APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
CAS Numbers: 309-00-2
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
CAS Numbers: 309-00-2
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
CAS Numbers: 309-00-2
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
CAS Numbers: 309-00-2
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.002 mg/kg/day (2 µg/kg/day)
Critical Effect: Neurodevelopmental toxicity in offspring
Reference: Al-Hachim 1971
Point of Departure: 2 mg/kg/day (LOAEL)
Uncertainty Factor: 1,000
LSE Graph Key: 7
Species: Mouse

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

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

[a]Mean ± SEM for 10 pups/group.

Source: Al-Hachim 1971

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

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

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

MRL = LOAEL ÷ uncertainty factor
2 mg/kg/day ÷ 1,000 = 0.002 mg/kg/day (2 µg/kg/day)

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
CAS Numbers: 309-00-2
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate

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

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

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

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

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

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

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Aldrin
CAS Numbers: 309-00-2
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.00004 mg/kg/day (0.04 µg/kg/day)
Critical Effect: Increased liver weight and histological alterations in liver
Reference: Fitzhugh et al. 1964
Point of Departure: 0.037 mg/kg/day (LOAEL)
Uncertainty Factor: 1,000
LSE Graph Key: 23
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.00004 mg/kg/day (0.04 µg/kg/day) has been derived for aldrin. The MRL is based on a LOAEL of 0.037 mg/kg/day for increased liver weight and hepatic histological alterations (enlarged centrilobular hepatocytes with cytoplasmic oxyphilia, and peripheral migration of basophilic granules) in rats receiving aldrin from the food for 2 years (Fitzhugh et al. 1964). The study did not identify a NOAEL. The LOAEL of 0.037 mg/kg/day was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MRL = LOAEL ÷ uncertainty factor
0.037 mg/kg/day ÷ 1,000 = 0.00004 mg/kg/day (0.04 µg/kg/day)

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
CAS Numbers: 60-57-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
CAS Numbers: 60-57-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
CAS Numbers: 60-57-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
CAS Numbers: 60-57-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Acute

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

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

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

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

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

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

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

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
CAS Numbers: 60-57-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.0001 mg/kg/day (0.1 µg/kg/day)
Critical Effect: Neurotoxicity
Reference: Smith et al. 1976
Point of Departure: 0.01 mg/kg/day (NOAEL)
Uncertainty Factor: 100
LSE Graph Key: 31
Species: Monkey

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

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

Calculations

Intermittent Exposure: Not applicable.

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

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

MRL = NOAEL ÷ uncertainty factor
0.01 mg/kg/day ÷ 100 = 0.0001 mg/kg/day (0.1 µg/kg/day)

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

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dieldrin
CAS Numbers: 60-57-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.00005 mg/kg/day (0.05 µg/kg/day)
Critical Effect: Hepatotoxicity
Reference: Walker et al. 1969
Point of Departure: 0.005 mg/kg/day (NOAEL)
Uncertainty Factor: 100
LSE Graph Key: 52
Species: Rat

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

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

Source: Walker et al. 1969

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

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

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

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

MRL = NOAEL ÷ uncertainty factor
0.005 mg/kg/day ÷ 100 = 0.00005 mg/kg/day (0.05 µg/kg/day)

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

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ALDRIN/DIELDRIN

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

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

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

Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for aldrin/dieldrin released for public comment in 2021; thus, the literature search was restricted to studies published between January 2018 and October 2021. The following main databases were searched in October 2021:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for aldrin/dieldrin. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to aldrin/dieldrin were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2021	(("Aldrin"[mh] OR 309-00-2[rn] OR "Dieldrin"[mh] OR 60-57-1[rn]) OR (("(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-"[tw] OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1.alpha.,4.alpha.,4a.beta.,5.alpha.,8.alpha.,8a.beta.)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-, endo, exo-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-

Table B-2. Database Query Strings

Database search date	Query string
	hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-"[tw] OR "Aldocit"[tw] OR "Aldrex"[tw] OR "Aldrin"[tw] OR "Aldrite"[tw] OR "Aldron"[tw] OR "Aldrosol"[tw] OR "Algran"[tw] OR "Altox"[tw] OR "Andrex"[tw] OR "Complex Hydrocarbon Adrex 30"[tw] OR "Compound 118"[tw] OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene"[tw] OR "HHDN"[tw] OR "Isodrin"[tw] OR "Kortofin"[tw] OR "NA 2761"[tw] OR "NA 2762"[tw] OR "Octalene"[tw] OR "SD 2794"[tw] OR "Seedrin"[tw] OR "Soilgrin"[tw] OR "Tatuzinho"[tw] OR "Tipula"[tw] OR ("dimethanonaphthalene"[tw] AND "hexachloro"[tw] AND "hexahydro"[tw])) OR ("(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-Dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene"[tw] OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-"[tw] OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-, endo, exo-"[tw] OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6.2.1.1 3,6.0 2,7)dodec-9-ene"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "2,7:3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a.alpha.,2.beta.,2a.alpha.,3.beta.,6.beta.,6a.alpha.,7.beta.,7a.alpha.)-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-"[tw] OR "3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "Alvit"[tw] OR "Compound 497"[tw] OR "Dieldren"[tw] OR "Dieldrex"[tw] OR "Dieldrin"[tw] OR "Dieldrite"[tw] OR "Dielmoth"[tw] OR "Dildrin"[tw] OR "Dorytox"[tw] OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4:5,8-dimethanonaphthalene"[tw] OR "endo, exo-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7:3,6-dimethenapth(2,3-b)oxirene"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"HEOD"[tw] OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene"[tw] OR "Illoxol"[tw] OR "Insecticide No. 497"[tw] OR "Insectlack"[tw] OR "Kombi-Albertan"[tw] OR "Moth Snub D"[tw] OR "NA 2761"[tw] OR "Octalox"[tw] OR "Panoram D-31"[tw] OR "Red Shield"[tw] OR "SD 3417"[tw] OR "Shelltox"[tw] OR "Termitox"[tw] OR ("dimethanonaphth"[tw] AND "oxirene"[tw] AND "hexachloro"[tw] AND "octahydro"[tw]) OR ("dimethanonaphthalene"[tw] AND "hexachloro"[tw] AND "octahydro"[tw] AND "epoxy"[tw]))))) AND (2018:3000[dp] OR 2019/04/01:3000[edat] OR 2019/04/01:3000[crdt] OR 2019/04/01:3000[mhda])
NTRL	
10/2021	"1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "Aldrex" OR "Aldrin" OR "Aldron" OR "Altox" OR "Compound 118" OR "HHDN" OR "Isodrin" OR "Octalene" OR "Tipula" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "Alvit" OR "Dieldren" OR "Dieldrex" OR "Dieldrin" OR "HEOD" OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene" OR "Shelltox" "(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "Aldocit" OR "Aldrite" OR "Aldrosol" OR "Algran" OR "Andrex" OR "Complex Hydrocarbon Adrex 30" OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene" OR "Kortofin" OR "NA 2761" OR "NA 2762" OR "SD 2794" OR "Seedrin" OR "Soilgrin" OR "Tatuzinho"

