2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of endrin, endrin ketone and endrin aldehydex. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

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

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

2.2.1 Inhalation Exposure

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

2.2.1.1 Death

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

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

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

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

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

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

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

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

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

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

Acute (≤14 days)

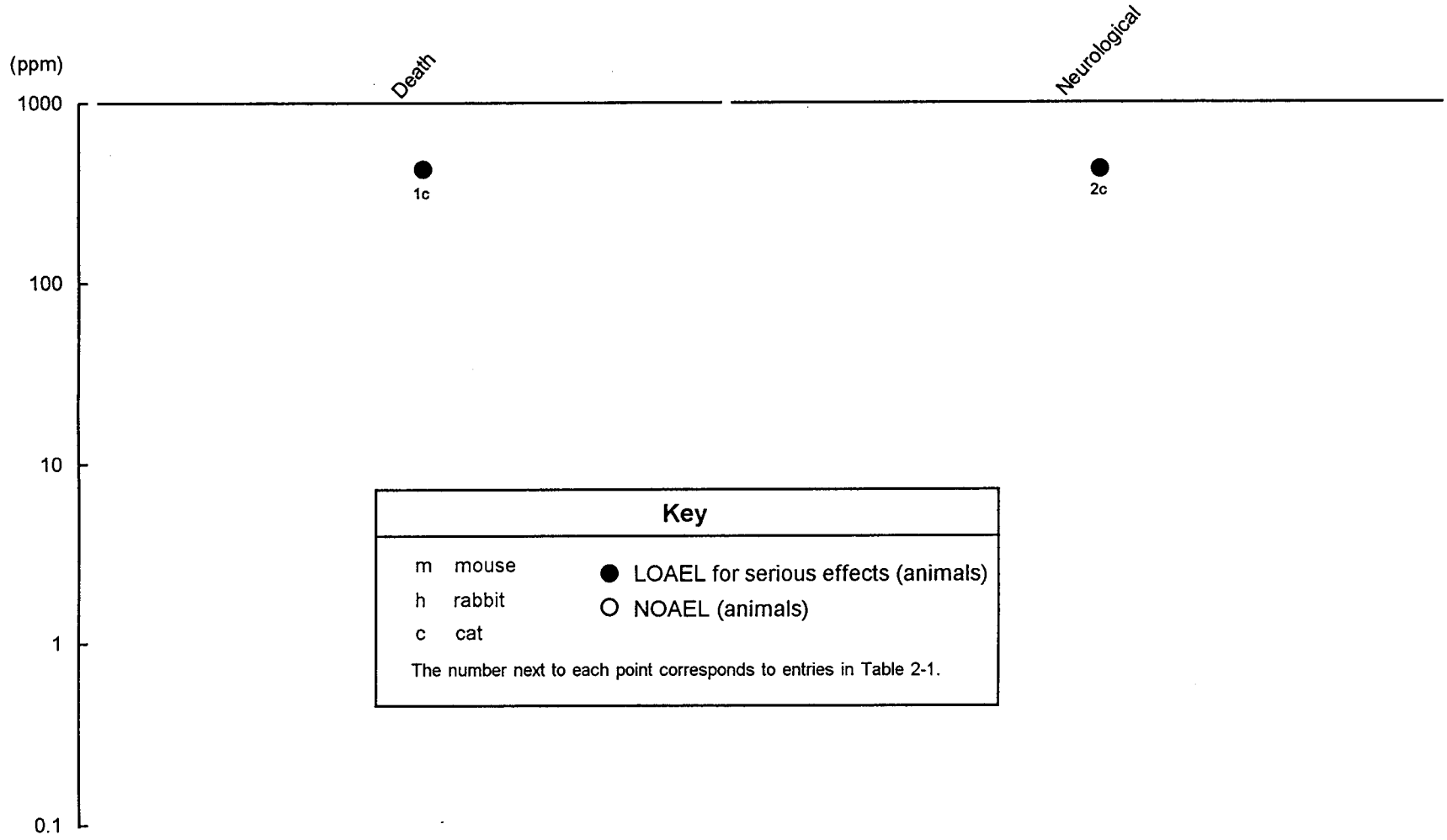
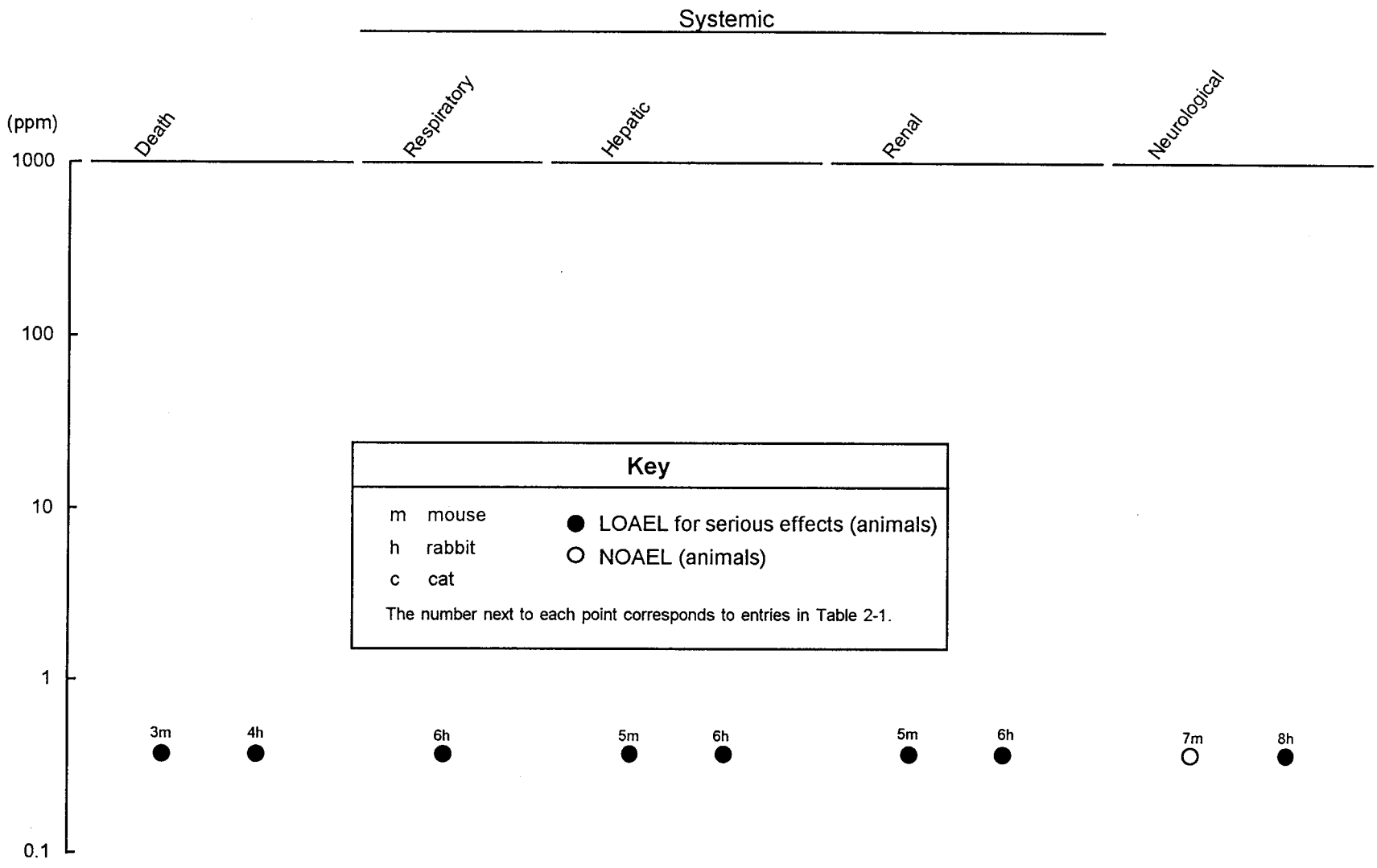


