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.

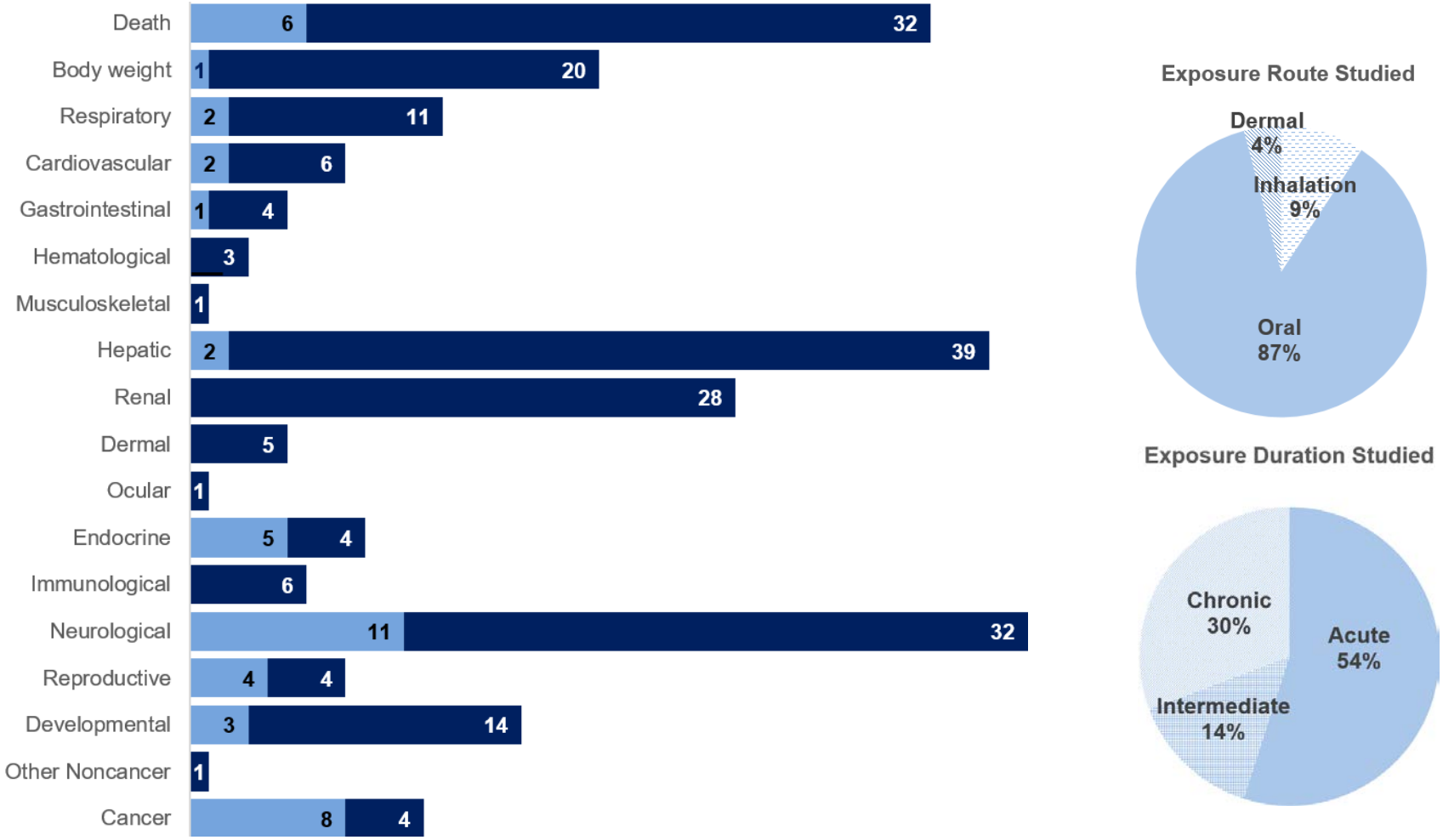
- **Cardiac and respiratory effects:** Limited data from human studies do not indicate that the cardiac and respiratory systems are sensitive targets of endrin toxicity. A few oral animal studies reported cardiac and respiratory effects; however, these effects were generally nonspecific (e.g., increased 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)