Table B-2. Database Query Strings

Database search date	Query string
	"(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-, endo, exo-" OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6 2 1 1 3,6 0 2,7)dodec-9-ene" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "Compound 497" OR "Dieldrite" OR "Dielmoth" OR "Dildrin" OR "Dorytox" OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4 5,8-dimethanonaphthalene" OR "endo, exo-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethenapth(2,3-b)oxirene" OR "Illoxol" OR "Insecticide No 497" OR "Insectlack" OR "Kombi-Albertan" OR "Moth Snub D" OR "NA 2761" OR "Octalox" OR "Panoram D-31" OR "Red Shield" OR "SD 3417" OR "Termitox"
Toxcenter	
10/2021	FILE 'TOXCENTER' ENTERED AT 15:42:58 ON 26 OCT 2021 CHARGED TO COST=EH038.12.01.LB.04 L1 10552 SEA FILE=TOXCENTER 309-00-2 L2 18530 SEA FILE=TOXCENTER 60-57-1 L3 21610 SEA FILE=TOXCENTER L1 OR L2 L4 21283 SEA FILE=TOXCENTER L3 NOT PATENT/DT L5 21251 SEA FILE=TOXCENTER L4 NOT TSCATS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L6 726 SEA FILE=TOXCENTER L5 AND ED>=20190401 ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L22 QUE (ENDOCRIN? AND DISRUPT?) L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)

Table B-2. Database Query Strings

Database search date	Query string
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L29 QUE (NEPHROTOX? OR HEPATOTOX?) L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L35 QUE L32 OR L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 468 SEA FILE=TOXCENTER L6 AND L37 L39 28 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 93 SEA FILE=TOXCENTER L38 AND BIOSIS/FS L41 347 SEA FILE=TOXCENTER L38 AND CAPLUS/FS L42 0 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 407 DUP REM L39 L40 L41 (61 DUPLICATES REMOVED) ANSWERS '1-407' FROM FILE TOXCENTER L*** DEL 28 S L38 AND MEDLINE/FS L*** DEL 28 S L38 AND MEDLINE/FS L44 28 SEA FILE=TOXCENTER L43 L*** DEL 93 S L38 AND BIOSIS/FS L*** DEL 93 S L38 AND BIOSIS/FS L45 82 SEA FILE=TOXCENTER L43 L*** DEL 347 S L38 AND CAPLUS/FS L*** DEL 347 S L38 AND CAPLUS/FS L46 297 SEA FILE=TOXCENTER L43 L47 379 SEA FILE=TOXCENTER (L44 OR L45 OR L46) NOT MEDLINE/FS D SCAN L47

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2021	Compounds searched: 309-00-2, 60-57-1
NTP	
10/2021	309-00-2 60-57-1 "aldrin" "dieldrin" "Isodrin" "Aldrex" "Aldron" "Altox" "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene" "Compound 118" "HHDN" "Octalene" "Tipula" "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene" "Alvit" "Dieldren" "Dieldrex" "HEOD" "Shelltox" "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene" "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene"
Regulations.gov	
10/2021	Documents and Dockets: limited to EPA, Notices, posted 01/01/2018-present aldrin dieldrin 309-00-2 60-57-1 HHDN isodrin dimethanonaphthalene
NIH RePORTER	
12/2021	Search Criteria Fiscal Year: Active ProjectsText Search: "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexachloro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "Aldrex" OR "Aldrin" OR "Aldron" OR "Altox" OR "Compound 118" OR "HHDN" OR "Isodrin" OR "Octalene" OR "Tipula" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene" OR "Alvit" OR "Dieldren" OR "Dieldrex" OR "Dieldrin" OR "HEOD" OR "Hexachloroepoxyoctahydro-endo, exo-dimethanonaphthalene" OR "Shelltox" (advanced)Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active ProjectsText Search: "(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "(1R, 4S, 4aS, 5S, 8R, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1a, 4a, 4ab, 5a, 8a, 8ab)-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)1,4 ,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-(1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-1,4,5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-1,4,5,8-endo, endodimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1,4,4a, 5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-10-hexachloro-1,4,4a, 5,8,8a-hexahydro-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	,(alpha, 4alpha, 4beta, 5alpha, 8alpha, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexa-chloro-1,4,4a, 5,8,8a, -hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro (1alpha, 4alpha, 4abeta, 5beta, 8beta, 8abeta)-" OR "1,4,5,8-Dimethanonaphthalene, 1,2,3,4,10,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1 alpha ,4 alpha ,4a beta ,5 alpha ,8 alpha ,8a beta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-,(1R, 4S, 4aS, 5S, 8R, 8aR)-rel-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a-hexahydro-, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a, 5,8,8a- hexahydro-(1alpha, 4alpha, 4abeta, 5alpha, 8alpha, 8abeta)-" OR "Aldocit" OR "Aldrite" OR "Aldrosol" OR "Algran" OR "Andrex" OR "Complex Hydrocarbon Adrex 30" OR "Hexachlorohexahydro-endo-exo-dimethanonaphthalene" OR "Kortofin" OR "NA 2761" OR "NA 2762" OR "SD 2794" OR "Seedrin" (advanced)Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active ProjectsText Search: "(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)Octahydro-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene" OR "(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth[2,3-b]oxirene" OR "(1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a, 5,6,7,8,8a-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1R, 4S, 4aS, 5R, 6R, 7S, 8S, 8aR-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo-" OR "1,4 5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a, 5,6,7,8,8a-octahydro-, endo, exo-" OR "1,8,9,10,11,11-Hexachloro-4,5-exo epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6 2 1 1 3,6 0 2,7)dodec-9-ene" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a,

