CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

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

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

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are

those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) are indicated in Table 2-1 and Figure 2-3 for aldrin and Table 2-2 and Figure 2-4 for dieldrin.

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

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

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

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

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

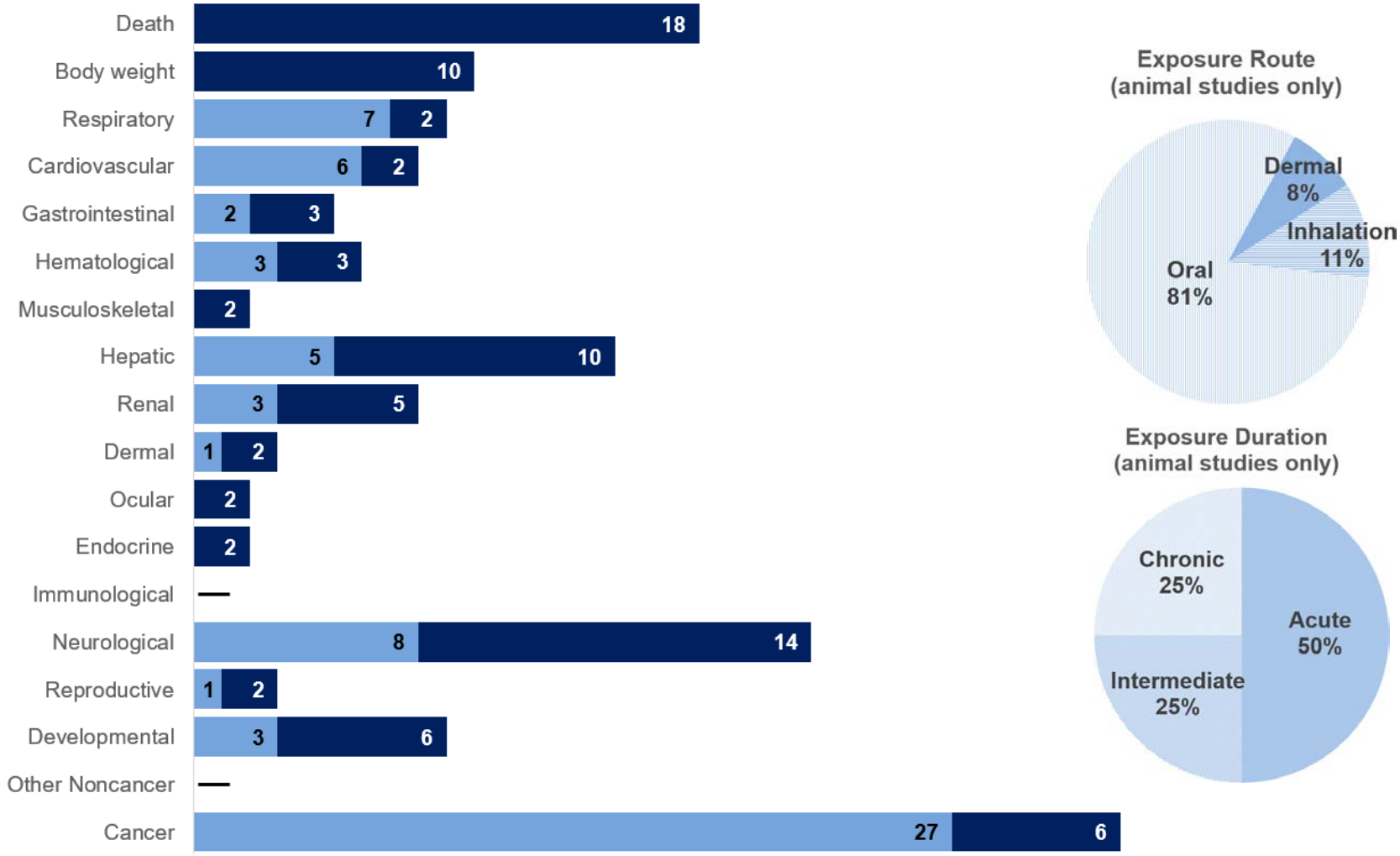
- **Reproductive effects.** Reproductive effects represent a presumed health effect endpoint for humans. Effects such as decreased fertility, delayed estrus, reduced libido, lack of mammary function and development, and increased numbers of stillbirths were reported in animal studies that employed oral exposure to aldrin or dieldrin.

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

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

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

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

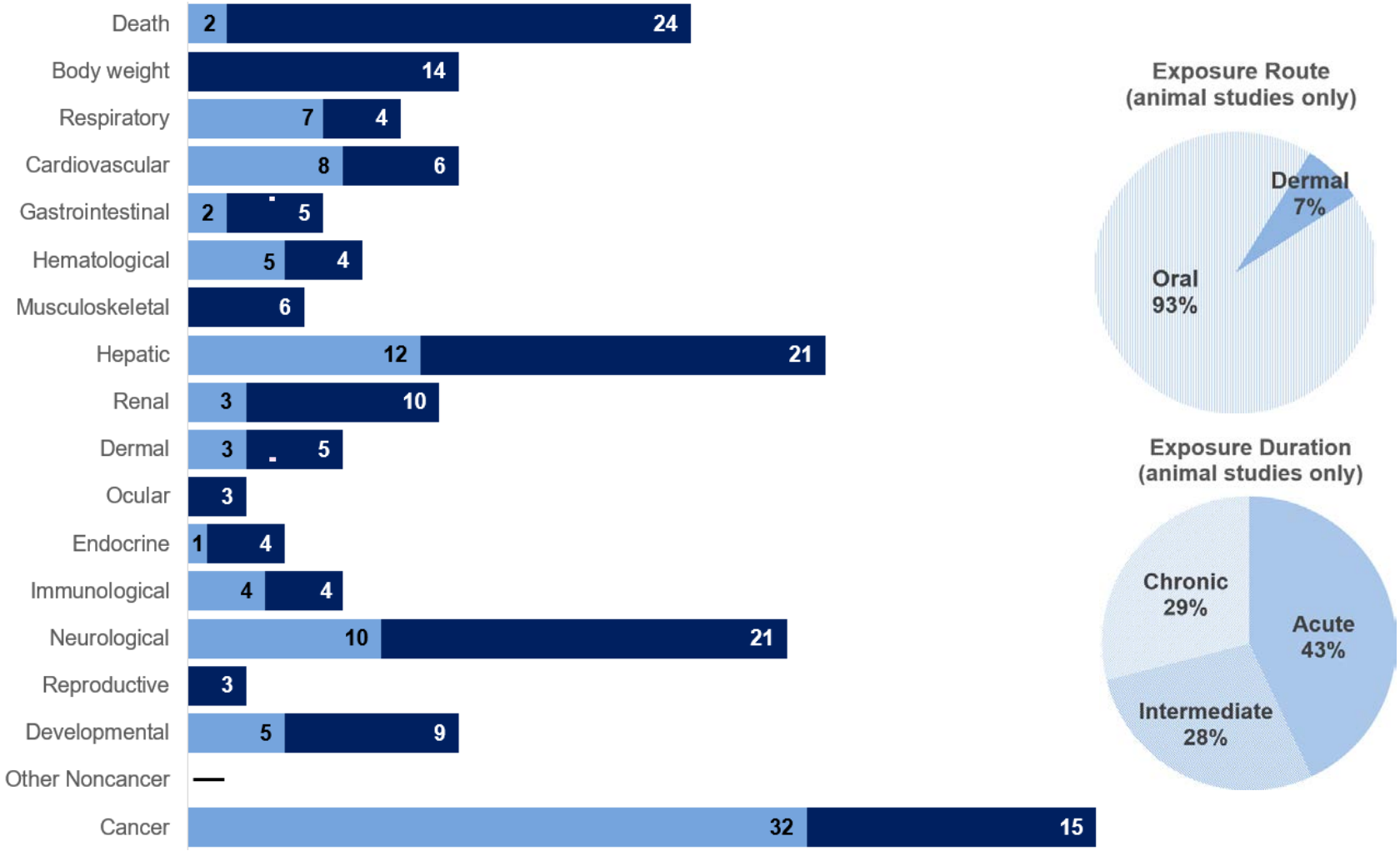


*Includes studies discussed in Chapter 2. A total of 148 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints. Exposure route and duration charts do not include human studies which likely involved multiple exposure routes of unspecified durations.

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

Most studies examined the potential hepatic and neurological effects of dieldrin

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



*Includes studies discussed in Chapter 2. A total of 247 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints. Exposure route and duration charts do not include human studies which likely involved multiple exposure routes of unspecified durations.

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

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

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
7	Rat (Sprague-Dawley) 4 M	3 days 1 time/day (GO)	0, 1, 5, 10	BI, CS	Neuro			10	Tremors, convulsions
Mehrotra et al. 1989 (grade and purity not specified)									
8	Rat (Carworth) 10 M, 10 F	Up to 2 weeks (F)	0, 55	CS, GN, HP, LE	Death			55	100% mortality
					Hepatic			55	Severe liver damage
					Neuro			55	Convulsions, degenerative brain lesions
Treon et al. 1951a (recrystallized 99% purity; technical grade 95% purity)									
9	Rat (Carworth) 10 F	Once (GO)	NS	CS, LE	Death			48.3	LD_{50}
Treon et al. 1952 (≥95% purity)									
10	Mouse (ICR/Ha Swiss) 7 F	Third trimester of pregnancy 1 time/day (GO)	0, 2, 4	BW, CS	Develop		2[b]		Depressed pup body weight, increased electroshock seizure threshold
Al-Hachim 1971 (technical grade; purity not specified)									
11	Mouse (CD1) 9–10 F	GD 9 (GO)	0, 25	CS, DX, TG	Develop			25	Webbed feet
Ottolenghi et al. 1974 (recrystallized; ≥99% purity)									
12	Hamster NS F	Once GD 7, 8, or 9 (GO)	0, 50	CS, DX, TG	Develop			50	Up to 38% fetal mortality; 19% depressed fetal weight; increased incidences of webbed foot, cleft palate, cleft lip
Ottolenghi et al. 1974 (recrystallized; ≥99% purity)									
INTERMEDIATE EXPOSURE									
13	Rat (Osborne-Mendel) 5 M, 5 F	6 weeks (F)	M: 0, 3.5, 7, 14, 28 F: 0, 3.8, 7.6, 15, 30.2	BW, LE	Death			28 M 30.2 F	3/5 males died; 5/5 females died

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NCI 1978a (technical grade >85% purity)									
14	Rat (Carworth) 10 M, 10 F	6 months (F)	0, 0.26, 0.53, 2.6, 7.9, 32	CS, GN, HP, LE	Death			32	100% mortality during the first 2 weeks of treatment
					Bd wt	7.9			
					Hepatic	0.53	2.6		Increased liver weight, histopathologic liver lesions
Treon et al. 1951a (recrystallized 99% purity; technical grade 95% purity)									
15	Rat (Carworth) 40 M, 40 F	27 weeks (F)	M: 0, 0.25, 1.25, 2.5 F: 0, 0.28, 1.4, 2.8	BW, HP, LE, OW	Bd wt	2.5 M 2.8 F			
					Hepatic	2.5 M 2.8 F			
					Renal	2.5 M 2.8 F			
Treon et al. 1953a (recrystallized 99% purity)									
16	Rat (Carworth) 16 M, 16 F	3 generations (F)	0, 0.26, 1.3, 2.6	CS, DX	Repro	0.26		1.3	40% decreased number of litters from first parental mating
					Develop			0.26	3.2-fold increased mortality of F1a pups
Treon et al. 1954a									
17	Mouse (Swiss white) 4 M, 14 F	6 generations (F)	0, 0.56, 0.94, 1.88, 4.70	DX, FX, LE, MX	Repro			0.56	Decreased number of pregnant dams
					Develop			0.56	Decreased pup survival to PPD 4
Keplinger et al. 1970									
18	Mouse (B6C3F1) 5 M, 5 F	6 weeks (F)	M: 0, 0.45, 0.9, 1.8, 3.6, 7.2, 14.4 F: 0, 0.49, 1, 2, 3.9, 7.8, 15.6	BW, LE	Death			7.2 M 7.8 F	100% mortality
NCI 1978a (technical grade >85% purity)									
19	Dog (NS)	Up to 9 months		BW, CS, HP, LE	Death			0.89	Death or moribund sacrifice at 5.7 or 6.7 months