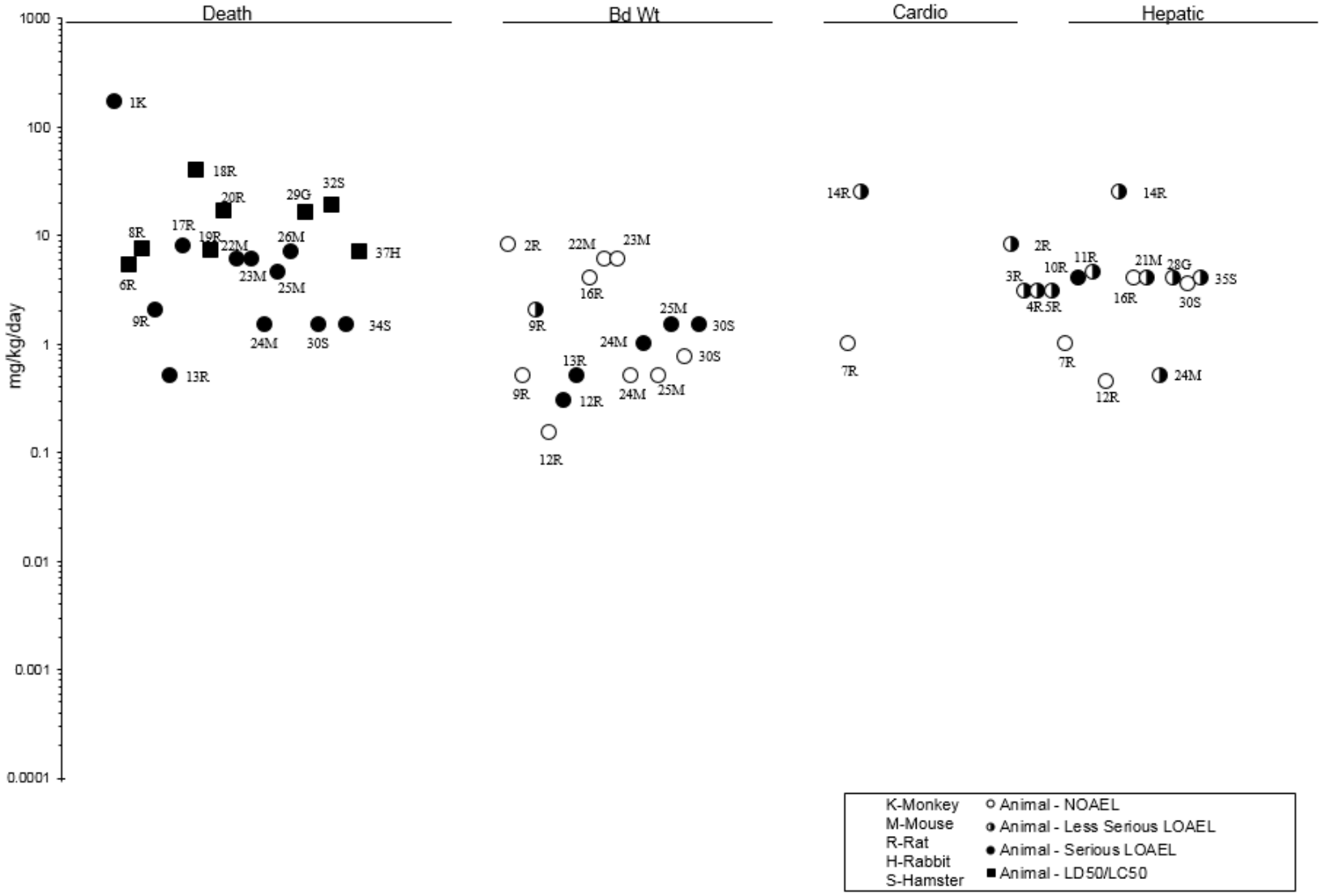


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Acute (≤14 days)