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "Soilgrin" OR "Tatuzinho" (advanced)Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active ProjectsText Search: "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1a alpha ,2 beta ,2a alpha ,3 beta ,6 beta ,6a alpha ,7 beta ,7a alpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aR, 2R, 2aS, 3S, 6R, 6aR, 7S, 7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9- hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-,(1aalpha, 2beta, 2aalpha, 3beta, 6beta, 6aalpha, 7beta, 7aalpha)-" OR "3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "Compound 497" OR "Dieldrite" OR "Dielmoth" OR "Dildrin" OR "Dorytox" OR "endo, exo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4 5,8-dimethanonaphthalene" OR "endo, exo-3,4,5,6,9,9-Hexachloro-1a, 2,2a, 3,6,6a, 7,7a-octahydro-2,7 3,6-dimethenapth(2,3-b)oxirene" OR "Illoxol" OR "Insecticide No 497" OR "Insectlack" OR "Kombi-Albertan" OR "Moth Snub D" OR "NA 2761" OR "Octalox" OR "Panoram D-31" OR "Red Shield" OR "SD 3417" OR "Termitox" (advanced)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 582
- Number of records identified from other strategies: 11
- Total number of records to undergo literature screening: 593

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

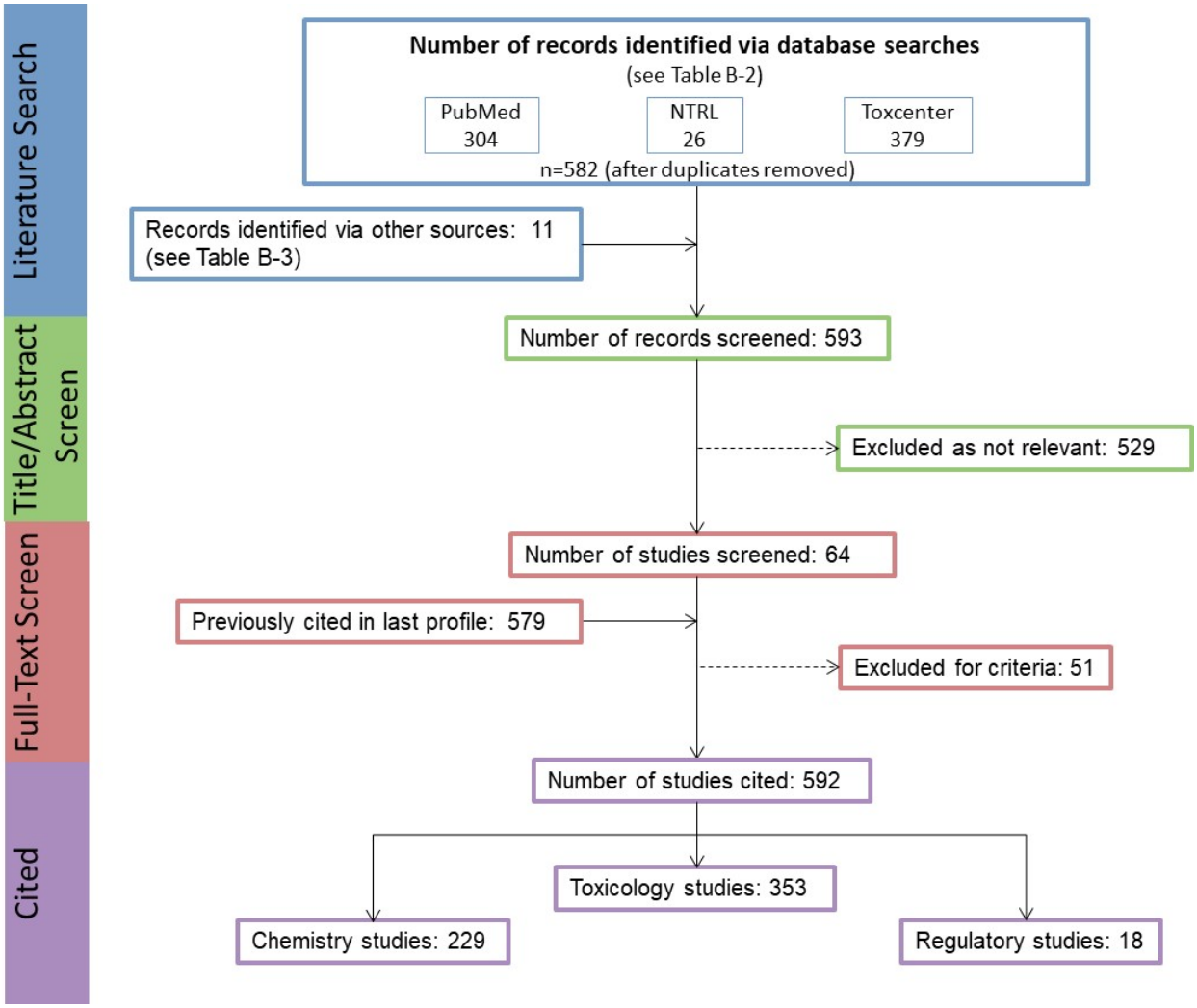
- Number of titles and abstracts screened: 593
- Number of studies considered relevant and moved to the next step: 64

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 64
- Number of studies cited in the pre-public draft of the toxicological profile: 579
- Total number of studies cited in the profile: 592

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

Figure B-1. October 2021 Literature Search Results and Screen for Aldrin/Dieldrin



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ALDRIN AND DIELDRIN

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to aldrin/dieldrin, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to aldrin and dieldrin:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

The systematic review for this profile is divided into three sections:

1. Steps 1, 2, and 3 for aldrin and dieldrin (Sections C.1, C.2, and C.3)
2. Steps 4, 5, 6, 7, and 8 for aldrin (Sections C.4, C.5, C.6, C.7, and C.8)
3. Steps 4, 5, 6, 7, and 8 for dieldrin (Sections C.9, C.10, C.11, C.12, and C.13)

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to aldrin and dieldrin. The inclusion criteria used to identify relevant studies examining the health effects of aldrin/dieldrin are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of aldrin/dieldrin. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for aldrin/dieldrin released for public comment in 2021. See Appendix B for the databases searched and the search strategy.