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	1 M, 1–2 F	(F)	0, 0.89-1.78, 1.25–4.39, 2.07–9.10		Gastro		0.89		Vomiting
					Hepatic		1.25		Degenerative liver lesions
					Neuro			0.89	Hypersensitivity, tremors, twitching convulsions prior to death; neuronal degeneration in brain
Treon et al. 1951b (purified, but purity not specified)									
20	Dog (mixed) 2 M, 1 F	Up to 37 days 5 days/week 1 time/day (C)	1.5, 3, 4.5	BW, CS, LE	Death			1.5	All three pups died
					Bd wt		1.5		Depressed body weight gain (weight loss prior to death)
					Neuro			1.5	Lethargy, intoxication
Treon et al. 1955 (recrystallized; purity not specified)									
CHRONIC EXPOSURE									
21	Rat (Osborne-Mendel) 50 M, 30 F	25 months (F)	0, 0.37	BW, GN, HE, HP, LE, OW	Bd wt	0.37			
					Hemato	0.37			
Deichmann et al. 1967 (technical grade; 95% purity)									
22	Rat (Osborne-Mendel) 50 M, 50 F	31 months (F)	M: 0, 1.4, 2.1, 3.5 F: 0, 1.54, 2.3, 3.9	BW, CS, HP, LE	Bd wt	2.1 M 3.9 F		3.5 M	12–22% depressed body weight gain
					Hepatic	1.4 M 3.9 F	2.1 M		23% increased relative liver weight
Deichmann et al. 1970 (grade and purity not specified)									
23	Rat (Osborne-Mendel) 12 M, 12 F	2 years (F)	0, 0.037, 0.15, 0.73, 3.65, 7.3, 11	BW, GN, HP, LE, OW	Death			7.3	58% decreased survival
					Bd wt	11			
					Hepatic		0.037[c]		34% increased relative liver weight in females, increasing severity of liver lesions at higher doses
Fitzhugh et al. 1964 (recrystallized; ≥99% purity)									
24	Rat	M: 74 weeks F: 80 weeks	M: 0, 2.1, 4.2 F: 0, 2.3, 4.6	BW, CS, HP, LE	Bd wt		2.1 M 2.3 F		10–12% depressed mean body weight

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	(Osborne-Mendel) 50 M, 50 F	(F)			Resp	4.2 M 4.6 F			
					Cardio	4.2 M 4.6 F			
					Gastro	4.2 M 4.6 F			
					Musc/skel	4.2 M 4.6 F			
					Hepatic	4.2 M 4.6 F			
					Renal	4.2 M 4.6 F			
					Dermal	4.2 M 4.6 F			
					Ocular	4.2 M 4.6 F			
					Endocr	4.2 M 4.6 F			
					Neuro		2.1 M 2.3 F		Hyperexcitability
NCI 1978a (technical grade; >85% purity)									
25	Mouse (C3HeB/Fe) 215 B	2 years (F)	0, 1.7	GN, HP	Cancer			1.7	CEL (liver tumors)
Davis and Fitzhugh 1962 (grade and purity not specified)									
26	Mouse (B6C3F1) 50 M, 50 F	80 weeks (F)	M: 0, 0.7, 1.4 F: 0, 0.5, 1	BW, CS, HP, LE	Death			1 F	Decreased survival
					Bd wt	1.4 M 1 F			
					Resp	1.4 M 1 F			
					Cardio	1.4 M 1 F			

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					Gastro	1.4 M 1 F			
					Musc/skel	1.4 M 1 F			
					Hepatic	1.4 M 1 F			
					Renal	1.4 M 1 F			
					Dermal	1.4 M 1 F			
					Ocular	1.4 M 1 F			
					Endocr	1.4 M 1 F			
					Neuro		0.7 M 0.5 F		Hyperexcitability
					Cancer			0.7 M	Hepatocellular carcinoma
NCI 1978a (technical grade; >85% purity)									
27	Dog (Mongrel) 1–2M, 1–2F	Up to 25 months 6 days/week 1 time/day (C)	0.2, 0.5, 1, 2, 5	BW, CS, HP, LE	Death			1	Decreased survival
					Bd wt	0.2		0.5	Body weight loss
					Hemato	0.5	1		Reduced bone marrow cellularity
					Hepatic	0.5	1		Fatty degenerative changes
					Renal	0.5	1		Fatty degenerative kidney changes
Fitzhugh et al. 1964 (recrystallized; ≥99% purity)									
28	Dog (Beagle) 2 M, 2 F	Up to 15.8 months 7 days/week (F)	0, 0.04-0.09, 0.12-0.25	BW, CS, LE, HP, OW	Bd wt	0.12			
					Hemato	0.12			
Treon et al. 1955 (recrystallized; purity not specified)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects

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

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

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

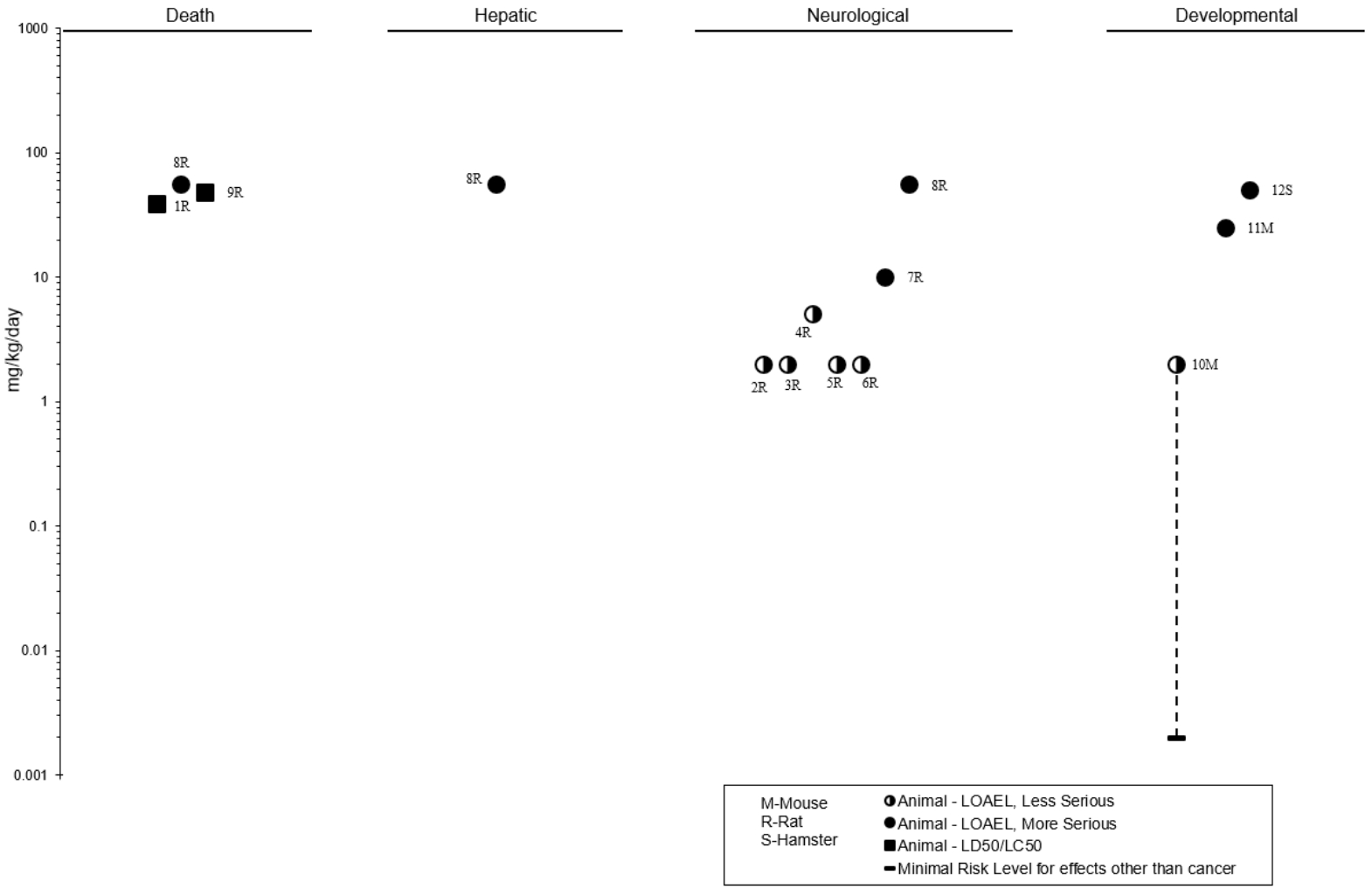


Figure 2-3. Levels of Significant Exposure to Aldrin – Oral
Intermediate (15-364 days)

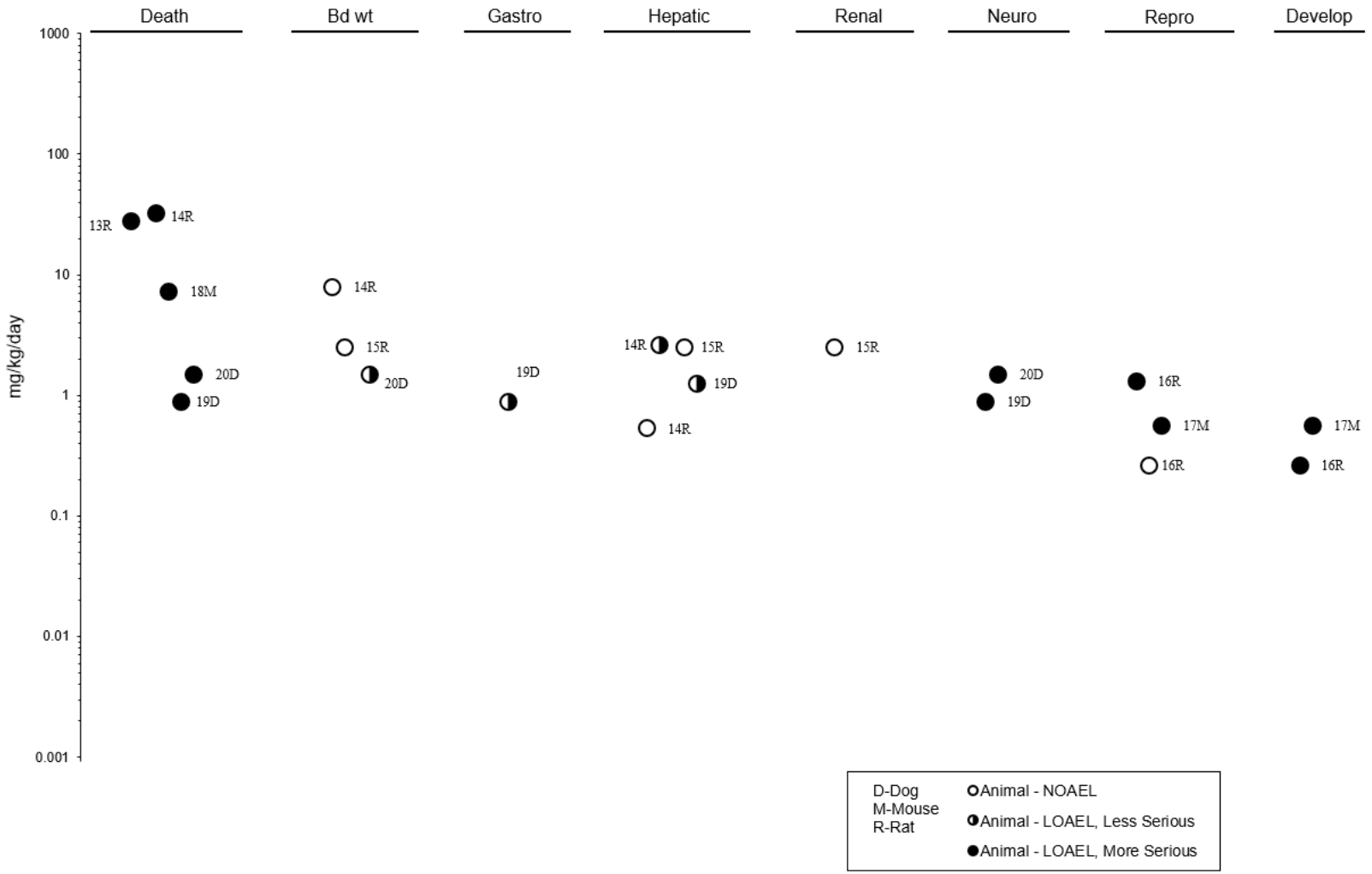


Figure 2-3. Levels of Significant Exposure to Aldrin – Oral
Chronic (≥365 days)

