, and microscopic examination of ovaries and uteri at termination of these dogs revealed no specific changes due to endrin. Furthermore, two of three control dogs failed to bring any pups to weaning and dogs were infected with *Brucella canis* infections. Due to these confounding factors, this study in considered inadequate to make a NOAEL/LOAEL determination for reproductive effects.

2.17 DEVELOPMENTAL

Data on the potential for endrin to cause developmental effects in humans are limited. In an Egyptian study of 123 pregnancies, associations between maternal or cord serum endrin levels and birth weight, length, or head circumference appear to be significant (reported p-values of $\leq$0.001); however, the associations are not marked as significant in study data tables, and the study authors only discuss the significant associations between birth outcomes and serum heptachlor and DDT levels (Samra and Selim 2009). The reasons for this apparent discrepancy are unclear based on the reported data. In a birth cohort with 220 mother-son pairs born in Granada between 2000 and 2002, detection of endrin in the placenta was associated with a significant 2-fold increase in the risk of “moderately” elevated cord blood TSH

levels, as defined by the World Health Organization (>5 mU/L) (Freire et al. 2011). A subset of mother-son pairs from this birth cohort were evaluated in a case-control study of male infant cryptorchidism and/or hypospadias; placental endrin levels were comparable between cases and controls (Fernandez et al. 2007).

Animal studies have observed malformations and variations in mice and hamsters following maternal exposure to endrin via gavage, predominantly at doses that caused maternal toxicity. Exposure of mice to 2.5 mg/kg on GD 9 resulted in significantly increased incidence of open eyes and cleft palate (Ottolenghi et al. 1974). Increased incidence of exencephaly, fused ribs, and supernumerary ribs were seen in offspring of pregnant mice treated with ≥7 mg/kg of endrin on GD 8; increased maternal mortality was also observed at this dose (Kavlock et al. 1985). There were no dose-related indications of skeletal or visceral malformations or anomalies in the mice following maternal exposure to doses up to 2 mg/kg/day via gavage on GDs 7–17, but delays in development (changes in the number of caudal vertebrae, development of the renal pelvis, and ossification of the supraoccipital bones) and maternal toxicity were observed at doses ≥1 mg/kg/day (Kavlock et al. 1981). Increased hydronephrosis was reported in mouse fetuses following maternal exposure to 6 mg/kg on GD 12 (Hassoun and Stohs 1996a). In hamsters, a statistically significant increase in the incidence of fused ribs and cleft palate was observed in fetuses from golden Syrian hamsters treated on GD 7, 8, or 9 with 5 mg/kg of endrin (Ottolenghi et al. 1974). A significant increase in open eyes and webbed feet occurred only in fetuses from dams treated on GD 8 (Ottolenghi et al. 1974). A single dose of endrin administered to hamsters on GD 8 produced meningo-encephaloceles at a doses of ≥5 mg /kg (Chernoff et al. 1979). Exposure of hamsters to ≥1.5 mg/kg/day on GDs 5–14 resulted in irregularly shaped supraoccipital bones and visceral abnormalities (Chernoff et al. 1979). In both the single and repeated studies by Chernoff et al. (1979), fetal effects occurred only at doses with significant maternal toxicity. In contrast, endrin did not cause fetal malformations or variations in a study in which pregnant hamsters were administered up to 2.5 mg/kg/day from GD 4 to 13 (Goldenthal 1978b). In rats, no malformations were observed in offspring following maternal exposure to doses up to 0.45 mg/kg/day from GD 7 to 20 (Kavlock et al. 1981) or 2 mg/kg/day on GDs 6–15 (Goldenthal 1978a). However, delayed ossification of sternebrae and skull along with maternal toxicity (decreased weight gain and death) were observed at 2 mg/kg/day (Goldenthal 1978a).

Gestational exposure studies have observed inconsistent effects on fetal survival and resorptions that may depend on the exposure window, dose, strain, and/or species. Increased incidence of dead or resorbed fetuses following gestational exposure occurred in C56BL/6J mice exposed to 6 mg/kg on GD 12 (Hassoun and Stohs 1996a) and hamsters exposed to either 5 mg/kg on GD 8 (Ottolenghi et al. 1974) or

≥1.5 mg/kg/day from GD 5 to 14 (Chernoff et al. 1979). Hassoun and Stohs (1996a) also reported significant reductions in placental weight in C57BL/6J mice at doses ≥4.5 mg/kg and DBA/2J mice at 6 mg/kg. Other studies did not observe changes in fetal survival in rats exposed to gavage doses up to 0.3 mg/kg/day from GD 7 to 15 (Gray et al. 1981), DBA/2J mice exposed to gavage doses up to 6 mg/kg on GD 12 (Hassoun and Stohs 1996b), CD-1 mice exposed to a single gavage dose of 2.5 mg/kg on GD 9 (Ottolenghi et al. 1974), hamsters exposed to gavage doses up to 1.5 mg/kg/day from GD 5 to 14 (Gray et al. 1981), or hamsters exposed to a single oral dose up to 10 mg/kg on GD 8 (Chernoff et al. 1979).

Gestational studies have also reported decreased fetal growth following gestational exposure to endrin, predominantly at maternally toxic doses (>0.5 mg/kg/day). In rats, nonsignificant decreases in fetal body weight and crown-rump length were observed following maternal exposure to 2 mg/kg/day from GD 6 to 15; this dose caused significant maternal toxicity and death (Goldenthal 1978a). No changes in fetal weight or growth were observed in rat offspring at maternal doses ≤0.5 mg/kg/day (Goldenthal 1978a; Gray et al. 1981; Kavlock et al. 1981). In mice, a 4–28% decrease in fetal body weight was reported in C57BL/6J and DBA/2J mice following a single maternal dose to 4.5 or 6 mg/kg/day on GD 12; no changes in maternal body weight were noted (Hassoun and Stohs 1996a). C57BL/6J mice also showed a 13–17% decrease in fetal thymus weights at ≥4.5 mg/kg/day. In CD-1 mice, decreased fetal body weight was observed following maternal exposure to doses ≥1 mg/kg/day from GD 7 to 17; decreased maternal weight gain was also observed at these doses (Kavlock et al. 1981). In hamsters, decreased fetal body weight was observed at maternally toxic doses ≥1.5 mg/kg/day (Chernoff et al. 1979; Ottolenghi et al. 1974). However, no changes in postnatal offspring growth or physical development were observed in hamsters following maternal exposure to gavage doses up to 1.5 mg/kg/day on GDs 5–14, respectively (Gray et al. 1981).

Data regarding pup survival and growth from generational exposure studies are difficult to interpret due to several study limitations. A 3-generation reproduction study in rats found no exposure-related changes in pup viability or survival through weaning at dietary doses up to 0.1 mg/kg/day (Eisenlord et al. 1968). The number of pups in the F3a litter of the high-dose group was significantly increased relative to controls, while F3a pup body weight in the low-dose group was significantly decreased. However, interpretation of the study results is confounded by a high death rate in controls attributed to putative viral pneumonitis. Lack of organ weight or morphologic changes in dog pups from a single-generation study evaluating dietary doses up to 0.059 mg/kg/day is also difficult to interpret due to the low number of treated animals, presence of a *Brucella canis* infection, and failure of two of three control dogs to bring any pups to weaning (Kettering 1971).

One study observed altered neurodevelopment in rat offspring following maternal exposure to endrin at doses ≥0.15 mg/kg/day from GD 7 to 15 (Gray et al. 1981). Exposed offspring showed increased activity in the last 30 minutes of a 45-minute figure-eight maze trail on postnatal day (PND) 15 and PND 20, indicating a lack of normal habituation to a new environment. This effect was no longer apparent on PND 90, and may have been a result of delayed maturation of cholinergic and serotonergic neurotransmission networks. A similar effect was observed in hamster offspring following maternal exposure to 1.5 mg/kg/day on GDs 5–14 (Gray et al. 1981). It should be noted that increases in maternal mortality were also observed at 1.5 mg/kg/day in the hamsters.

2.18 OTHER NONCANCER

Acute exposure to 8.2 mg/kg/day endrin in the diet for 1–2 days resulted in a significant 41–51% decrease in serum glucose (Ali and Shakoori 1993). In the absence of additional data, the biological significance of this finding is unclear.

2.19 CANCER

Studies of workers in the endrin manufacturing industry have not shown an association between occupational exposure to endrin and overall mortality rates due to cancer (Ditraglia et al. 1981; Ribbens 1985; Versteeg and Jager 1973); see Table 2-1 for study details. While there was no specific cancer risk at any of the manufacturing sites, several cancer mortalities reported in aldrin/ dieldrin/endrin plants in one study may warrant further investigation, including slight excesses of cancer of the esophagus, liver, rectum, and the lymphatic and hematopoietic systems (Ditraglia et al. 1981). However, the study authors noted that excesses were not statistically significant, and acknowledged that the elevated standardized mortality ratios (SMRs) were based on small numbers of observed deaths (one to three deaths except for lymphatic/hematopoietic cancers, which were based on six deaths). Limitations of these studies include small cohort size, limited follow-up, and lack of control for confounding factors (e.g., smoking, alcohol consumption).

Several case-control studies have evaluated potential associations between organochlorine pesticide exposure and specific types of cancer. Available studies on breast cancer (Boada et al. 2012; Ward et al. 2000), bladder cancer (Boada et al. 2016), prostate cancer (Pi et al. 2016), and lymphoma (Cocco et al. 2008) did not find detectable endrin levels in any of the cancer subjects. In these studies, detection of endrin levels varied widely in control subjects (endrin detected in 0–58% of controls). These studies are

inadequate to evaluate potential associations between endrin and cancer due to the low detection rate and unknown exposure potentials.

Endrin was found not to be carcinogenic in Osborne-Mendel rats exposed to dietary doses up to 0.25 mg/kg/day (males) or 0.30 mg/kg/day (females) or B6C3F1 mice exposed to dietary doses up to 0.42 mg/kg/day (males) or 0.65 mg/kg/day (females) for 80 weeks (NCI 1979). However, the study's less-than-lifetime exposure duration limits its conclusions. Deichmann et al. (1970) also reported a lack of exposure-related neoplastic findings in Osborn-Mendel rats in a lifetime dietary study; however, this study was also limited because it only included microscope examination of the liver, kidneys, and lungs.

Only one study reported carcinogenic effects of endrin, but its design limitations render the findings unreliable. Reuber (1979) observed increased incidence of sarcoma and carcinomas in multiple tissues combined (e.g., mammary glands, lungs, liver, lymph nodes, thyroid, uterus and kidneys) in Osborne-Mendel rats following lifetime dietary exposure to doses ranging from 0.005 to 1.25 mg/kg/day. However, the findings were not dose-related (higher incidence at the lower doses). Based on statistics performed for this review, only mammary gland carcinoma incidence in female rats exposed to 0.5 mg/kg/day (14/23) and 0.25 mg/kg/day (13/20) and thyroid carcinoma in female rats exposed to 1.25 mg/kg/day (4/19) were significantly elevated compared with controls (6/23 and 0/23, respectively). With the exception of mammary gland and thyroid carcinomas, tumor incidence per organ was only one to two animals. Study limitations include the low number of animals studied (15–23/sex/group), several inconsistencies in data reporting, and concerns regarding Reuber's methods for classifying tissues as tumorigenic (as identified by IRIS 2002), including a lack of slide-by-slide tabulation of study findings as well as no attempt to distinguish between primary and metastatic tumors in the liver. Due to these reasons, the reliability of these findings is questionable, and this study is not included in the LSE.

The EPA has classified endrin in Group D, not classifiable as to carcinogenicity in humans (IRIS 2002). IARC has classified endrin in Group 3, not classifiable as to its carcinogenicity in humans (IARC 1987). HHS has not classified the potential for endrin to cause cancer in humans (NTP 2016).

2.20 GENOTOXICITY

Available evidence indicates that endrin is not mutagenetic. There is limited evidence that it is capable of causing DNA damage and chromosomal alterations under certain conditions; however, endrin-mediated oxidative damage generally causes the observed DNA damage, rather than direct interaction with DNA. Tables 2-5 and 2-6 summarize the results of *in vitro* and *in vivo* genotoxicity studies with endrin, respectively.

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

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium strains TA98, TA100	Gene mutation	–	–	Glatt et al. 1983
S. typhimurium strains TA97, TA98, TA100, TA102, A1535, TA1537	Gene mutation	–	–	Mersch-Sundermann et al. 1994
S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	Moriya et al. 1983
S. typhimurium strains TA98, TA1000, TA1535, TA1537, TA1538, C3076, D3052, G46	Gene mutation	–	–	Probst et al. 1981
Salmonella typhimurium strains TA98, TA100, A1535, TA1537	Gene mutation	–	–	Zeiger 1987
Escherichia coli strain WP2	Gene mutation	–	–	Moriya et al. 1983
E. coli strains WP2, WP2 uvrA-	Gene mutation	–	–	Probst et al. 1981
E. coli strain PQ37	DNA damage (modified SOS chromotest)	NA	+	Venkat et al. 1995
E. coli strain PQ37	DNA damage (SOS chromotest)	–	–	Mersch-Sundermann et al. 1994
Mammalian cells				
Rat (liver epithelial ARL cells)	HGPRT mutations	NA	–	Williams 1980
Mouse (lymphoma L5178Y tk+/- cells)	Gene mutation	–	–	McGregor et al. 1991
Human (lymphoid cells)	Sister chromatid exchange	–	–	Sobti et al. 1983

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

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Rat (primary hepatocytes)	DNA damage/repair	–	NA	Maslansky and Williams 1981
Rat (primary hepatocytes)	Unscheduled DNA synthesis	–	NA	Probst et al. 1981
Rat (primary hepatocytes)	DNA damage/repair	–	NA	Williams 1980
Rat (neuroactive adrenal pheochromocytoma PC-12 cells)	DNA damage (single strand breaks)	NA	+	Bagchi et al. 1995a
Mouse (primary hepatocytes)	DNA damage/repair	–	–	Maslansky and Williams 1981
Hamster (primary hepatocytes)	DNA damage/repair	–	NA	Maslansky and Williams 1981
Hamster (primary hepatocytes)	DNA damage/repair	–	NA	Williams 1980

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

Table 2-6. Genotoxicity of Endrin *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Rat (oral)	DNA damage in brain and liver (single strand breaks)	+	Bagchi et al. 1995a
Rat (oral)	DNA damage in brain and liver (single strand breaks)	+	Bagchi et al. 1995b
Rat (oral)	DNA damage in liver (single strand breaks)	+	Bagchi et al. 1992a
Rat (oral)	DNA damage in liver (single strand breaks)	+	Bagchi et al. 1993a
Rat (oral)	DNA damage in liver (single strand breaks)	+	Bagchi et al. 1993b
Rat (oral)	DNA damage in liver (single strand breaks)	+	Hassoun et al. 1993
Mice (oral)	DNA damage in brain and liver(Fragmentation)	+	Bagchi et al. 2000
Mice (oral)	DNA damage in brain and liver (Fragmentation)	+	Bagchi et al. 2002
Mice (oral)	DNA damage in fetuses, placenta, and fetal liver tissues (Single strand breaks)	+	Hassoun and Stohs 1996b

Table 2-6. Genotoxicity of Endrin *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Rat (intratesticular injection)	Chromosomal aberrations in testes	+	Dikshith and Datta 1973
Eukaryotic organisms			
Drosophila melanogaster (oral)	Somatic mutation (wing spot test)	+/–	Osaba et al. 1999
D. melanogaster (oral)	Recombination	+	Pontecorvo and Fantaccione 2006

– = negative result; + = positive result; +/– = inconclusive result; DNA = deoxyribonucleic acid

Mutagenicity. Endrin was not mutagenic in microbial systems (Glatt et al. 1983; Mersch-Sundermann et al. 1994; Moriya et al. 1983; Probst et al. 1981; Zeiger 1987), rat liver epithelial ARL cells (Williams 1980), or mouse lymphoma L5178Y tk +/- cells (McGregor et al. 1991). In a *Drosophila* wing spot test, the mutagenicity of endrin was inconclusive due to toxicity, even at the lowest concentrations tested (0.001 mM); however, the study authors interpreted the results as primarily negative (Osaba et al. 1999). No studies evaluating *in vivo* mutagenicity of endrin in mammals were located.

Clastogenicity. Sister chromatid exchanges were not observed in human lymphoid cells exposed to endrin *in vitro* (Sobti et al. 1983). *In vivo,* chromosomal aberrations in rat testicular cells were observed following an intratesticular injection of endrin (Dikshith and Datta 1973). The number of recombination events was slightly, but significantly, increased in *Drosophila melanogaster* males (cross overs detected in 3 out of 60 males; p=0.05) (Pontecorvo and Fantaccione 2006).

DNA Damage. In *Escherichia coli,* DNA damage was not observed using the standard SOS chromotest (Mersch-Sunderann et al. 1994); however, DNA damage was observed when endrin was tested in a modified SOS chromotest using sodium taurocholate micelles to better simulate conditions in the small intestine (Venkat et al. 1995). In mammalian cells, endrin did not cause DNA damage or repair or unscheduled DNA synthesis in rat, mouse, or hamster primary hepatocytes (Maslansky and Williams 1981; Probst et al. 1981; Williams 1980). A small, but significant (2.5-fold) increase in nuclear DNA single-strand breaks was detected in rat neuroactive adrenal pheochromocytoma PC-12 cells cultured with 100 nM endrin, compared with controls (Bagchi et al. 1995a).

Several studies reported increased DNA single strand breaks in liver (up to 4.4-fold) and brain tissues (up to 4.3-fold) of rats and mice following acute oral exposure to endrin (Bagchi et al. 1995a, 1995b, 1992a, 1993a, 1993b, 2000, 2002; Hassoun et al. 1993). Evidence of concurrent production of reactive oxidative

species was observed in these studies, indicating that DNA damage was secondary to oxidative injury caused by endrin. Additionally, pre-administration of lazaroid U74389F (16-desmethyl tirilazad) decreased both generation of reactive oxidative species and DNA single strand breaks (Bagchi et al. 1995b). DNA damage was greater in p53-deficient mice (up to 3.9- and 4.4-fold increase in liver and brain tissue, respectively) compared with wild-type mice (up to 2.6- and 1.8-fold increase in liver and brain tissue, respectively), indicating a role for the *p53* tumor suppressor gene in observed oxidative DNA damage (Bagchi et al. 2000).

Hassoun and Stohs (1996b) evaluated the potential role of the Ah receptor in observed DNA damage in placental, fetal, and fetal liver tissue following a single oral exposure to endrin on GD 12. Results showed a greater increase in DNA single strand breaks in Ah-responsive C57BL/6J mice than in Ah-unresponsive DBA/2J mice, particularly in placenta (3.2- and 2-fold, respectively) and fetal liver tissues (4.67- and 1.39-fold, respectively).

2.21 MECHANISMS OF TOXICITY

General, systemic mechanisms of endrin toxicity may include altered metal homeostasis, generation of reactive oxygen species, and glutathione depletion.

Several oral rat studies reported altered metal homeostasis following exposure to endrin. Altered trace metal distribution was observed systemically in rats exposed once to a gavage dose of 25 mg/kg/day (Lawrence et al. 1968). Changes included significant increases in zinc concentrations in the liver, kidney, spleen, brain, and heart with decreased blood cell zinc levels; decreases copper concentrations in the liver, spleen, brain, and heart with elevated serum plasma levels; increases in magnesium concentration in kidney, spleen, and heart; decreases in magnesium concentrations in the liver, brain, red blood cells, and plasma; and increases in iron concentrations of the liver, kidney, spleen, and heart. Similarly, altered metal homeostasis was reported in rats following administration of 8 mg/kg of endrin over 8 days (3 mg/kg on day 1, 2 mg/kg on days 3 and 5, and 1 mg/kg on day 8, with findings indicating increased magnesium excretion and decreased zinc excretion (Coleman et al. 1968). Bagchi et al. (1992c) also reported altered metal homeostasis in the liver following a single exposure to ≥3 mg/kg, including increases in mitochondrial iron and calcium, decreases in microsomal and nuclear iron, and increases in microsomal and nuclear calcium.