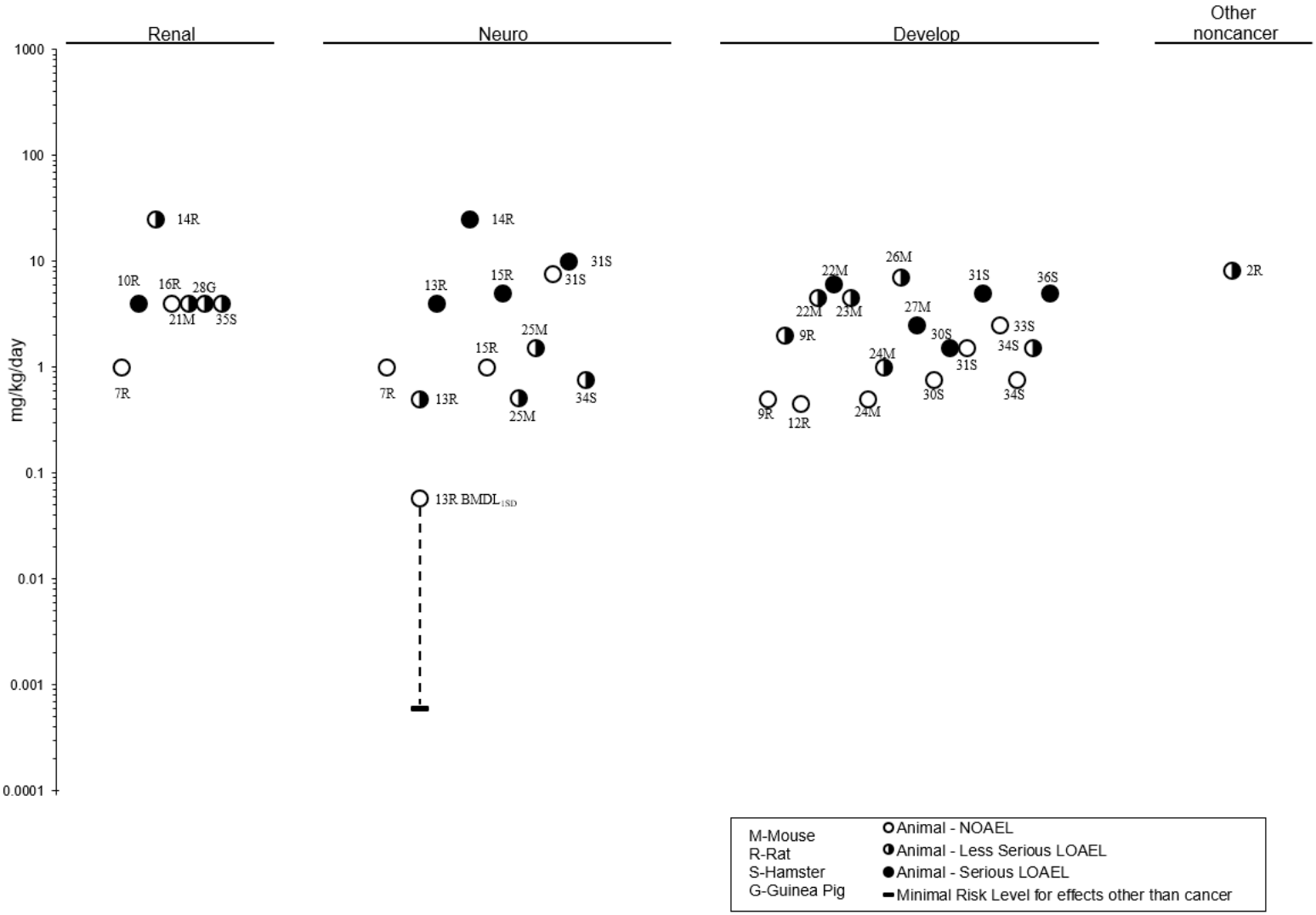


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Intermediate (15-364 days)