Figure 2-1. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Inhalation (cont.)

Intermediate (15-364 days)



2.2.1.2 Systemic Effects

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

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

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

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

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

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

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

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

2.2.1.3 Immunological and Lymphoreticular Effects

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

2.2.1.4 Neurological Effects

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

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

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

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

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

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

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

2.2.2 Oral Exposure

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

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

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

2.2.2.1 Death

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

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

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

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

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

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

2.2.2.2 Systemic Effects

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Acute (≤14 days)

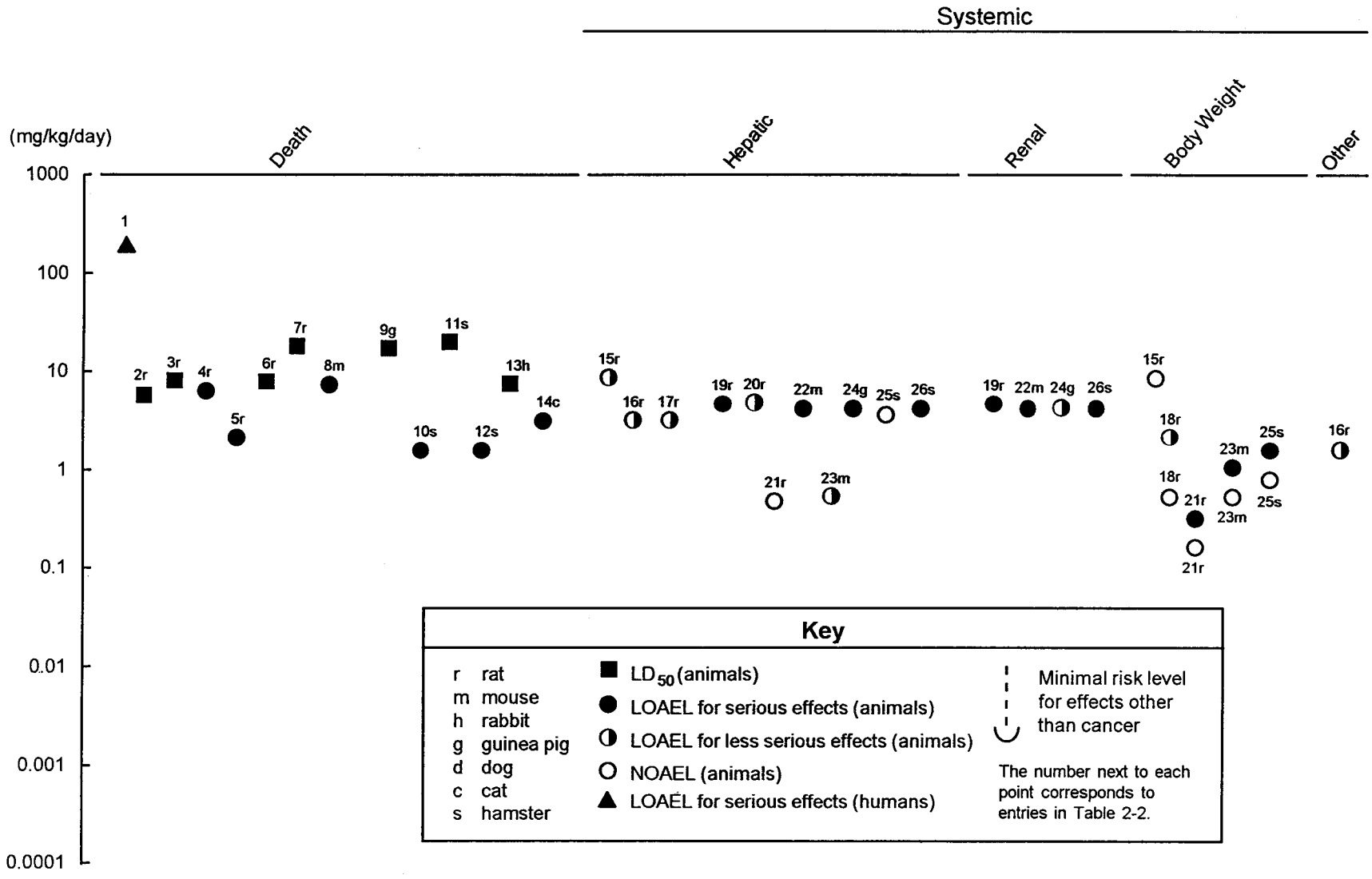


Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continued)

Acute (≤14 days)