Oral administration of endrin to rats was associated with increased lipid peroxidation, increased excretion of metabolites indicative of lipid peroxidation, decreased membrane fluidity, DNA damage (single strand breaks), and induction of protective heat shock (stress) proteins in hepatocytes and brain tissue (Bagchi et al. 1995a, 1995b, 1992a, 1992b, 1993a, 1993b, 1996, 2000, 2002; Hassoun and Stohs 1996b; Hassoun et al. 1993, 1996). Administration of antioxidants ameliorated some of the adverse observations. Similar effects have been observed in placental tissue, fetal tissue, and fetal livers (Hassoun and Stohs 1996b), and increased levels of metabolites indicative of lipid peroxidation have been reported in urine, maternal sera, amniotic fluids, and placenta following acute exposure to endrin (Bagchi et al. 1992b; Hassoun and Stohs 1996b; Hassoun et al. 1996). Therefore, generation of reactive oxygen species may represent a general mechanism by which endrin exerts toxicity, potentially through activation of the PKC pathway, which could lead to altered cell proliferation and differentiation (Bagchi et al. 1997).

Limited evidence indicates that endrin may deplete glutathione. Numan et al. (1990a, 1990b) reported that endrin exposure was associated with decreased glutathione concentrations in liver, kidneys, heart, spleen, brain, and lungs, and altered glutathione-regulating enzymes in liver and kidneys.

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

3.1 TOXICOKINETICS

Limited data were found regarding the absorption, distribution, metabolism, and excretion of endrin in humans and animals after inhalation, oral, or dermal exposure. Available data are summarized below.

- Toxic effects following oral, inhalation, or dermal exposure indicate that the body absorbs endrin via all routes; however, data regarding absorption rates are very limited.
- Endrin is primarily distributed to fat.
- The major biotransformation product of endrin is anti-12-hydroxyendrin and the corresponding sulfate and glucuronide metabolites.
- Endrin is excreted in urine and feces.
- No studies were found that described the toxicokinetics of endrin aldehyde or endrin ketone.

3.1.1 Absorption

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

Reported toxic effects in case studies indicate that humans absorb endrin following ingestion (Coble et al. 1967; Curley et al. 1970; Kintz et al. 1992; Rowley et al. 1987; Runhaar et al. 1985; Weeks 1967). Similarly, numerous animal studies reported serious adverse biological effects following oral exposure, indicating absorption. However, no studies have been located that report the rate or extent of absorption that occurs in orally exposed humans or animals.

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

Dermal exposure of rats and rabbits to endrin resulted in toxicity and death (Gaines 1960; Treon et al. 1955), indicating that percutaneous absorption of endrin occurs. Data describing the rate or extent of dermal absorption in animals were not located.

3.1.2 Distribution

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

Measurable tissue concentrations of endrin have been observed in cases of acute oral poisoning. The time of sample collection is critical, as endrin residues in tissues decline rapidly after exposure has ceased (Coble et al. 1967). Evaluations shortly after exposure (<1 hour) have shown the highest concentrations in the gastrointestinal system and liver, followed by the kidneys, spleen, and heart (Coble et al. 1967; Curley et al. 1970; Kintz et al. 1992; Moriya and Hashimoto 1999; Tewari and Sharma 1978). Blood and bile concentrations were low compared to organ levels in all cases except those with rapid death (Kintz et al. 1992). Evaluations at a later time point show a different pattern; 11 days after a suicide attempt, the highest concentration was identified in the adipose tissue, followed by much lower levels in the liver, heart, brain, kidneys, and blood (Runhaar et al. 1985). In the general population, low levels of endrin in the adipose tissue of Jordanian men and woman generally increased with age (Alawi et al. 1999); however, studies in the United States and Canada did not find measurable levels of endrin in adipose tissue of the general population (EPA 1986b; Williams et al. 1984).

Endrin tends to bioaccumulate in fat because of its high lipid solubility. Three days after an acute oral dose of 2.5 mg/kg of radio-labeled endrin, the percentages of the administered dose in male rat organs were 1.2% in liver, 0.6% in kidneys, 1.7% in fat, 2.3% in skin, and 12.2% in the carcass. Female rats retained higher concentrations in tissues: 2% of the dose in liver, 0.35% in kidneys, 8% in fat, 4% in skin, and 28.2% in carcass (Hutson et al. 1975). Richardson et al. (1970) also reported an unidentified metabolite of endrin in the brain, liver, and adipose tissue of male rats following a single oral exposure. Following administration of radiolabeled endrin to lactating cows, the highest tissue concentrations were in the fat (about 8% of the total dose). Residues in liver, muscle, kidneys, and fat primarily contained unchanged endrin (Baldwin et al. 1976). Endrin and 12-ketoendrin were detected in the maternal liver and fetal tissue of rats and hamsters administered endrin during gestation (Chernoff et al. 1979; Kavlock et al. 1981). Concentrations of endrin in fetal tissue ranged from 2 to 8% of those measured in maternal livers, indicating that endrin can cross the placenta.

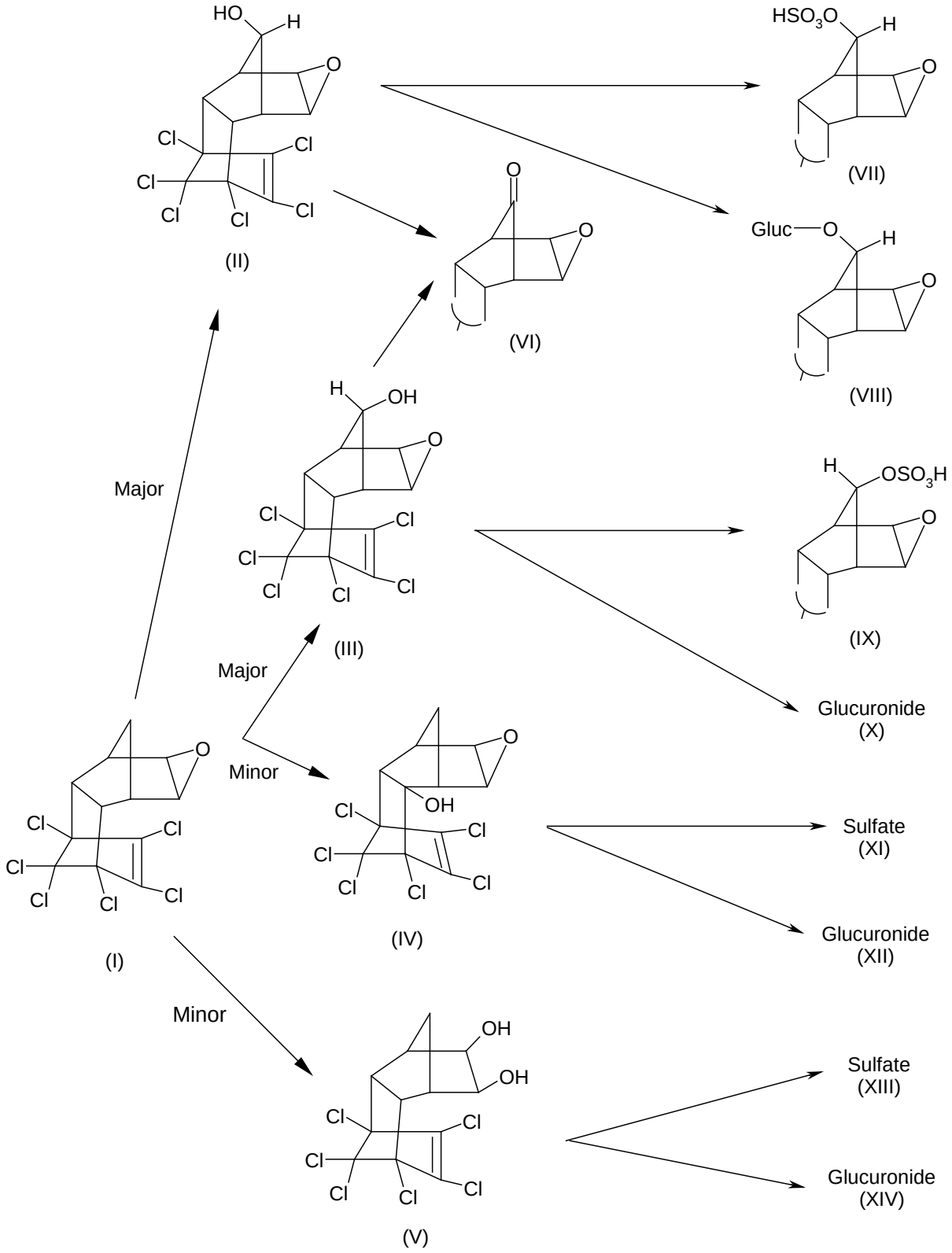
In Beagle dogs that had died after apparent ingestion of endrin-containing bait, the stomach contents contained 34–5,000 mg/kg endrin (Quick et al. 1989). The highest tissue concentrations were found in the fat (5.4–40 mg/kg), followed by liver (0.82–4.5 mg/kg) and brain (0.34–2.7 mg/kg). Lower concentrations were found in lungs and muscles. Following administration of 0.1 mg/kg/day in the feed for 128 days, concentrations of endrin in the blood of Beagle dogs showed no accumulation over time (Richardson et al. 1967). At termination, there was no correlation between the concentration of endrin in blood with that in heart, pancreas, liver, kidneys, spleen, and lungs, although a trend of high concentrations in fat (250–760 ppb) and high concentrations in blood (1–8 ppb) were noted. The highest tissue concentrations of endrin were generally found in fat, followed by muscle (120–310 ppb), heart (125–170 ppb), pancreas (87–280), liver (77–84 ppb), kidneys (38–82 ppb), and lungs (17–33 ppb). Concentrations in the spleen were highly variable (7–2,620 ppb). Results from this study may be somewhat confounded by a potential feeding error, as dieldrin (being fed to a concurrent group) was detected in the blood and tissues of the three endrin-treated dogs.

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

3.1.3 Metabolism

The metabolism of endrin varies among species, regardless of the route of exposure. In all species, oxidation of the methylene bridge in endrin (Compound I in Figure 3-1) to syn-, but mostly anti-12-hydroxyendrin occurs (Compounds II and III), followed by dehydrogenation to 12-ketoendrin (Compound VI). Minor independent pathways involve the hydrolysis of the epoxide to a transdiol (Compound V in Figure 3-1) and hydroxylation of the C-3 position (Compound IV) (Bedford et al. 1975b; Hutson 1981; Petrella et al. 1977). Hydroxylation at C-3 and C-4 is inhibited by the presence of the bulky hexachlorinated fragment (Hutson 1981). In rats, both anti-12-hydroxyendrin and 12-ketoendrin are produced at higher rates in the male rat, with higher formation of anti-12-hydroxy-endrin O-sulphate in female rats (Hutson et al. 1975). Richardson et al. (1970) also reported sex differences in the proportion of fecal metabolites in rats; however, metabolites were identified as “1” and “2” and not further characterized except to state that they were not ketone rearrangement products of endrin. In mice, strains resistant to acute endrin toxicity produce anti-12-hydroxyendrin at higher rates (~2-fold) compared with strains that are susceptible to acute endrin toxicity (Petrella et al. 1977).

Figure 3-1. Proposed Metabolism Scheme for Endrin in Mammals



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

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

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

3.1.4 Excretion

Measurements of human serum concentrations of endrin following incidents of acute poisoning indicate rapid decline in concentration after exposure, suggesting rapid excretion (Coble et al. 1967; Rowley et al. 1987). Anti-12-hydroxyendrin and 12-ketoendrin were detected in the feces of pesticide manufacturing workers and its glucuronide conjugate and 12-ketoendrin have been detected in the urine (Baldwin and Hutson 1980). In another study, the levels of anti-12-hydroxyendrin increased accompanied by a sharp rise in D-glucaric acid levels in 29 workers after 7 days of exposure (Ottevanger and Van Sittert 1979; Vrij-Standhardt et al. 1979). Endrin has also been detected in human breast milk, cord blood, and placental tissues in several studies worldwide (Alawi et al. 1992; Bedi et al. 2013; Bordet et al. 1993; Fujii et al. 2012; Gladen et al. 1999; Guillette et al. 1998; Lopez-Espinosa et al. 2007; Polanco-Rodriguez 2017; Romero et al. 2000; Schaalan et al. 2012). Endrin, endrin aldehyde, and endrin ketone may also be excreted in humans via sweat (Genuis et al. 2016).

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

In rats, the major route of elimination is the feces, with a smaller percentage eliminated in the urine, and there are apparent sex differences. Twenty-four hours after oral exposure to 0.5–2.5 mg/kg, 55–57% of ^{14}C-endrin was metabolized in the bile; the predominant metabolite was the glucuronide of anti-12-hydroxyendrin (Hutson et al. 1975). Other minor components (<10%) were the glucuronides of 3-hydroxy- and 12-ketoendrin. Male rats eliminated 69% of the radioactive label within 3 days and females eliminated 45%. Another study in male rats reported elimination of 49% of the radioactive label within 3 days following oral exposure (Richardson et al. 1970). In studies with isolated perfused livers, ^{14}C-endrin was excreted in the bile of livers from male rats at a rate 2–12 times higher than that for females (Klevay 1971). In urine, the major metabolites in males and females were 12-ketoendrin and 12-hydroxyendrin-O-sulfate, respectively, following oral exposure (Hutson et al. 1975). Baldwin et al. (1970) also detected 9-ketoendrin in the urine of rats.

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

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

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 chemical-specific PBPK models have been developed for endrin.

3.1.6 Animal-to-Human Extrapolations

No studies were identified that could evaluate potential differences in the toxicity or toxicokinetics of endrin between humans and animals. However, the primary toxicity target (nervous system) is consistent between exposed humans and animals. Some species differences were observed between different laboratory species; however, the targets of toxicity appear to be similar. Available mechanistic data are inadequate to evaluate potential species differences.

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 endrin are discussed in Section 5.7, Populations with Potentially High Exposures.

Persons with a history of convulsive disorders are expected to be at increased risk of nervous system effects if exposed to endrin. Data are inadequate to determine if children may be more sensitive than adults to the acute toxic effects of endrin. In an endrin poisoning episode in Pakistan, children 1–9 years old represented about 70% of the cases of convulsions (Rowley et al. 1987). The causative factor responsible for the outbreak was not identified, however, so it is unclear whether the age distribution of cases is due to increased susceptibility in children or age-specific exposure situations. In general, following oral administration, female animals appear to be more susceptible to endrin toxicity than males (Gaines 1960; Treon et al. 1955). The difference may be due to the more rapid excretion of endrin by

male versus female rats (Hutson et al. 1975; Klevay 1971; Korte et al. 1970). A sex-related difference in toxicity was not apparent following dermal exposure (Gaines 1960, 1969). No sex-based differences in endrin-related human toxicity have been documented. For example, an equal number of male and female patients were affected in the endrin poisoning episode in Pakistan (Rowley et al. 1987). Genetic differences in metabolism may also alter susceptibility to endrin toxicity as well, as a heritable resistance in pine mice to endrin raises the LD50 from as low as 1.37 mg/kg in sensitive strains to as high as 36.4 mg/kg in resistant strains (Webb et al. 1973). This trait is correlated with the higher amounts of detoxifying enzymes in resistant mice.

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 endrin 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 endrin 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 endrin 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

Levels of endrin or endrin metabolites can be measured in tissue and excreta, thereby serving as biomarkers of exposure. Further, measurements of endrin in blood are best suited for detecting recent exposures because endrin is cleared rapidly from blood. The lack of persistence of endrin in human tissues and blood seen in the study of Coble et al. (1967) indicates a brief half-life for endrin on the order of 1–2 days. Sera levels of endrin (time to sample not specified) in Pakistani patients who were poisoned with endrin ranged from 0.3 to 254 ppb (0.3–254 µg/L); survivors had sera levels that ranged from 1.3 to 17.4 ppb (1.3–17.4 µg/L) (Rowley et al. 1987). An endrin concentration of 0.3 ppb was detected in the cerebrospinal fluid. Hair may be a useful biomarker for prior exposure to endrin. Smith-Baker and Saleh (2011) demonstrated a sensitive method of endrin detection in hair that accurately distinguished occupationally exposed workers from the general public.

Measurements of endrin metabolites can also be useful in monitoring endrin exposure. The glucuronides of anti-12-hydroxyendrin and 12-ketoendrin have been detected in feces and urine (Baldwin and Hutson 1980). The anti-12-hydroxyendrin glucuronide marker is the most sensitive and specific urinary marker. D-glucaric acid is a nonspecific marker that may indicate prior exposure to endrin (Hunter et al. 1972; Ottevanger and Van Sittert 1979; Vrij-Standhardt et al. 1979). High levels of D-glucaric acid were detected in workers for up to 6 weeks, after which levels returned to normal ranges (Ottevanger and Van Sittert 1979).

Endrin levels in fat tissues may only be a useful biomarker after high occupational exposure, as endrin has only been detected in the adipose tissue of workers after very high exposures and not in the general population (EPA 1986b; Williams et al. 1988). Endrin has been detected in the milk of lactating women (0.02–6.24 mg/kg milk fat) (Alawi et al. 1992; Bordet et al. 1993).

3.3.2 Biomarkers of Effect

Changes in the nervous system are the most common effects associated with human exposure to endrin. Various signs and symptoms of exposure include twitching of muscles, dizziness, mental confusion, and epileptiform seizures (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Hoogendam et al. 1962, 1965; Rowley et al. 1987; Runhaar et al. 1985; Waller et al. 1992; Weeks 1967). However, these effects also occur following exposure to other organochlorine pesticides and other drugs, and are not specific to endrin.

3.4 INTERACTIONS WITH OTHER CHEMICALS

The toxicity of endrin may be influenced by interactions with other chemicals and physical agents, particularly other organochlorine pesticides.

Quails treated with endrin and chlordane had significantly lower endrin residues in brain tissue ($p<0.025$) than birds treated with endrin alone (Ludke 1976). It is not clear how co-administration of chlordane altered tissue distribution of endrin; however, the authors attributed this difference to the presence of one or more metabolites of chlordane in the nervous system. However, despite differences in endrin residues, toxicity of endrin was not altered by prior exposure to chlordane; 15/20 animals died within 10 days of daily endrin exposure and 14/20 animals died within 10 days of daily endrin exposure following 10 weeks of chlordane exposure (Ludke 1976).

Keplinger and Deichmann (1967) evaluated potential interactions between endrin and several other pesticides based on observed versus expected LD_{50} values in mice. After determining LD_{50} values for each compound, the expected LD_{50} value of a mixture was calculated and compared to the observed LD_{50} value of the mixture. The study authors considered ratios between 0.79 and 1.27 essentially additive, with higher ratios indicating greater-than-additive effects, and lower ratios indicating less-than-additive effects. Greater-than-additive effects were noted for endrin and chlordane (ratio of 2.22) and for endrin and aldrin (ratio of 1.83). The interactions observed for endrin plus dieldrin, diazinon, toxaphene, or malathion were additive, and the interactions observed for endrin plus parathion, DDT, and Delnav were less than additive (ratios of 0.65, 0.53, and 0.44, respectively). When a mixture of aldrin, chlordane, and endrin was administered, observed effects were considered additive (ratio of 1.27).

In an *in vitro* estrogenic potential assay, binary mixtures of organochlorine compounds (DDT, DDD, DDE, aldrin, dieldrin, endrin) did not increase estrogenic activity compared with estradiol; additional

testing with individual compounds also found no significant dose-related estrogenic activity (Mumtaz et al. 2002; Tully et al. 2000). More studies are needed to better identify and characterize potential synergistic effects of endrin with other compounds.

Pohl and Tylenda (2000) conducted binary weight-of-evidence (WOE) determinations of the potential for joint toxic action between endrin and other organochlorine pesticides. Based on their analyses, there is direct mechanistic data indicating a synergistic effect between endrin and the following organochlorines: DDT, aldrin, dieldrin, chlordane, hexachlorobenzene (HCB), and α-, β-, and δ-hexachlorocyclohexane (HCH). For γ-HCH, there is direct mechanistic data indicating an antagonistic effect on endrin. Demonstrated toxicological significance was only available for chlordane (see Ludke 1976 above); for the remaining compounds, Pohl and Tylenda (2000) inferred toxicological significance.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

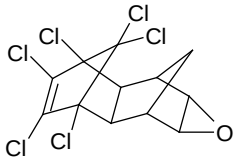
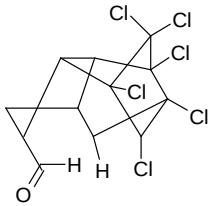
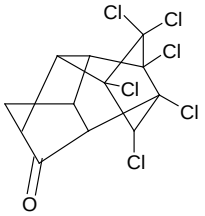
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of endrin, endrin aldehyde, and endrin ketone is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of endrin, endrin aldehyde, and endrin ketone is located in Table 4-2.