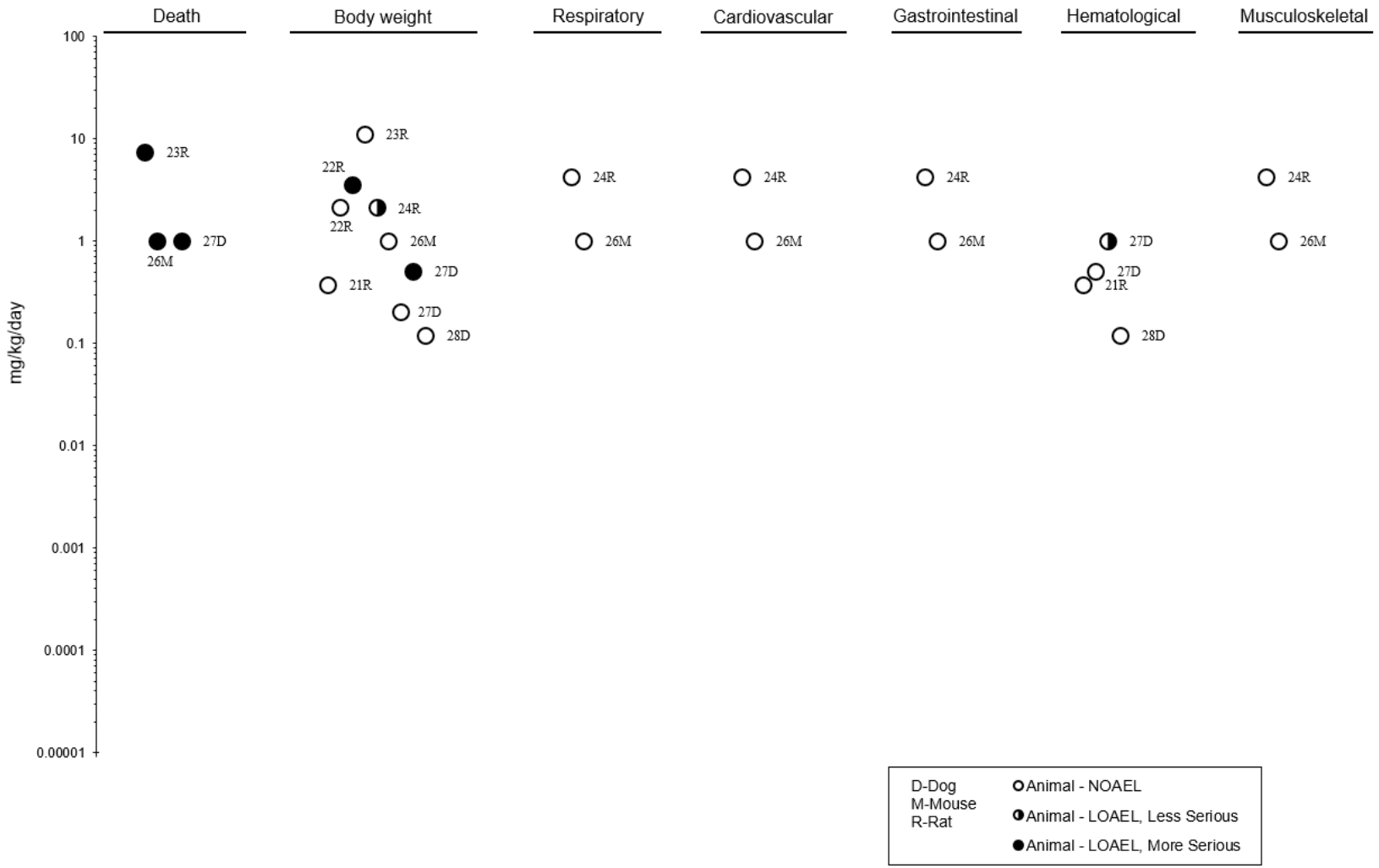


Figure 2-3. Levels of Significant Exposure to Aldrin – Oral

Chronic (≥365 days)

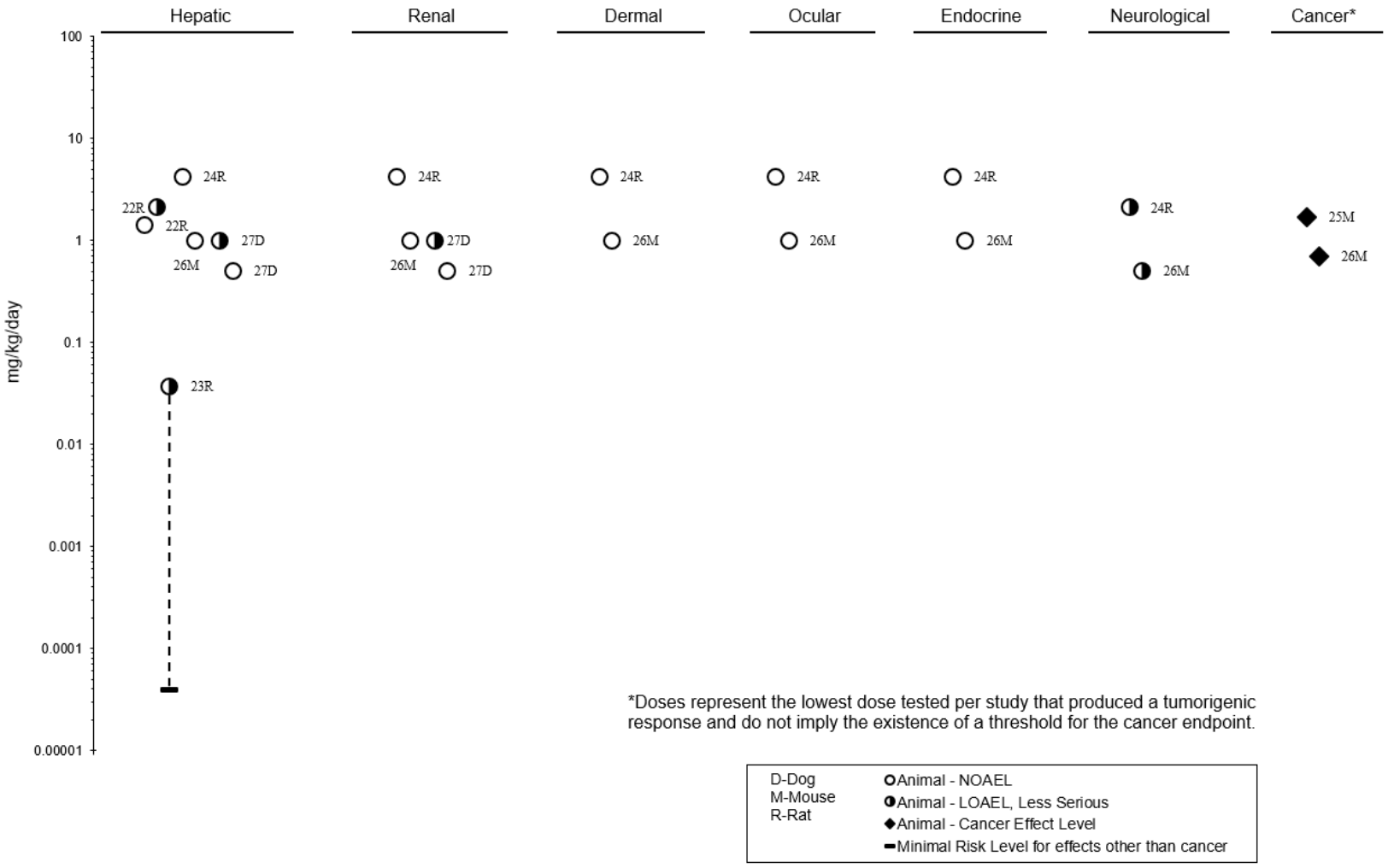


Table 2-2. Levels of Significant Exposure to Dieldrin – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Wistar) 14 or 16 M	Once (GO)	0, 16.7	OF	Neuro			16.7	Impaired maze performance
Burt 1975 (technical grade; 100%)									
2	Rat (Wistar) NS M	Once (GO)	2.5, 5	OF	Neuro			2.5	Disrupted operant behavior
Burt 1975 (technical grade 100%)									
3	Rat (Wistar) NS B	Once (GO)	0, 8.4, 16.7	OF	Neuro	8.4		16.7	Disrupted operant behavior
Burt 1975 (technical grade 100%)									
4	Rat (Sprague-Dawley) 4 M	Once (GO)	0, 0.5, 1.5, 4.5	OF	Neuro			0.5	Impaired escape behavior
Carlson and Rosellini 1987 (95% purity)									
5	Rat (CD) 14–32 F	GDs 7–16 1 time/day (GO)	0, 1.5, 3, 6	BW, CS, DX, LE, MX	Death			6	13 of 32 inseminated females died
					Bd wt	3		6	32% depressed maternal body weight gain
					Develop	6			
Chernoff et al. 1975 (87% purity)									
6	Rat (Sherman) NS	Once (GO)	NS	CS	Death			46	LD_{50}
Gaines 1960 (technical grade; purity not specified)									
7	Rat (Sprague-Dawley) 4–8 F	Once (GO)	0, 26	BI	Hepatic		26		3-fold increase in lipid peroxidation
Goel et al. 1988 (grade and purity not specified)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
8	Rat (Wistar) 5–10 M	Once (GO)	0, 30	BI, OW	Hepatic		30		23% increased liver weight, increased lipid peroxidation
Kohli et al. 1977 ("analar" grade; purity not specified)									
9	Rat (Wistar) 10 M	Once (GO)	NS	LE	Death			167.8	LD_{50} for newborn male rats
Lu et al. 1965 (grade and purity not specified)									
10	Rat (Wistar) 10 M	Once (GO)	NS	LE	Death			24.9	LD_{50} for 14–16-day-old male rats
Lu et al. 1965 (grade and purity not specified)									
11	Rat (Wistar) 10 M	Once (GO)	NS	LE	Death			37	LD_{50} for 3–4-month-old male rats
Lu et al. 1965 (grade and purity not specified)									
12	Rat (Wistar) 10 M	4 days 1 time/day (GO)	NS	LE	Death			9.04	4-day LD_{50} for 14–16-day-old male rats
Lu et al. 1965 (grade and purity not specified)									
13	Rat (Wistar) 10 M	4 days 1 time/day (GO)	NS	LE	Death			54.8	4-day LD_{50} for 3–4-month-old male rats
Lu et al. 1965 (grade and purity not specified)									
14	Rat (Sprague-Dawley) 4 M	3 days 1 time/day (GO)	0, 1, 5, 10	BI, CS	Neuro			10	Tremors, convulsions
Mehrotra et al. 1989 (grade and purity not specified)									
15	Rat (Fischer-344) 15 M, 15 F	Up to 2 weeks (F)	0, 2.6, 5.3, 10.5, 21, 31.6	CS, HP	Death			21	100% mortality

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
NCI 1978b (purified technical grade)									
16	Rat (Carworth) 10 F	Once (GO)	NS	CS, LE	Death			38.3	LD_{50}
Treon et al. 1952 (99% purity)									
17	Rat (Carworth) 10 M, 10 F	Up to 2 weeks (F)	0, 55	CS, GN, HP, LE	Death			55	100% mortality
					Hepatic			55	Severe liver damage
					Neuro			55	Hypersensitivity, degenerative brain lesions
Treon et al. 1951a (recrystallized 99% purity; technical grade 85% purity)									
18	Rat (NS) NS	Once (GO)	0, 12.5, 25, 40	CS, OF	Neuro	12.5	25		Increased evoked potentials
Woolley et al. 1985									
19	Mouse (CD-1) 12–23 F	GDs 7–16 1 time/day (GO)	0, 1.5, 3, 6	BW, CS, DX, MX, OW	Bd wt	3		6	Essentially no maternal body weight gain
					Hepatic	1.5	3		25% increased mean maternal liver weight
					Develop	1.5	3		Increased incidence of supernumerary ribs (42 versus 6% among controls)
Chernoff et al. 1975 (87% purity)									
20	Mouse (CD-1) 30–86 NS	Once (GO)	2-200	LE	Death			27	LD_{50}
Costella and Virgo 1980 (technical grade; 86.1% purity)									
21	Mouse (BALB/c) 24 F	Up to 2 weeks 1 time/day (GO)	0, 0.45, 2.25, 4.5, 22.5	CS, LE	Death			22.5	Unspecified number of high-dose mice died during the first week
					Neuro			22.5	Seizures, hypersalivation, loss of consciousness
Foster et al. 2008 (grade and purity not specified)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
22	Mouse (BALB/c) 12 or 13 F	5 days prior to mating 1 time/week from gestation day 9 to weaning (GO)	0, 0.45, 2.25, 4.5	BW, CS, DX, FX, GN, HP, MX	Bd wt	4.5			
					Neuro	2.25	4.5		Mild seizures in postweaning female pups
Foster et al. 2008 (grade and purity not specified)									
23	Mouse (C57B1/6) 4-5 F	Twice 7 days apart (GO)	0, 16.6	OF	Immuno		16.6 F		Impaired T-cell activity
Fournier et al. 1988 (99% purity)									
24	Mouse (three strains) 10 F	Once (GO)	0, 4, 12, 18, 30	CS, LE, OF	Immuno	12		18	Increased lethality in two strains following viral infection
Krzystyniak et al. 1985 (99.9% purity)									
25	Mouse (BALB/c) 10 M	2 weeks (F)	0, 0.09, 0.9, 9	OF	Immuno		0.09		Impaired antigen processing by macrophages
Loose et al. 1981 (grade and purity not specified)									
26	Mouse (CD1) 10 F	GD 9 (GO)	0, 15	CS, TG	Develop			15	Webbed foot; cleft palate
Ottolenghi et al. 1974 (recrystallized; ≥99% purity)									
27	Mouse (C57BL/6J) NS F	2 weeks prior to mating and during gestation and lactation; every 3 days	0, 0.3, 1, 3	BW, CS, DX	Bd wt	3			
Richardson et al. 2006 (≥98% purity)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
28	Mouse (Carworth Farm No. 1) NS F	Up to 10 days (F)	0, 0.16, 1.6, 7.5	HP, LE, OW,	Death			7.5	4/4 mice died during the first 10 days of treatment
					Hepatic	0.16	1.6		Liver lesions after 7 days of treatment
Wright et al. 1972 (recrystallized; >99.5% purity)									
29	Hamster (Syrian golden) NS F	Once GD 7, 8, or 9 (GO)	0, 30	CS, DX, TG	Develop			30	Up to 25% fetal mortality; 26% depressed fetal weight; increased incidences of webbed foot, cleft palate, cleft lip
Ottolenghi et al. 1974 (recrystallized; ≥99% purity)									
30	Sheep (NS) 4 F	4 days 1 time/day (C)	20	CS, OF	Neuro			20	Impaired operant behavior, EEG changes
Sandler et al. 1969 (technical grade; purity not specified)									
INTERMEDIATE EXPOSURE									
31	Monkey (Squirrel) 2–4 M	55 days 1 time/day (F)	0, 0.01, 0.1	CS, OF	Neuro	0.01[b]		0.1	Learning deficit
Smith et al. 1976 (technical grade; purity not specified)									
32	Rat (NS) 65 M, 65 F	6 months (F)	0, 22	HP	Hepatic		22		Increased serum AST and AP, decreased serum cholesterol and total protein, necrosis in Kupffer cells
					Renal			22	Degenerative changes in kidney epithelial cells; focal aggregation of lymphocytes and macrophages associated with edema and fibroblastic proliferation
Ahmed et al. 1986 (technical grade; 85.6% purity)									
33	Rat (Wistar) 5 M	15 days (GO)	0, 5	HP	Hepatic		5		Diffuse necrosis in the liver
					Renal		5		Glomerulonephritis; renal tubular nephrosis