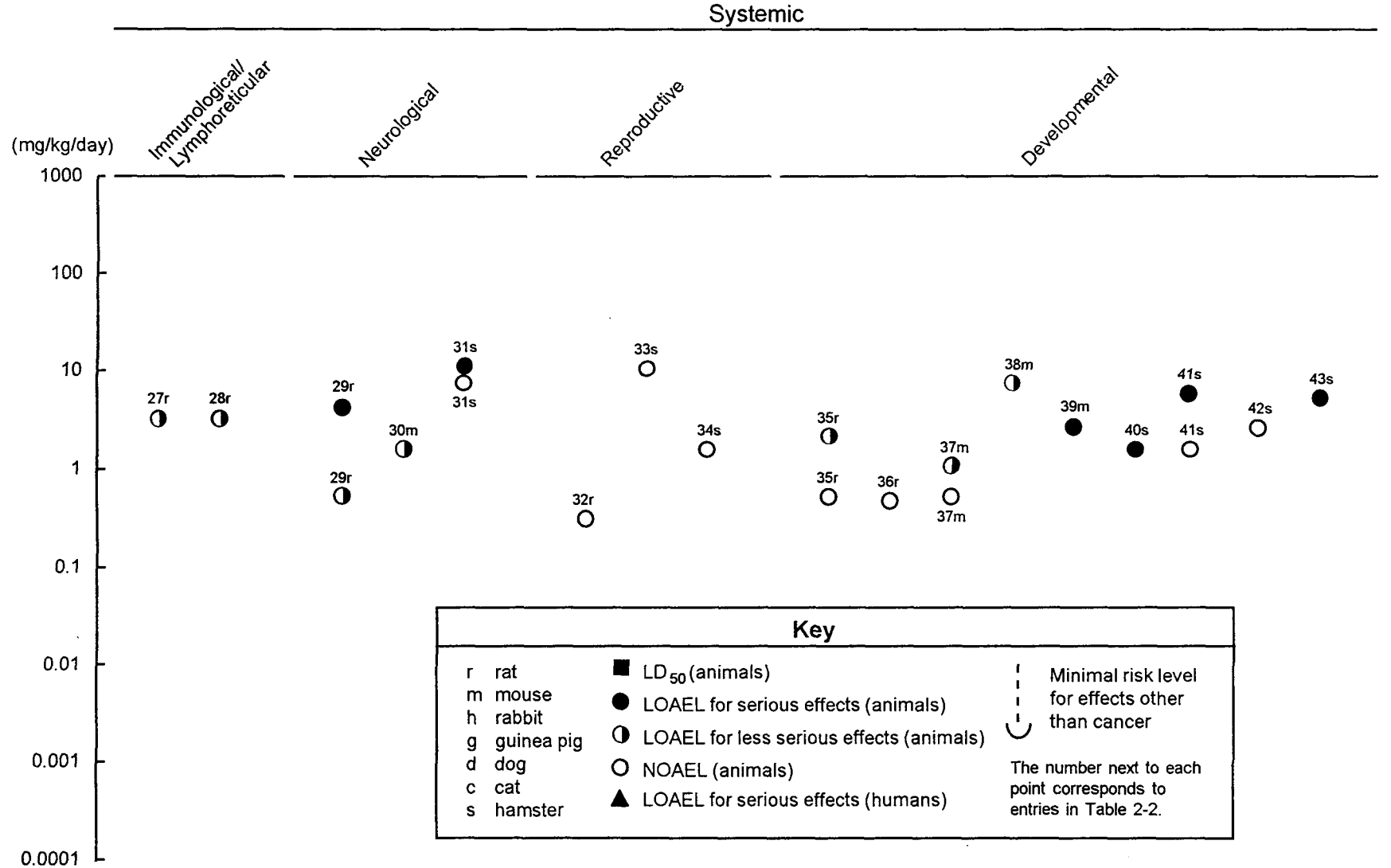


Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continued)

Intermediate (15-364 days)