Table 4-1. Chemical Identity of Endrin, Endrin Aldehyde, and Endrin Ketone

Characteristic	Endrin	Endrin aldehyde	Endrin ketone	Reference
Chemical name	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- (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-	1,2,4-Methenocyclopenta(cd)-entalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro- (1α,2β,2aβ,4β,4aβ,5β,6aβ,6bβ,7R*)	2,5,7-Metheno-3H-cyclopenta(a)entalen-3-one,3b,4,5,6,6a-hexachlorodecahydro-(2α,3aβ,3bβ,4β,5β,6aβ, 7α,7aβ,8R*)	EPA 1984b
Synonym(s)	Endrin; 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4A,5,6,7,8,8A- octahydro-endo, endo-1,4:5,8-dimethanonaphthalene, and others	Endrin aldehyde; 1,2,4-methanecyclopenta(c,d)pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro	Endrin ketone	NLM 2020
Registered trade name(s)	*Mendrin, Hexacrin, Endrex* experimental insecticide 269	No data	Delta-keto 153	NLM 2020; Sittig 1980
Chemical formula	$C_{12}H_8Cl_6O$	$C_{12}H_8Cl_6O$	$C_{12}H_8Cl_6O$	EPA 1984b
Chemical structure				EPA 1984b
CAS registry	72-20-8	7421-93-4	53494-70-5	EPA 1984b

CAS = Chemical Abstracts Services

Table 4-2. Physical and Chemical Properties of Endrin, Endrin Aldehyde, and Endrin Ketone

Property	Endrin	Endrin aldehyde	Endrin ketone	Reference
Molecular weight	380.9	381.9	380.9	EPA 1984b
Color	White, colorless	No data	No data	IARC 1974; NLM 2020; Worthing and Walker 1983
Physical state	Crystalline solid	Solid	Solid	EPA 1984b; IARC 1974; NLM 2020
Melting point	235°C; 226–230°C (decomposes)	145–149°C; 235°C (decomposes)	No data	EPA 1981; NLM 2020; Worthing and Walker 1983
Boiling point	Decomposes at 246°C; decomposes above 200°C	No data	No data	ACGIH 1986; IARC 1974; NLM 2020
Density at 20°C	No data	No data	No data	
Odor	1.7 at 20°C	No data	No data	EPA 1980; NLM 2020
Odor threshold:				
Water	0.041 mg/L			Verschueren 1983
Air	$1.8x10^{-2}$ ppm	No data	No data	Fazzalari 1978
Solubility:				
Water	200 µg/L at 20°C	50 mg/L; 0.25–0.26 ppm	No data	EPA 1981
Organic solvents	Acetone:17 g/100 mL; benzene 13.8 g/100 mL; carbon tetrachloride: 3.3 g/100 mg/L; hexane: 7.1 g/100 mL; xylene: 18.3 g/100 mL	No data	No data	Budavari 1989; NLM 2020
Partition coefficients:				
Log K_{ow}	5.6, 5.34 (calculated), 5.45 (calculated)	3.146, 4.7, 5.6 (calculated)	4.99 (calculated)	EPA 1981, 1995a; NLM 2020
K_{oc}	4.532 (calculated); 5.195 (±0.005)	4.80 (calculated); 3.929–4.653 (calculated)	No data	De Bruijin et al. 1989; Kenaga 1980; NLM 2020
Vapor pressure	$2.0x10^{-7}$ mmHg	$2.0x10^{-7}$ mmHg	No data	EPA 1981; NLM 2020; Worthing and Walker 1983

Table 4-2. Physical and Chemical Properties of Endrin, Endrin Aldehyde, and Endrin Ketone

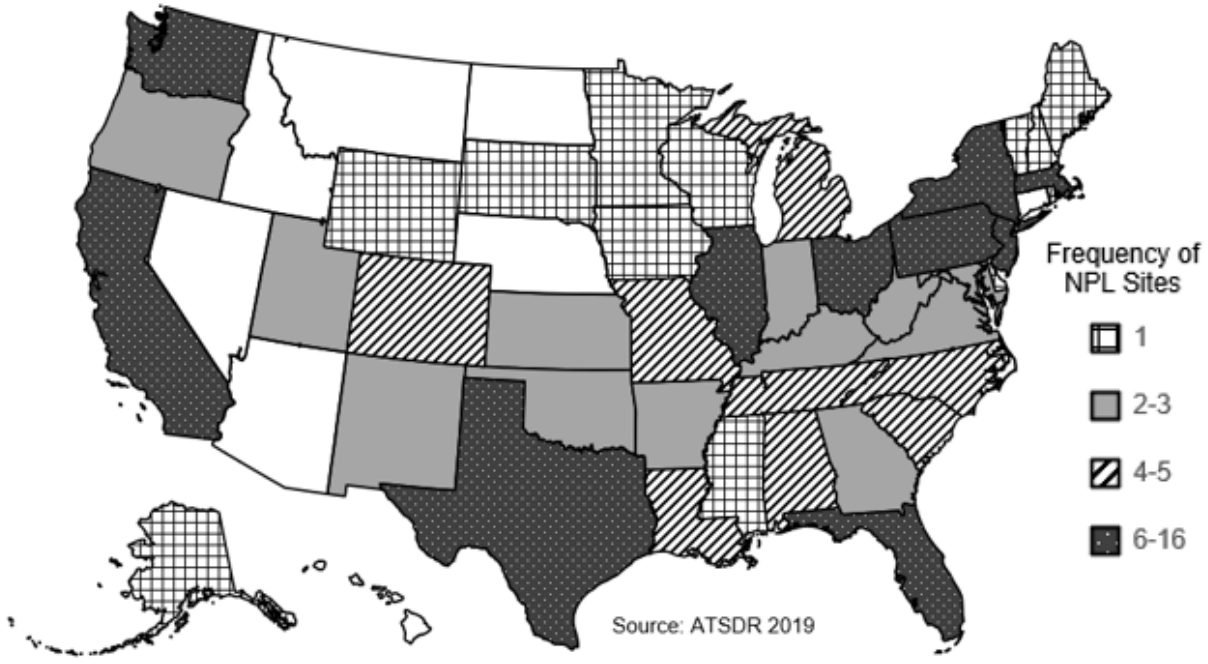
Property	Endrin	Endrin aldehyde	Endrin ketone	Reference
Henry's law constant	$4.0x10^{-7}$ atm-m^3/mol (calculated); $5.4x10^{-7}$ atm-m^3/mol (calculated)	$2x10^{-9}$ atm-m^3/mol; $2.9x10^{-9}$ atm-m^3/mol; $3.67x10^{-8}$ atm-m^3/mol (calculated)	$2.02x10^{-8}$ atm-m^3/mol	EPA 1981; NLM 2020; EPA 1994; Thomas 1982
Autoignition temperature	No data	No data	No data	
Flashpoint	Non-flammable	Non-flammable	No data	NLM 2020
Flammability limits	No data	No data	No data	
Conversion factors	1 ppm=15.6 mg/m^3 1 mg/m^3=0.06 ppm	1 ppm=15.6 mg/m^3 1 mg/m^3=0.06 ppm	1 ppm=15.6 mg/m^3 1 mg/m^3=0.06 ppm	
Explosive limits	No data	No data	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Endrin, endrin aldehyde, or endrin ketone has been identified in at least 176 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 endrin, endrin aldehyde, or endrin ketone has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 175 are located within the United States and 1 is located in the Virgin Islands (not shown).

Figure 5-1. Number of NPL Sites with Endrin, Endrin Aldehyde, or Endrin Ketone Contamination



- The most likely route of exposure to endrin for the general population is via ingestion of endrin residues on imported food items. Endrin is no longer used in the United States.
- Environmental exposure is expected to be low. Exposure to small amounts may occur following unregistered use, inappropriate disposal, or at hazardous waste sites.
- Currently, there are no significant releases of endrin into the environment, but endrin persists in sorbed forms to sediments and soil from previous use.
- The estimated half-life of endrin in soil is approximately 14 years. It is not expected to migrate from soil to groundwater.

- Endrin transformation products including endrin ketone, endrin aldehyde, and endrin alcohol, can be detected in plants grown in soils treated at least 16 years prior to planting.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

No information is available in the TRI database on facilities that manufacture or process endrin because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

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

Endrin is no longer manufactured in the United States. Velsicol Chemical Company, Memphis, Tennessee, was the producer of endrin until the final voluntary cancellation of registration with the Office of Pesticide Programs in 1991 (EPA 1984a, 1985a, 1986a, 1993; USDA 1993). It is estimated that 2.345 million kg (5.1–9.9 million pounds) of endrin were sold in the United States in 1962, while <450,000 kg (990,000 pounds) were produced in 1971 (IARC 1974). More recent estimates of domestic production of endrin could not be found (NLM 2020). As with many toxic chemicals, information on production or use of pesticides is often proprietary, and quantitative estimates of production of endrin are virtually impossible to obtain (Bason and Colborn 1992). Chemical manufacturers in the United States, however, can legally produce pesticides for export that are currently banned or not registered for use in the United States (FASE 1996).

Endrin aldehyde and endrin ketone were never commercial products but occurred as impurities of endrin or as degradation products (EPA 1985b; IARC 1974; SRI 1987). While commercial preparations of solid endrin were typically 95–98% pure, the following chemicals (in addition to endrin aldehyde and endrin ketone) have been found as trace impurities: aldrin, dieldrin, isodrin, heptachloronorbornadiene, and heptachloronorborene (NLM 2020). The active ingredient would often be mixed with one or more

organic solvents for application in a liquid form. Carriers included xylene, hexane, and cyclohexane (NLM 2020; Zabik et al. 1971).

5.2.2 Import/Export

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

5.2.3 Use

Endrin was first used as an insecticide, rodenticide, and avicide beginning in 1951 to control cutworms, voles, grasshoppers, borers, and other pests on cotton, sugarcane, tobacco, apple orchards, and grain (EPA 1979a; NLM 2020). It was also used as an avicide on enclosed bird perches (EPA 1985c). Unlike aldrin/dieldrin, with which it has many chemical similarities, endrin apparently was never used extensively for termite-proofing or other applications in urban areas (Blus et al. 1989; NLM 2020). Endrin's toxicity to nontarget populations of raptors (birds of prey) and migratory birds was a major reason for its cancellation as a pesticide agent (Blus et al. 1989; EPA 1979b; USDA 1993). Except for use as an avicide on bird perches, which was canceled in 1991, all other uses of endrin in the United States were voluntarily canceled by the manufacturer in 1986 (EPA 1984a, 1985a, 1986a, 1993; USDA 1993). It has been estimated that 6,250 kg (13,780 pounds) of endrin were used annually in the United States prior to 1983 (EPA 1986c). Since endrin may still be used as a pesticide agent in foreign countries, residues on imported food items are still of some concern (FDA 1990, 1991, 1992; Hundley et al. 1988). Both the EPA and the Food and Drug Administration (FDA) revoked all food tolerances for endrin in 1993 (USDA 1993).

5.2.4 Disposal

Because endrin and endrin aldehyde are listed as hazardous substances, disposal of wastes containing these compounds is controlled by a number of federal regulations (see Chapter 7). Land disposal restrictions apply to wastes containing endrin or endrin aldehyde (EPA 1987a). Chemical treatment

(reductive dechlorination) or incineration are possible disposal methods (IRPTC 1985; NLM 2020). Past disposal methods included land disposal (EPA 1987b; Sittig 1980). In general, disposal methods for endrin residues or endrin-containing wastes are similar to those for wastes containing aldrin/dieldrin (NLM 2020). No information was found in the available literature on regulations or methods for the disposal of endrin ketone.

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

5.3 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 2005). 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 2005).

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

5.3.1 Air

There is no information on releases of endrin to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

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

There is also a potential for atmospheric release of endrin, endrin aldehyde, and endrin ketone from hazardous waste sites.

5.3.2 Water

There is no information on releases of endrin to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

In the past, endrin could have been released to surface water from manufacturing and processing facilities. No information on direct discharges or loadings of endrin into surface water was found. Based on amounts measured in rainfall at various stations in Canada, loading estimates for endrin and a number of other organochlorine pesticides have been attempted for portions of the Great Lakes basin (Strachan 1988). The sources for such loadings to receiving waters are not clear, but would likely involve in-place contaminants related to endrin's past uses as a pesticide agent. A 1995 study conducted in Oklahoma indicates that in some areas of the United States, endrin can be released to surface water from farmland soils that have been treated with endrin in the past (Petty et al. 1995).

There is also a potential for release of endrin, endrin aldehyde, and endrin ketone to water from hazardous waste sites.

5.3.3 Soil

There is no information on releases of endrin to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Past use of endrin as an agricultural pesticide has been the principal source of its release to soils or aquatic sediments. There is also a potential for release of endrin, endrin aldehyde, and endrin ketone to soils and sediments from hazardous waste sites.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Endrin is extremely persistent when released to the soil. It adsorbs strongly to soil particles and tends to be immobile, based on an estimated K_{oc} of 34,000 (Kenaga 1980; Swann et al. 1983). Endrin on soil may be transported to surface water via runoff from rain or irrigation. Since endrin in solid form is hydrophobic and sorbs strongly to soil particles, migration into groundwater would not generally be expected from normal agricultural application. In laboratory studies, endrin was found to be almost completely adsorbed to samples of sandy loam and organic soil (Sharom et al. 1980a). In sandy soil, only 13.6% of the endrin was leached from the soil after 10 successive 200 mL water rinses. In organic soil, only 1.5% of the endrin was leached from the soil after 10 successive 200 mL water rinses. The mobility factors calculated for the sandy soil and organic soil were 0.52 and 0.040, respectively. Only dieldrin, leptophos, and *p,p'*-DDT were less mobile than endrin in the two soil types.

However, endrin has been detected in groundwater, suggesting that leaching may be possible in some soils under certain conditions (CSWRCB 1986; EPA 1988). Furthermore, because endrin formulations in solvent carriers such as xylene or hexane were also commonly used, endrin could move into groundwater from spills of such formulations. Similarly, migration to groundwater might also occur at waste sites where endrin residues become mixed with organic solvents (Jaquess et al. 1989).

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

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

Because of its high log K_{oc} and log K_{ow} values (4.53 and 5.34–5.6, respectively; see Table 4-2), when released to water, endrin strongly adsorbs to sediment (Kenaga 1980; Swann et al. 1983) and bioconcentrates significantly in aquatic organisms (ASTER 1995; EPA 1980; Metcalf et al. 1973).

Typical bioconcentration factors (BCFs) for freshwater and marine organisms range from 80 to 49,000 (Table 5-1). Biomagnification of endrin with increasing trophic level is not expected to be significant (Leblanc 1995). Metcalf et al. (1973) reported a ratio of biomagnification through the aquatic food chain to bioconcentration by direct uptake from water to be 2 for endrin compared to 2.50 for DDT. These authors used a model laboratory aquatic ecosystem containing algae (*Oedogonium cardiacurn*), snails (*Physa* sp.), water fleas (*Daphnia magna*), mosquito larvae (*Culex pipiens quinquefasciatus*), and mosquito fish (*Gambusia afinis*).

Table 5-1. Bioconcentration Data for Endrin

Species common name (scientific name)	Exposure type	Duration (days)	BCF[a]	Reference
Freshwater				
Algae (*Microcystis aeruginosa*)	–	7	200	EPA 1980
Algae (*Anabaena cylindrica*)	–	7	222	EPA 1980
Algae (*Scenedesmus quadricauda*)	–	7	156	EPA 1980
Algae (*Oedogonium* sp.)	–	7	140	EPA 1980
Water flea (*Daphnia magna*)	S	1	2,600	Metcalf et al. 1973
Mosquito (*Culex pipiens quinquefasciata*)	S	1	2,100	Metcalf et al. 1973
Stonefly (*Pteronarcys dorsata*)	F	28	1,000	Anderson and Defoe 1980
Pouch snail (*Physa* sp.)	S	33	49,000	Metcalf et al. 1973
Mussels (mixed species)	–	21	3,000	Jarvinen and Tyo 1978
Channel catfish (*Ictalurua punctatus*)	–	41–55	2,000	EPA 1980
Flagfish (*Jordanella floridae*)	–	65	15,000	Hermanutz 1978
Flagfish (*J. floridae*)	F	15	7,000	Hermanutz et al. 1985
Fathead minnow (*Pimephales promelas*)	F	47	10,000	EPA 1980
Fathead minnow (*P. promelas*)	–	56–300	7,000	Jarvinen and Tyo 1978
Fathead minnow (*P. promelas*)	F	2–304	80b	Veith and Kosian 1983
Black bullhead (*Ictalurus melas*)	F	4	3,700	Anderson and Defoe 1980
Black bullhead (*I. melas*)	F	7	6,200	Anderson and Defoe 1980
Saltwater				
Grass shrimp (*Palaemonetes pugio*)	F	145	1,600	Tyler-Schroeder 1979
American oyster (*Crassostrea virginica*)	F	2	1,670	Mason and Rowe 1976
American oyster (*C. virginica*)	F	7	2,780	Mason and Rowe 1976
Sheepshead minnow, embryo-juveniles (*Cyprinodon variegatus*)	–	33	4,800	EPA 1980
Sheepshead minnow (*C. variegatus*)	–	141–161	6,400	Hansen et al. 1977
Spot (*Leiostomos xanthurus*)	–	5–8 months	1,450	EPA 1980

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

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

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

In air, endrin is expected to be associated primarily with particulate matter based on its low vapor pressure and high K_{oc} (Kenaga 1980). However, small amounts of endrin in the atmosphere may exist in the vapor phase (Eisenreich et al. 1981). Because of its low solubility (200 µg/L, see Table 4-2), endrin would not be expected to be removed significantly from the atmosphere by wet deposition. Particle-adsorbed endrin will be removed from the atmosphere by both wet and dry deposition. Endrin was found in 5% of 450 wet deposition (rain/snow) samples collected between 1986 and 1991 in the Great Lakes area, at volume weighted mean concentrations ranging from 0.02 to 0.98 ng/L (ppt) (Chan et al. 1994).

No studies on the environmental transport and partitioning of endrin aldehyde could be found in the available literature. Values of the estimated log K_{ow} for endrin aldehyde vary widely, ranging from 3.1 to 5.6 (see Table 4-2). Based on the lowest estimated log K_{ow}, the K_{oc} value for endrin aldehyde can be estimated to be approximately 1,000 (Lyman 1990), indicating a low mobility in soil (Swann et al. 1983). Using the higher estimated values of log K_{ow} (4.7–5.6), the K_{oc} value for endrin aldehyde can be estimated to range from 8,500 to 380,000 (Lyman 1990), indicating that this compound will be virtually immobile in most soils (Swann et al. 1983). Because of its low vapor pressure of $2.0x10^{-7}$ mmHg and Henry's Law constant ranging from $2x10^{-9}$ to $3.7x10^{-8}$ atm-m^3/mol (see Table 4-2), endrin aldehyde would not be expected to volatilize significantly from soil or water (Eisenreich et al. 1981; Thomas 1990). Any endrin aldehyde in air should exist predominantly in the adsorbed phase (Eisenreich et al. 1981). Atmospheric endrin aldehyde will be transported to soil and surface water via wet and dry deposition of associated particles. In water, adsorption to sediments and bioconcentration are likely to be significant partitioning processes. Based on the lowest estimated value of 3.1 for log K_{ow} (see Table 4-2), the BCF value for endrin aldehyde can be estimated to be only 86 (Veith et al. 1979), indicating little tendency to bioconcentrate in aquatic organisms. Using the higher estimates of 4.7–5.6 for log K_{ow} (see Table 4-2), BCF values for endrin aldehyde are estimated to range from to 2,000 to 11,000 (Veith et al. 1979), indicating a much higher tendency for bioconcentration.

No studies on the environmental transport or partitioning of endrin ketone could be found in the available literature, and only limited information was found on estimated values of physical and chemical properties. The very low estimated value of 2.02×10^{-8} atm-m^3/mole for Henry's Law constant for endrin ketone (see Table 4-2) indicates that this compound will not volatilize from water. Based on the estimated log K_{ow} of 4.99 (see Table 4-2), the BCF value for endrin ketone can be estimated to be 3,500 (Veith et al. 1979), indicating that endrin ketone may be removed from water via bioconcentration in aquatic organisms. Also based on an estimated log K_{ow} of 4.99, the K_{oc} value for endrin ketone can be estimated to range from 5,500 to 90,000 (Lyman 1990), indicating that this compound will be virtually immobile in soil and sediments (Swann et al. 1983).