A total of 593 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of aldrin/dieldrin.

Title and Abstract Screen. In the Title and Abstract Screen step, 593 records were reviewed; 22 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 154 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 154 documents, 226 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Aldrin/Dieldrin and overviews of the results are presented in Sections 2.2–2.18 of the profile. Results from oral exposure studies are summarized in the Table 2-1 (Levels of Significant Exposure to Aldrin) and Table 2-2 (Levels of Significant Exposure to Dieldrin). Limited information regarding the effects of inhalation or dermal exposure to aldrin or dieldrin mainly involves evaluation of acute lethality. Results from animal studies that employed inhalation or dermal exposure routes are summarized in the appropriate sections of Chapter 2 but are not presented in tables summarizing levels of significant exposure.

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—ALDRIN

Overviews of the potential health effect outcomes for aldrin identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Multiple occupational cohorts were evaluated for possible associations between aldrin and/or dieldrin exposure and risk of death from selected noncancer or cancer endpoints. Cohorts with potential exposure to both aldrin and dieldrin are included in sections C.4–C-8 for aldrin and Sections C.9–C.13 for dieldrin. Studies in which the reported exposure was to aldrin during its production or use are assumed to have primarily involved the inhalation exposure route and exposure duration was considered to be chronic unless otherwise indicated. Other human studies involving aldrin include case-control studies, self-reported use, and individual case reports. Data from human studies evaluating possible associations between serum dieldrin levels and selected health outcomes are presented in sections C.9–C.13 under the assumption that exposures were to dieldrin, although some exposures may have been to aldrin because dieldrin is readily formed from aldrin in biological systems. Animal studies of aldrin predominantly employed the oral exposure route. Collectively, the animal studies examined a number of endpoints. The most sensitive endpoints (outcomes) were body weight, hepatic, neurological, reproductive, and developmental. Animal studies evaluating these potential outcomes were carried through Steps 4–8 of the systematic review. Human studies evaluating potential hepatic, neurological, reproductive, and developmental outcomes were also carried through Steps 4–8 of the systematic review. No human studies evaluated body weight.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Aldrin Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		6	5	1	1		4	2	1				3		1		14
		2											2				4
Case control													1		2		3
Population																	6
																	1
Case series					1								2				
					1								2				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series								1					2	1			
								1					2	1			
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

APPENDIX C

Table C-4. Overview of the Health Outcomes for Aldrin Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration							1 1						8 8		3 3		
Intermediate-duration	3 1			1 1			3 2	1 0					2 2	2 2	2 2		
Chronic-duration	7 2	2 0	2 0	2 0	3 1	2 0	6 4	4 2	2 0	2 0	2 0		3 3		1 1		2 2
Dermal studies																	
Acute-duration													1 1				
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—ALDRIN

C.5.1 Risk of Bias Assessment—Aldrin

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of aldrin health effects studies (observational epidemiology studies and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for Aldrin—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Hepatic effects							
Cohort							
de Jong 1991	+	–	+	–	+	+	Second
Hoogendam et al. 1965	+	–	+	–	+	+	Second
Hunter et al. 1972	+	–	+	–	+	+	Second
Jager 1970	+	–	+	–	+	+	Second
van Sittert and de Jong 1987	+	–	+	–	+	+	Second
Outcome: Neurological effects							
Cohort							
de Jong 1991	+	–	+	–	+	+	Second
Hoogendam et al. 1962	NA	–	+	–	+	+	Second
Hoogendam et al. 1965	NA	–	+	–	+	+	Second
Case-Control							
Zhang et al. 2021	++	–	+	–	+	+	Second
Case reports							
Avar and Czegledi-Janko 1970	NA	–	+	–	+	+	Second
Gupta 1975	NA	–	+	–	+	+	Second
Kazantzis et al. 1964	NA	–	+	–	+	+	Second
Spiotta 1951	NA	+	+	–	+	+	Second