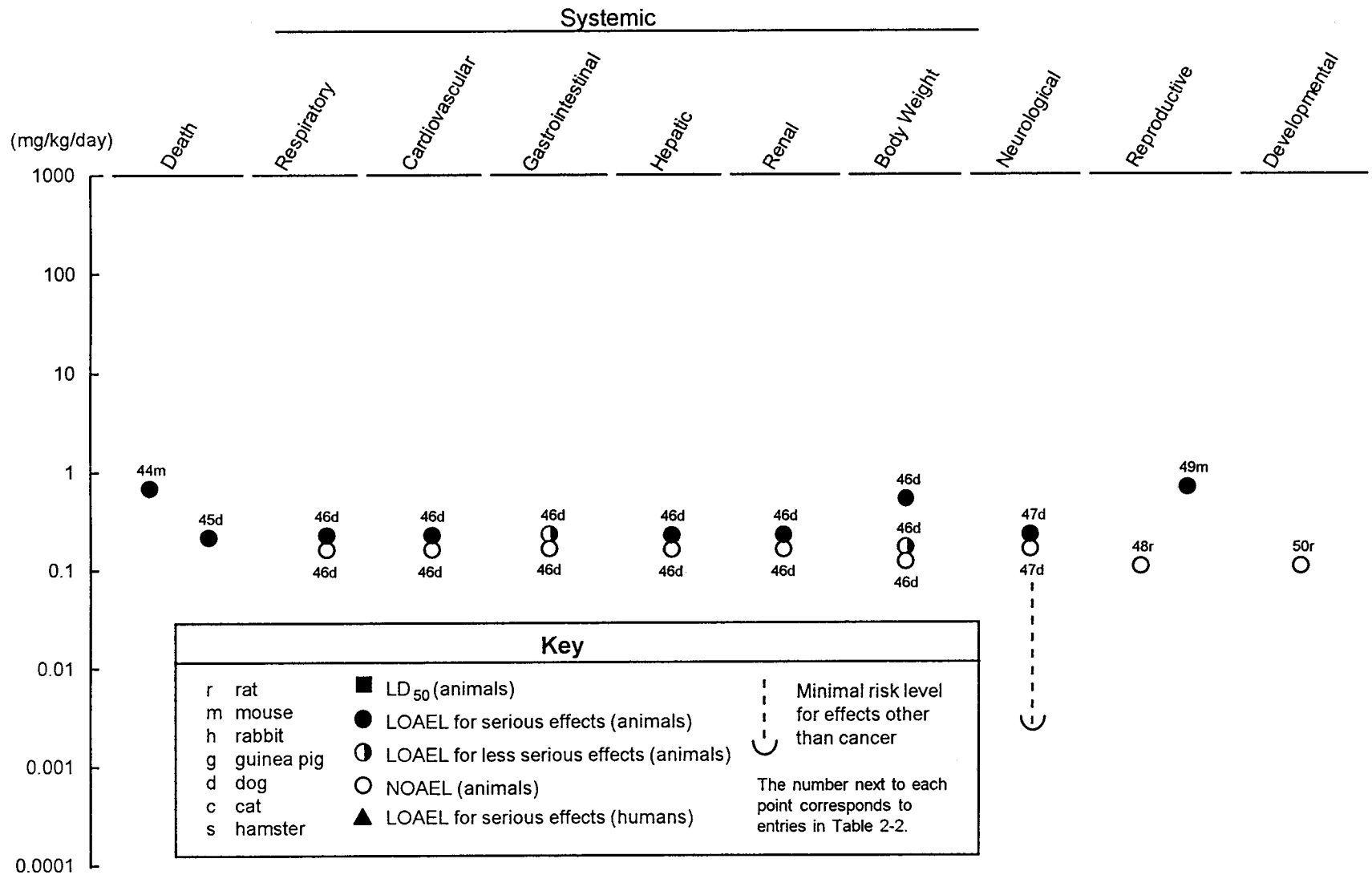
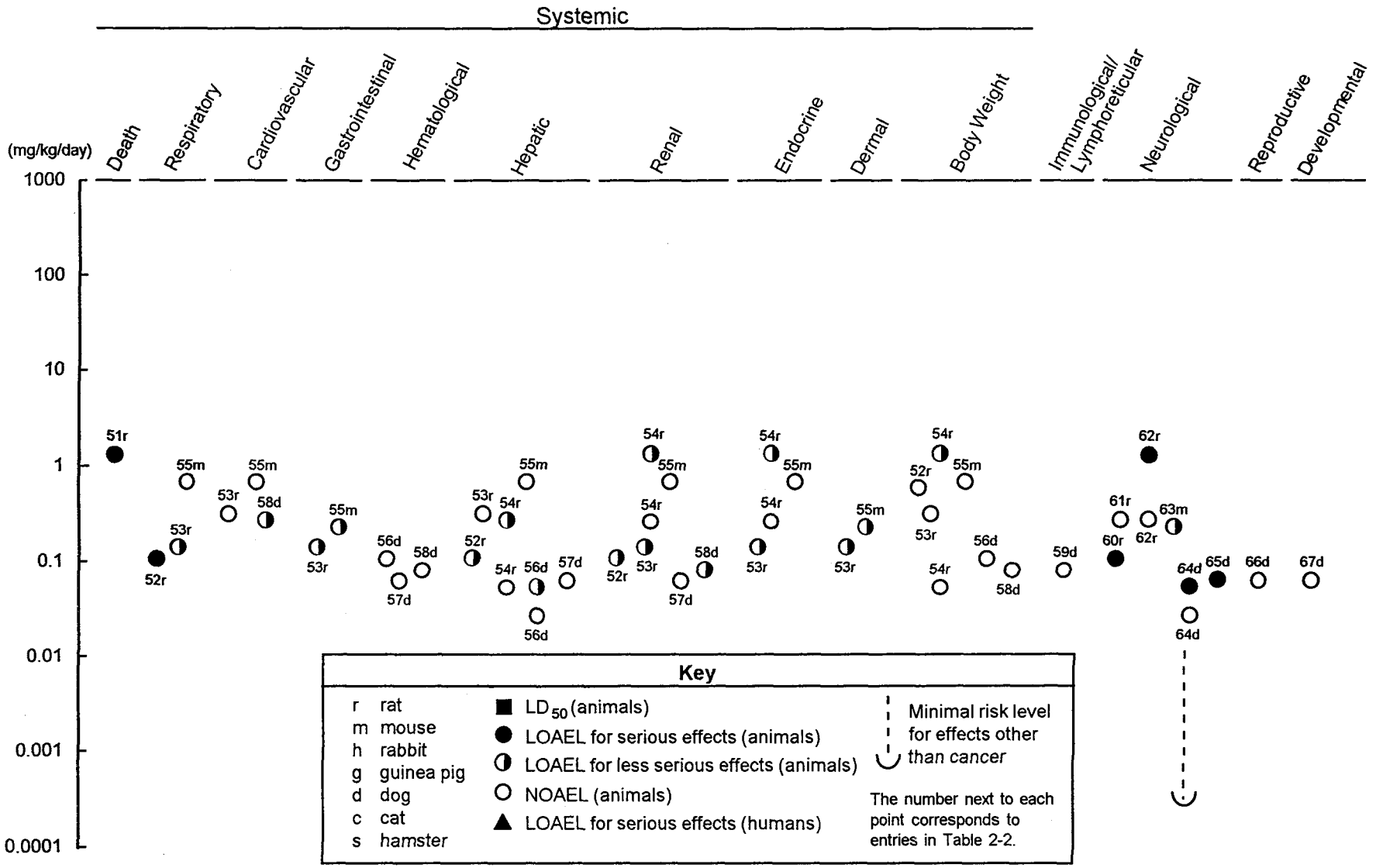