5.4.2 Transformation and Degradation

Air. Field studies on the transformation of endrin in the atmosphere were not located in the available literature. Photochemical isomerization of endrin, primarily to the pentacyclic ketone commonly called delta ketoendrin or endrin ketone, was observed after exposure of thin layers of solid endrin on glass to sunlight (Burton and Pollard 1974). Minor amounts of endrin aldehyde were also formed in this reaction. Results of seasonal studies indicated that this isomerization would proceed with a half-life (first-order kinetics) of 5–9 days in intense summer sunlight, with complete conversion to the pentacyclic ketone in 15–19 days. Knoevenagel and Himmelreich (1976) reported that photodegradation of solid endrin in the laboratory proceeded with a half-life (first-order kinetics) of 20–40 hours. In laboratory studies conducted by Zabik et al. (1971) on endrin formulations in hexane and cyclohexane (similar to those commonly used for pesticide applications), endrin was found to undergo photolytic dechlorination when exposed to ultraviolet radiation, yielding a pentachlorinated half-cage ketone as the major product. This degradation product was also detected in environmental samples. Endrin may also be transformed by heat in the atmosphere, yielding primarily the pentacylic ketone and endrin aldehyde (EPA 1979c; Phillips et al. 1962). Endrin may also react with photochemically generated hydroxyl radicals in air, with a predicted half-life (first-order kinetics) ranging from 1.45 hours (Howard 1991) to 1.8 days (EPA 1995b). No information could be found on the products of this reaction. The reaction of endrin with ozone in air is not significant. The predicted first-order rate constant for this reaction is 3.6×10^{-20} cm^3/molecule-second, corresponding to a half-life of 320 days (EPA 1995b).

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

Water. Laboratory studies of the fate of endrin in water samples suggest a significant degree of stability, although there is evidence of varying degrees of biodegradation in some systems. Endrin was among the more stable of 12 insecticides incubated in water collected from the drainage canal of a vegetable-growing site near Toronto, with about 80% of endrin remaining in the natural water after incubation for 16 weeks (Sharom et al. 1980b). There was little indication of chemical degradation of endrin in these studies. Studies in which sealed water samples from the Little Miami River were exposed to sunlight and artificial fluorescent light showed no measurable degradation of endrin over an 8-week period (Eichelberger and Lichtenberg 1971). However, microorganisms in fish pond water and algae from a fish pond were able to metabolize endrin (Patil et al. 1972). In the case of the algae, the metabolite was 12-ketoendrin. The rate of metabolism was 35% for the water sample and 24% for the algal culture in 1 month. Using the static culture procedure, Tabak et al. (1981) found no biodegradation of endrin in domestic waste water samples.

Based on laboratory experiments on solid endrin (Burton and Pollard 1974) and on endrin in organic solvents (Zabik et al. 1971), it is likely that endrin released to surface water will undergo photo-isomerization to endrin ketone, with minor amounts of endrin aldehyde also being formed. Under real world conditions, endrin released to surface waters would not be expected to biodegrade or hydrolyze to any significant extent (Eichelberger and Lichtenberg 1971; EPA 1979c). Endrin is very resistant to hydrolysis, with an estimated half-life (first-order kinetics) of >4 years (EPA 1979c). The predominant removal of endrin from water by photodegradation and sorption to suspended particulates or sediments is consistent with the observed low incidence of detected endrin in ambient surface waters based on analyses of EPA National Urban Runoff Program (Cole et al. 1984) and STORET (Staples et al. 1985) data.

Little information could be found in the available literature on the transformation and degradation of endrin aldehyde in water. Neither hydrolysis nor oxidation (via peroxy radicals or singlet oxygen) are expected to be significant in aquatic systems (EPA 1981). By analogy to endrin, the hydrolysis half-life (first-order kinetics) of endrin aldehyde in water is probably >4 years (EPA 1979c). No information could be found on the biodegradation of endrin aldehyde in aquatic systems.

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

Sediment and Soil. Biodegradation does not appear to be a significant degradation process for endrin in soils. The actual measurement of biodegradation of endrin under field conditions on well-drained agricultural soil indicates a biodegradation half-disappearance time of approximately 14 years (Nash and Woolson 1967), suggesting that endrin is resistant to biodegradation in soils under natural conditions. In this study, 41% of the initial endrin applied to an agricultural field was present in the soil after 14 years.

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

biodegradation of endrin in laboratory microcosms within 4 days has been reported; however, the researchers caution that under natural conditions, redox environments in many soils will not be suitable for anaerobic degradation, and that endrin residues sorbed to soil particles would often be rendered unavailable to bacteria (Maule et al. 1987).

In combination, losses from volatilization, photodegradation (Burton and Pollard 1974; EPA 1985b; Knoevenagel and Himmelreich 1976; Zabik et al. 1971), and heat transformation (primarily to endrin ketone, with minor amounts of endrin aldehyde) (EPA 1979c; Phillips et al. 1962) are likely to account for a rapid decrease in endrin residues on soil or plant surfaces exposed to bright sunlight. Studies have also been conducted indicating significant concentrations of endrin transformation products (including endrin ketone, endrin aldehyde, and endrin alcohol) in plants grown in endrin-treated soil (Nash et al. 1972; Nash and Harris 1973).

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

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

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to endrin depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of endrin 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 endrin 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 5-2 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-2. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	No data	Harkov 1986; Ligocki and Pankow 1985
Water	0.006 ppb	EPA 1982
Soil/sediment	2–3 ppb	Carey et al. 1976
Blood serum	5.09–7.8 ng/g lipid	CDC 2018

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Detections of endrin, endrin aldehyde, and endrin ketone in air, water, and soil at NPL sites are summarized in Table 5-3.

Table 5-3. Endrin, Endrin Aldehyde and Endrin Ketone 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
Endrin					
Water (ppb)	0.355	0.651	62.2	16	13
Soil (ppb)	1,810	1,160	53.7	25	24
Air (ppbv)	0.0013	0.0024	61	7	4
Endrin aldehyde					
Water (ppb)	0.17	0.099	29	6	5
Soil (ppb)	6.05	86.8	10.4	20	17
Air (ppbv)			No data		
Endrin ketone					
Water (ppb)	0.465	0.622	18.2	12	8
Soil (ppb)	52	202	27.7	27	20
Air (ppbv)			No data		

[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.

5.5.1 Air

Endrin is relatively nonvolatile with a vapor pressure of 2.0×10^{-7} mmHg (EPA 1981; Worthing and Walker 1983). Despite its low volatility, initial loss of agriculturally applied endrin through volatilization was found to be comparable to more volatile pesticides (Nash 1983). Endrin was detected in seven of

132 ambient air samples collected by the EPA Great Lakes National Program in 2018; reported concentrations were 0.143–0.688 pg/m^3 (NWQMC 2020). In 2 of 29 dry fall material samples collected, reported concentrations were 0.774 and 0.847 pg/m^3 (NWQMC 2020).

Limited information was found on atmospheric concentrations of endrin between 1970 and the mid-1980s, prior to cancellation of virtually all uses (EPA 1984a, 1985a, 1986a, 1993; USDA 1993). The data were insufficient to identify any trends. The mean and maximum airborne concentrations of endrin in the United States in 1970–1971 were reported to be 0.2 and 19.2 ng/m^3, respectively (Lee 1977). For that same time period, mean airborne concentrations at suburban sites near Jackson, Mississippi, and Columbia, South Carolina, were reported to be 0.1 and 0.2 ng/m^3, respectively (Bidleman 1981; Kutz et al. 1976). Endrin was not detected at Boston, Massachusetts, suburban sites (Bidleman 1981). A survey of airborne contaminants in the Great Lakes area in 1981 did not detect endrin (Eisenreich et al. 1981).

Atmospheric concentrations of endrin in the vicinity of manufacturing facilities were higher than those found in non-source areas of the United States. Eight hundred meters from two formulation plants in Arkansas and 275 meters from one formulation plant in Tennessee, mean airborne concentrations of endrin were reported to be 3.3 and 3.5 ng/m^3, respectively, during 1970–1972 (Lewis and Lee 1976). Endrin was also detected in air in industrial or source-dominated regions of the Mississippi Delta in 1972–1974, and in Tennessee in 1971 (EPA 1985b).

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

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

5.5.2 Water

Endrin was not reported above the lower quantification limit of 6.0–60 ng/L (ppt) in over 3,600 ambient surface water data points compiled for 2016–2020 from EPA STOrage and RETrieval (STORET) and National Water Information System (NWIS) databases (NWQMC 2020). Endrin aldehyde was also not reported above the lower quantification limit of 5.0–68 ng/L (ppt) in approximately 2,700 surface water data points reported (NWQMC 2020). Unlike DDT, chlordane, aldrin/dieldrin, and a variety of other chlorinated pesticides, endrin was never used extensively in urban areas. This is reflected in the results from EPA's Nationwide Urban Runoff Program, which showed no detections in 86 high-flow water samples from 51 urbanized watersheds from 19 cities (Cole et al. 1984). Endrin was not detected (detection limit 49 ng/L [0.045 ppb]) in surface water from the Yakima River Basin, Washington (Foster et al. 1993). However, in 1991–1992, endrin was detected in first flush (first 20 minutes) stormwater runoff samples at four of six sites in Louisville, Kentucky, at levels that exceeded U.S. federal criteria (0.003 µg/L, [ppb]) (Marsh 1993). Maximum, minimum, and mean concentrations at the four sites were 0.03–0.05, 0.02–0.04, and 0.03–0.04 (ppb), respectively. Endrin was not detected (detection limit not specified) in 3-hour composite samples of stormwater runoff from any of the six sites.

Endrin is rarely detected in drinking water and any trace amounts of endrin that might be encountered in raw drinking water supplies will likely be removed in the treatment systems used by most communities. In 1966 and 1967, when the use of endrin was not restricted, endrin was detected in 5 of 67 raw water samples from the Mississippi and Missouri Rivers (Schafer et al. 1969). When endrin use was substantially restricted, an Iowa study of 33 community water supplies using surface water found no detectable concentrations of endrin in the distribution systems (IDNR 1987). In an extensive water quality monitoring program conducted by the California Department of Health Services, endrin was detected (detection limit not specified) in only 2 of 5,109 public drinking water sources sampled from 1984 to 1992, at mean and maximum concentrations of 0.06 and 0.10 ppb, respectively (Storm 1994). Concentrations did not exceed the maximum concentration level of 0.2 ppb. Endrin was not detected (detection limit not specified) in 32 samples each of raw water and highly treated reclaimed waste water undergoing evaluation as a possible supplement to raw water sources in San Diego, California (De Peyster et al. 1993). Recent data concerning endrin concentrations in drinking water were not available.

Detections of endrin in groundwater are also rare except from wells near hazardous waste sites. The EPA Pesticides in Groundwater Data Base (EPA 1988) contains groundwater data collected with good quality assurance/quality control (QA/QC) provisions from areas with significant agricultural land uses as well as

from urban areas. Analysis of these data indicated there were only two wells with detectable levels of endrin within the entire United States. A detection occurred in a well in California (concentration not reported) where point source problems or spills were deemed the likely sources. Endrin contamination found in an Illinois well at an average concentration of 0.02 ppb was considered likely to have resulted from ordinary agricultural uses. In a groundwater contamination study of California's 58 counties, in which over 50 pesticides were evaluated from both point and nonpoint sources, endrin was detected in only one sample (CSWRCB 1986). Endrin was detected at 0.9% of 178 Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) sites and 1.3% of 156 Resource Conservation and Recovery Act (RCRA) sites sampled; however, endrin concentrations were not reported (Plumb 1987). Endrin was not reported above the lower quantification limit of 10–28 ng/L (ppt) in 480 groundwater data points compiled for 2016–2020 from EPA STORET and NWIS databases (NWQMC 2020). Endrin aldehyde was also not reported above the lower quantification limit of 21–28 ng/L (ppt) in 360 groundwater data points reported (NWQMC 2020).

No information was found in the available literature on levels of endrin ketone in surface or groundwater.

5.5.3 Sediment and Soil

In general, endrin was found infrequently and at relatively low levels in both urban and cropland soils in the United States. Endrin was detected in only 10 of 1,483 cropland soil samples in 1972 at concentrations up to 2.13 ppm (detection limit of 0.01 ppm) (Carey et al. 1979). These studies were part of the National Soils Monitoring Program carried out by EPA and the U.S. Department of Agriculture (USDA) under the National Pesticide Monitoring Program, which covered a total of 1,533 sampling sites in 37 states. Endrin detections were documented in the following states: Alabama, Arkansas, Georgia, Illinois, Louisiana, Nebraska, New York, North Carolina, and South Dakota, as well as at sites from one or more of the mid-Atlantic states of Delaware, Maryland, and New Jersey. Endrin was also detected at a level of 0.017 ppm at a single site in California in a study that targeted rice-growing cropland soils in Arkansas, California, Louisiana, Mississippi, and Texas (Carey et al. 1980). Endrin was not detected in urban soils from 13 of 14 U.S. cities included in a 1970 study of pesticide residues in urban soils (25–30 soil sampling sites were used for each of the urban areas) (Carey et al. 1976). The only detection was at a single site near Memphis, Tennessee, where the Velsicol Chemical Company (which produced endrin at that time) is located. The reported concentration for this site was 0.07 ppm; the mean concentration for all 28 Memphis sites was <0.01 ppm. Endrin and endrin aldehyde was detected in 6 of 119 soil data

points compiled from EPA STORET; concentrations were 22.9–42 µg/kg (ppb) for endrin and 17.5–26.6 µg/kg (ppb) for endrin aldehyde (NWQMC 2020).

Relatively little literature was identified concerning the analysis of endrin in aquatic sediments. The available data indicate that, historically, sediment concentrations of endrin have been very low. In a study of sediment contaminants in Casco Bay, Maine, endrin was found at concentrations near or below the method detection limit (<0.25 ppb) (Kennicutt et al. 1994). In the National Surface Water Monitoring Program conducted from 1976 to 1980, endrin was detected in 1.3% of the sediment samples analyzed (detection limit not reported), with a maximum concentration of 2.9 ppb (Carey and Kutz 1985). In a study by Ford and Hill (1991) to evaluate organochlorine pesticide residues in sediments and aquatic animals in the vicinity of the Yazoo National Wildlife Refuge in the Mississippi Delta, a region that has experienced very high usage of pesticide agents, detectable levels of endrin were not found in sediments (detection limit 0.01 ppm [10 ppb]). Similarly, endrin was not detected in sediment or pore water samples (detection limits 0.49 and 0.01 ppm [490 and 10 ppb], respectively) from 18 mosquito control impoundments in St. Lucie County, Florida, where organochlorine pesticides had been heavily used through the early 1960s (Parkinson et al. 1993). Endrin was detected in 42 of 973 sediment data points compiled for 2016 to 2020 from EPA STORET; concentrations were 0.52–16.24 µg/kg (ppb) (NWQMC 2020). Endrin aldehyde was not detected (detection limit 0.017–2.9 µg/kg [ppb]) in 678 sediment data points reported (NWQMC 2020).

No information was found in the available literature on levels of endrin aldehyde in soil or endrin ketone in sediment or soil.

5.5.4 Other Media

Endrin had been found in many foods, but current levels appear to be very low and not of concern for human health. The FDA has concluded that endrin is no longer present in the environment to the extent that it may be contaminating food or feed at levels of regulatory concern (USDA 1993). An FDA survey of pesticide residues in samples of domestic and imported food and feed commodities from Fiscal Year (FY) 1982 to 1986 lists endrin levels for specific food items up to 0.50 ppm (500 ppb) (Hundley et al. 1988). This study was conducted by surveillance sampling with follow-up compliance sampling for sources of foodstuffs where the concentrations in surveillance samples violated EPA tolerance levels. In surveillance sampling, endrin was detected in 0.05% (3 of 6,391 samples) and 1.5% (183 of 12,044 samples) of domestic and imported foods, respectively. The incidence of violative surveillance

samples (endrin residues ≥0.05 ppm [50 ppb]) was higher for imported foods (0.1%; 12 violations) than for food items from domestic sources (0.02%; 1 violation). In follow-up compliance monitoring of 1,239 samples of imported foods, endrin was found in 11 samples (0.9%); 2 of these samples (0.2%) were violative. In imported foods, endrin was detected in mung beans, cucumbers, pickling cucumbers, cantaloupe, acorn squash, cabocha squash, Italian squash, summer squash, and yellow squash (Hundley et al. 1988). In another study of pesticide residues in food conducted in 10 states between 1988 and 1989, endrin was not detected in any of the 13,980 samples analyzed in 1988. In 1989, the detection frequencies for endrin and endrin ketone were 0.084 and 0.007%, respectively, for the 13,085 samples analyzed (Minyard and Roberts 1991). Endrin was detected each year in regulatory monitoring of domestic and imported foods conducted by the FDA from 1989 to 1994 as part of its Pesticide Residue Monitoring Program (FDA 1990, 1991, 1992, 1993, 1994, 1995). Concentrations were not reported; however, <1% of the surveillance samples had any pesticide residue levels that were above established tolerances. In the most recent FDA survey of pesticide residues in U.S. domestic food, endrin was not detected in the 1,931 food samples (FDA 2017a).

Endrin was also detected in the FDA Total Diet Studies in 1987, 1988, 1989, and 1991, but not in 1990 (FDA 1988, 1989, 1990, 1991, 1992). Overall, in 234 ready-to-eat foods tested 37 times each as part of the FDA Total Diet Studies from 1982 to 1991, endrin was found only 26 times at an average concentration of 0.0027 µg /g (2.7 ppb) in nine different foods: broccoli, cantaloupe, collards, cucumbers, onion rings, dill pickles, pumpkin pie, summer squash, and winter squash (Kan-Do Office 1995). Concentrations ranged from 0.0011 µg/g (1.1 ppb) (broccoli) to 0.0041 µg/g (4.1 ppb) (summer squash). In a summary of 1985–1991 FDA pesticide residue findings, endrin was not reported in >10,000 surveillance samples of domestic and imported foods that may be eaten by infants or children, or in >4,000 analyses of Total Diet Study foods eaten by infants and children (Yess et al. 1993). In FDA Total Diet Studies between 1991–1993 and 2003–2004, endrin was detected in seven food items (canned evaporated milk, cantaloupe, cucumber, summer squash, winter squash, radish, and cheese pizza); it was only detected in 10 of the 296 samples (0.03%) with levels ranging from 0. 2 to 2.0 ppb (FDA 2006). In 2017, endrin was not detected in whole milk samples (limit of detection of 1.5 ppb) (FDA 2017b). In an overall summary for the 5-year period 1986–1991, average dietary intakes of endrin for eight age/sex groups (6–11-month-old infants, 2-year-old children, 14–16-year-old males and females, 25–30-year-old males and females, and 60–65-year-old males and females) were all estimated to be <0.000l µg/kg body weight/day (FDA 1993).

Other studies further indicate that the occurrence of endrin in the U.S. food supply is very low. In a 1990–1991 FDA survey of pesticide residues in milk representing most of the U.S. supply consumed in metropolitan areas, endrin was detected at trace levels (0.0005–0.001 ppm [0.5–1.0 ppb]) in only 2 of 806 composite samples (one sample each from Atlanta, Georgia and Dover, Delaware) (Trotter and Dickerson 1993). In another statistically based FDA study in 1992–1993, endrin was not found as a violative residue in any of 710 domestic or 949 imported pear samples (Roy et al. 1995). Endrin was not reported among the pesticides detected in a 1994 FDA survey of pesticide levels in 160 samples of catfish, crayfish, shrimp, trout, salmon, oysters, and various other species from important aquaculture areas of the United States (FDA 1995). Comparable results were found in similar studies conducted by the FDA in 1990–1993 (FDA 1995). A food basket survey patterned after the FDA approach that was conducted in San Antonio, Texas did not find detectable concentrations of endrin (detection limit 0.050 ppm [50 ppb]) in 6,970 produce items (Schattenberg and Hsu 1992).