Table C-8. Summary of Risk of Bias Assessment for Aldrin—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate?	Confounding bias — **Study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — **Confidence in the exposure characterization?***	Detection bias — **Confidence in the outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Risk of bias tier
Outcome: Reproductive effects							
Population-based case-control							
Saxena et al. 1980	+	–	+	–	+	+	Second
Outcome: Developmental effects							
Case-control							
Pi et al. 2020	+	–	+	–	+	+	Second
Yin et al. 2021	+	–	+	–	+	+	Second
Cross-sectional							
Dwivedi et al. 2021	NA	–	+	–	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in the exposure characterization?	Detection bias: **Confidence in the outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Other bias: Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Body weight										
Oral intermediate exposure										
Treon et al. 1951a rat	+	+	+	+	+	+	+	+	+	First
Treon et al. 1953a rat	+	+	+	+	+	+	+	+	+	First
Treon et al. 1955 dog	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Deichmann et al. 1967 rat	+	+	+	+	+	+	+	+	+	First
Deichmann et al. 1970 rat	+	+	+	+	+	+	+	+	+	First
Fitzhugh et al. 1964 rat	+	+	+	+	+	+	+	+	+	First
Fitzhugh et al. 1964 dog	+	+	+	+	+	+	+	+	+	First
NCI 1978a rat	++	+	+	+	+	+	+	+	+	First
NCI 1978a mouse	++	+	+	+	+	+	+	+	+	First
Treon et al. 1955 dog	+	+	+	+	+	+	+	+	+	First
Outcome: Hepatic effects										
Oral acute exposure										
Treon et al. 1951a rat	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure										
Treon et al. 1951a rat	+	+	+	+	+	+	+	+	+	First
Treon et al. 1951b dog	+	+	+	+	+	+	+	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in the exposure characterization?	Detection bias: **Confidence in the outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Other bias: Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Treon et al. 1953a rat	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Deichmann et al. 1970 rat	+	+	+	+	+	+	+	+	+	First
Fitzhugh et al. 1964 rat	+	+	+	+	+	+	+	+	+	First
Fitzhugh et al. 1964 dog	+	+	+	+	+	+	+	+	+	First
Kitselman 1953 dog	+	+	+	+	+	+	+	+	+	First
NCI 1978a rat	++	+	+	+	+	+	+	+	+	First
NCI 1978a mouse	++	+	+	+	+	+	+	+	+	First
Outcome: Neurological effects										
Oral acute exposure										
Jamaluddin and Poddar 2001a rat	+	+	+	+	+	+	+	+	+	First
Jamaluddin and Poddar 2001b rat	+	+	+	+	+	+	+	+	+	First
Jamaluddin and Poddar 2003 rat	+	+	+	+	+	+	+	+	+	First
Mehrotra et al. 1989 rat	+	+	+	+	+	+	+	+	+	First
Treon et al. 1951a rat	+	+	+	+	+	+	+	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Oral intermediate exposure										
Treon et al. 1951b dog	+	+	+	+	+	+	+	+	+	First
Treon et al. 1955 dog	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Kitselman 1953 dog	+	+	+	+	+	+	+	+	+	First
NCI 1978a rat	++	+	+	+	+	+	+	+	+	First
NCI 1978a mouse	++	+	+	+	+	+	+	+	+	First
Dermal acute exposure										
Treon et al. 1953b rabbit	+	+	+	+	+	+	+	+	+	First
Outcome: Reproductive effects										
Oral intermediate exposure										
Keplinger et al. 1970 mouse	+	+	+	+	+	+	+	+	+	First
Treon et al. 1954a rat	+	+	+	+	+	+	+	+	+	First
Outcome: Developmental effects										
Oral acute exposure										
Al-Hachim 1971 mouse	+	+	+	+	+	+	+	+	+	First
Ottolenghi et al. 1974 mouse	+	+	+	+	+	+	+	+	+	First
Ottolenghi et al. 1974 hamster	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure										

Table C-9. Summary of Risk of Bias Assessment for Aldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Keplinger et al. 1970 mouse	+	+	+	+	+	+	+	+	+	First
Treon et al. 1954a rat	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Kitselman 1953 dog	+	+	+	+	+	+	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—ALDRIN

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to aldrin and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating—Aldrin

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to aldrin and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining hepatic, neurological, and reproductive outcomes in the observational epidemiology studies; and body weight, hepatic, neurological, reproductive, and developmental outcomes in animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Aldrin—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Developmental					
Case-control					
Pi et al. 2020	No	Yes	Yes	Yes	Moderate
Yin et al. 2021	No	Yes	Yes	Yes	Moderate

Table C-13. Presence of Key Features of Study Design for Aldrin—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Cross-sectional					
Dwivedi et al. 2021	No	Yes	Yes	No	Low
Outcome: Hepatic effects					
Cohort					
de Jong 1991	No	Yes	Yes	Yes	Moderate
Hoogendam et al. 1965	No	Yes	Yes	No	Low
Hunter et al. 1972	No	Yes	Yes	Yes	Moderate
Jager 1970	No	Yes	Yes	Yes	Moderate
van Sittert and de Jong 1987	No	Yes	Yes	Yes	Moderate
Outcome: Neurological effects					
Cohort					
de Jong 1991	No	Yes	Yes	Yes	Moderate
Hoogendam et al. 1962	No	Yes	Yes	No	Low
Hoogendam et al. 1965	No	Yes	Yes	No	Low
Case-control					
Zhang et al. 2021	No	Yes	Yes	Yes	Moderate
Case reports					
Avar and Czegledi-Janko 1970	No	Yes	Yes	No	Low
Gupta 1975	No	Yes	Yes	No	Low
Kazantzis et al. 1964	No	Yes	Yes	No	Low
Spiotta 1951	No	Yes	Yes	No	Low
Outcome: Reproductive effects					
Population-based case-control					
Saxena et al. 1980	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Aldrin—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Body weight effects					
Oral intermediate exposure					
Treon et al. 1951a rat	Yes	Yes	Yes	Yes	High
Treon et al. 1953a rat	Yes	Yes	Yes	Yes	High
Treon et al. 1955 dog	Yes	No	Yes	No	Low
Oral chronic exposure					
Deichmann et al. 1967 rat	Yes	Yes	Yes	Yes	High
Deichmann et al. 1970 rat	Yes	Yes	Yes	Yes	High
Fitzhugh et al. 1964 rat	Yes	Yes	Yes	Yes	High
Fitzhugh et al. 1964 dog	Yes	No	Yes	Yes	Moderate
NCI 1978a rat	Yes	Yes	Yes	Yes	High
NCI 1978a mouse	Yes	Yes	Yes	Yes	High
Treon et al. 1955 dog	Yes	No	Yes	No	Low
Outcome: Hepatic effects					
Oral acute exposure					
Treon et al. 1951a rat	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Treon et al. 1951a rat	Yes	Yes	Yes	Yes	High
Treon et al. 1951b dog	Yes	No	No	No	Very low
Treon et al. 1953a rat	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Deichmann et al. 1970 rat	Yes	Yes	Yes	Yes	High
Fitzhugh et al. 1964 rat	Yes	Yes	Yes	Yes	High
Fitzhugh et al. 1964 dog	Yes	No	Yes	Yes	Moderate
Kitselman 1953 dog	Yes	No	No	No	Very low
NCI 1978a rat	Yes	Yes	Yes	Yes	High
NCI 1978a mouse	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Oral acute exposure					
Jamaluddin and Poddar 2001a rat	Yes	No	Yes	Yes	Moderate
Jamaluddin and Poddar 2001b rat	Yes	No	Yes	Yes	Moderate
Jamaluddin and Poddar 2003 rat	Yes	No	Yes	Yes	Moderate
Mehrotra et al. 1989 rat	Yes	No	Yes	Yes	Moderate
Treon et al. 1951a rat	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for Aldrin—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Oral intermediate exposure					
Treon et al. 1951b dog	Yes	No	No	No	Very low
Treon et al. 1955 dog	Yes	No	Yes	No	Low
Oral chronic exposure					
Kitselman 1953 dog	Yes	No	No	No	Very low
NCI 1978a rat	Yes	Yes	Yes	No	Moderate
NCI 1978a mouse	Yes	Yes	Yes	No	Moderate
Dermal acute exposure					
Treon et al. 1953b rabbit					
Outcome: Reproductive effects					
Oral intermediate exposure					
Keplinger et al. 1970 mouse	Yes	Yes	Yes	Yes	High
Treon et al. 1954a rat	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Oral acute exposure					
Al-Hachim 1971 mouse	Yes	No	Yes	Yes	Moderate
Ottolenghi et al. 1974 mouse	Yes	No	Yes	Yes	Moderate
Ottolenghi et al. 1974 hamster	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Keplinger et al. 1970 mouse	Yes	Yes	Yes	Yes	High
Treon et al. 1954a rat	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Kitselman 1953 dog	Yes	No	No	No	Very low