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Bandyopadhyay et al. 1982b (grade and purity not specified)									
34	Rat (Wistar) 8–15 M	60–120 days (F)	0.046, 0.46, 1.8	OF	Neuro	0.046		0.46	Disrupted operant behavior
Burt 1975 (technical grade 100%)									
35	Rat (Osborne-Mendel) 5 M, 5 F	6 weeks (F)	M: 0, 4, 8, 16, 32 F: 0, 4.5, 9, 18, 36	BW, LE	Death			32 M 36 F	2/5 males died; 5/5 females died
NCI 1978a (technical grade; >85% purity)									
36	Rat (Fischer-344) 15 M, 15 F	Up to 8 weeks (F)	0, 2.6, 5.3, 10.5, 21, 31.6	CS, HP	Neuro	5.3		10.5	Neuronal necrosis of brain
NCI 1978b (purified technical grade)									
37	Rat (Albino) 3–6 M	1–6 months (F)	0, 2	BI, HP	Hepatic		2		Decreased hepatic protein; hepatocellular necrosis
Shakoori et al. 1982 (grade and purity not specified)									
38	Rat (Carworth) 10 M, 10 F	6 months (F)	0, 0.26, 0.53, 2.6, 7.9, 32	CS, GN, HP, LE	Bd wt	7.9			
					Hepatic	0.53	2.6		Increased liver weight, histopathologic liver lesions
Treon et al. 1951a (recrystallized 99% purity; technical grade 95% purity)									
39	Rat (Carworth) 40 M, 40 F	27 weeks (F)	M: 0, 0.25, 1.25, 2.5 F: 0, 0.28, 1.4, 2.8	BW, HP, LE, OW	Bd wt	2.5 M 2.8 F			
					Hepatic	2.5 M 2.8 F			
					Renal	2.5 M 2.8 F			
Treon et al. 1953a (recrystallized 99% purity)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
40	Rat (Carworth) 16 M, 16 F	3 generations (F)	0, 0.26, 1.3, 2.6	CS, DX	Repro			0.26	34% decreased number of litters from first parental mating
					Develop	0.26		1.3	1.9-fold increased 5-day mortality of F3a pups
Treon et al. 1954a									
41	Mouse (FVB-MMTV) 29–30 F	5 days premating 1 time/week during gestation and lactation	0, 0.45, 2.25, 4.5	BW, CS, DX, FX, GN, HP, MX	Cancer			4.5	CEL (mammary tumor burden)
Cameron and Foster 2009									
42	Mouse (CFW Swiss) 101 B	120 days (F)	0, 0.93	CS	Repro	0.93			
Good and Ware 1969 (technical grade; 85% purity)									
43	Mouse (BALB/c) 10 M	3, 6, or 18 weeks (F)	0, 0.18, 0.9	OF	Immuno			0.18	Increased lethality following tumor implant
Loose et al. 1981 (grade and purity not specified)									
44	Mouse (B6C3F1) 5 M, 5 F	6 weeks (F)	M: 0, 0.45, 0.9, 1.8, 3.6; F: 0, 0.49, 1, 2, 3.9	BW, LE	Death			3.6 M 3.9 F	M: 3/5 died F: 4/5 died
NCI 1978a (technical grade >85% purity)									
45	Mouse (B6C3F1) 4 M	28 days (F)	0, 0.18, 0.54, 1.8	BC, BW, EA, FI, HP, OF, OW	Hepatic	1.8 M			
Stevenson et al. 1995 (grade and purity not specified)									
46	Mouse (Swiss-Vancouver) 18–19 F	4 weeks premating to postpartum day 28	0, 0.5, 1, 2, 2.9, 3.9, 4.9	CS, DX, LE, OF	Death			3.9	7/18 maternal mice died prior to mating
					Repro	1		2	18% of bred females did not become pregnant

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
		(F)			Develop	0.5		1	Increased pup mortality
Virgo and Bellward 1975 (technical grade; 86.1% purity)									
47	Dog (NS) 1 M, 1–2 F	Up to 9 months (F)	0, 0.73–1.85, 1.95–4.24, 2.45–9.80	BW, CS, HP, LE	Death			1.95	3/3 died
					Gastro	0.73	1.95		Vomiting
					Hepatic		0.73		Degenerative liver lesions
					Neuro			0.73	Hypersensitivity, tremors, twitching convulsions prior to death; neuronal degeneration in brain
Treon et al. 1951b (purified, but purity not specified)									
CHRONIC EXPOSURE									
48	Human 3-4 M	18 months 1 time/day (C)	0, 0.00014, 0.00071, 0.003	BC, BI	Hemato	0.003 M			
					Hepatic	0.003 M			
					Neuro	0.003 M			
Hunter and Robinson 1967									
49	Rat (Osborne-Mendel) 50 M, 50 F	31 months (F)	M: 0, 1.4, 2.1, 3.5 F: 0, 1.54, 2.3, 3.9	BW, CS, HP, LE	Death			2.3 F	Decreased survival
					Bd wt	3.5 M 3.9 F			
					Hepatic	3.5 M 3.9 F			
Deichmann et al. 1970 (grade and purity not specified)									
50	Rat (Osborne-Mendel) 12 M, 12 F	2 years (F)	0, 0.037, 0.15, 0.73, 3.65, 7.3, 11	BW, GN, HP, LE, OW	Death			3.65	42% decreased survival
					Bd wt	11			
					Hepatic		0.037		34% increased relative liver weight in females; dose-related increasing incidence and severity of liver lesions
Fitzhugh et al. 1964 (recrystallized; ≥99% purity)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
51	Rat (Osborne-Mendel) 50 M, 50 F	59–80 weeks (F)	M: 0, 2.0, 4.6 F: 0. 2.2, 5.0	BW, CS, HP, LE	Bd wt	4.6 M 5.0 F			
					Resp		2 M 2.2 F		Dyspnea, tachypnea
					Cardio	4.6 M 5.0 F			
					Gastro		2 M 2.2 F		Diarrhea
					Musc/skel	4.6 M 5.0 F			
					Hepatic	4.6 M 5.0 F			
					Renal	4.6 M 5.0 F			
					Dermal		2 M 2.2 F		Rough coat, discolored hair coat, alopecia
					Ocular	4.6 M 5.0 F			
					Endocr	4.6 M 5.0 F			
NCI 1978a (technical grade; >85% purity)									
52	Rat (Fischer-344) 24 M, 24 F	104–105 weeks (F)	0, 0.17, 0.85, 4.25	CS	Neuro	0.85		4.25	Convulsions
NCI 1978b (purified technical grade)									
53	Rat (Carworth Farm E) 25 M, 25 F	2 years (F)	0, 0.005, 0.05, 0.5	BC, BW, CS, FI, GN, HP, LE, OW	Bd wt	0.5			
					Resp	0.5			
					Cardio	0.5			
					Gastro	0.5			
					Hemato	0.5			
					Musc/skel	0.5			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	0.5 M 0.005[c] F	0.05 F		13% increased liver weight; parenchymal cell changes at 0.5 mg/kg/day in females
					Renal	0.5			
					Dermal	0.5			
					Endocr	0.5			
					Neuro	0.05		0.5	Tremors and occasional convulsions
Walker et al. 1969 (>99% purity)									
54	Mouse (C3HeB/Fe) 218 B	2 years (F)	0, 1.7	GN, HP	Cancer			1.7	CEL (liver tumors)
Davis and Fitzhugh 1962 (grade and purity not specified)									
55	Mouse (BALB/c) 90 M	75 weeks (F)	0, 1.7	HP	Cancer			1.7	CEL (liver tumors)
Lipsky et al. 1989 (grade and purity not specified)									
56	Mouse (three strains) 50–75 M	85 weeks (F)	0, 1.7	GN, HP	Cancer			1.7	CEL (liver tumors)
Meierhenry et al. 1983 (98.5% purity)									
57	Mouse (B6C3F1) 50 M, 50 F	80 weeks (F)	0, 0.43, 0.86	BW, CS, HP, LE	Bd wt	0.86			
					Resp	0.86			
					Cardio	0.86			
					Gastro	0.86			
					Musc/skel	0.86			
					Hepatic	0.86			
					Renal	0.86			
					Dermal	0.86			
					Ocular	0.86			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Endocr	0.86			
					Neuro		0.43		Hyperexcitability, tremors
					Cancer			0.86M	CEL (liver tumors)
NCI 1978a (technical grade; >85% purity)									
58	Mouse (C3H) 11–21 M	2 years (F)	0, 1.7	HP	Cancer			1.7	CEL (hepatocellular adenomas)
Ruebner et al. 1984 (>99% purity)									
59	Mouse (Carworth Farm No. 1) 19–82 M	Up to 92 weeks (F)	0, 1.7	BW, GN, HP, OF, OW	Bd wt	1.7			
					Cancer			1.7	CEL (liver tumors)
Tennekes et al. 1981 (>99% purity)									
60	Mouse (CF1) 30–45 M 30–45 F	2 years (F)	0, 1.7	CS, GN, HP, LE	Death			1.7	Decreased survival in latter portion of the treatment period
					Cancer			1.7	CEL (liver tumors)
Thorpe and Walker 1973 (>99% purity)									
61	Mouse (Carworth Farm No. 1) 58 NS	Up to 64 weeks (F)	0, 1.7	HP	Cancer			1.7	CEL (liver tumors)
Walker et al. 1973 (>99% purity)									
62	Mouse (Carworth Farm No. 1) 60 B	Up to 128 weeks (F)	0, 0.2, 0.43, 0.86, 1.7, 3.4	CS	Death			1.7	Decreased survival
					Neuro	1.7		3.4	Body tremors, convulsions
					Cancer			0.43	CEL: Liver tumors
Walker et al. 1973 (>99% purity)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
63	Mouse (Carworth Farm No. 1) 250–600 B	Up to 132 weeks (F)	0, 0.017, 0.17, 1.7	CS, GN, HP, LE	Death			1.7	(50% mortality reached at 15 months versus 20–24 months in controls)
					Cancer			1.7	CEL (liver tumors)
Walker et al. 1973 (>99% purity)									
64	Dog (Mongrel) 1–2 M, 1–2 F	Up to 25 months 6 days/week (C)	0.2, 0.5, 1, 2, 5, 10	BW, CS, HP, LE	Death			0.5	Decreased survival
					Hemato	0.5	1		Reduced bone marrow cellularity
					Hepatic	0.5	1		Fatty degenerative changes in liver
					Renal	0.5	1		Fatty degenerative changes in kidney
Fitzhugh et al. 1964 (recrystallized; ≥99% purity)									
65	Dog (Beagle) 2 M, 2 F	Up to 15.8 months 7 days/week (F)	0, 0.03–0.10, 0.14–0.23	BW, CS, LE, HP, OW	Bd wt	0.14			
					Hemato	0.14			
Treon et al. 1955 (recrystallized; purity not specified)									
66	Dog (Beagle) 5 M, 5 F	2 years 1 time/day (C)	0, 0.005, 0.05	BC, BH, BW, CS, FI, GN, HP, LE, OW, UR	Bd wt	0.05			
					Resp	0.05			
					Cardio	0.05			
					Gastro	0.05			
					Hemato	0.05			
					Musc/skel	0.05			
					Hepatic	0.05			
					Renal	0.05			
					Dermal	0.05			
					Ocular	0.05			
					Endocr	0.05			
					Neuro	0.05			
Walker et al. 1969 (>99% purity)									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects

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

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

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

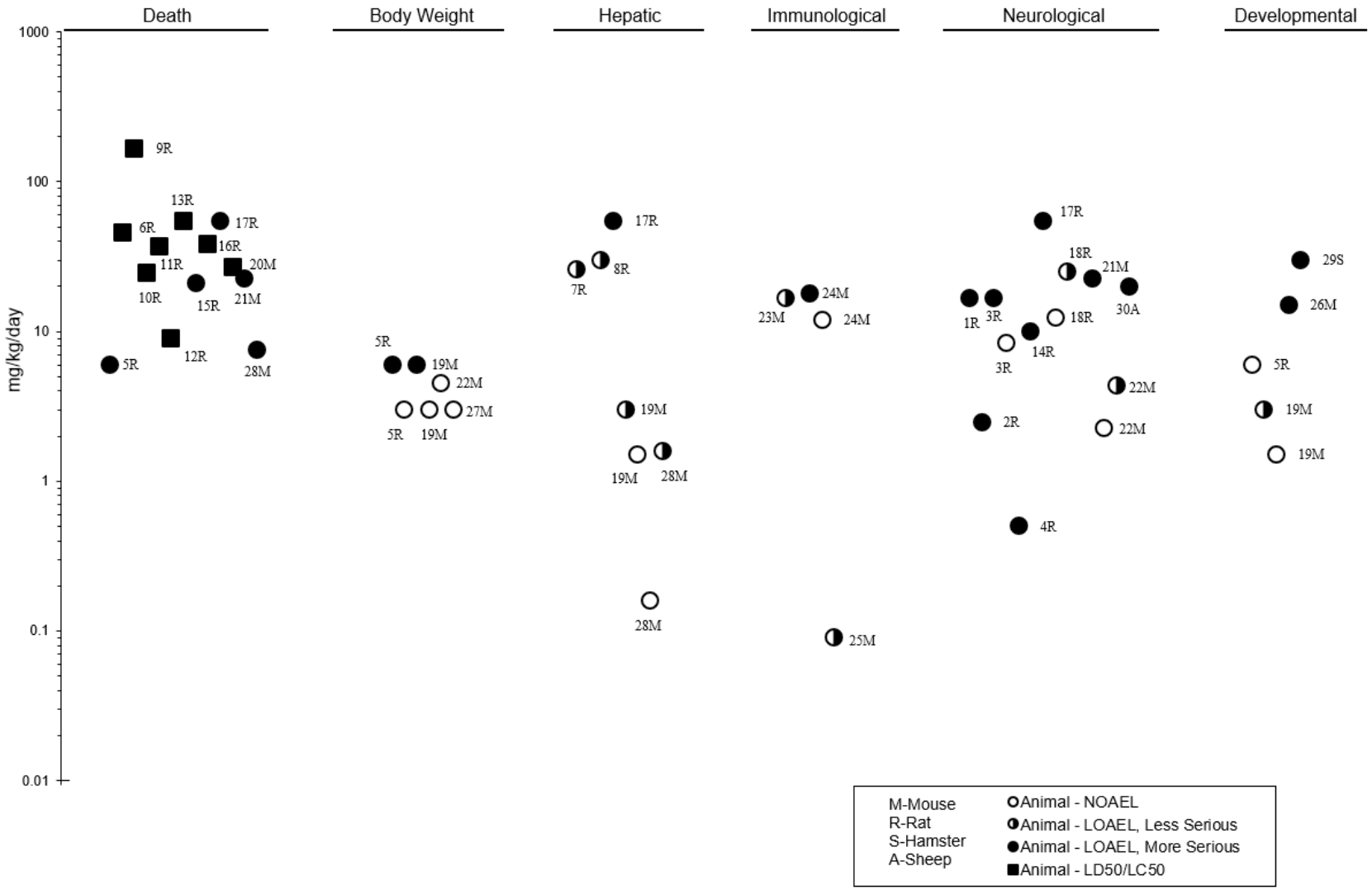


Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral
Intermediate (15-364 days)

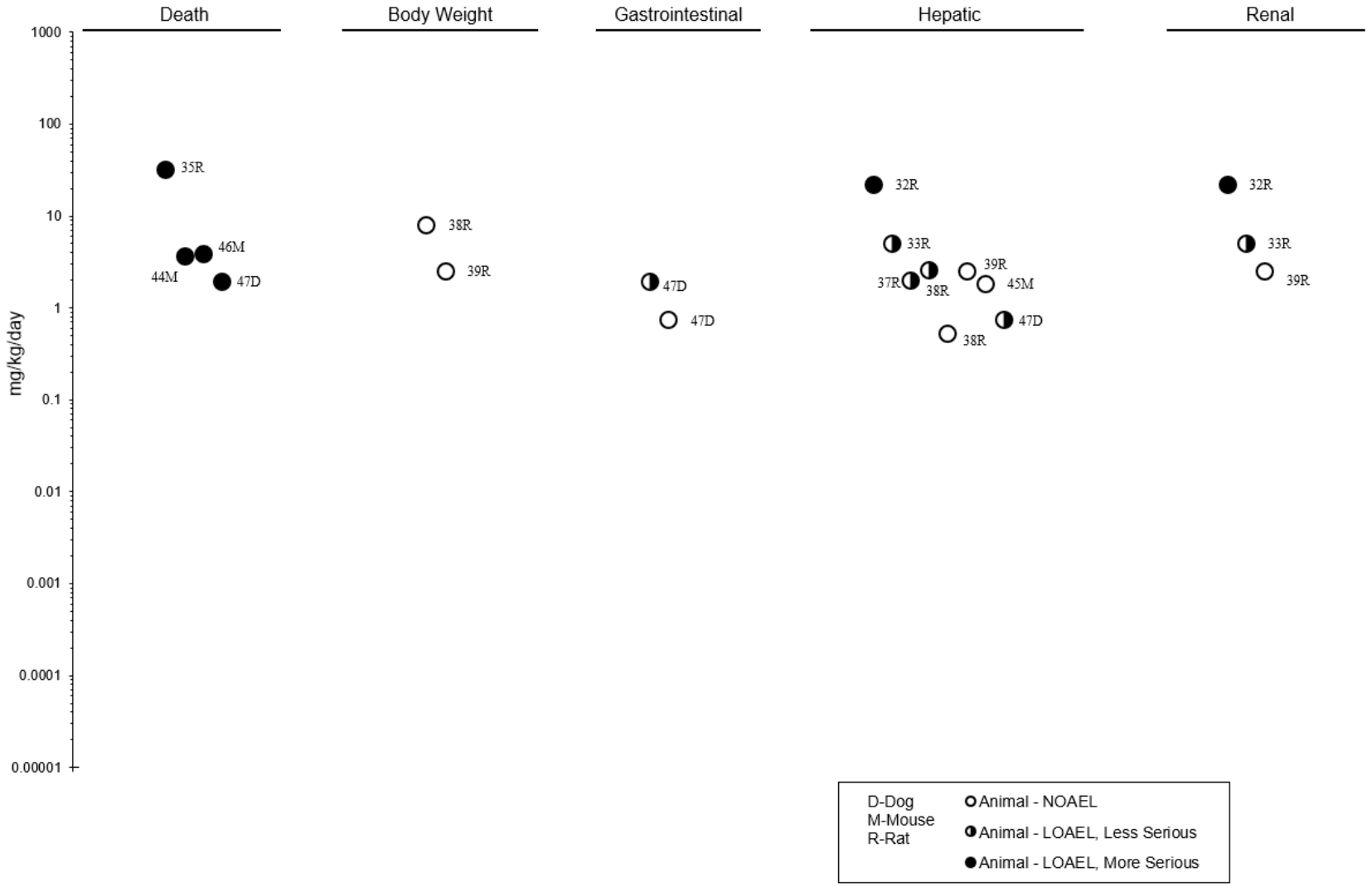


Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral
Intermediate (15-364 days)

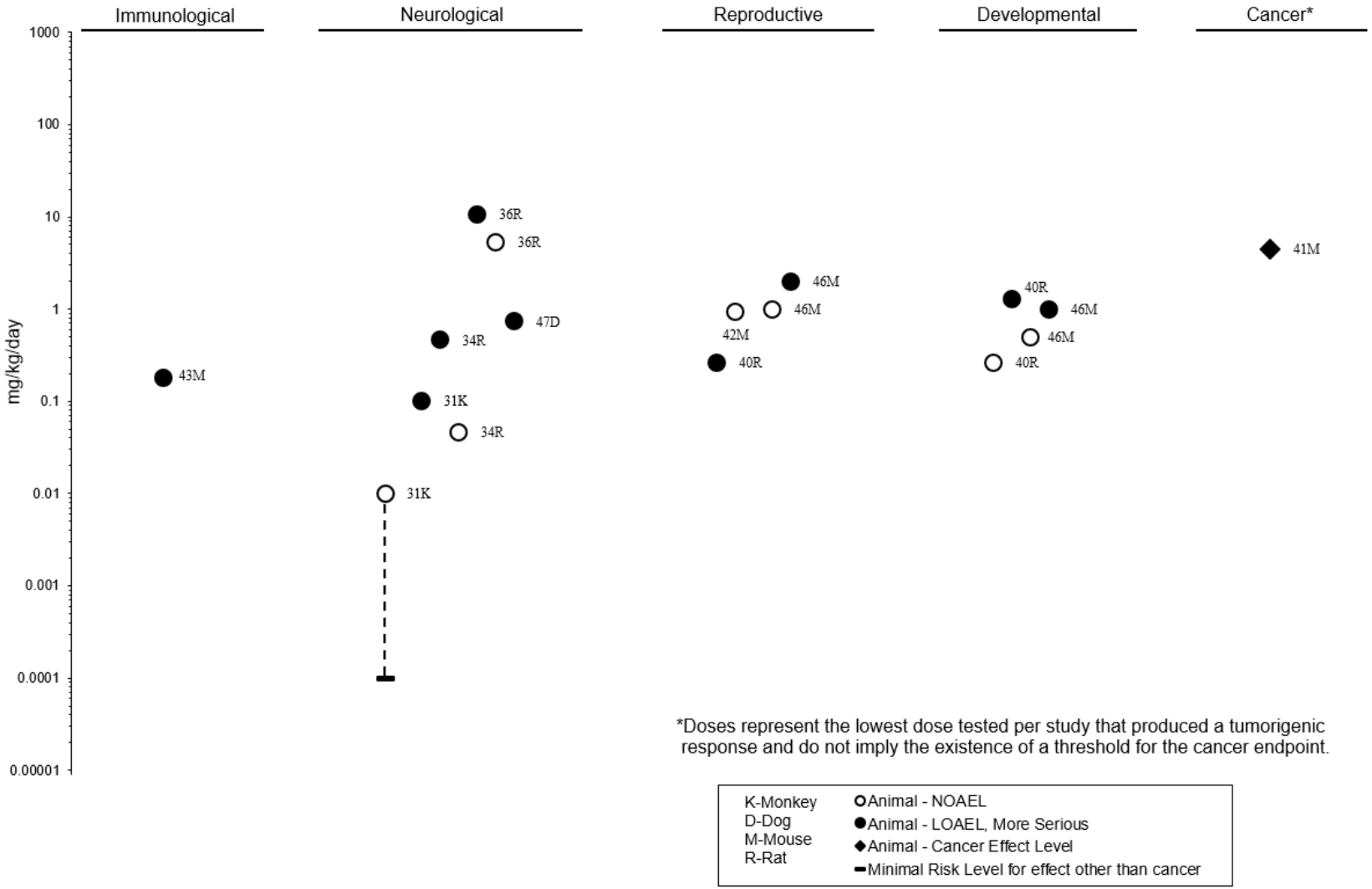


Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral
Chronic (≥365 days)

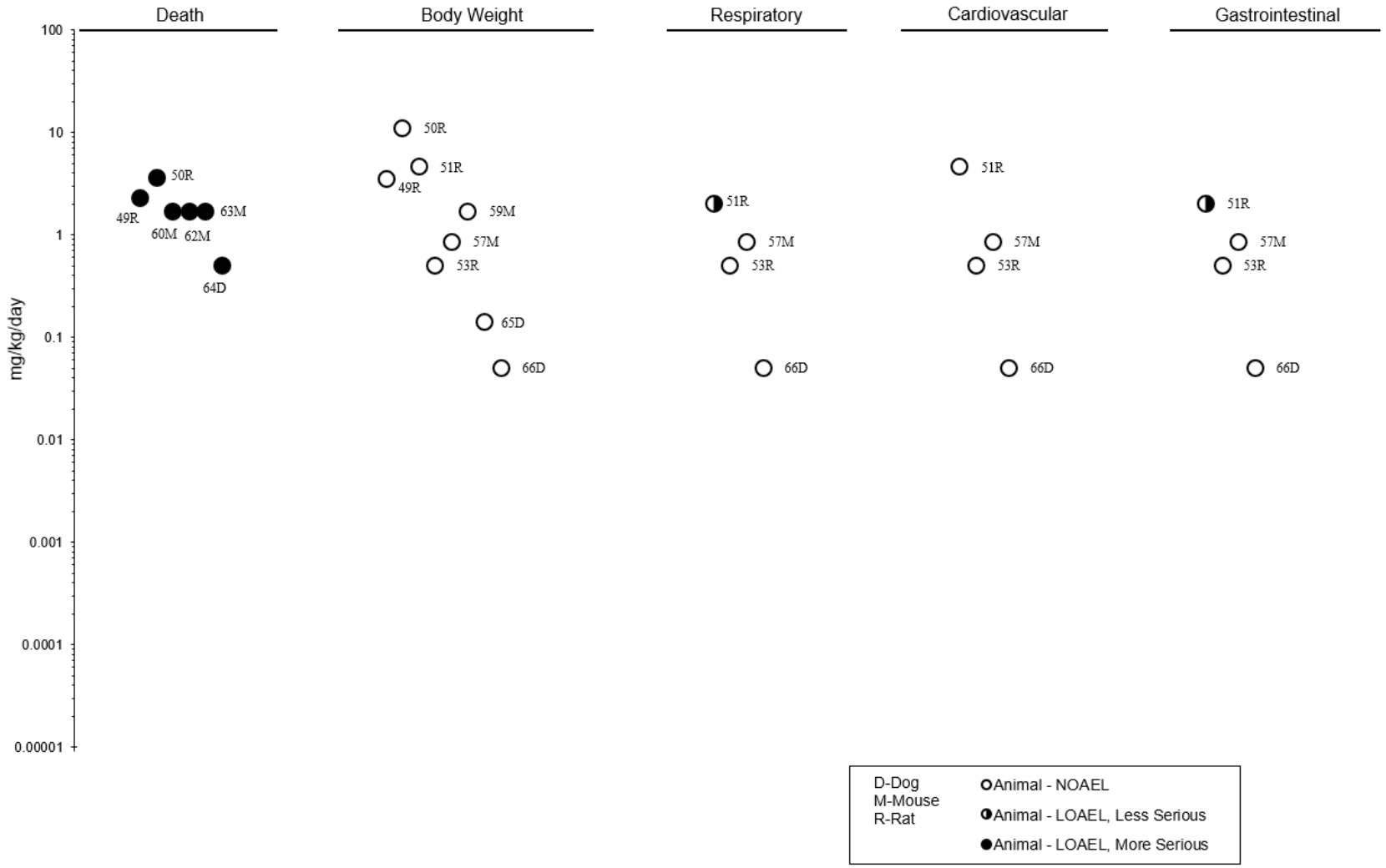


Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral
Chronic (≥365 days)