Because of the persistence of endrin in the environment and its potential to bioconcentrate significantly in aquatic organisms, there has been continued concern over the levels of endrin in fish and shellfish. This concern, however, appears to be limited primarily to specific sites where endrin was used heavily in agriculture or was discharged by industrial plants. In 1963, at the height of agricultural endrin use, endrin levels in catfish poisoned by endrin exceeded 4 ppm (4,000 ppb) during a fish kill (Mount and Putnicki 1966). Endrin was detected in two species of commercial Penaeus shrimp collected at 21 of 31 stations in the Calcasieu River Estuary in Louisiana, a Gulf Coast estuary receiving both industrial discharges and urban and agricultural runoff (Murray and Beck 1990). The maximum, mean, and median concentrations of endrin reported were 9.47, 1.07, and 0.25 ppm (9,470, 1,070, and 250 ppb), respectively. Several other national studies, however, indicated that contaminated fish or shellfish currently are not a likely source of potentially high human exposure to endrin. In the National Contaminant Biomonitoring Program, maximum endrin concentrations in whole fish from around the United States for the periods 1976–1777, 1978–1979, 1980–1981, and 1984 were 0.40, 0.11, 0.30, and 0.22 ppm (400, 110, 300, and 220 ppb), respectively. Corresponding geometric mean concentrations were ≤0.01 ppm (10 ppb) (Schmitt et al. 1985, 1990). The percentage of stations where detectable endrin residues were present also showed a relatively steady decline from 47.2% in 1976–1977 to 28% in 1984. The maximum concentration of 0.22 ppm (220 ppb) in 1984 was recorded near Memphis in the vicinity of the Velsicol Chemical Company. In portions of the Mississippi Delta within or bordering the Yazoo National Wildlife Refuge, endrin was found at the 0.01 ppm (10 ppb) detection limit in whole-body tissue samples from such rough fish as carp, smallmouth buffalo, bowfin, and spotted gar collected in 1988 (Ford and Hill 1991). In the 1986 National Study of Chemical Residues in Fish conducted by the EPA, endrin was detected in fish

tissue samples at 11% of the 362 sites surveyed. The maximum, mean, and median concentrations of endrin reported were 0.162 ppm, 0.002 ppm, and not detected (<0.0025 ppm) (162, 2, and <2.5 ppb), respectively (EPA 1992a).

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

In the 2009 National Study of Chemical Residues in Lake Fish Tissues, endrin was detected in 3 of 486 samples from predator fish with a maximum concentration of 12 ppb (EPA 2009). It was also detected in 14 of 395 samples of bottom dweller fish with a maximum concentration of 20 ppb (EPA 2009); only 1 sample exceeded the minimum level of 10 ppb.

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

There may be a potential for contamination of fish and wildlife in the vicinity of hazardous waste sites.

5.6 GENERAL POPULATION EXPOSURE

Endrin is no longer registered for use in the United States. Consequently, the current potential for exposure of the general population to endrin appears to be very limited and will likely continue to diminish even more over time. Members of the general population may be exposed to very low levels of endrin through ingestion of contaminated foodstuffs, particularly those that are imported from areas where endrin is still being used. However, FDA concluded that endrin is no longer present enough in the environment to contaminate food or feed at levels of regulatory concern (USDA 1993). Several studies indicate that human exposures are far below the levels of concern for human health. Based on results of FDA Total Diet Studies conducted from 1978 to 1982, estimated average dietary intakes were <0.001 µg/kg (ppb) body weight/day for infants and toddlers for all 5 years (Gartrell et al. 1986). However, actual intakes must have been lower than these estimates because the reported average dietary intakes were based on the mean concentration of the positive samples only. A report summarizing the FDA Total Diet Studies from April 1982 to April 1984 indicated an estimated daily intake for 6–11-month-old infants of 0.0003 µg/kg (ppb)body weight/day for that period, with estimated daily intakes for 14–16-year-old males and 60–65-year-old females essentially zero (Gunderson 1988). Endrin intakes, in µg/kg (ppb) body weight/day, estimated from the Total Diet Study analyses were <0.0001, <0.0001, and 0.0001 in FY 1989 for 6–11-month-old infants, 14–16-year-old males, and 60–65-year-old females, respectively (FDA 1990), and <0.000l in FY 1991 for all age categories (FDA 1992). Estimated endrin intakes were not reported for FY 1990 (FDA 1991). In an overall summary of FDA Total Diet Studies for the 5-year period 1986–1991, average dietary intakes of endrin for eight age/sex groups (6–11-month-old infants, 2-year-old children, 14–16-year-old males and females, 25–30-year-old males and females, and 60–65-year-old males and females) were all estimated to be <0.0001 µg/kg (ppb) body weight per day (FDA 1993). In Canada, where endrin was registered for use from 1954 to 1990, a dietary intake study estimated the adult annual intake of endrin at approximately 32 µg (0.001 µg/kg [ppb] body weight/day) (Davies 1988).

The National Health and Nutrition Examination Survey (NHANES) uses biomonitoring to provide estimates of exposure to the civilian U.S. population. Chemicals and their metabolites are measured in subsets of participants aged 6–59 years old, meant to be a representative sample of the general U.S. population. Serum endrin values were surveyed during the years 2001–2004; endrin was pooled with other organochlorines in subsequent NHANES surveys (CDC 2019). As shown in Table 5-4, endrin was below the limit of detection (LOD) in most samples. The LODs for survey years 2001–2002 and 2003–

2004 are 5.09 and 7.8 ng/g lipid, respectively. The analytical method used for the analysis was gas chromatography with high-resolution mass spectrometry.

Although endrin bioaccumulates significantly in aquatic organisms (ASTER 1995; EPA 1980; Metcalf et al. 1973), studies indicate that endrin levels in fish and shellfish in the United States are not of concern for human health (EPA 1992b; Ford and Hill 1991; Murray and Beck 1990; Schmitt et al. 1985, 1990). Dietary exposures to endrin from domestic fish were estimated from 1984 to 1988 FDA surveillance data to be $1.7x10^{-5}$ µg/kg (ppb) body weight/day (Ahmed et al. 1993). As of 1995, there were no fish consumption advisories for endrin in effect in the United States (EPA 1995c).

In the 1982 National Human Adipose Tissue Survey, endrin was not detected in adipose tissues from the general U.S. population (EPA 1986b). Endrin also was not detected in adipose breast tissue from breast cancer patients (n=5) or controls (n=5) in the United States (Djordjevic et al. 1994). A 1984 study based on autopsied adipose tissue from 141 cadavers from six Canadian Great Lakes municipalities showed no detectable concentrations of endrin (detection limit 2.4 ppb) (Williams et al. 1988). In a 1990–1991 survey, only very low levels of endrin (average concentration 3.27 ng/g (ppb); range 0.23–8.56 ng/g [ppb] lipid) were found in adipose tissue samples from 3 of 41 residents of British Columbia, Canada, where endrin was registered for use from 1954 to 1990 (Teshke et al. 1993).

Table 5-4. Serum Endrin Levels (Lipid-Adjusted) in the NHANES U.S. Population[a]

	Survey years[b]	Geometric mean (95% CI) (ng/g lipid)	Selected percentiles (95% confidence interval) (ng/g lipid)				Sample size
			50th	75th	90th	95th	
Total	2001–2002	Not calculated[c]	<LOD	<LOD	<LOD	5.10 (<LOD–5.40)	2,187
	2003–2004	Not calculated	<LOD	<LOD	<LOD	LOD	1,825
Age group							
12–19 years	2001–2002	Not calculated	<LOD	<LOD	5.20 (<LOD–5.50)	5.60 (5.40–5.70)	730
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	539
≥20 years	2001–2002	Not calculated	<LOD	<LOD	<LOD	<LOD	1,457
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	1,286
Sex							
Males	2001–2002	Not calculated	<LOD	<LOD	<LOD	5.20 (<LOD–5.40)	1,022
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	885
Females	2001–2002	Not calculated	<LOD	<LOD	<LOD	<LOD	1,165
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	940
Race/ethnicity							
Mexican Americans	2001–2002	Not calculated	<LOD	<LOD	<LOD	5.30 (<LOD–6.50)	547
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	433
Non-Hispanic blacks	2001–2002	Not calculated	<LOD	<LOD	<LOD	5.40 (<LOD–6.30)	487
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	446
Non-Hispanic whites	2001–2002	Not calculated	<LOD	<LOD	<LOD	5.10 (<LOD–5.40)	1,000
	2003–2004	Not calculated	<LOD	<LOD	<LOD	<LOD	831

[a]Serum endrin levels not adjusted for lipid levels are available at https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume2_Jan2019-508.pdf.
[b]The limit of detection for survey years 2001–2002 and 2003–2004 were 5.09 and 7.8 ng/g lipid, respectively. Serum endrin levels were not measured after NHANES 2004.
[c]Not calculated: proportion of results below LOD was too high to provide valid results.

LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2019

Endrin has been detected in the milk of lactating women living outside the United States; however, no data from the United States could be located. Data from other countries indicate that there is some correlation between the levels of endrin used in, or transported to, an area and concentrations found in breast milk. Endrin was not detected in breast milk samples from a remote area of Papua, New Guinea (Spicer and Kereu 1993). In a recent investigation of Inuit exposure to organochlorine pesticides through the aquatic food chain in Arctic Quebec, endrin was detected in only 1 of 107 breast milk samples from Inuit women, at a concentration of <8 ng/g (ppb) in milk fat, and in none of 50 samples from southern Quebec Caucasian women (Dewailly et al. 1993). In France, where endrin has not been used for over 20 years, endrin was detected in 8 of 20 human milk samples collected 20–90 days after parturition. Concentrations ranged from 0.02 to 0.84 ppm (20–840 ppb) in milk fat, with a mean concentration of 0.06 ppm (60 ppb) (Bordet et al. 1993). Higher levels of endrin were found in human milk in a study conducted in Jordan, where endrin was widely used over the previous 40 years (Alawi et al. 1992). In this study, endrin was detected in samples from 3 of 15 donors at concentrations ranging from 0.26 to 6.24 ppm (260–6,240 ppb) in milk fat. The median and maximum daily intakes of endrin for breastfed infants were estimated to be 1.55 and 12.70 mg/kg (ppm) (1,550 and 12,700 ppb) body weight, respectively. The relevance of these findings to the U.S. population is unclear.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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

Although all uses of endrin in the United States were canceled by 1991 (EPA 1984a, 1985a, 1986a, 1993; USDA 1993), occupational exposures to endrin, endrin aldehyde, and endrin ketone may occur among workers involved in the handling and treatment of materials at hazardous waste sites, and among agricultural workers at sites formerly treated with endrin. No information was found in the available literature on current occupational exposures. In the past, exposures of agricultural workers were

significant. Seasonal agricultural workers dusting potatoes with 1% endrin dust were calculated to be exposed to a dermal dose of 2.0 mg/kg (ppm) body weight/day and an inhalation dose of 0.04 mg/kg (ppm) body weight/day at a time when agricultural use of endrin was near its peak (Wolfe et al. 1963).

Occupational exposure to endrin was not evaluated during the National Occupational Exposure Survey (NOES) conducted from 1981 to 1983 or its predecessor, the National Occupational Hazard Survey (NOHS) conducted from 1972 to 1974. The surveys conducted by the National Institute for Occupational Safety and Health (NIOSH) were designed to provide data necessary to describe potential exposure agents and profile health and safety programs in United States workplaces.

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 endrin 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 endrin.

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.

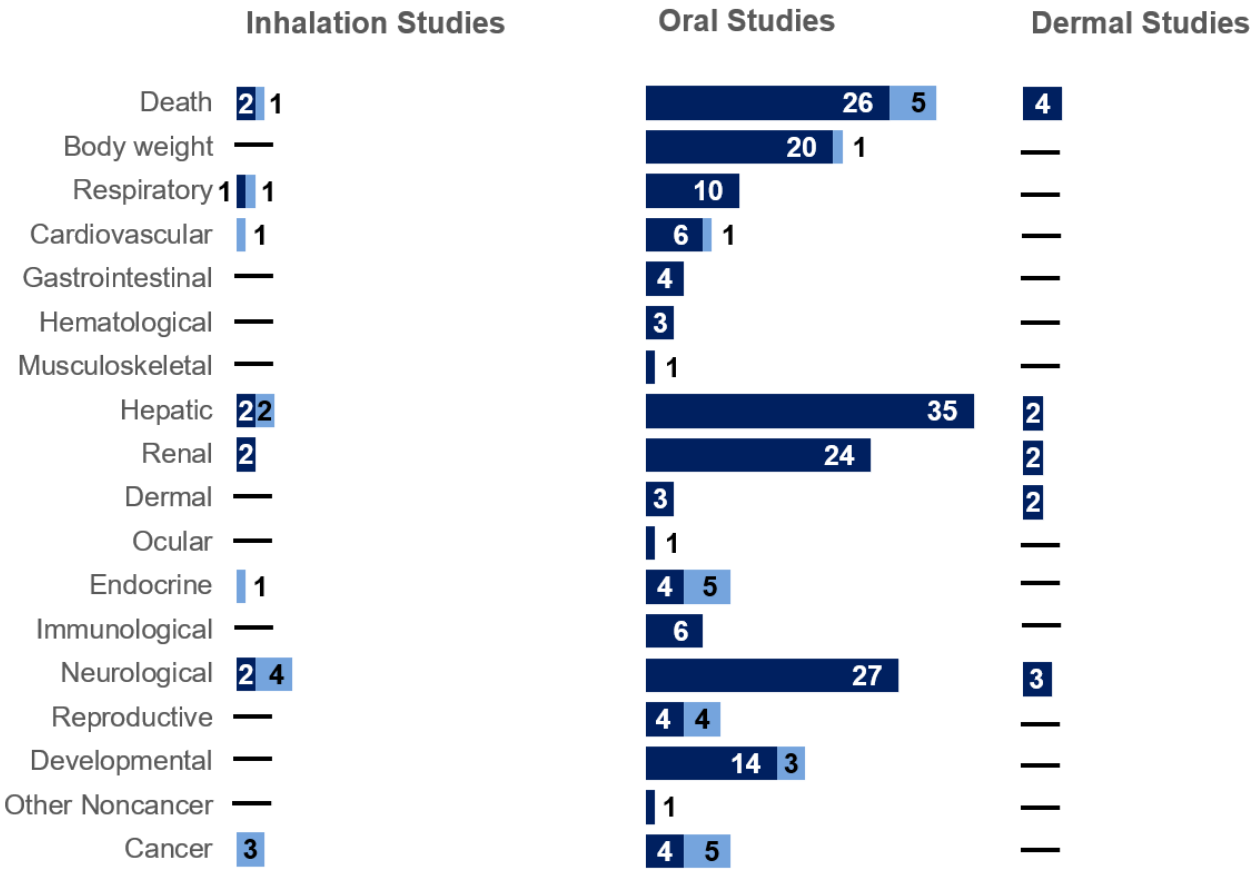
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to endrin that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of endrin. 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.

As illustrated in Figure 6-1, most of the data on the toxicity of endrin come from oral studies in laboratory animals. The most examined endpoints were neurological, hepatic, renal, body weight, and developmental effects. The available human studies include occupational health surveys, population-based studies, and case series predominantly focused on neurological effects and cancer. However, more recent human studies evaluated potential endocrine, reproductive, and developmental effects. For the purposes of Figure 6-1, all occupational studies were classified as inhalation studies and all population-based studies were classified as oral studies; however, it is acknowledged that humans were likely exposed via multiple exposure routes in both occupational and environmental settings. The laboratory animal inhalation and dermal toxicity database consists of a small number of studies evaluating limited endpoints. Only one study (Young and Mehendale 1986) was found on the health effects of endrin aldehyde or endrin ketone in animals following oral exposure; all other animal studies in Figure 6-1 evaluate endrin.

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

Most studies examined the potential hepatic and neurological effects of endrin
The majority of the studies examined oral exposure in **animals** (versus **humans**)



Includes studies discussed in Chapter 2. A total of 95 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints. All occupational studies were classified as inhalation studies and all population-based studies were classified as oral studies to avoid double counting these studies; however, it is acknowledged that humans were likely exposed via multiple exposure routes in both occupational and environmental settings.

6.2 Identification of Data Needs

Missing information in Figure 6-1 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.

Acute-Duration MRLs. The inhalation database is inadequate to derive an acute-duration inhalation MRL; available human studies do not provide exposure data and the animal database is limited to a single study reporting lethality and histological alterations in the brain of a single cat (Ressang et al. 1959). Well-designed acute studies evaluating a comprehensive set of endpoints, including neurotoxicity, could potentially identify a point of departure (POD) to use as the basis for an acute inhalation MRL. The oral database is adequate to derive an acute-duration oral MRL based on neurobehavioral changes in rats. Additional well-designed, low-dose acute studies designed to evaluate a wide-array of neurological endpoints, including neurobehavior, could potentially identify a NOAEL for neurological effects following acute exposure and decrease the uncertainty in the acute oral MRL.

Intermediate-Duration MRLs. The inhalation database is not adequate to derive an intermediate-duration inhalation MRL; there are no available human studies and the animal database is limited to a single study evaluating mice and rabbits exposed to lethal concentrations (Treon et al. 1955). The oral database is also inadequate to derive an intermediate-duration oral MRL due to inadequate low-dose information; however, the acute-duration oral MRL was adopted as the intermediate-duration oral MRL. Well-designed, intermediate-duration inhalation and oral studies designed to evaluate a wide array of endpoints at low exposure levels, particularly neurological endpoints, could potentially identify an appropriate POD to use as the basis for intermediate-duration MRLs.

Chronic-Duration MRLs. The inhalation database is inadequate to derive a chronic-duration inhalation MRL; available human studies do not provide exposure data and there are no animal studies. Low-exposure inhalation studies designed to identify a NOAEL for neurological effects could potentially identify a POD to use as the basis for a chronic-duration inhalation MRL. The oral database is adequate to derive a chronic-duration oral MRL. Additional well-designed, low-dose chronic studies designed to evaluate a wide-array of neurological endpoints, including neurobehavior, could decreased the uncertainty in the chronic oral MRL.

Health Effects.

Neurotoxicity. While overt neurological effects are well characterized following oral exposures and, to a lesser extent, inhalation and dermal exposures, additional studies specifically to evaluate a wide array of neurological endpoints, including neurobehavior, would be helpful to establish dose-response relationships. Studies in humans indicate that endrin causes changes in the nervous system after occupational and oral exposure. Clinical symptoms including twitching and jerking of muscles, seizures, dizziness, and mental confusion within 2 hours following occupational exposure. Studies in animals confirm the neurotoxic potential of endrin.

Hepatic Toxicity. Additional low-exposure studies may better define the dose-response relationships. There is limited evidence of changes in liver function in endrin-exposed workers. Animal studies confirm that hepatotoxicity occurs following exposure at or near lethal doses. Hepatotoxicity has been observed following chronic exposure to sublethal doses.

Renal Toxicity. Additional low-exposure studies may better define the dose-response relationships. There are no data in humans regarding changes in renal function in endrin-exposed individuals. Inhalation, oral, and dermal exposure at or near lethal levels of endrin caused diffuse degenerative lesions in the kidneys of various species. There is limited evidence of renal effects (cloudy swelling of tubule epithelial cells) at nonlethal doses from one chronic study in rats (Deichmann et al. 1970); however, this finding was not confirmed in rats or mice at sublethal chronic doses in an NCI (1979) bioassay.

Respiratory Toxicity. Additional epidemiological studies and low-exposure animal studies in several species may better define potential respiratory effects and inform the dose-response relationships. No clear associations have been observed between altered respiratory function or disease and occupational endrin exposure in humans; however, human data are limited to two studies. In animals, most respiratory tract effects were associated with lethal exposure levels, and were attributed to widespread systemic failure. However, one chronic rat study reported focal hemorrhage and congestion of the lungs at sublethal levels.

Cardiovascular Toxicity. Additional epidemiological studies and low-exposure animal studies in several species may better define potential cardiac effects and inform the dose-response

relationships. No clear associations have been observed between environmental or occupational endrin exposure in humans; however, available human data are extremely limited. In dogs, diffuse degenerative lesions have been reported at lethal doses and elevated heart weight has been reported at sublethal doses. These findings have not been observed in other animal species.

Endocrine Toxicity. Additional epidemiological studies and low-exposure animal studies in several species may better define potential endocrine effects and inform the dose-response relationships. No clear associations have been observed between environmental exposure to endrin and endocrine effects in humans. In animals, chronic exposure to sublethal dietary doses caused thyroid hyperplasia and pituitary cysts in rats, but not mice.

Immunotoxicity. *In vivo* studies designed specifically to assess immune function (inhalation, oral, and dermal exposure routes), as well as additional *in vitro* testing involving humoral mediated immunity and nonspecific immunity, could be useful in assessing the immunotoxic potential of endrin. No *in vivo* studies evaluating immune function are available in humans or animals following exposure to endrin after inhalation, oral, or dermal exposure. Results of *in vitro* assays evaluating inhibition of lymphocyte responses and neutrophilic chemotaxis were negative. Animal studies are limited to oral studies reporting inconsistent organ weight changes in immune organs; the only study evaluating immune organ histopathology did not observe any histopathological lesions after chronic exposure.