Figure 2-2. Levels of Significant Exposure to Endrin/Endrin Aldehyde - Oral (continued)

Chronic (≥365 days)



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2.2.3 Immunological and Lymphoreticular Effects

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

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

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

2.2.2.4 Neurological Effects

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

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

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

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

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

2.2.2.5 Reproductive Effects

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

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

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

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

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

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

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

2.2.2.6 Developmental Effects

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

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

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

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

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

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

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

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

2.2.2.7 Genotoxic Effects

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

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

2.2.2.8 Cancer

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

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

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

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

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

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

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

2.2.3 Dermal Exposure

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

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

2.2.3.1 Death

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

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

2.2.3.2 Systemic Effects

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

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

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

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

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

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL			Reference Chemical Form
				Less Serious (mg/kg)		Serious (mg/kg)	
INTERMEDIATE EXPOSURE							
Death							
Rabbit (NS)	25-45x total, 5 d/wk 2 hr/d					27-44 F (1/4 rabbit died)	Treon et al. 1955 Endrin
Rabbit (NS)	19-70 x total, 5 d/wk 2 hr/d					20-42 F (1/3 rabbits died)	Treon et al. 1955 Endrin
Systemic							
Rabbit (NS)	19-70 x total, 5 d/wk 2 hr/d	Hepatic				20-42 F (fatty degeneration)	Treon et al. 1955 Endrin
		Renal				20-42 F (degenerative changes)	
		Dermal	67-91 F				
Neurological							
Rabbit (NS)	19-70 x total, 5 d/wk 2 hr/d					20-42 F (convulsions, tremors, twitching of facial muscles, brain necrosis)	Treon et al. 1955 Endrin