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Aldrin Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Body weight effects		
Oral intermediate exposure		
Animal studies		
Treon et al. 1951a rat	High	High
Treon et al. 1953a rat	High	
Treon et al. 1955 dog	Low	
Oral chronic exposure		
Animal studies		
Deichmann et al. 1967 rat	High	High
Deichmann et al. 1970 rat	Moderate	
Fitzhugh et al. 1964 rat	Moderate	
Fitzhugh et al. 1964 dog	Very low	
NCI 1978a rat	High	
NCI 1978a mouse	High	
Treon et al. 1955 dog	High	
Outcome: Hepatic effects		
Inhalation chronic exposure		
Human studies		
de Jong 1991	Moderate	Moderate
Hoogendam et al. 1965	Low	
Hunter et al. 1972	Moderate	
Jager 1970	Moderate	
van Sittert and de Jong 1987	Moderate	
Oral acute exposure		
Animal studies		
Treon et al. 1951a rat	Moderate	Moderate
Oral intermediate exposure		
Animal studies		
Treon et al. 1951a rat	High	High
Treon et al. 1951b dog	Very low	
Treon et al. 1953a rat	High	
Oral chronic exposure		
Animal studies		
Deichmann et al. 1970 rat	High	High
Fitzhugh et al. 1964 rat	Moderate	
Fitzhugh et al. 1964 dog	Moderate	
Kitselman 1953 dog	Very low	
NCI 1978a rat	High	
NCI 1978a mouse	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Human studies		
Kazantzis et al. 1964	Low	Low

Table C-15. Initial Confidence Rating for Aldrin Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation chronic exposure		
Human studies		
Avar and Czegledi-Janko 1970	Low	Moderate
de Jong 1981	Moderate	
Hoogendam et al. 1962	Low	
Hoogendam et al. 1965	Low	
Oral acute exposure		
Human studies		
Spiotta 1951	Low	Low
Animal studies		
Jamaluddin and Poddar 2001a rat	Moderate	Moderate
Jamaluddin and Poddar 2001b rat	Moderate	
Jamaluddin and Poddar 2003 rat	Moderate	
Mehrotra et al. 1989 rat	Moderate	
Treon et al. 1951a rat	Moderate	
Oral intermediate exposure		
Human studies		
Gupta 1975	Low	Low
Animal studies		
Treon et al. 1951b dog	Very low	Low
Treon et al. 1955 dog	Low	
Oral chronic exposure		
Human studies		
Zhang et al. 2021	Moderate	Moderate
Animal studies		
Kitselman 1953 dog	Very low	Moderate
NCI 1978a rat	Moderate	
NCI 1978a mouse	Moderate	
Dermal acute exposure		
Animal studies		
Treon et al. 1953b rabbit		
Outcome: Reproductive effects		
Oral intermediate exposure		
Human studies		
Saxena et al. 1980	Moderate	Moderate
Animal studies		
Keplinger et al. 1970 mouse	High	High
Treon et al. 1954a rat	High	
Oral chronic exposure		
Human studies		
Saxena et al. 1980	High	High
Outcome: Developmental effects		
Oral acute exposure		
Animal studies		

Table C-15. Initial Confidence Rating for Aldrin Health Effects Studies

	Initial study confidence	Initial confidence rating
Al-Hachim 1971 mouse	Moderate	Moderate
Ottolenghi et al. 1974 mouse	Moderate	
Ottolenghi et al. 1974 hamster	Moderate	
Oral intermediate exposure		
Animal studies		
Keplinger et al. 1970 mouse	High	High
Treon et al. 1954a rat	High	
Oral chronic exposure		
Human studies		
Dwivedi et al. 2021	Low	Moderate
Pi et al. 2020	Moderate	
Yin et al. 2021	Moderate	
Animal Studies		
Kitselman 1953 dog	Very low	Very low

C.6.2 Adjustment of the Confidence Rating—Aldrin

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for body weight, hepatic, neurological, reproductive, and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with aldrin exposure is presented in Table C-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome

  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels;

confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Body weight effects:			
Animal studies	High	No adjustments	High
Hepatic effects:			
Human studies	Moderate	Downgrade one confidence level; all studies in risk of bias second tier	Low
Animal studies	High	No adjustments	High
Neurological effects:			
Human studies	Moderate	Downgrade one confidence level; all studies in risk of bias second tier	Low
Animal studies	Moderate	No adjustments	Moderate
Reproductive effects:			
Human studies	Moderate	Downgrade one confidence level; all studies in risk of bias second tier	Low
Animal studies	High	No adjustments	High
Developmental effects:			
Human	Moderate	Downgrade one confidence level; all studies in risk of bias second tier	Low
Animal studies	High	No adjustments	High

Table C-17. Confidence in the Body of Evidence for Aldrin

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Body weight effects		High
Hepatic effects	Low	High
Neurological effects	Low	Moderate
Reproductive effects	Low	High
Developmental effects	Low	High

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—ALDRIN

In the seventh step of the systematic review of the health effects data for aldrin, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for aldrin is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Aldrin

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	Low	Health effect	Moderate
Neurological effects	Low	Health effect	Moderate
Reproductive effects	Low	Health effect	Low
Developmental effects	Low	Health effect	Low
Animal studies			
Body weight effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Neurological effects	Moderate	Health effect	Moderate
Reproductive effects	High	Health effect	High
Developmental effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—ALDRIN