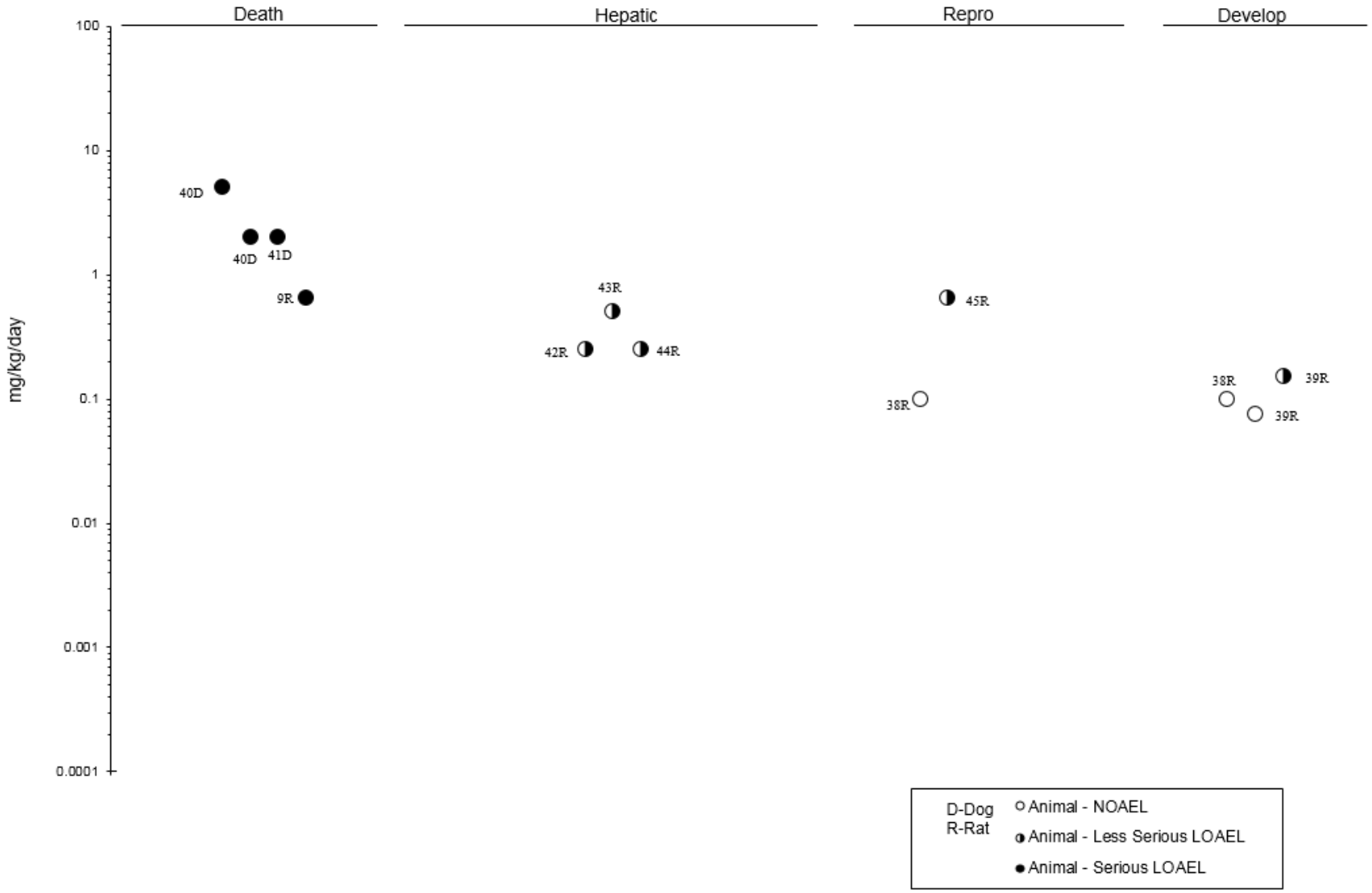


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Chronic (≥365 days)