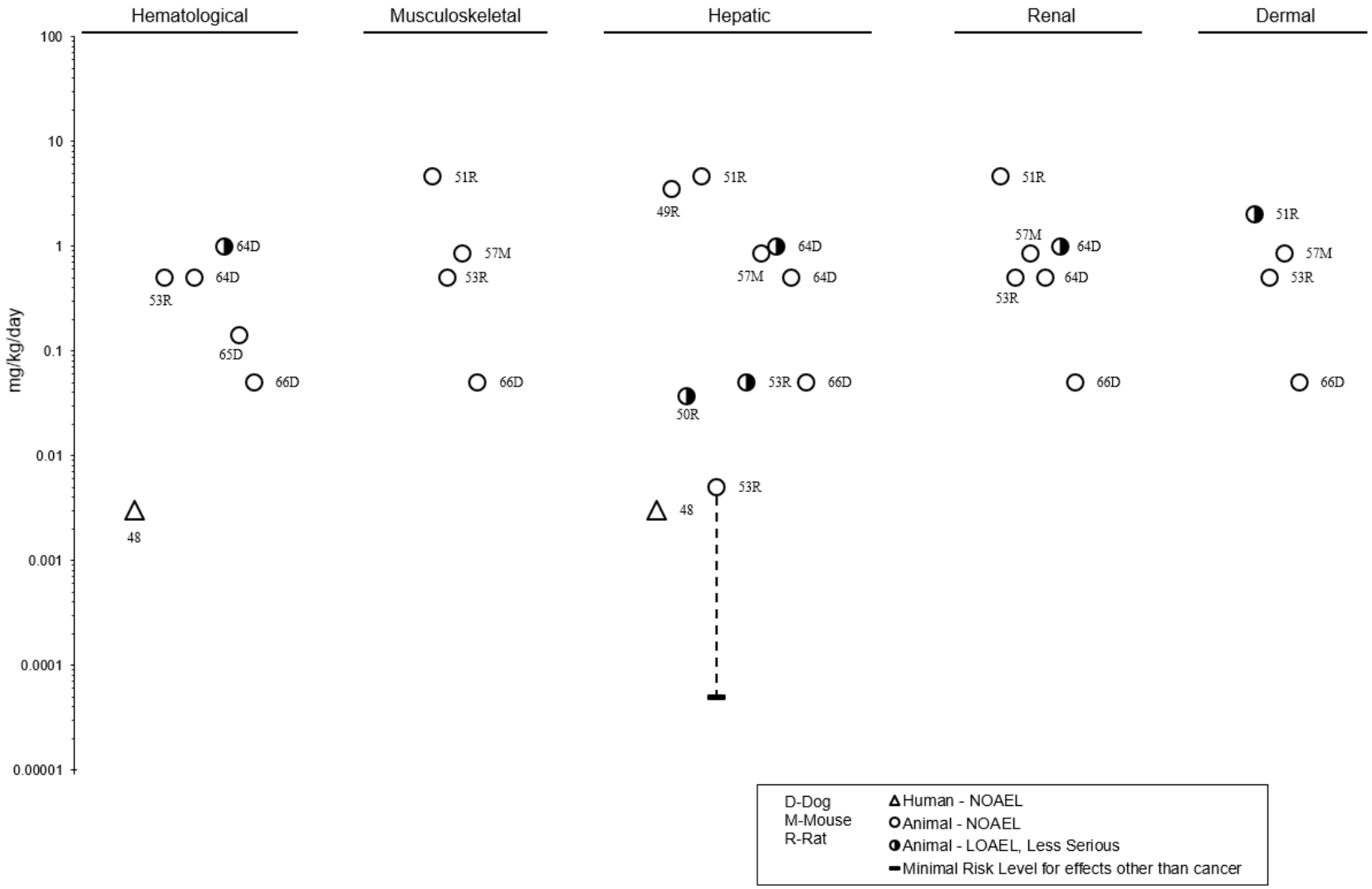
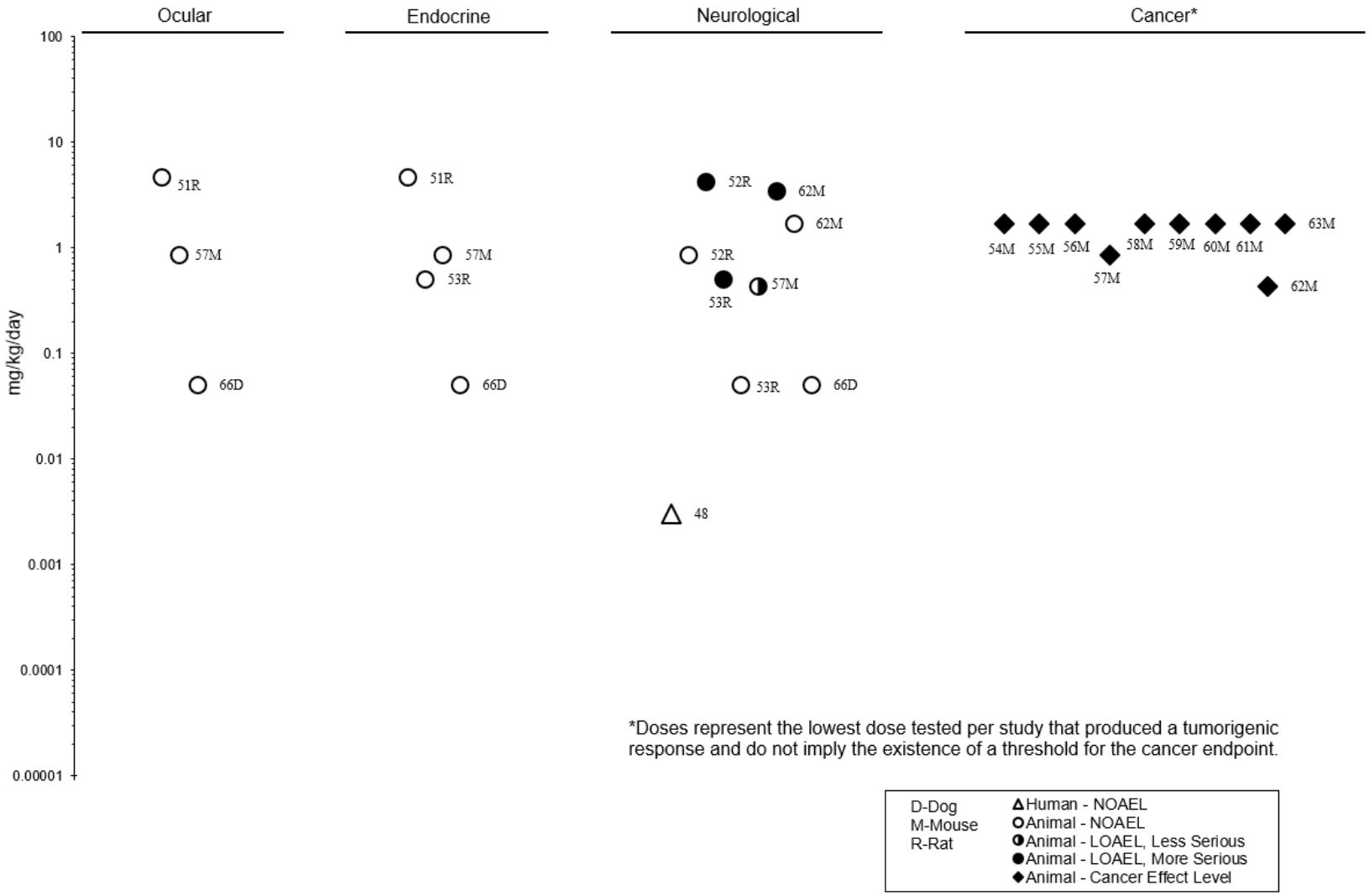


Figure 2-4. Levels of Significant Exposure to Dieldrin – Oral
Chronic (≥365 days)



2.2 DEATH

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

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

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

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

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

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

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

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

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

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

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

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

2.3 BODY WEIGHT

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

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

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

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

2.4 RESPIRATORY

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

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

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

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

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

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

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

2.5 CARDIOVASCULAR

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

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

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

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

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

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

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

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

2.6 GASTROINTESTINAL

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

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

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

2.7 HEMATOLOGICAL

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

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

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

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

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

2.8 MUSCULOSKELETAL

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

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

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

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

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

2.9 HEPATIC

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.10 RENAL

Epidemiological Studies. No evidence of renal damage was seen in workers employed for ≥4 years in the manufacture of aldrin or dieldrin (Jager 1970). A survey study of farmers found no associations between exposure to aldrin and/or dieldrin and glomerular filtration rate or chronic kidney disease (Shearer et al. 2021). A man who attempted suicide by consuming an estimated 25.6 mg/kg of aldrin had elevated blood urea nitrogen, gross hematuria, and albuminuria upon admission to the hospital (Spiotta 1951). By 17 days after admission, levels of nitrogen, blood, and protein in the urine had returned to normal. Six weeks after the suicide attempt, the ability to concentrate the urine was poor. Another man who reportedly ingested 120 mg/kg of dieldrin exhibited no evidence of renal damage (Black 1974). In both of these case reports, the actual dose available for absorption was unknown because efforts were made to limit absorption of the chemicals from the gastrointestinal tract.

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

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

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

2.11 DERMAL

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

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

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

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

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

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

2.12 OCULAR

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

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

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

2.13 ENDOCRINE

Epidemiological Studies. One study evaluated associations between serum levels of dieldrin and blood thyroid hormones in pregnant women (Yamazaki et al. 2020). This prospective study included 333 pregnant women in Japan with a median maternal serum dieldrin level of 16.3 pg/g wet weight. Results of multivariate regression analysis showed an inverse association between serum dieldrin and free thyroxine (T4) (β: -0.08; 95% confidence interval (CI): -0.14, -0.02; p=0.01). No association was observed between dieldrin and thyroid stimulating hormone (TSH) levels. This study also assessed thyroid effects in infants (discussed in Section 2.17). No studies were located regarding endocrine effects in humans following inhalation, oral, or dermal exposure to aldrin.

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

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

2.14 IMMUNOLOGICAL

Epidemiological Studies. Limited information is available regarding the possible immunological effects of aldrin or dieldrin in humans. In one case report, a pesticide sprayer developed immunohemolytic anemia after multiple exposures to dieldrin, heptachlor, and toxaphene (Muirhead et al. 1959). Antibodies for dieldrin-coated or heptachlor-coated red blood cells were found in the subject's serum. However, this study is limited because the subject was exposed to other pesticides as well. In another case report, a man developed immunohemolytic anemia after eating fish that contained high levels of dieldrin (Hamilton et al. 1978). Testing of the patient's serum revealed a positive antibody test for

dieldrin-coated red blood cells. No sensitization was observed in volunteers challenged with fabric containing up to 0.5% dieldrin 2 weeks following 4-day induction exposure (Suskind 1959). In a study of 98 breastfed and 73 bottle-fed Inuit infants from Nunavik (Arctic Quebec, Canada), risk of experiencing otitis media (three or more episodes) over the first year of life was reportedly increased with prenatal exposure to dieldrin (Dewailly et al. 2000). No clinically relevant differences were noted between breastfed and bottle-fed infants with regard to immunologic parameters.

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

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

I*n vitr*o studies have shown dieldrin to cause increased superoxide production in human neutrophils (Pelletier and Girard 2002; Pelletier et al. 2001), presumably via protein kinases C and tyrosine kinases,

and apoptotic alterations in human peripheral blood lymphocytes (Michalowicz et al. 2013). Cytotoxicity and oxidative stress were observed in BALB/c 3T3 fibroblasts exposed to aldrin (Lonare et al. 2016).

2.15 NEUROLOGICAL

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

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

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

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

Results from a comprehensive neurological examination of 27 workers involved in either the manufacture or application of dieldrin were compared to those of a group of unexposed workers (Sandifer et al. 1981). Scores on five psychological tests were significantly different from those of the unexposed controls. However, the importance of the results was questioned by the authors because of differences in the degree of literacy between the two groups. Also, three exposed workers had abnormal electromyograms (EMGs), suggesting a peripheral neuropathy. However, EMGs were not obtained in the control group; thus, the significance of these results is unknown.