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

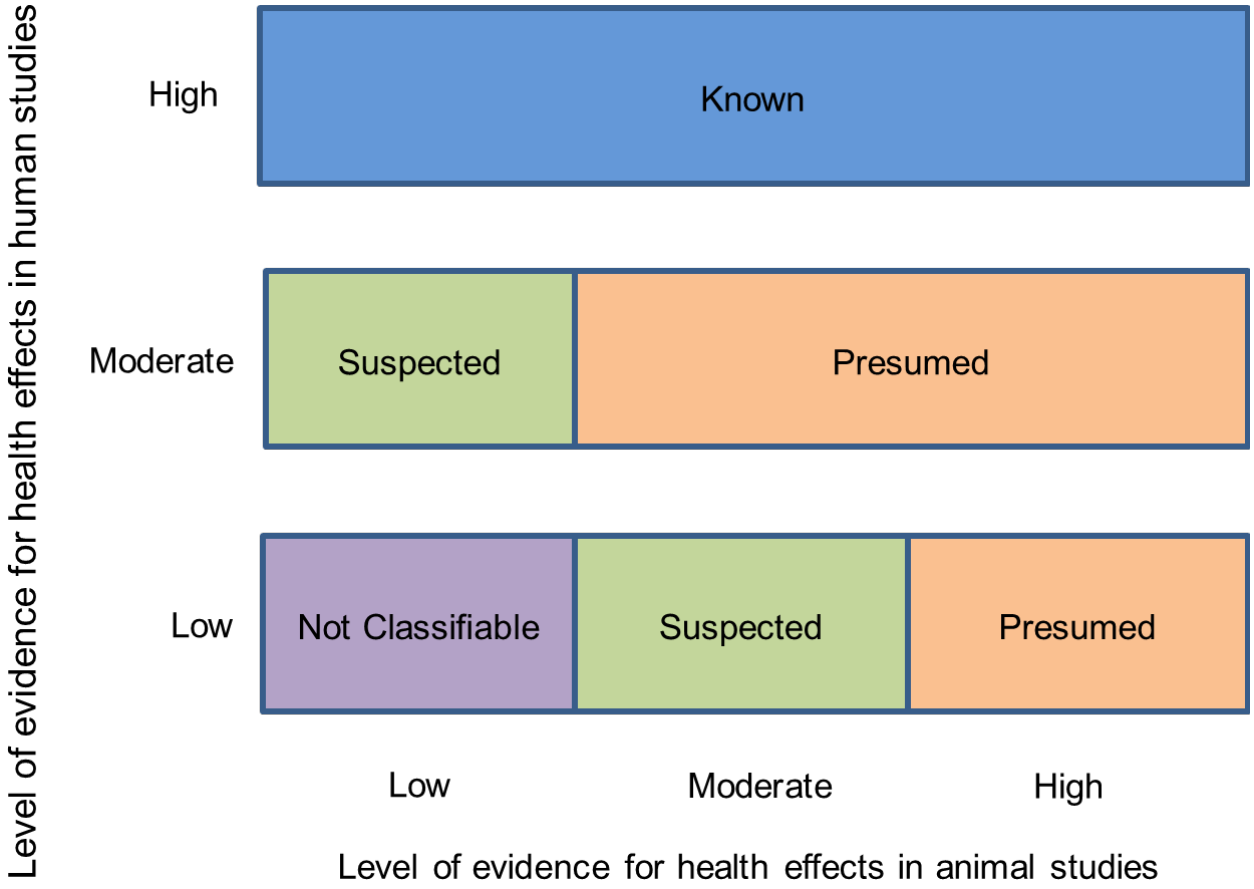
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies

- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for aldrin are listed below and summarized in Table C-19.

Presumed Health Effects

- Body weight effects
  - No human studies evaluated body weight effects.
  - Depressed body weight or actual body weight loss have been reported in intermediate- and chronic-duration oral studies in laboratory animals (Deichmann et al. 1970; Fitzhugh et al. 1964; Treon et al. 1955).

- Hepatic effects
  - Human studies evaluating hepatic endpoints have not provided convincing evidence of aldrin-induced liver effects.
  - Increased liver weight and histopathologic hepatic changes have been observed in laboratory animals following oral exposure to aldrin (Fitzhugh et al. 1964; Treon et al. 1951a, 1955).

- Neurological effects
  - Various clinical signs and abnormal EEGs have been observed among workers involved in the production of aldrin or its use as an insecticide (Avar and Czegledi-Janko 1970; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). Neurological effects were observed in individuals inadvertently ingesting wheat containing aldrin and lindane (Gupta 1975). A study in a general population did not find evidence that aldrin exposure was related to hearing loss (Zhang et al. 2021).
  - Increased locomotor activity was observed in rats following single or repeated oral exposure to aldrin (Jamaluddin and Poddar 2001a, 2001b, 2003). Repeated oral dosing of laboratory animals with aldrin has resulted in increased locomotor activity, convulsions, tremors, and neuronal degeneration (Jamaluddin and Poddar 2001a, 2001b, 2003; Kitselman 1953; NCI 1978a, 1978b; Treon et al. 1951b; Walker et al. 1969).

- Reproductive effects
  - A limited human study reported significantly higher aldrin blood levels in a group of women who had premature labor or spontaneous abortion when compared to a group of controls (Saxena et al. 1980).
  - A variety of adverse reproductive effects were reported in dogs administered aldrin orally for 14 months prior to mating (Deichmann et al. 1971).

- Developmental effects
  - Studies did not find associations between aldrin blood levels and neural tube defects (Yin et al. 2021) or orofacial clefts (Pi et al. 2020). One study found an inverse correlation between maternal blood dieldrin and birth weight (Dwivedi et al. 2021).
  - Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975). Aldrin or dieldrin exposure during gestation has resulted in some evidence of external malformations or skeletal anomalies in animals (Chernoff et al. 1975; Ottolenghi et al. 1974).