Reproductive Toxicity. Additional, well-designed reproductive assays evaluating various species and several dose levels via the oral route (and other routes as well) would be useful in assessing the potential reproductive toxicity of endrin. No clear associations have been observed between environmental endrin exposure and preterm labor or birth outcomes in humans; however, there is limited evidence of a potential association between delayed female physical and sexual development in adolescents living in a highly contaminated region in Kazakhstan. Additional well-designed epidemiological studies with appropriate statistical power and control for confounding variables would be useful to further evaluate this potential association. No studies are available on the reproductive effects of endrin in animals after inhalation or dermal exposure. Reproductive toxicity data in animals are limited to two 1-generation studies, one in mice limited to a single dose level (Good and Ware 1969) and one in dogs with several experimental flaws (Kettering 1971), and a low-dose 3-generation study in rats (Eisenlord et al. 1968). Only the mouse study indicated potential reproductive effects (decreased litter size).

Developmental Toxicity. Additional low-exposure studies could determine if any additional developmental effects occur at oral doses below maternal toxicity or following inhalation or dermal exposure. Conducting these studies in multiple species could be helpful in identifying potential species differences. Limited evidence in humans indicate that endrin is not associated with adverse birth outcomes or impaired male reproductive development; however, one study reported an association between endrin exposure and cord blood thyroid hormone levels. Offspring of mice and hamsters exposed to endrin during gestation showed statistically significant increases in the incidence of fused ribs, cleft palate, exencephaly, and meningoencephaloceles at maternally toxic doses. In rats, only delayed ossification was observed at maternally toxic doses. However, perinatal studies in rats suggest altered neurobehavior in offspring at doses below those associated with maternal toxicity.

Epidemiology and Human Dosimetry Studies. Additional quantitative exposure data obtained from individuals occupationally exposed to low levels of endrin would be useful in evaluating potential risk to people living near hazardous waste sites. There are reports on the adverse effects of endrin in humans. These reports involve acute exposures in people who ingested endrin-contaminated food, occupational surveys and case reports, and population-based studies. Most studies have poor control for confounding variables, particularly exposure to other organochlorine pesticides, and/or have low statistical power. Despite limitations, existing studies identify the nervous system as a major target associated with exposure to endrin. However, reliable quantitative exposure levels that lead to these effects are lacking.

Biomarkers of Exposure and Effect. Measurement of endrin and its metabolites can be useful indicators of exposure. Since endrin is cleared from the blood rapidly, such measurements are suitable only for recent exposures. Changes in the nervous system appear to be the main effect associated with human exposure to endrin. Effects on the nervous system can be monitored in exposed individuals by measuring the incidence of signs and symptoms such as myoclonic jerking, seizures, convulsions, dizziness, and mental confusion. Because these effects also occur following exposure to other organochlorine pesticides and drugs, the development of more specific biomarkers of endrin exposure would be useful for studying potential endrin-related adverse health effects.

Absorption, Distribution, Metabolism, and Excretion. Additional studies are needed to determine absorption rates following exposure by all routes. There are limited data on the absorption of

endrin in humans and animals. Limited studies provide qualitative evidence that endrin is absorbed following inhalation, oral, and dermal exposures; however, no information is available on the rate or extent of absorption that occurs by any of these routes.

Data are sparse on the distribution of endrin. Limited data in humans indicate that significant amounts of endrin residues are found in adipose tissue of people acutely exposed to high levels, but not typically in the general population. However, endrin has been detected in breast milk and placental tissues. Low levels of endrin are found in the liver, kidneys, and brain in people exposed to endrin or endrin-contaminated food. The time of sample collection is critical since endrin residues in tissues decline rapidly after exposure has ceased.

Additional studies in different species, as well as inhalation and dermal exposure studies, would be helpful. No studies were found regarding the metabolism of endrin in humans, excretion patterns in workers show metabolites similar to those identified in animal studies. Metabolism following oral exposure in animals has been fairly well characterized and shows some species differences.

Additional studies on the excretion of endrin and its metabolites via the dermal route would be useful since differences in urinary metabolite profiles have been observed following exposure to endrin by other routes. Excretion patterns following oral and inhalation exposure have been fairly well characterized.

Comparative Toxicokinetics. Additional studies using all three potential routes of human exposure would be useful in understanding differences in species and in determining which animal species is the most appropriate model for human exposure. There are limited data on the kinetics of endrin in humans. Studies in animals suggest that metabolism and urinary metabolite profiles vary among species.

Children's Susceptibility. Developmental effects have not been evaluated in animals following inhalation or dermal exposure. Studies in young animals and/or epidemiological data for children would be useful to address these data gaps. Data are inadequate to determine if children are more susceptible to acute toxic effects of endrin. In an endrin poisoning episode in Pakistan (of unknown origin), children 1–9 years old represented about 70% of the cases of convulsions (Rowley et al. 1987). The causative factor responsible for the outbreak was not identified, however, so it is unclear whether the age distribution of cases was due to increased susceptibility in children or age-specific exposure situations. Available data from oral developmental studies in animals do not indicate that developing animals are uniquely susceptible to toxicity following exposure to endrin.

Physical and Chemical Properties. More complete information on the physical and chemical properties of endrin aldehyde and endrin ketone would be useful. However, the physical and chemical properties of endrin have been sufficiently documented to permit estimation of its environmental fate.

Production, Import/Export, Use, Release, and Disposal. Information as to whether endrin is currently being produced and the export volumes for endrin are needed to evaluate existing routes of exposure for the general population and occupationally exposed individuals. Endrin is no longer registered for use and is not likely to be imported into the United States. Consequently, the risk of human exposure to endrin (and to endrin aldehyde and endrin ketone, which occur as impurities or transformation products of endrin) from these activities is expected to be minimal. However, recent information suggests that several organochlorine pesticides that have been banned from use or have been voluntarily cancelled in the United States are still being manufactured in large quantities for export abroad.

Environmental Fate. Anaerobic biodegradation, which may occur in river bottoms and in Superfund sites, has been studied in the laboratory, but not under natural conditions. Further information on these processes, including identification of degradation products, would be useful in determining potential mechanisms and the potential for contamination of groundwater by endrin released from soils. The partitioning of endrin released to the environment and the potential for bioaccumulation is well characterized. Information on biodegradation of endrin in soil under aerobic conditions exists, but degradation products have not been identified.

Bioavailability from Environmental Media. Additional information regarding the bioavailability of endrin from both ingestion of soil-bound endrin and dermal contact with endrin-contaminated soils would be helpful, particularly for populations living near hazardous waste sites. Information on absorption following inhalation and oral exposure, however, is well characterized under most conditions.

Food Chain Bioaccumulation. Data on bioaccumulation and bioconcentration of endrin generally appear to be adequate, particularly since endrin has not been registered for use in the United States since the mid-1980s. Although bioconcentration data are available for several species, it may be useful to obtain information on bioconcentration in the species with the highest BCF factor (snail) since data are only available in the pouch snail.

Exposure Levels in Environmental Media. There are possibilities of exposure from foodstuffs imported from countries that still use endrin and potential localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin. Additional data on environmental concentrations of endrin, endrin aldehyde, and endrin ketone from these possible sources of exposure would be useful. In addition, reliable monitoring data for the levels of endrin, endrin aldehyde, and endrin ketone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of these substances in the environment can be used in combination with their known body burdens to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Endrin has been reported to occur at very low levels in food and air. It has only rarely been detected in a number of national and regional surveys of drinking water supplies. Because endrin is no longer commercially used in the United States, future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low.

Exposure Levels in Humans. No studies specifically evaluating levels of endrin, endrin aldehyde, or endrin ketone in blood and other tissues of people near hazardous waste sites were located. This information is necessary for assessing the need to conduct health studies on these populations. Data on the concentrations of endrin in breast milk from U.S. women would be particularly useful, given that it has been detected in the milk of lactating women in other countries. However, metabolism of endrin in humans is relatively rapid compared with other organochlorine pesticides. Thus, levels in human blood and tissue may only be useful for acute exposures or very high occupational exposures. Endrin was not found in adipose tissue samples of the general U.S. population, or in adipose breast tissue from breast cancer patients in the United States.

Exposures of Children. Children may be exposed to endrin through the same routes as adults, as well as via placental transfer and breastfeeding. Monitoring of children's exposure to endrin would be useful, particularly in heavily contaminated areas, in combination with children's health and susceptibility information, to assess the potential risk for deleterious effects.

6.3 Ongoing Studies

No ongoing studies were identified for endrin.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding endrin 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 endrin.

Table 7-1. Regulations and Guidelines Applicable to Endrin

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 2002
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)	0.02 mg/L	
	10-Day health advisory (10-kg child)	0.005 mg/L	
	DWEL	0.01 mg/L	
	Lifetime health advisory	0.002 mg/L	
	10^{-4} Cancer risk	No data	
	National primary drinking water regulations		EPA 2009
	MCL	0.002 mg/L	
	PHG	0.002 mg/L	
	RfD	$3x10^{-4}$ mg/kg/day	IRIS 2002
WHO	Drinking water quality guidelines		WHO 2017
	Guideline value	0.0006 mg/L (0.6 µg/L)	
	PTDI	0.2 µg/kg body weight	
FDA	Substances Added to Food[a]	No data	FDA 2020
	Allowable level in bottled water	0.002 mg/L	FDA 2017c
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	D[b]	IRIS 2002
IARC	Carcinogenicity classification	Group 3[c]	IARC 1987

Table 7-1. Regulations and Guidelines Applicable to Endrin

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	0.1 mg/m^3 [d]	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	0.1 mg/m^3 [d]	NIOSH 2016
	IDLH	2 mg/m^3	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[e]	1.8 mg/m^3	
	PAC-2[e]	20 mg/m^3	
	PAC-3[e]	2,000 mg/m^3	

[a]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 from use in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group D: not classifiable as to human carcinogenicity.
[c]Group 3: not classifiable as to its carcinogenicity to humans.
[d]Skin designation.
[e]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; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; PHG = public health goal; PTDI = provisional tolerable daily intake; 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.

APPENDIX A

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.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Endrin
CAS Numbers: 72-20-8
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute inhalation MRL.

Rationale for Not Deriving an MRL: The limited number of human studies available do not contain quantitative data needed for MRL derivation and often report co-exposure to other chemicals (e.g., aldrin, dieldrin). Acute inhalation data in laboratory animals are limited to one study reporting brain lesions and mortality in a single cat exposed twice to endrin at 417 ppm (1 hour/session) (Ressang et al. 1959).

Agency Contacts (Chemical Manager): Susan Zells Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Endrin
CAS Numbers: 72-20-8
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: The limited number of human studies available do not contain quantitative data needed for MRL derivation and often report co-exposure to other chemicals (e.g., aldrin, dieldrin). The intermediate-duration inhalation database in laboratory animals consists of a single study evaluating survival in cats, guinea pigs, hamsters, rats, rabbits, and mice exposed to endrin at 0.36 ppm for 107–130 days (5 days/week, 7 hours/day) (Treon et al. 1955). Necropsy was only performed on animals that died (1/3 mice, 2/4 rabbits), and no controls were used.

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Endrin
CAS Numbers: 72-20-8
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: The limited number of human studies available do not contain quantitative data needed for MRL derivation and often report co-exposure to other chemicals (e.g., aldrin, dieldrin). No chronic-duration inhalation studies in laboratory animals were identified for endrin.

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Endrin
CAS Numbers: 72-20-8
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Acute
MRL 0.0006 mg/kg/day
Critical Effect: Decreased locomotor activity
Reference: Kavlock et al. 1981
Point of Departure: $BMDL_{1SD}$ of 0.057 mg/kg
Uncertainty Factor: 100
LSE Graph Key: 13
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.0006 mg/kg/day was derived for endrin based on evidence of neurotoxicity (decreased locomotor activity) in rats following a single exposure to endrin at gavage doses ≥0.5 mg/kg (Kavlock et al. 1981). The MRL is based on the $BMDL_{1SD}$ of 0.057 mg/kg for depressed locomotor activity and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: The lowest LOAELs identified in the acute oral database include a serious LOAEL of 0.3 mg/kg/day for a 38% decrease in maternal body weight gain in rats exposed to endrin for 14 days during gestation (Kavlock et al. 1981), a LOAEL of 0.5 mg/kg/day for decreased locomotion in female rats on day 1 of a 14-day exposure (Kavlock et al. 1981), and a LOAEL of 0.5 mg/kg/day for increased liver weights in maternal rats exposed to endrin for 11 days during gestation (Kavlock et al. 1981). A NOAEL of 0.15 mg/kg/day was established for maternal body weight effects; no NOAELs were identified for neurological or hepatic effects in the Kavlock et al. (1981) study. Other reported body weight, neurological, and hepatic effects following acute exposure to endrin are reviewed in Table A-1. Observed effects in other systems, including the developing fetus, occurred at doses ≥1 mg/kg (see Table 2-3), and were not considered as candidate critical effects. It should be noted that increased mortality occurred in female CD rats exposed to ≥0.5 mg/kg/day for up to 14 days (Kavlock et al. 1981); however, the same authors observed 100% survival in a second study of female CD rats exposed to doses up to 0.45 mg/kg/day for 14 days (Kavlock et al. 1981). In other rat strains and other species, reported lethal doses following acute exposure were ≥1.5 mg/kg.

Since decreased maternal body weight in rats, decreased locomotion in female rats, and increased maternal liver weight in mice occurred at similar doses in the various experiments conducted by Kavlock et al. (1981), all were considered for MRL derivation.

Table A-1. Summary of Candidate Critical Effects for Acute Oral MRL for Endrin

Species	Duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
CD rat	14 days (GO)	ND	0.5	Depressed locomotor activity on day 1	Kavlock et al. 1981 (range-finding)

Table A-1. Summary of Candidate Critical Effects for Acute Oral MRL for Endrin

Species	Duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Holtzman albino rat	8 days, every 2–3 days (GO)	1	ND	No clinical signs of neurotoxicity	Coleman et al. 1968
Holtzman albino rat	Once (GO)	ND	25 (serious LOAEL)	Convulsions	Lawrence et al. 1968
CD-1 mouse	Up to 11 days	0.5	1.5	Decreased locomotor activity on days 1 and 3	Kavlock et al. 1981 (range-finding)
Golden Syrian hamster	Once GD 8 (GO)	7.5	10 (serious LOAEL)	Convulsions	Chernoff et al. 1979
Hepatic effects					
CD rat	14 days GDs 7–20 (GO)	0.45		No change in maternal liver weight	Kavlock et al. 1981 (main study)
CD-1 mouse	11 days GDs 7–17 (GO)	ND	0.5	Increased relative maternal liver weight	Kavlock et al. 1981 (main study)
Holtzman albino rat	8 days, every 2–3 days	1 (TWA)	ND	No change in liver weight	Coleman et al. 1968
Sprague-Dawley rat	Once (GO)	ND	3	Increased relative liver weight	Bagchi et al. 1992a, 1992b, 1992c
Golden Syrian hamster	10 days GDs 5–14 (GO)	3.5	ND	No change in liver weight	Chernoff et al. 1979
Sprague-Dawley rat	Once (GO)	4	ND	No change in liver weight	Numan et al. 1990a
Sprague-Dawley rat; Swiss Webster mouse; guinea pig; golden Syrian hamster	Once (GO)	ND	4	Necrosis, fatty degeneration, inflammation, cell regeneration, lipid peroxidation	Hassan et al. 1991
Sprague-Dawley rat	1–2 days (F)		8.2	Altered serum chemistry, vacuolization, fatty infiltration	Ali and Shakoori 1993
Body weight effects					
CD rat	14 days GDs 7–20 (GO)	0.15	0.3 (serious LOAEL)	38% decrease in maternal body weight gain	Kavlock et al. 1981 (main study)

Table A-1. Summary of Candidate Critical Effects for Acute Oral MRL for Endrin

Species	Duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sherman rat	10 days GDs 6–15 (G)	0.5	2	12% decrease in maternal weight gain (2/25 dams died at this dose)	Goldenthal 1978a
CD-1 mouse	11 days GDs 7–17 (GO)	0.5	1 (serious LOAEL)	24% decrease in maternal body weight gain	Kavlock et al. 1981 (main study)
CD-1 mouse	11 days (GO)	0.5	1.5 (serious LOAEL)	43% decrease in body weight gain	Kavlock et al. 1981 (range-finding)
Golden Syrian hamster	10 days GDs 5–14 (GO)	ND	1.5 (serious LOAEL)	19-fold increase in weight loss (37% mortality rate at this dose)	Chernoff et al. 1979
C57BL/6J or DBA/2J mouse	Once GD 12 (GO)	6	ND	No change in body weight in surviving dams (25% mortality at 6 mg/kg)	Hassoun and Stohs 1996b
Sprague-Dawley rat	1–2 days (F)	8.2			Ali and Shakoori 1993

(F) = feed; GD = gestation day; (GO) = gavage-oil; LOAEL = lowest observed adverse effect level; MRL = minimal risk level; ND = not determined; NOAEL = no-observed-adverse-effect level; TWA = time-weighted average

Selection of the Principal Study: The Kavlock et al. (1981) range finding study in rats was selected as the principal study because it identified the lowest POD (see next section) for a sensitive target of endrin toxicity.

Summary of the Principal Study:

Kavlock RJ, Chernoff N, Hanisch RC, et al. 1981. Perinatal toxicity of endrin in rodents. II. Fetotoxic effects of prenatal exposure in rats and mice. Toxicology 21:141-150.

Kavlock et al. (1981) conducted two studies in CD rats, a preliminary range-finding study in nonpregnant females and a main teratology study in pregnant females.

Range-Finding Study. In the range finding study, groups of 5–9 nonpregnant female rats were administered doses of 0, 0.5, 1.0, 2.0, and 4.0 mg/kg/day endrin (>99% pure) via gavage in corn oil for up to 14 days. This preliminary range-finding study only evaluated mortality, body weight, and locomotor activity. Reactive locomotor activity was measured for 30 minutes on day 1 in figure-eight mazes (2–4 hours after initial dosing).

Increased mortality occurred in all treated groups, with 60% mortality at 0.5 mg/kg/day and 100% mortality at higher doses. Survival time decreased in a time-related manner. Average times-to-death at 0.5, 1.0, 2.0, and 4.0 mg/kg/day were 7.7, 5.5, 3.4, and 1.3 days, respectively. All control animals survived. Body weight gain in the two surviving rats at the lowest dose was decreased 94% compared to controls (1.8 g gained versus 32.4 g gained). Two of the six animals in the 4 mg/kg exposure group

experienced convulsions within 2–4 hours of the first exposure; these animals were excluded from the locomotor activity assessment. In other treated animals, a dose-related decrease in locomotor activity was observed 2–4 hours after the first administration. Activity was significantly depressed by 40, 72, and 88% at 0.5, 1.0, and 2.0 mg/kg, respectively. The study authors reported that activity was also decreased by 88% in the four rats at 4 mg/kg/day that did not experience convulsions; however, statistics and quantitative data for this group were not reported.

***Main Teratology Study*.** Based on findings from the range-finding study, groups of 15–32 pregnant female rats were administered doses of 0, 0.075, 0.15, 0.3, and 0.45 mg/kg/day via gavage in corn oil from GD 7 to 20. Dams were observed for mortality and maternal body weight gain was monitored. All dams were sacrificed on GD 21. At sacrifice, the uterus and liver were removed and weighed. The uterus was examined for the number of live, dead, and resorbed fetuses. The fetuses were weighed, examined for gross anomalies, and divided equally for examination for skeletal and visceral malformations and variations.

Despite 60% mortality at 0.5 mg/kg/day in the range-finding study, no mortalities occurred in the main study at doses up to 0.45 mg/kg/day (highest dose tested). The study authors did not discuss potential reasons for this apparent steep dose-response curve for lethality. However, results from the main study are consistent with findings in other rat strains, which only reported increased mortality after exposure to acute doses ≥2 mg/kg/day (Bedford et al. 1975a; Gaines 1960, 1969; Goldenthal 1978a; Numan et al. 1990b; Speck and Maaske 1958; Treon et al. 1955). Maternal body weight gain was significantly decreased by 38–87% at ≥0.3 mg/kg/day. No exposure-related changes were observed in maternal liver weight. There were exposure-related changes in fetal endpoints.