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

A small group of persons who consumed wheat mixed with aldrin and lindane over a period of 6–12 months developed a variety of central nervous system symptoms (Gupta 1975); exposure levels were not estimated. These included bilateral myoclonic jerks, generalized seizures, auditory and visual auras, hyperexcitability, and irritability. In some cases, the onset of symptoms was abrupt. EEGs showed spike and wave activity and abnormal bursts of slow delta-wave discharges. After exposure was discontinued,

the symptoms slowly improved. However, 1 year after exposure, infrequent myoclonic jerks were observed in several of the subjects. One subject also complained of memory loss and irritability, and a 7-year-old child was believed to have developed mild mental retardation as a result of the exposure. Although both aldrin and lindane had been mixed with the wheat, the author concluded that the effects observed were due to the aldrin exposure because in previous years wheat had been routinely mixed with lindane and consumed with no apparent adverse effects.

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

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

A case-control study in China evaluated potential associations between serum concentrations of aldrin and hearing loss (Zhang et al. 2021). The study population was recruited from the general population and included 174 adults (87 per group). No association was observed between serum aldrin concentrations and hearing loss. Serum levels of aldrin, adjusted for serum lipid, were similar (p=0.417) in case (20.99 mg/mL) and control (21.8 ng/mL in controls) groups.

Aldrin. Single or repeated gavage dosing of rats with aldrin at 2–25 mg/kg/day resulted in increased locomotor activity (Jamaluddin and Poddar 2001a, 2001b, 2003). Peak responses occurred at 2 hours postdosing. In a study designed to evaluate dose-response characteristics following single dosing at 1–25 mg/kg, the greatest increase in locomotor activity occurred at 10 mg/kg; there was no significant difference in locomotor activity between controls and rats dosed at 25 mg/kg (Jamaluddin and Poddar 2001b). In studies that employed dosing at 5 or 10 mg/kg/day for up to 30 days, the peak of aldrin-induced increased locomotor activity occurred at treatment day 12; by treatment day 30, locomotor

activity had returned to near control levels (Jamaluddin and Poddar 2001b, 2003). Tremors and convulsions were observed in rats administered 10 mg/kg/day aldrin for 3 days (Mehrotra et al. 1989). Neurotoxic signs observed in cattle poisoned with unspecified dietary concentrations of aldrin included tremors, running, hyperirritability, and seizures (Buck and Van Note 1968).

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

Dogs orally administered aldrin at 0.89–1.78 mg/kg/day for up to 9 months experienced convulsions and neuronal degeneration in the cerebral cortex (Treon et al. 1951b). At this dose, aldrin-treated dogs also exhibited hypersensitivity to stimulation, twitching, and tremors. At higher doses, degenerative changes were observed in basal ganglia and cerebellum. In another chronic dog study, moderate neuronal degeneration was reported in dogs following 1 year of oral exposure to aldrin at 0.2 mg/kg/day (Kitselman 1953). The small number of animals tested and the poor reporting of the results limit the interpretation of this study.

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

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

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

Chronic-duration oral exposure of rats resulted in irritability, tremors, and/or convulsions at 0.5–4.25 mg/kg/day (NCI 1978a, 1978b; Walker et al. 1969). In 80-week bioassays of mice, hyper-excitability, fighting and/or tremors were reported at oral doses of 0.43 mg dieldrin/kg/day (NCI 1978a). Body tremors and convulsions were also reported in mice exposed to 3.4 mg/kg/day dieldrin in the diet for up to 128 weeks (Walker et al. 1973).

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

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

Mechanisms of Action. A number of studies have investigated possible mechanisms of aldrin and dieldrin neurotoxicity. Aldrin and dieldrin characteristically stimulate the central nervous system causing hyperexcitation and generalized seizures (convulsions). It is generally believed that the hyperexcitatory effects of these chemicals result from a generalized activation of synaptic activity throughout the central nervous system. It is unclear whether aldrin and dieldrin act at the nerve terminal to facilitate

neurotransmitter release, or if they cause excitation by depressing activity of inhibitory neurotransmitters within the central nervous system (Joy 1982; Shankland 1982).

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

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

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

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

Results from a number of studies indicate a potential role for dieldrin in the etiology of Parkinson's disease that includes oxidative damage and/or apoptosis (e.g., Hatcher et al. 2007; Kanthasamy et al. 2008; Kitazawa et al. 2001, 2003; Russo et al. 2020; Saminathan et al. 2011; Schmidt et al. 2017; Sharma et al. 2010; Sun et al. 2005). Possible underlying mechanisms in aldrin and/or dieldrin-induced oxidative damage and/or apoptosis in dopaminergic neuronal cells include changes such as increased expression of α-synuclein resulting in proteasomal dysfunction, mitochondrial dysfunction, promotion of caspase-3-dependent proteolytic cleavage of protein kinase c, activation of a nonreceptor tyrosine kinase, and impaired protein degradation pathways through gene disruption.

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

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

2.16 REPRODUCTIVE

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

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

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

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

A significant but slight decrease in fertility was observed in female mice receiving dieldrin from the diet at 2 or 2.9 mg/kg/day from 4 weeks prior to mating through weaning (Virgo and Bellward 1975). In this study, males were exposed to test material only during the 2-week mating period. In a 3-generation reproduction study, male and female weanling rats receiving test substance from the diet at doses as low as 0.26 mg/kg/day dieldrin exhibited decreased fertility (decreased number of litters) during the first mating of the parental generation (Treon et al. 1954a). A subsequent mating of the parental rats receiving dieldrin failed to show a consistent dose-related effect on fertility. At matings of the offspring, no effect

on fertility (number of litters) was observed at 0.26 mg dieldrin/kg/day; effects on fertility due to higher doses were difficult to assess because few offspring survived to be mated. No consistent effect of doses as high as 2 mg/kg/day dieldrin was found on the conception rate of male and female rats exposed from the time they were 28 days old through the period of mating (initiated when the rats were 146 days old) (Harr et al. 1970). These results are limited in that no statistical analysis of the data was presented. In addition, male and female mice exposed to 0.93 mg/kg/day dieldrin for 30 days prior to mating and then for 90 days thereafter exhibited no adverse effects on fertility, fecundity, or length of gestation (Good and Ware 1969). The only adverse reproductive effect observed in this study was a slight decrease in litter size. However, this study is limited in that only one dose level of dieldrin was tested.

A number of adverse reproductive effects were observed in dogs administered aldrin orally (males and females) at 0.15 or 0.30 mg/kg/day for 14 months prior to mating (Deichmann et al. 1971). The effects included delayed estrus, reduced libido, lack of mammary function and development, and an increased number of stillbirths. However, this study is limited by the small number of animals tested.

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

Mechanisms of Action. Mechanisms of action for reproductive effects have not been established. Results of a study in cultured buffalo ovarian granulosa cells showed that dieldrin upregulated expression of the CYP19A1 gene and increased cellular production of estradiol-17b (Sharma et al. 2021).

2.17 DEVELOPMENTAL

Epidemiological Studies. Little information is available on the potential developmental effects of aldrin and dieldrin in humans. Available epidemiological studies were conducted in general populations and evaluated numerous chemicals; however, results did not apply adjustments for co-exposure to other chemicals. Thus, interpretation is limited. Results of a case-control study (119 cases and 119 controls) did not find an association between aldrin in umbilical cord tissue and neural tube defects (Yin et al. 2021). No association between placental tissue levels of aldrin and fetal orofacial clefts were observed in a case-control study of 103 cases and 103 controls in China (Pi et al. 2020). A cross-sectional study in

221 mother-infant pairs in India found inverse correlations between maternal blood dieldrin and birth weight (Pearson's correlation coefficient: -0.205; p=0.002) and cord blood dieldrin and birth weight (Pearson's correlation coefficient: -0.305; p<0.001) (Dwivedi et al. 2021). No correlations were observed between maternal or cord blood aldrin and birth weight. In a cohort study of 311 pregnant women in France, a positive association was observed between hair levels of dieldrin in the 75th percentile (0.61 pg/mg) and birth length in boys (β_{adj}: 0.94 cm; 95% CI: 0.14, 1.74) compared to the lower 25th percentile (less than the limit of detection); no association was observed for girls (Beranger et al. 2020). No associations were observed between hair levels of dieldrin and birth weight or head circumference in boys or girls. A cross-sectional study of 81 pregnant women in Egypt did not find an association between the presence of dieldrin in maternal blood (level not reported) and infant gender (Abdel Hamid et al. 2020).

In addition to birth outcomes, studies have evaluated associations between dieldrin and infant thyroid hormones and neurodevelopment. A prospective study evaluated associations between maternal serum levels of dieldrin and infant blood thyroid hormones in 333 mother-infant pairs in Japan (Yamazaki et al. 2020). The median maternal serum dieldrin level was 16.3 pg/g wet weight. Based on multivariate regression analysis, no association was observed between maternal serum dieldrin and infant TSH or free T4 levels. A cross-sectional study of 55 mother-infant pairs assessed associations between breast milk dieldrin and infant neurodevelopment using the Bayley Scales of Infant and Toddler Development (Kao et al. 2019a). Test results for cognitive, language, and social-emotions scales were stratified into lower and higher scores. For the Bayley language scale, higher infant scores were associated with higher breast milk concentration of dieldrin (0.392 ng/g lipid) compared to lower language scores (0.114 ng/g lipid). No differences in breast milk dieldrin levels were observed for higher and lower performance scores for Bayley cognitive or social-emotional tests.

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

Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin. Increased mortality of offspring during the first 5 days postpartum was observed at 0.26 mg/kg/day of aldrin in the first mating of a 3-generation reproduction study in rats (Treon et al. 1954a). Decreased pup survival to postpartum day 4 was observed in a multigeneration study in which mice were exposed to 0.56 mg/kg/day aldrin (Keplinger et al. 1970). Poor litter survival was also reported in a study of dogs treated orally for up to 1 year at doses of aldrin as low as 0.2 mg/kg/day

(Kitselman 1953). In some instances, apparently normal puppies died after a few days of nursing. Although maternal toxicity was not specifically addressed in this study, dogs receiving similar doses of aldrin exhibited histopathologic evidence of hepatic and renal toxicity. This study is limited because too few dogs were tested, pregnancies were incidental to the study protocol, and adequate controls were not used. Dogs mated 2 weeks to 9 months after 14 months of oral exposure to aldrin at doses as low as 0.15 mg/kg/day also exhibited high levels of offspring mortality (Deichmann et al. 1971). However, this study was also limited by the small number of animals tested. An increase in fetal mortality was observed in hamsters administered single gavage doses of 50 mg/kg aldrin on GD 7, 8, or 9 (Ottolenghi et al. 1974).

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

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

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

gluconeogenesis. Cardiac failure, secondary to cardiac glycogen depletion, has been proposed as the cause of death (Costella and Virgo 1980).

Conflicting results have been obtained in animal studies designed to evaluate the ability of dieldrin to cause external malformations or skeletal anomalies. Such effects have been observed in mice and hamsters following a single very large dose of dieldrin in mid-gestation (Ottolenghi et al. 1974). Significant increases in cleft palate and webbed foot were observed in mice following a dose of 15 mg/kg dieldrin on GD 9. Significant increases in cleft palate, open eye, and webbed foot were observed in fetuses from hamsters dosed once on gestation day 7, 8, or 9 at 30 mg/kg dieldrin. Other developmental effects included increased fetal mortality and depressed fetal weight. A significant increase in supernumerary ribs was observed in mice from dams administered dieldrin orally on GDs 7–16 at 3 or 6 mg/kg/day (Chernoff et al. 1975). No developmental defects were observed in studies of rats administered dieldrin orally during GDs 7–16 at doses as high as 6 mg/kg/day (Chernoff et al. 1975) or in mice exposed to 1–4 mg/kg/day on GDs 6–14 (Dix et al. 1977).

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

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

2.18 OTHER NONCANCER

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

2.19 CANCER

Cancer Classification

Aldrin. The Department of Health and Human Services (HHS) has not evaluated the carcinogenicity of aldrin (NTP 2016a). EPA classified aldrin as Group B2 (probable human carcinogen) based on sufficient evidence in animals (significantly increased liver tumor responses in three strains of male and female mice) and noted that tumor induction was also observed in structurally related chemicals (including dieldrin, a pesticide and metabolite of aldrin) (EPA 2003; IRIS 1987). EPA considered the human carcinogenicity data for aldrin to be inadequate.

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

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

Dieldrin. The HHS has not evaluated the carcinogenicity of dieldrin (NTP 2016a). EPA classified dieldrin as Group B2 (probable human carcinogen) based on sufficient evidence of carcinogenicity (liver tumors) in seven strains of mice treated orally (IRIS 1988). EPA noted that dieldrin is structurally related to other compounds (including aldrin) that produce tumors in rodents. EPA considered the human carcinogenicity data for dieldrin to be inadequate.

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

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

Epidemiological Studies. The database of information regarding the potential human carcinogenicity of aldrin and dieldrin includes evaluation of cohorts involved in aldrin and dieldrin production, cohort or case-control studies employing self-reported usage of aldrin and/or dieldrin, and case-control studies using blood or tissue aldrin or dieldrin levels as evidence of exposure. A major limitation common to the epidemiological studies for aldrin and dieldrin is the lack of quantitative measures of exposure. Other limitations include exposure to other pesticides, relatively small numbers of cases for selected cancer types, and possible exposure to other known human carcinogens.

The potential carcinogenicity of aldrin and dieldrin was evaluated in a cohort of 1,155 workers at an organochlorine manufacturing plant in Colorado (Ditraglia et al. 1981). All workers in the study had been employed for at least 6 months prior to December 31, 1964. Vital status was ascertained through December 31, 1976. There was no increased risk of death from all malignant neoplasms, or cancers of the esophagus, stomach, intestines, rectum, liver, pancreas, respiratory system, bladder and urinary system, or lymphatic and hematopoietic system. Numbers of observed deaths from these selected cancer types ranged from one to seven. Follow-up evaluation of this cohort through December 31, 1987 revealed 5 deaths from liver biliary/gallbladder cancer (1.27 expected) (Brown 1992). Amoateng-Adjepong et al.