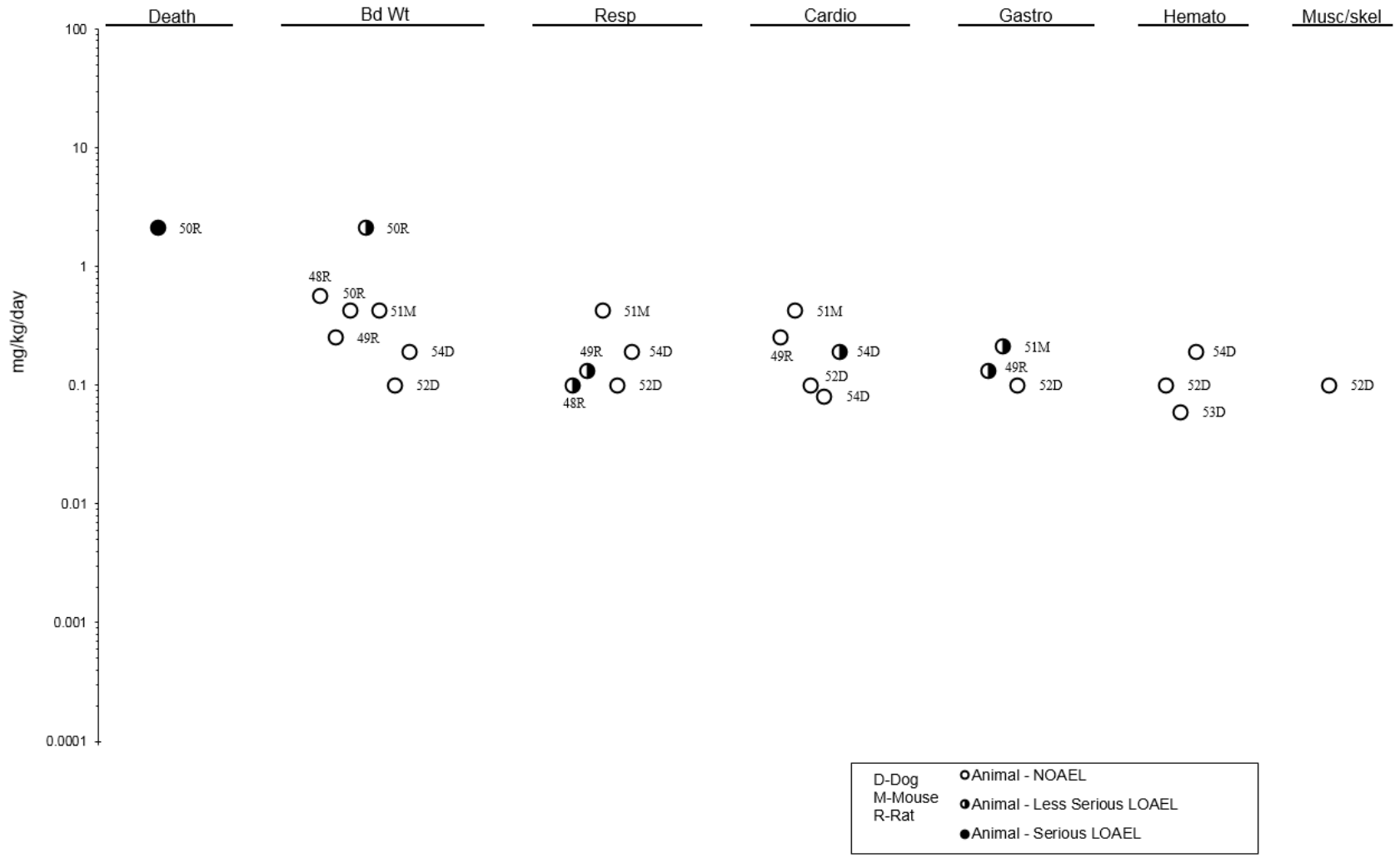


Figure 2-3. Levels of Significant Exposure to Endrin/Endrin Aldehyde/Endrin Ketone – Oral
Chronic (≥365 days)