Selection of the Point of Departure: A $BMDL_{1SD}$ of 0.057 mg/kg was selected as the POD for the acute-duration oral MRL.

In order to identify the study providing the most sensitive POD, BMD modeling was attempted for the most sensitive data for each critical endpoint identified in Table A-1: decreased locomotor activity in female rats, increased relative liver weight in mouse dams, and decreased maternal body weight in rat dams. The data for these three endpoints are presented in Tables A-2, A-3, and A-4, respectively. The data were fit to all continuous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2) using a benchmark response (BMR) of 1 standard deviation (locomotor activity) or 10% relative deviation (body and organ weight data). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) was chosen.

Table A-2. Locomotor Activity in Female Rats Following a Single Gavage Administration of Endrin

	Dose (mg/kg)			
	0	0.5	1.0	2.0
Locomotor activity (number of photocell beam interruptions) Mean±SD (N)	665±82 (6)	400±33 (5)	186±49 (6)	83±51 (4)

N = number; SD = standard deviation

Source: Kavlock et al. 1981

Table A-3. Relative Liver Weight in Mouse Dams Following Gavage Administration of Endrin on GDs 7–17

	Dose (mg/kg/day)				
	0	0.5	1.0	1.5	2.0
Relative maternal liver weight (%) Mean±SD (N)	6.7±1.0 (27)	7.2±0.6 (31)	7.4±0.6 (32)	8.1±0.7 (12)	7.2±NR (2)

GD = gestation day; N = number; NR = not reported (no variance data reported by study authors); SD = standard deviation (SD calculated for this review from reported standard error of the mean and animal number)

Source: Kavlock et al. 1981

Table A-4. Maternal Body Weight Gain in Rat Dams Following Gavage Administration of Endrin on GDs 7–17

	Dose (mg/kg/day)				
	0	0.075	0.150	0.300	0.450
Maternal body weight gain (g) Mean±SD (N)	69.0±21.5 (29)	73.0±11.2 (14)	66.8±19.7 (27)	42.9±26.4 (29)	8.8±19.4 (12)

GD = gestation day; N = number; SD = standard deviation (SD calculated for this review from reported standard error of the mean and animal number)

Source: Kavlock et al. 1981

Three models provided adequate fit to the locomotor activity data (Exponential 2, 3, and 4); the remaining models did not provide adequate fit; the results of the modeling are presented in Table A-5. The $BMDL_{1SD}$ values were sufficiently close and the model with the lowest AIC (Exponential 2) was recommended. The Exponential 2 model estimated a BMD_{1SD} of 0.075 mg/kg and $BMDL_{1SD}$ of 0.057 mg/kg. For the maternal relative liver weight data, all but the Exponential 4, Exponential 5, and Polynomial 2-degree models provided adequate fit to the data with nonconstant variance; the model results are presented in Table A-6. The BMDLs were sufficiently close, and the Exponential 2 model with a BMD_{RD10} of 0.820 mg/kg/day and $BMDL_{RD10}$ of 0.642 mg/kg/day were selected. None of the models (with or without the highest dose group dropped) provided adequate fit to the maternal body weight gain data.

Table A-5. Model Predictions (Constant Variance) for Locomotor Activity in Female Rats Following a Single Gavage Administration of Endrin (Kavlock et al. 1981)

Model	BMD_{1SD}[a] (mg/kg)	$BMDL_{1SD}$[a] (mg/kg)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Exponential 2[d,e]	**0.075**	**0.057**	**0.261**	**234.60**	**-0.199**	**-0.199**
Exponential 3[d]	0.092	0.058	0.124	236.28	-0.102	-0.102
Exponential 4[d]	0.074	0.055	0.103	236.57	-0.222	-0.222
Exponential 5[d]			NA	235.91	-0.020	-0.020
Hill[d]			NA	235.93	-0.067	-0.067
Polynomial Degree 3[d]			<0.0001	257.88	-0.903	1.931
Polynomial Degree 2[d]			<0.0001	257.88	-0.903	1.930
Power[d]			<0.0001	257.88	-0.903	1.930
Linear			<0.0001	257.88	-0.904	1.930

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Exponential 2).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure dose associated with a 10% relative deviation from control)

Table A-6. Model Predictions (Nonconstant Variance) for Relative Liver Weight in Female Rats Following a Single Gavage Administration of Endrin (Kavlock et al. 1981)

Model	BMD_{1SD}[a] (mg/kg)	$BMDL_{1SD}$[a] (mg/kg)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Exponential 2[d,e]	**0.820**	**0.642**	**0.253**	**228.08**	**-1.13**	**-0.0149**
Exponential 3[d]	0.822	0.642	0.252	228.09	-1.13	-0.0257
Exponential 4[d]			0.096	230.10	-1.21	0.0609
Exponential 5[d]			0.096	230.11	-1.21	0.0715
Hill[d]	0.777	0.592	0.248	228.12	-1.24	0.099
Polynomial Degree 3[d]	0.851	0.605	0.106	229.95	-1.02	-0.085
Polynomial Degree 2[d]			0.097	230.09	-1.16	0.0097
Power[d]	0.790	0.602	0.250	228.10	-1.21	0.0625
Linear	0.790	0.601	0.250	228.10	-1.21	0.0625

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Exponential 2).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure dose associated with a 10% relative deviation from control)

The candidate PODs are summarized in Table A-7. Neurological effects in female rats (0.075 mg/kg) had the lowest effect level (BMD or LOAEL). The BMD_{1SD} for this endpoint is 0.057 mg/kg estimated using the Exponential 2 model which is presented in Figure A-1. The POD is 5 times lower than the LOAEL for decreased maternal body weight gain and nearly 10 times lower than the lethal dose reported in the range-finding study by Kavlock et al. (1981). Furthermore, the central nervous system is the primary target system for endrin toxicity (*Other Additional Studies or Pertinent Information* below).

Table A-7. Summary of Candidate Critical Effects and PODs for the Acute Oral MRL for Endrin

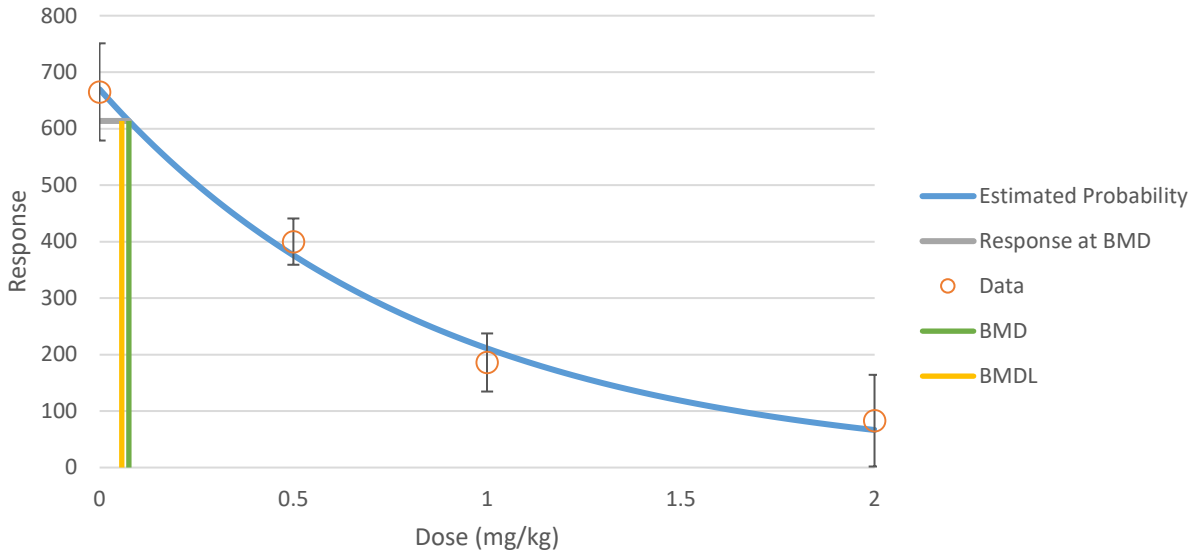
Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Decreased locomotor activity on day 1 in rats (Kavlock et al. 1981)	ND	0.5	0.075 (BMD_{1SD})	0.057[a] ($BMDL_{1SD}$)
Increased relative liver weight in mouse dams (Kavlock et al. 1981)	ND	0.5	0.82 (BMD_{RD10})	0.642 ($BMDL_{RD10}$)

Table A-7. Summary of Candidate Critical Effects and PODs for the Acute Oral MRL for Endrin

Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Decreased maternal body weight gain in rat dams (Kavlock et al. 1981)	0.15	0.3 (serious LOAEL)	NA	NA

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NA = not applicable; NOAEL = no-observed-adverse-effect level; POD = point of departure; RD = relative deviation; SD = standard deviation

Figure A-1. Fit of Exponential 2 Model (with Constant Variance) for Decreased Locomotor Activity in Rats Administered Endrin on Day 1 (Kavlock et al. 1981)



Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{1SD} \div$ uncertainty factors

$0.057 \text{ mg/kg/day} \div (10 \times 10) = 0.00057 \text{ mg/kg/day} \approx 0.0006 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information: The POD based on neurological effects ($BMDL_{1SD}$ of 0.057 mg/kg/day) is 5 times lower than the LOAEL for decreased maternal body weight gain and nearly 10 times lower than the lethal dose reported in the range-finding study by Kavlock et al. (1981), resulting in an MRL that is 500–1,000 times lower than any doses associated with adverse health effects or mortality. Therefore, the MRL based on neurological effects is protective of other known endpoints. Identification of neurotoxicity as the critical effect of endrin is supported by reports of neurologic effects including convulsions and tremors in humans acutely poisoned with endrin (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Rowley et al. 1987; Waller et al. 1992; Weeks 1967) and various animal species following oral exposure (Chernoff et al. 1979; Deichmann

et al. 1970; Kavlock et al. 1981; Kettering 1969; Mehrotra et al. 1989; Treon et al. 1955). Acute neurotoxic effects have also been observed following high occupational exposure (Hoogendam et al. 1962, 1965). There is also limited animal evidence for neurotoxicity following acute inhalation or dermal exposure (Gaines 1960; Pandy 1978; Ressang et al. 1959; Treon et al. 1955).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Endrin
CAS Numbers: 72-20-8
Date: March 2021
Profile Status: Final
Duration: Intermediate
MRL: 0.0006 mg/kg/day (adopt acute oral MRL)
Critical Effect: Decreased locomotor activity
Reference: Kavlock et al. 1981
Point of Departure: $BMDL_{1SD}$ of 0.057 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 13
Species: Rat

MRL Summary: The acute-duration oral MRL of 0.006 mg/kg/day based on a $BMDL_{1SD}$ of 0.057 mg/kg decreased locomotor activity in rats (Kavlock et al. 1981) was adopted for the intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: An MRL was not derived for intermediate-duration oral exposure because the MRL derived from the available data in the limited database would be higher than the acute-duration MRL. The acute-duration MRL is expected to be protective of intermediate-duration exposures; therefore, the acute oral MRL is adopted as the intermediate oral MRL.

The intermediate-duration oral database for endrin is limited (see Table A-8). The lowest identified effect level is for altered habituation in locomotor testing in PND 16 and 20 offspring following maternal exposure to 0.15 mg/kg/day endrin via gavage from GD 7 to PND 15 (Gray et al. 1981). Young and Mehendale (1986) reported hepatic LOAELs at slightly higher doses based on altered hepatic enzyme levels or hepatobiliary function in rats exposed to endrin, endrin aldehyde, or endrin ketone at 0.25–0.5 mg/kg/day for 15 days (Young and Mehendale 1986). The only other available studies reported serious LOAELs for death in one dog exposed to endrin doses of 0.20–0.27 mg/kg/day for 47 days (midpoint 0.24 mg/kg/day) (Treon et al. 1955) and mouse dams exposed to 0.65 mg/kg/day during gestation (Good and Ware 1969).

Table A-8. Summary of Effects Following Intermediate Oral Exposure to Endrin

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sublethal effects					
CD rat	28 days GD 7–PND 15 (GO)	0.075[a]	0.15	Altered habituation in locomotor testing in offspring on PND 16 and 20	Gray et al. 1981
Sprague-Dawley rat	15 days (F)	ND	0.25	Altered hepatobiliary function (no change in serum chemistry; organ weight and histology not assessed)	Young and Mehendale 1986

Table A-8. Summary of Effects Following Intermediate Oral Exposure to Endrin

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sprague-Dawley rat	15 days (F)	ND	0.5 (endrin aldehyde)	10-fold increase in serum ALT and 5-fold increase in serum AST (no changes in hepatobiliary function; organ weight and histology not assessed)	Young and Mehendale 1986
Sprague-Dawley rat	15 days (F)	ND	0.25 (endrin ketone)	8-fold increase in serum ALT (no changes in hepatobiliary function; organ weight and histology not assessed)	Young and Mehendale 1986
Lethality					
Beagle dog	Up to 9.9 months; 6 days/week (F)	NA	0.23	Death	Treon et al. 1955
Swiss mouse	120 days (F)	NA	0.65	Maternal death	Good and Ware 1969

[a]Selected POD.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = feed; GD = gestation day; GO = gavage-oil; LOAEL = lowest observed adverse effect level; MRL = minimal risk level; NA = not applicable; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure

Altered locomotion in offspring from the Gray et al. (1981) study was selected as the critical effect because it was the most sensitive effect observed in available studies. BMD modeling was conducted for locomotor data from the final 15 minutes of the 45-minute locomotor trial, which showed the most significant increases in locomotion compared with control (Table A-9). Values for modeling were extracted from Figure 3B in the report using GrabIt! software. Using the BMD modeling approach described in the acute-duration oral MRL worksheet, no adequate models were identified with either the full dataset or the highest dose dropped. Therefore, the NOAEL of 0.075 mg/kg/day was selected as the point-of-departure. Using a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), the intermediate-duration oral MRL would be 0.0008 mg/kg/day. This value is higher than the acute-duration oral MRL of 0.0006 mg/kg/day based on a $BMDL_{1SD}$ of 0.057 mg/kg/day for decreased activity in adult female rats (Kavlock et al. 1981). Therefore, there are no sufficient low-dose data to derive an intermediate-duration oral MRL.

Table A-9. Locomotor Activity in PND 16–20 Rat Offspring Following Maternal Exposure to Endrin from GD 7 to PND 15 via Gavage

	Dose (mg/kg/day)			
	0	0.075	0.15	0.3
Locomotor activity (number of photocell beam interruptions) Mean±SD[a] (N)	43±8 (35)	39±6 (34)	71±10 (34)	83±13 (8)

[a]Values extracted from graphically presented data (Figure 3B) using GrabIt! Software.

GD = gestation day; N = number; PND = postnatal day; SD = standard deviation

Source: Gray et al. 1981

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Endrin
CAS Numbers: 72-20-8
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.0003 mg/kg/day
Critical Effect: Hepatic lesions and occasional convulsions
Reference: Kettering 1969
Point of Departure: NOAEL of 0.025 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 52
Species: Dog

MRL Summary: A chronic oral MRL of 0.0003 mg/kg/day was derived for endrin based on convulsions and hepatic lesions in dogs exposed to dietary endrin for 2 years (Kettering 1969). The MRL is based on the NOAEL of 0.025 mg/kg/day for neurological and hepatic effects and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: The lowest LOAEL identified in the chronic oral database was 0.05 mg/kg/day in dogs exposed to dietary endrin for 2 years (Kettering 1969). Effects observed at this dose included hepatic vacuolation in female dogs and occasional convulsions in one female dog; hepatic and neurological effects were also observed in males at the next dose (0.1 mg/kg/day). Other reported hepatic and neurological effects following chronic exposure to endrin are reviewed in Table A-10. Observed effects in other systems occurred at doses ≥0.1 mg/kg.

Table A-10. Summary of Candidate Critical Effects for Chronic Oral MRL for Endrin

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Beagle dog	2 years (F)	0.025[a] (females) 0.05 (males)	0.05 (females) 0.10 (males) (serious LOAEL)	Occasional convulsions	Kettering 1969
Beagle dog	64–156 weeks (F)	ND	0.059 (serious LOAEL)	Seizures	Kettering 1971
Beagle dog	16.4–18.7 months 6 days/week (F)	0.12	ND		Treon et al. 1955
Carworth rat	2 years (F)	0.25	1.25 (serious LOAEL)	Diffuse degeneration of the brain	Treon et al. 1955
Osborne-Mendel rat	17.6–20.8 months (F)	ND	0.1 (serious LOAEL)	Convulsions and tremors	Deichmann et al. 1970

Table A-10. Summary of Candidate Critical Effects for Chronic Oral MRL for Endrin

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Osborne-Mendel rat	80 weeks (F)	0.3	ND		NCI 1979
B5C3F1 mouse	80 weeks (F)	ND	0.21 M 0.33 F	Hyperexcitability	NCI 1979
Hepatic effects					
Beagle dog	2 years (F)	0.025[a] (females) 0.05 (males)	0.05 (females) 0.10 (males)	Hepatic cell vacuolation	Kettering 1969
Beagle dog	64–156 weeks (F)	0.059	ND		Kettering 1971
Carworth rat	2 years (F)	0.05	0.25	Increased liver weight	Treon et al. 1955
Osborne-Mendel rat	17.6–20.8 months (F)	ND	0.1	Cloudy swelling of centrilobular cells	Deichmann et al. 1970
Osborne-Mendel rat	80 weeks (F)	0.3	ND		NCI 1979
B6C3F1 mouse	80 weeks (F)	0.42	ND		NCI 1979

[a]Selected POD.

(F) = feed; LOAEL = lowest observed adverse effect level; MRL = minimal risk level; ND = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure

While convulsions only occurred in one of six dogs at 0.05 mg/kg/day, neurological effects were considered co-critical effects (along with hepatic effects) because the central nervous system is the primary target system for endrin, as evidenced by reports of neurologic effects including convulsions and tremors in humans and other animal species (Curley et al. 1970; Deichmann et al. 1970; Kettering 1969; Treon et al. 1955; Waller et al. 1992).

Selection of the Principal Study: The study with the lowest candidate POD (Kettering 1969) was selected as the principal study.

Summary of the Principal Study:

Kettering Laboratory. 1969. Effects exerted upon beagle dogs during a period of two years by the introduction of 1,2,3,4,10,10-hexachloro-6,7- epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo, endo-5,8-dimethanonaphthalene into their daily diets. Cincinnati, OH. Report to Velsicol Chemical Corporation.

Groups of Beagle dogs (3/sex/group) were fed diets containing 0, 0.1, 0.5, 1.0, 2.0, or 4.0 ppm endrin for 2 years. Additional animals (4/sex/group) were included in the 0-, 1.0-, and 4.0-ppm groups for interim sacrifice at 6 or 12 months (2/sex/group at each sacrifice). Using assumed food consumption of 0.32 kg feed/day and body weights of 12.7 kg, estimated daily endrin intake levels were calculated to be 0.0025, 0.125, 0.025, 0.05, and 0.1 mg/kg/day for the 0.1, 0.5, 1.0, 2.0, and 4.0 ppm dose groups, respectively. Dogs were observed daily for clinical signs of toxicity, and body weights were recorded weekly. Blood

was collected for hematological and clinical chemistry evaluation at 2 weeks and 1, 3, 6, 12, 18, and 24 months. Urine was collected for analysis at the same intervals. After 24 months, all females and two males/group were sacrificed (the remaining male/group was retained for a special reproductive study, results of this study not included in this report). The liver, heart, lungs, kidneys, spleen, brain, gonads, pituitary, adrenals, and thyroid were weighed. The authors also microscopically examined these organs, along with the gall bladder, aorta, stomach, duodenum-pylorus, small and large intestines, pancreas, mesenteric lymph nodes, urinary bladder, prostate, uterus, thymus, spinal cord, eyes, bone marrow, bone, skeletal muscle, fat tissue, and skin.

The authors reported no deaths and no exposure-related changes in rate of growth, food consumption, hematology, clinical chemistry, or urinalysis.

Convulsions (or physical evidence of having had a convulsion) were observed in one female and two male dogs at 0.1 mg/kg/day and one female dog at 0.05 mg/kg/day. The study authors indicate that the female from the 0.05 mg/kg/day group convulsed on two successive days after eating at 25 months (this is unclear, since animals were scheduled for sacrifice after 24 months). At 0.1 mg/kg/day, one male showed physical evidence of having had a convulsion after 5 months (not observed at any other time point), a second male dog had several convulsions between 10 and 12 months of feeding (scheduled for interim sacrifice at 12 months), and a female dog "probably" had a convulsion at 12 and 21 months and had multiple observed convulsions at 23 months. Petechial hemorrhages and cerebral edema were observed in the brain of one male dog having convulsions at the time of necropsy.