(1995) expanded the cohort to include all employees who ever worked at the plant during 1952 through 1982 and for whom social security numbers and dates of employment and birth were known (n=2,384). Among white male workers in hourly jobs, five deaths from hepatobiliary cancer were observed (two expected). Observed deaths from other cancers (digestive system, colon/rectum, respiratory system, lung, brain and central nervous system, lymphopoietic) and all cancer types were similar to those expected based on Colorado rates. A major limitation of this cohort is the production of numerous other pesticide compounds at the plant in addition to aldrin and dieldrin, which limits the usefulness of the results.

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

A number of cohort or case-control studies have used data collected as part of the Agricultural Health Study of pesticide applicators in Iowa and North Carolina to evaluate possible associations between self-reported use of aldrin or dieldrin and risk of non-Hodgkin's lymphoma (Alavanja et al. 2014; Cantor et al. 1992; De Roos et al. 2003; Lee et al. 2004a; McDuffie et al. 2001; Purdue et al. 2006; Schroeder et al. 2001); multiple myeloma (Alavanja et al. 2014); female breast cancer (Engel et al. 2005; Louis et al. 2017); prostate cancer (Koutros et al. 2013a, 2013b; Purdue et al. 2006); bladder cancer (Koutros et al. 2016; Purdue et al. 2006); leukemia (Brown et al. 1990; Purdue et al. 2006); lung cancer (Bonner et al. 2017; Purdue et al. 2006); stomach/esophageal cancer (Lee et al. 2004b); pancreatic cancer (Clary and Ritz 2003); colon cancer (Purdue et al. 2006); rectal cancer (Purdue et al. 2006); melanoma (Dennis et al. 2010; Purdue et al. 2006); soft tissue sarcoma (Pahwa et al. 2011); or childhood cancer (Flower et al. 2004). As shown in Table 2-3, most studies found no association between self-reported aldrin or dieldrin use and risk of selected cancer types.

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

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

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

Cancer type	Association[a]	No association[b]
Rectum		Purdue et al. 2006
Melanoma		Purdue et al. 2006

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

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

Some studies evaluated possible associations between dieldrin in blood or adipose tissue and risk of non-Hodgkin's lymphoma (Cantor et al. 2003; Chen et al. 2020; De Roos et al. 2005; Quintana et al. 2004); female breast cancer (Gammon et al. 2002; Hoyer et al. 1998, 2001, 2002; Mathur et al. 2002; Ward et al. 2000); or prostate cancer (Ritchie et al. 2003). Table 2-4 provides a summary list of reported association/lack of association between dieldrin in blood or adipose tissue and risk of selected cancer types. The most convincing evidence for an association between blood or adipose tissue dieldrin levels and cancer risk was for female breast cancer among estrogen receptor negative (ER^-) breast cancer cases (Hoyer et al. 2001). Three studies examined the possible association between blood aldrin levels and the risk of female breast cancer. Ward et al. (2000) did not find an association in a case control study of women aged 18–60 years. No association was observed between aldrin levels and female breast cancer in a case control study of women (mean age: 47.8 years) in China (Miao et al. 2021). Ibarluzea et al. (2004) found an association among postmenopausal women.

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

Cancer type	Association[a]	No association[b]
Non-Hodgkin's lymphoma	Quintana et al. 2004	Cantor et al. 2003 Chen et al. 2020 De Roos et al. 2005
Female breast cancer	Hoyer et al. 1998 Hoyer et al. 2001[c] Ibarluzea et al. 2004[d] Miao et al. 2021	Gammon et al. 2002 Hoyer et al. 2002 Ibarluzea et al. 2004[e] Ward et al. 2000
Prostate cancer		Ritchie et al. 2003

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

Animal Studies

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

NCI (1978a) observed significantly increased incidences of follicular cell adenoma and carcinoma of the thyroid in Osborne-Mendel male rats receiving 2.1 mg/kg/day aldrin in the diet for up to 74–80 weeks, but not at 4.2 mg/kg/day. Similarly-treated female rats exhibited significantly increased incidences of adrenal cortical adenoma and combined adenoma and carcinoma at 2.3 mg/kg/day; however, incidences of these tumor types were not significantly increased at 4.6 mg/kg/day. The study authors considered the lack of a dose-response to suggest the lack of a carcinogenic response.

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

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

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

the reporting of the number of females examined at the 0.017 and 0.17 mg/kg/day treatment levels (Hunt et al. 1975). Increased incidence of hepatocellular adenoma and carcinoma (combined) was also observed among CF1 mice administered dieldrin in the diet for up to 128 weeks at 0.43 mg/kg/day (Walker et al. (1973).

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

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

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

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

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

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

The effects of dieldrin on changes in hepatocyte DNA synthesis, mitosis, apoptosis, and ploidy were studied in rats and mice treated with 0, 1, 3, or 10 mg dieldrin/kg in the diet (Kamendulis et al. 2001). No changes were observed in rat liver. Liver from mice fed only the highest dose (10 mg dieldrin/kg) exhibited significantly increased DNA synthesis and mitosis at 14, 28, or 90 days on the diet and a

significant increase in octaploid (8N) hepatocytes. The apoptotic index in the liver of mice in any treatment group did not change over a 90-day treatment and study period.

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

Wang et al. (2020) proposed that dieldrin-induced liver cancer is mediated through the nuclear constitutive androstane receptor (CAR), a nuclear receptor subfamily. Oral exposure of mice to dieldrin resulted in expression of genes that are associated with CAR. In addition, Wang et al. (2020) concluded that dieldrin-induced oxidative stress and damage contributed to hepatocarcinogenesis.

2.20 GENOTOXICITY

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

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

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

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

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

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium				
TA98, TA1535, TA 1537, TA1538	Gene mutation	–	–	NTP 2016b
TA100	Gene mutation	–	+/–	NTP 2016b
TA98, TA 100, TA1535, TA1537, TA1538	Gene mutation	–	–	Moriya et al. 1983
TA1535, TA1536, TA1537, TA1538	Gene mutation		–	Shirasu 1975; Shirasu et al. 1976
TA98, TA 100, TA1535, TA1537, TA1538	Gene mutation	–		EPA 1977
Escherichia coli				
WP2, WP67, CM871	Gene mutation	–	–	De Flora et al. 1984
WP2 *hcr*	Gene mutation	–	–	Moriya et al. 1983
WP2	Gene mutation		–	Shirasu 1975; Shirasu et al. 1976

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

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Bacillus subtilis				
H17 Rec$^+$, M45 Rec$^-$	DNA damage	–	–	De Flora et al. 1984
H17 Rec$^+$, M45 Rec$^-$	DNA damage		–	Shirasu et al. 1976
Mammalian cells:				
Human				
Lymphocytes	Chromosomal aberrations		(+)	Georgian 1975
Lymphocytes	Unscheduled DNA synthesis		(+)	Rocchi et al. 1980
SV-40 transformed fibroblasts	Unscheduled DNA synthesis	+	+	Ahmed et al. 1977a

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

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

Aldrin did not induce mutagenicity in a variety of *in vitro* test systems (see Table 2-6) or DNA damage in *Bacillus subtilis* in the presence (De Flora et al. 1984) or absence (De Flora et al. 1984; Shirasu et al. 1976) of exogenous metabolic activation. Ahmed et al. (1977a) reported unscheduled DNA synthesis in SV-40 transformed human fibroblasts. *In vitro* assays that employed human lymphocytes provided equivocal results for chromosomal aberrations (Georgian 1975) and unscheduled DNA synthesis (Rocchi et al. 1980).

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

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

Species/test substance (exposure route)	Endpoint	Results	Reference
Human			
Lymphocytes (dieldrin plant workers)	Chromosomal aberrations	–	Dean et al. 1975
Mouse			
Liver (oral)	DNA damage	+	Wang et al. 2020
Liver (oral)	Gene mutation	–	Bauer-Hofmann et al. 1990
Liver (oral)	Gene mutation	–	Bauer-Hofmann et al. 1992
Liver tumors (oral)	Gene mutation	–	Bauer-Hofmann et al. 1990
Liver tumors (oral)	Gene mutation	–	Bauer-Hofmann et al. 1990
Bone marrow (oral)	Unscheduled DNA synthesis	–	Bachowksi et al. 1998
Bone marrow (i.p.)	Chromosomal aberrations	+	Majumdar et al. 1976
Bone marrow (i.p.)	Chromosomal aberrations	+	Markaryan 1966
Bone marrow (i.p.)	Micronuclei	+	Cicchetti et al. 1999
Germinal tissue (oral)	Dominant lethality	–	Dean et al. 1975
Germinal tissue (oral)	Dominant lethality	–	Epstein et al. 1972
Germinal tissue (i.p.)	Dominant lethality	–	Epstein et al. 1972
Chinese hamster			
Bone marrow (oral)	Chromosomal aberrations	–	Dean et al. 1975
Drosophila melanogaster			
Wing spot test (oral)	Gene mutation	–	Osaba et al. 1999

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

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

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium				
TA98, TA 100, TA1535, TA1537, TA1538	Gene mutation	–	–	De Flora et al. 1984
TA98, TA100	Gene mutation		–	De Flora et al. 1989
TA98, TA100	Gene mutation		–	Glatt et al. 1983
TA98, TA100, TA1535, TA1538	Gene mutation	–		Anderson and Styles 1978
TA1535, TA1537	Gene mutation		–	Glatt et al. 1983
TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Haworth et al. 1983

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

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
TA98, 100	Gene mutation	+	+	Majumdar et al. 1977
TA1535	Gene mutation	+	–	Majumdar et al. 1977
TA1535, TA1536, TA1537, TA1538	Gene mutation	–	–	Marshall et al. 1976
TA98, TA 100, TA1535, TA1537, TA1538	Gene mutation	–	–	Moriya et al. 1983
TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 2016c
TA1535, TA1536, TA1537, TA1538	Gene mutation		–	Shirasu 1975; Shirasu et al. 1976
TA98, TA100	Gene mutation	–	–	Wade et al. 1979
Escherichia coli				
WP2 *Try*$^-$	Gene mutation		–	Ashwood-Smith et al. 1972
WP2, WP67, CM871	Gene mutation	–	–	De Flora et al. 1984
Strain not specified	Gene mutation		–	Fahrig 1974
WP2 *hcr*	Gene mutation	–	–	Moriya et al. 1983
WP2	Gene mutation		–	Shirasu 1975; Shirasu et al. 1976
ColE1 plasmid DNA	DNA strand breaks		–	Griffin and Hill 1978
Bacillus subtilis				
H17 Rec$^+$, M45 Rec$^-$	DNA damage	–	–	De Flora et al. 1984
H17 Rec$^+$, M45 Rec$^-$	DNA damage		–	Shirasu et al. 1976
Eukaryotic organisms:				
Saccharomyces cerevisiae				
D4	Mitotic gene conversion		–	Dean et al. 1975
RS112	Mitotic gene conversion		–	Fahrig 1974
Aspergillus nidulans				
35 (haploid)	Gene mutation		–	Crebelli et al. 1986
P1 (diploid)	Aneuploidy		–	Crebelli et al. 1986
Mammalian cells:				
Human				
Lymphocytes	Unscheduled DNA synthesis		(+)	Rocchi et al. 1980
Ovary epithelial cells	DNA damage		+	Shah et al. 2020
SV-40 transformed fibroblasts	Unscheduled DNA synthesis	+	+	Ahmed et al. 1977a
Embryonic lung WI-38	Chromosomal aberrations	+		Majumdar et al. 1976

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

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

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

Dieldrin has been evaluated for potential genotoxicity in a number of *in vivo* evaluations. There was no evidence of dieldrin-related increases in chromosomal aberrations in cultured lymphocytes from workers at a dieldrin production facility (Dean et al. 1975). Negative results were obtained from tests of dieldrin-induced gene mutations in livers or liver tumors from orally-exposed mice (Bauer-Hofmann et al. 1990, 1992) or orally-exposed *Drosophila melanogaster* (Osaba et al. 1999). Dieldrin did not induce chromosomal aberrations in bone marrow from orally-exposed Chinese hamsters (Dean et al. 1975). Dieldrin did not induce dominant lethality in mice exposed via oral or intraperitoneal injection routes (Dean et al. 1975; Epstein et al. 1972). However, dieldrin induced chromosomal aberrations (Majumdar et al. 1976) and micronuclei (Cicchetti et al. 1999) in bone marrow from mice exposed by intraperitoneal injection.

In vitro assays for dieldrin-induced mutagenicity in a variety of bacterial test systems were predominantly negative. Dieldrin did not induce mutagenicity in the fungus, *Aspergillus nidulans* (Crebelli et al. 1986). However, positive results were obtained for gene mutation in mouse L5178Y lymphoma cells (McGregor

et al. 1991) and Chinese hamster V79 lung fibroblasts (Ahmed et al. 1977b) in the absence of exogenous metabolic activation. Dieldrin did not induce mitotic gene conversion in two strains of *Saccharomyces cerevisiae* (Dean et al. 1975; Fahrig 1974).

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

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

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