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

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

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

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

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

2.2.3.3 Immunological and Lymphoreticular Effects

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

2.2.3.4 Neurological Effects

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

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

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

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

2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

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

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

2.3 TOXICOKINETICS

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

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

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

2.3.1.2 Oral Exposure

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

2.3.1.3 Dermal Exposure

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

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

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

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

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

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

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

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

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

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

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

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

2.3.2.3 Dermal Exposure

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

2.3.3 Metabolism

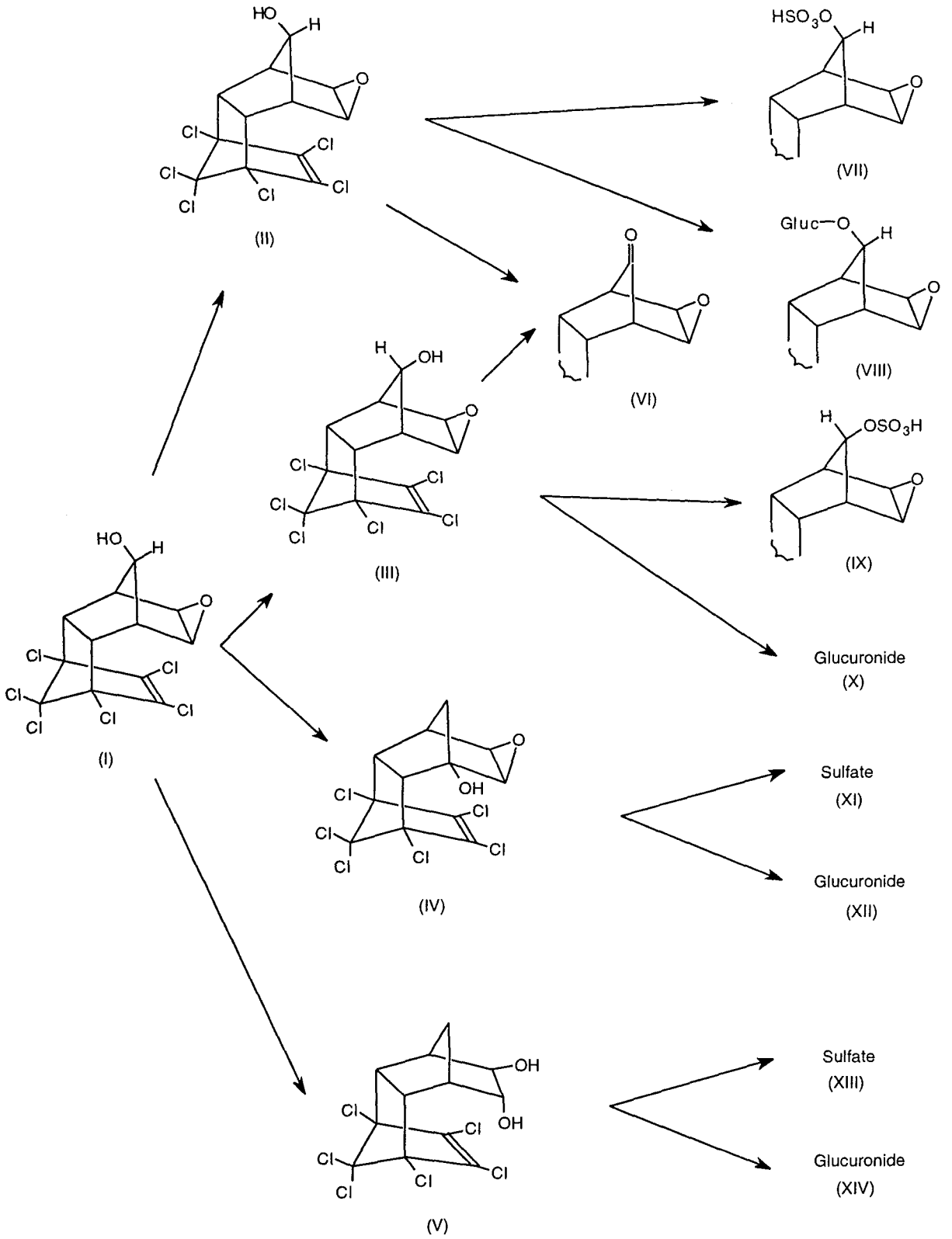
The metabolism of endrin varies among species, regardless of the route of exposure. In all species, oxidation of the methylene bridge in endrin (Compound I in Figure 2-3) to syn-, but mostly anti-12-hydroxyendrin occurs (Compounds II and III), followed by dehydrogenation to 12-ketoendrin (Compound VI).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

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

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

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

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



2.3.4 Excretion

2.3.4.1 Inhalation Exposure

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

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

2.3.4.2 Oral Exposure

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

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

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

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

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

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

2.3.4.3 Dermal Exposure

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

2.4 MECHANISMS OF ACTION

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

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

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

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

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

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

2.5 RELEVANCE TO PUBLIC HEALTH

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

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

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

Minimum Risk Levels for Endrin.

Inhalation MRLs

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

Oral MRLs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

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

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction, such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance-specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by endrin are discussed in Section 2.6.2.