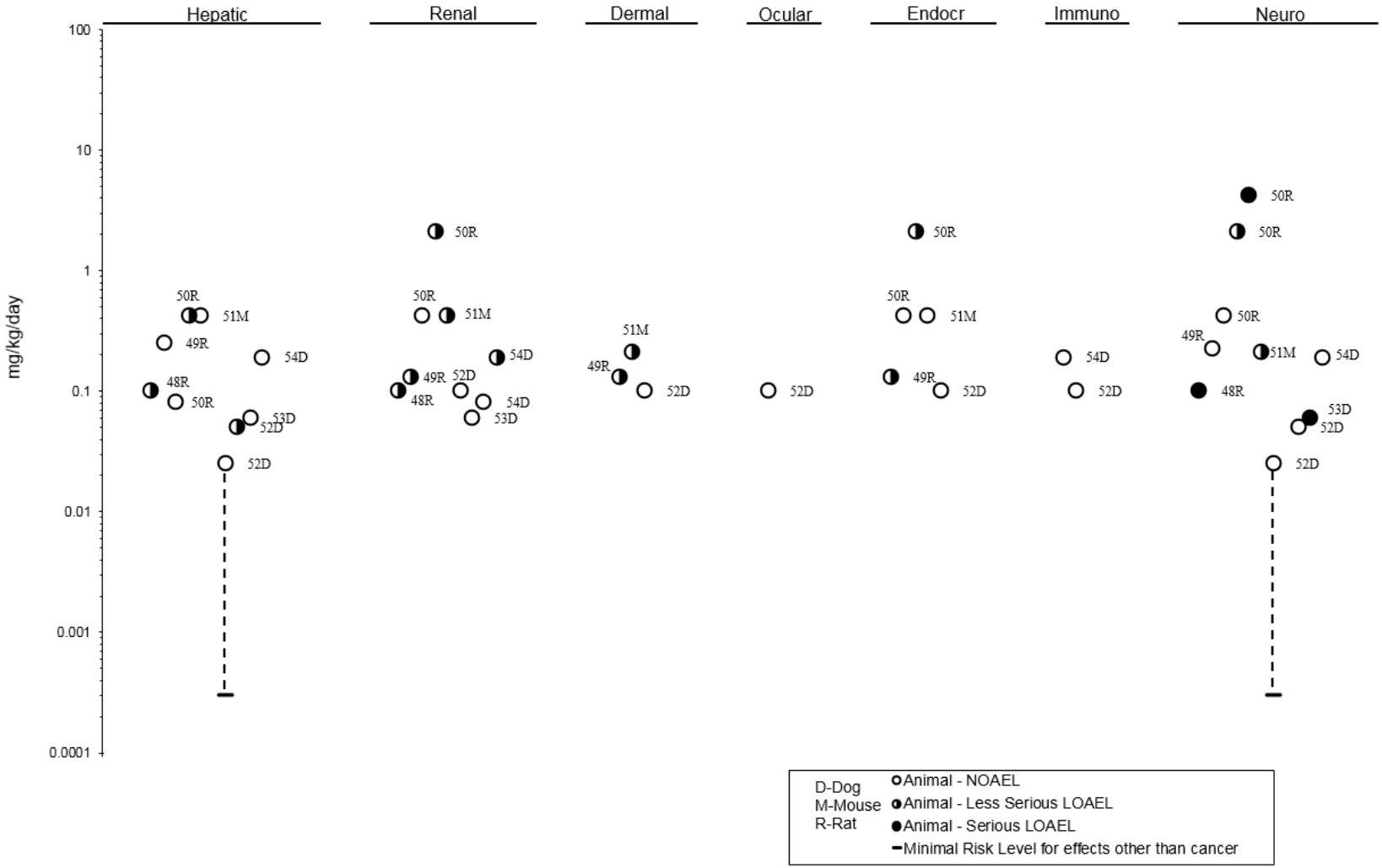


Table 2-4. Levels of Significant Exposure to Endrin – Dermal

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.