The study observed hepatic effects at the gross and microscopic levels. There were occasional slight increases in the absolute weight of livers from dogs fed diets containing endrin at 0.05 and 0.1 mg/kg/day, compared with control; however, average weights remained within 10% of control. Relative liver weights at 0.05 and 0.1 mg/kg/day were decreased by 3 and 17% in males, respectively, and increased by 24 and 2% in females, respectively. No other potentially exposure-related organ weight changes were observed. All dogs exposed to 0.1 mg/kg/day endrin showed moderate vacuolar degeneration in the hepatic cells with diffuse brown pigment. One female exposed to 0.05 mg/kg/day also showed vacuolar degeneration and pigmentation, and one male exposed to 0.05 showed brown pigmentation without vacuolar degeneration. Concentrations of 0.05 and 0.1 mg/kg/day endrin were associated with slight to moderate vacuolation of hepatic cells.

Based on hepatic and neurological effects, a NOAEL of 0.025 mg/kg/day and a LOAEL of 0.05 mg/kg/day were identified for this study.

Selection of the Point of Departure: The NOAEL of 0.025 mg/kg/day for neurological and hepatic effects was selected as the POD.

Due to the small number of animals per group (3/sex/group), the data were considered inadequate for BMD modeling. Thus, the NOAEL/LOAEL approach was used to identify the POD.

Uncertainty Factor: The NOAEL is divided by a total uncertainty factor of 100:

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

MRL = NOAEL ÷ uncertainty factors

0.025 mg/kg/day ÷ (10x10) = 0.00025 ≈ 0.0003 mg/kg/day

Other Additional Studies or Pertinent Information: The central nervous system is the primary target system for endrin as evidenced by reports of neurologic effects including convulsions and tremors in humans acutely poisoned with endrin (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Rowley et al. 1987; Waller et al. 1992; Weeks 1967) and various animal species following oral exposure (Chernoff et al. 1979; Deichmann et al. 1970; Kavlock et al. 1981; Kettering 1969; Mehrotra et al. 1989; Treon et al. 1955). Acute neurotoxic effects have also been observed following high occupational exposure (Hoogendam et al. 1962, 1965). Limited animal evidence also reports neurotoxicity following acute inhalation or dermal exposure (Gaines 1960; Pandy 1978; Ressang et al. 1959; Treon et al. 1955).

The liver also appears to be a potential toxicity target of endrin. In laboratory animals, hepatic effects been consistently reported following inhalation, oral, or dermal exposure at or near lethal levels in several species, including increased liver weight, altered liver serum enzymes, diffuse degenerative lesions, necrosis, vacuolation, fatty degeneration, and lipid peroxidation (Ali and Shakoori 1993; Bagchi et al. 1992a, 1992b, 1992c; Hassan et al. 1991; Hassoun et al. 1993; Kavlock et al. 1981; Lawrence et al. 1968, Treon et al. 1955; Young and Mehendale 1986). In low-dose oral chronic studies, hepatic effects were reported at sublethal effects in rats and dogs, including increased liver weight, cloudy swelling of centrilobular cells, and vacuolation (Deichmann et al. 1970; Kettering 1969; Treon et al. 1955).

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ENDRIN

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 endrin.

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 endrin. 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 endrin 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 endrin 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
Other noncancer effects

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

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 draft toxicological profile for endrin released for public comment in 2019; thus, the literature search was restricted to studies published between April 2017 and June 2020. The following main databases were searched in June 2020:

- PubMed
- National Technical Reports Library (NTRL)
- 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 endrin. 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 endrin 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	
06/2020	("Endrin"[mh] OR 72-20-8[rn] OR 7421-93-4[rn] OR 53494-70-5[rn] OR "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,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,5S,6S,7R,8R,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,5S,6,7R,8R,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-endo,endo-1,4 5,8-dimethanonaphthalene"[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 "3,4,5,6,9,9-Hexachloro-1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aR,2R,2aR,3R,6S,6aS,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 "Compound 269"[tw] OR "Endrex"[tw] OR "Endricol"[tw] OR "endrin"[tw] OR "Experimental Insecticide 269"[tw] OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene"[tw] OR "Hexadrin"[tw] OR "Mendrin"[tw] OR "Nendrin"[tw] OR "Oktanex"[tw] OR "SD 3419"[tw] OR "Stardrin"[tw] OR "1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-"[tw] OR "SD 7442"[tw] OR "delta-Keto 153"[tw] OR "delta-Ketoendrin"[tw] OR "SD 2614"[tw] OR "(2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one"[tw] OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one"[tw]) AND (2017/04/01:3000[mhda] OR 2017/04/01:3000[crdt] OR 2017/04/01:3000[edat] OR 2016/04/01:3000[dp]) "Compd. 269"[tw] OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene"[tw] OR "(1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde"[tw] OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,7.beta.,7a.alpha.)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octa-hydro-2,7 3,6-Dimethanonaphth[2,3-b]oxirene"[tw] OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,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 "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,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 "(1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde"[tw] OR "(1aR,2R,2aR,3R,6S,6aS,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

Table B-2. Database Query Strings

Database search date	Query string
	"(1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-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 "(2.alpha.,3a.beta., 3b.beta., 4.beta., 5.beta., 6a.beta., 7.alpha., 7a.beta., 8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one"[tw] OR "(2.alpha.,3a.beta., 3b.beta.,4.beta.,5.beta.,6a.beta.,7.alpha.,7a.beta.,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one"[tw] OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene"[tw] OR "1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-"[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,endo-"[tw] OR "2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-"[tw] OR "2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-"[tw] OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2.alpha.,3a.beta., 3b.beta., 4.beta., 5.beta., 6a.beta., 7.alpha., 7a.beta., 8R)"[tw] OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2.alpha.,3a.beta., 3b.beta.,4.beta.,5.beta.,6a.beta.,7.alpha.,7a.beta.,8R)"[tw] OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-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.beta.,3.alpha.,6.alpha.,6a.beta.,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,2abeta,3alpha,6alpha,6abeta,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,2aR,3R,6S,6aS,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-octa-hydro-, (1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,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,2aR,3R,6S,6aS,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-, (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-"[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,[1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.]"[tw] OR "endo,endo-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]
NTRL	
06/2020	"(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,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,5S,6S,7R,8R,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,5S,6,7R,8R,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-endo,endo-1,4 5,8-dimethanonaphthalene" 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 "3,4,5,6,9,9-Hexachloro-1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR,2R,2aR,3R,6S,6aS,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

Table B-2. Database Query Strings

Database search date	Query string
	"Compound 269" OR "Endrex" OR "Endricol" OR "endrin" OR "Experimental Insecticide 269" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene" OR "Hexadrin" OR "Mendrin" OR "Nendrin" OR "Oktanex" OR "SD 3419" OR "Stardrin" OR "Endrin aldehyde" OR "Endrin ketone" "Compd. 269" OR "delta-Keto 153" OR "delta-Ketoendrin" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene" OR "SD 2614" OR "SD 7442" OR "(1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde" OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,7.beta.,7a.alpha.)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octa-hydro-2,7 3,6-Dimethanonaphth[2,3-b]oxirene" OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,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 "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,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" "(1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde" OR "(1aR,2R,2aR,3R,6S,6aS,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 "(1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-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 "(2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one" OR "(2.alpha.,3a.beta., 3b.beta., 4.beta., 5.beta., 6a.beta., 7.alpha., 7a.beta., 8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one" OR "(2.alpha.,3a.beta., 3b.beta.,4.beta.,5.beta.,6a.beta.,7.alpha.,7a.beta.,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one" OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one" "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene" OR "1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-" OR "1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-" 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,endo-" OR "2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-" "2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-" OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2.alpha.,3a.beta., 3b.beta., 4.beta., 5.beta., 6a.beta., 7.alpha., 7a.beta., 8R)" OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2.alpha.,3a.beta., 3b.beta.,4.beta.,5.beta.,6a.beta.,7.alpha.,7a.beta.,8R)" OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-,

Table B-2. Database Query Strings

Database search date	Query string
	(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-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.beta.,3.alpha.,6.alpha.,6a.beta.,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,2abeta,3alpha,6alpha,6abeta,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,2aR,3R,6S,6aS,7S,7aS)-rel-" "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.beta.,3.alpha.,6.alpha., 6a.beta.,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,2aR,3R,6S,6aS,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-, (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-" 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,[1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.]" OR "endo,endo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4 5,8-Dimethanonaphthalene"
Toxcenter	
06/2020	FILE 'TOXCENTER' ENTERED AT 18:13:03 ON 14 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 7788 SEA FILE=TOXCENTER 72-20-8 OR 7421-93-4 OR 53494-70-5 L2 7648 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 532 SEA FILE=TOXCENTER L2 AND ED>=2016 ACT TOXQUERY/Q --------- L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR L7 OR 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
	L30 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?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L32 QUE L29 OR L30 OR L31
	L33 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L34 QUE L32 OR L33

	L35 275 SEA FILE=TOXCENTER L3 AND L34
	L36 0 SEA FILE=TOXCENTER L35 AND MEDLINE/SB
	L37 3 SEA FILE=TOXCENTER L35 AND MEDLINE/FS
	L38 266 DUP REM L35 (9 DUPLICATES REMOVED)
	ANSWERS '1-266' FROM FILE TOXCENTER
	D SCAN L38

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2020	Compounds searched: 72-20-8; 7421-93-4; 53494-70-5
NTP	
06/2020	72-20-8 7421-93-4 53494-70-5 "Compound 269" "Endrex" "Endricol" "endrin" "Experimental Insecticide 269" "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene" "Hexadrin" "Mendrin" "Nendrin" "Oktanex" "SD 3419" "Stardrin" "Compd. 269" "delta-Keto 153" "delta-Ketoendrin" "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene" "SD 2614" "SD 7442"
Regulations.gov	
06/2020	Compounds searched: 72-20-8; 7421-93-4; 53494-70-5
NIH RePORTER	
08/2020	Text Search: "Compound 269" OR "Endrex" OR "Endricol" OR "endrin" OR "Experimental Insecticide 269" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene" OR "Hexadrin" OR "Mendrin" OR "Nendrin" OR "Oktanex" OR "SD 3419" OR "Stardrin" OR "1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-" OR "SD 7442" OR "delta-Keto 153" OR "delta-Ketoendrin" OR "SD 2614" OR "(2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one" OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,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,5S,6S,7R,8R,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,5S,6,7R,8R,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-endo,endo-1,4 5,8-dimethanonaphthalene" 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 "3,4,5,6,9,9-Hexachloro-1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR,2R,2aR,3R,6S,6aS,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" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "Compd. 269" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene" OR "(1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta[cd]pentalene-5-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	carboxaldehyde" OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,7.beta.,7a.alpha.)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octa-hydro-2,7 3,6-Dimethanonaphth[2,3-b]oxirene" OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,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 "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,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 "(1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde" OR "(1aR,2R,2aR,3R,6S,6aS,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 "(1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-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 "(2.alpha.,3a.beta., 3b.beta., 4.beta., 5.beta., 6a.beta., 7.alpha., 7a.beta., 8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one" OR "(2.alpha.,3a.beta., 3b.beta.,4.beta.,5.beta.,6a.beta.,7.alpha.,7a.beta.,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one" OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene" OR "1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "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,endo-" OR "2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-" OR "2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-" OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2.alpha.,3a.beta., 3b.beta., 4.beta., 5.beta., 6a.beta., 7.alpha., 7a.beta., 8R)" OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2.alpha.,3a.beta., 3b.beta.,4.beta.,5.beta.,6a.beta.,7.alpha.,7a.beta.,8R)" OR "2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b,4,5,6,6,6a-hexachlorodecahydro-, (2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-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.beta.,3.alpha.,6.alpha.,6a.beta.,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,2abeta,3alpha,6alpha,6abeta,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,2aR,3R,6S,6aS,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-octa-hydro-, (1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,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,2aR,3R,6S,6aS,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-, (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-" OR "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-[2,7 3,6-dimethanonaphth[2,3-b]oxirene,[1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.]" OR "endo,endo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4 5,8-Dimethanonaphthalene" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 320
- Number of records identified from other strategies: 13
- Total number of records to undergo literature screening: 333

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on endrin:

- 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.

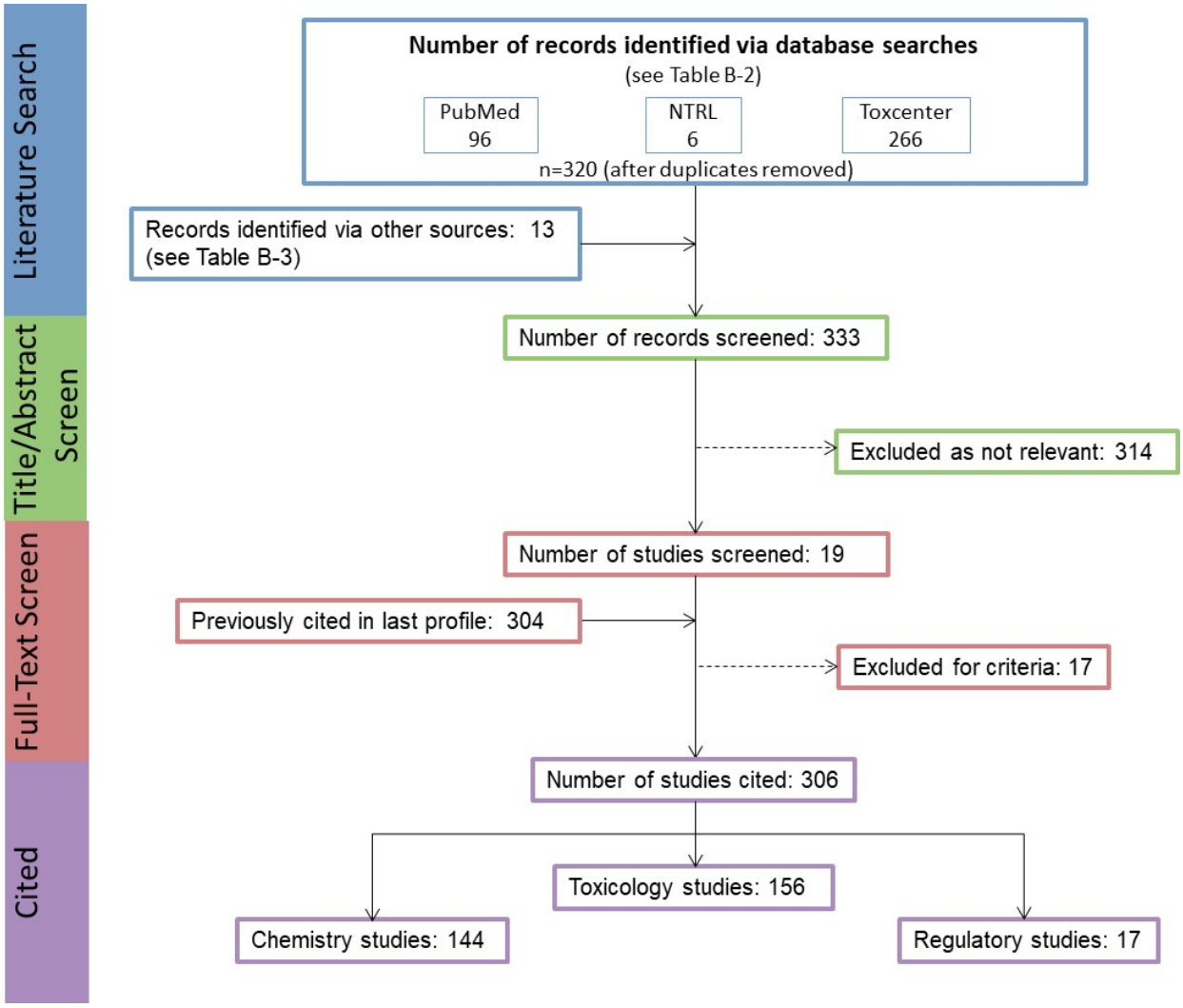
- Number of titles and abstracts screened: 333
- Number of studies considered relevant and moved to the next step: 17

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: 17
- Number of studies cited in the pre-public draft of the toxicological profile: 304
- Total number of studies cited in the profile: 306

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. June 2020 Literature Search Results and Screen for Endrin



APPENDIX C. 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 C-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), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), 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 C-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.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

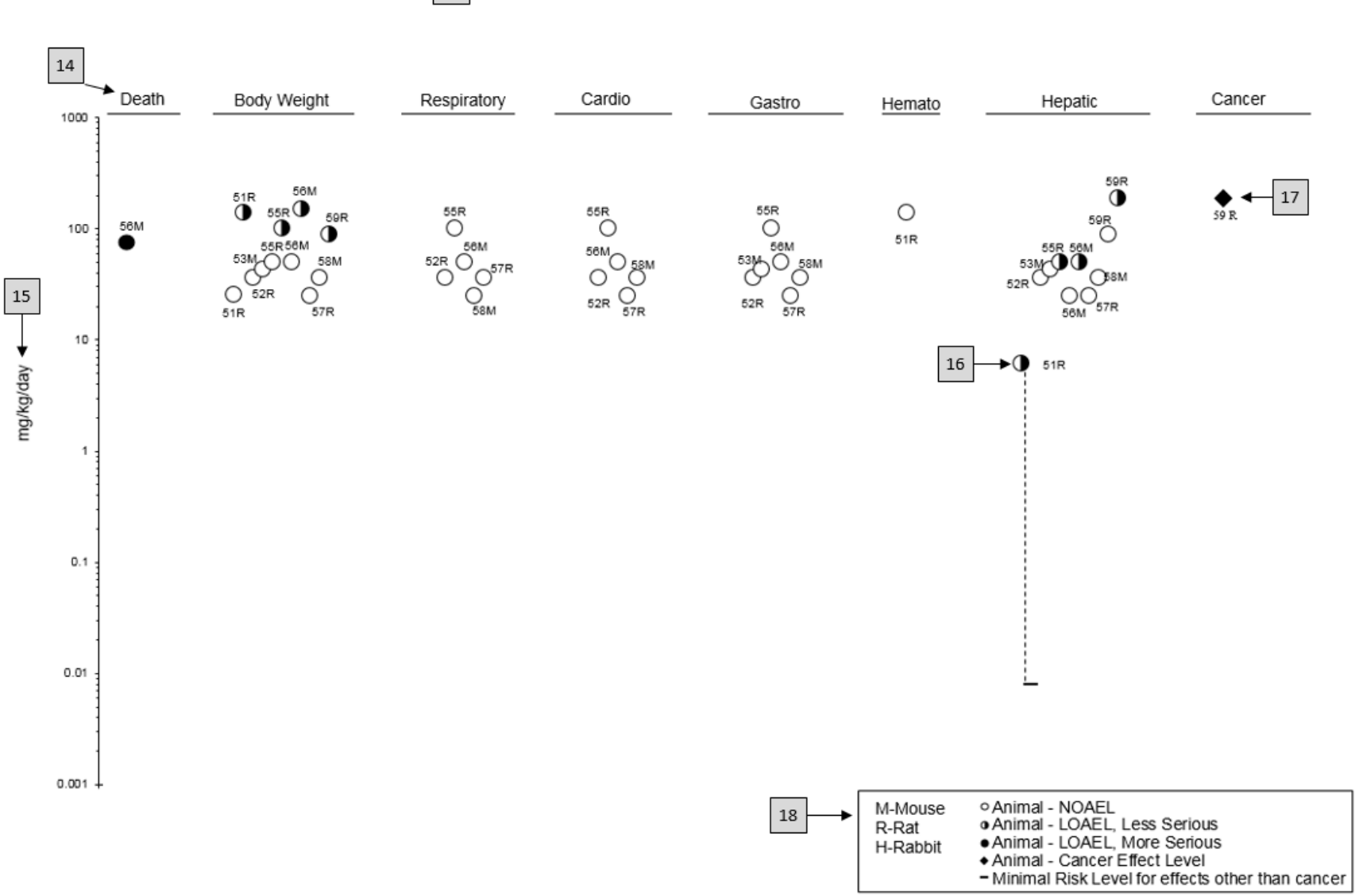
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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 D. 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.

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

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).

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/.

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 E. 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 F. 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