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

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Endrin

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

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

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

2.6.2 Biomarkers Used to Characterize Effects Caused by Endrin

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

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

2.7 INTERACTIONS WITH OTHER CHEMICALS

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

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

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to endrin. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to it. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

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

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

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

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

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

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

2.9.2 Reducing Body Burden

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

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

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

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

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

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

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

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

2.10 ADEQUACY OF THE DATABASE

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

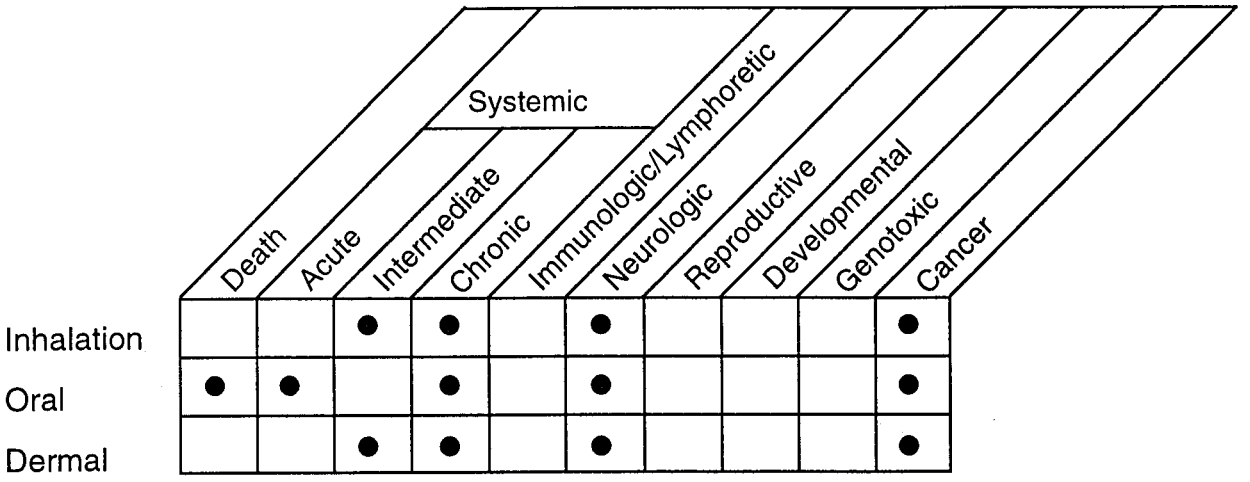
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.10.1 Existing Information on Health Effects of Endrin

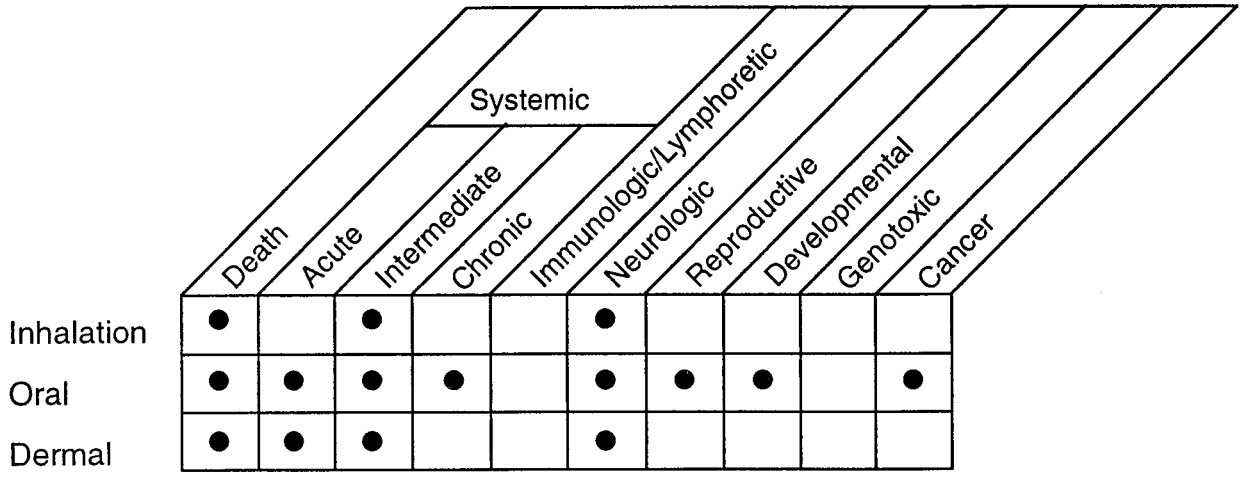
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to endrin are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of endrin. Each dot in the figure indicates that one or more studies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

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

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



Human



Animal

● Existing Studies

2.10.2 Identification of Data Needs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Biomarkers of Exposure and Effect.

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

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

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

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

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

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

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

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

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

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

2.10.3 Ongoing Studies

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

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

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