Table C-19. Hazard Identification Conclusions for Aldrin

Outcome	Hazard identification
Body weight effects	Presumed health effect in humans
Hepatic effects	Presumed health effect in humans
Neurological effects	Presumed health effect in humans
Reproductive effects	Presumed health effect in humans
Developmental effects	Presumed health effect in humans

C.9 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—DIELDRIN

Overviews of the potential health effect outcomes for dieldrin identified in human and animal studies are presented in Tables C-20 and C-21, respectively. Multiple cohorts were evaluated for possible associations between aldrin and/or dieldrin exposure and risk of death from selected noncancer or cancer endpoints. Cohorts with potential exposure to both aldrin and dieldrin are included in sections C.4–C-8 for aldrin and Sections C.9–C.13 for dieldrin. Studies involving production or use are assumed to have primarily involved the inhalation exposure route; exposure duration was considered to be chronic unless otherwise indicated. Other human studies involving dieldrin include case-control studies, self-reported use, and individual case reports. Data from human studies evaluating possible associations between serum dieldrin levels and selected health outcomes are presented in Sections C.9–C.13 under the assumption that exposures were to dieldrin, although some exposures may have been to aldrin because dieldrin is readily formed from aldrin in biological systems. Animal studies of dieldrin predominantly employed the oral exposure route. Collectively, these studies examined a number of endpoints. The most sensitive endpoints (outcomes) were hepatic, neurological, reproductive, and developmental. Animal studies examining these potential outcomes were carried through Steps 4–8 of the systematic review. Human studies evaluating potential hepatic, neurological, and developmental outcomes were also carried through Steps 4–8 of the systematic review. No human studies evaluated reproductive outcomes.

Table C-20. Overview of the Health Outcomes for Dieldrin Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		7	7	2	3		8	2	1		1		3		1		15
		2	0	0	0		0	0	0		1		2		1		2
Case control													1				11
													1				5
Population															4		8
															2		
Case series												1	1				
												1	1				
Oral studies																	
Cohort																	
Case control													2				
													2				
Population																	1
Case series			1		1		3	1				1	2				1
			1				3					1	2				1
Dermal studies																	
Cohort																	
Case control																	
Population												1					
												1					
Case series									1								
									1								

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

Table C-21. Overview of the Health Outcomes for Dieldrin Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	4 3						4 4					3 3	8 8		5 4		
Intermediate-duration	2 0			1 1			7 5	3 2				1 1	5 5	3 2	3 3		
Chronic-duration	8 0	4 1	5 1	4 1	4 1	6 2	9 5	7 3	4 1	3 0	4 0		7 6		1 1		9 8
Dermal studies																	
Acute-duration													1 1				
Intermediate-duration			1 0				1 0		1 0								
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.10 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES— DIELDRIN

C.10.1 Risk of Bias Assessment—Dieldrin

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies were presented above in Tables C-5, C-6, and C-7, respectively. As described in Section C.5.1, each risk of bias question was answered on a four-point scale and studies were assigned to one of three risk of bias tiers.

The results of the risk of bias assessment for the different types of dieldrin health effects studies (observational epidemiology, human controlled-exposure studies, and animal experimental studies) are presented in Tables C-22, C-23, and C-24, respectively.

Table C-22. Summary of Risk of Bias Assessment for Dieldrin—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Hepatic effects							
Cohort							
de Jong 1991	+	-	+	-	+	+	Second
Hoogendam et al. 1965	+	-	+	-	+	+	Second
Hunter et al. 1972	+	-	+	-	+	+	Second
Jager 1970	+	-	+	-	+	+	Second
Morgan and Lin 1978	-	-	+	-	+	+	Second
Morgan and Roan 1974	+	-	+	-	+	+	Second
van Sittert and de Jong 1987	+	-	+	-	+	+	Second
Warnick and Carter 1972	+	-	+	-	+	+	Second
Case series							
Black 1974	NA	**NA**	+	-	+	+	Second
Garrettson and Curley 1969	NA	**NA**	+	-	+	+	Second
Radomski et al. 1968	+	**NA**	+	-	+	+	Second
Outcome: Neurological effects							
Cohort							
de Jong 1991	+	-	+	-	+	+	Second
Hoogendam et al. 1962	NA	-	+	-	+	+	Second
Hoogendam et al. 1965	+	-	+	-	+	+	Second

Table C-22. Summary of Risk of Bias Assessment for Dieldrin—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate?	Confounding bias — **Study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — **Confidence in the exposure characterization?***	Detection bias — **Confidence in the outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Risk of bias tier
Case-control							
Sandifer et al. 1981	+	–	+	–	+	+	Second
Weisskopf et al. 2010	+	–	+	–	+	+	Second
Case series							
Black 1974	NA	**NA**	+	–	+	+	Second
Garrettson and Curley 1969	NA	**NA**	+	–	+	+	Second
Patel and Rao 1958	NA	**NA**	+	–	+	+	Second
Pennell et al. 2006	NA	–	+	–	+	+	Second
Outcome: Developmental effects							
Cohort							
Beranger et al. 2020	NA	–	+	–	+	+	Second
Yamazaki et al. 2020	NA	–	+	–	+	+	Second
Cross-sectional							
Abdel Hamid et al. 2020	NA	–	+	–	+	+	
Dwivedi et al. 2021	NA	–	+	–	+	+	Second
Kao et al. 2019a	NA	–	+	–	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-23. Summary of Risk of Bias Assessment for Dieldrin—Human Controlled-Exposure Studies

Reference	Risk of bias criteria and ratings							Risk of bias tier
	Selection bias		Performance bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately randomized	**Researchers, human subjects blinded to study group?***	Outcome data complete without attrition or exclusion?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Hepatic effects								
Oral chronic exposure								
Hunter and Robinson 1967	++	++	++	++	++	++	++	First
Outcome: Neurological effects								
Oral chronic exposure								
Hunter and Robinson 1967	++	++	++	++	++	++	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Hepatic effects										
Oral acute exposure										
Chernoff et al. 1975 mouse	+	+	+	+	+	+	+	+	+	First
Goel et al. 1988 rat	+	+	+	+	+	+	+	+	+	First
Kohli et al. 1977 rat	+	+	+	+	+	+	+	+	+	First
Wright et al. 1972 mouse	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure										
Ahmed et al. 1986 rat	+	+	+	+	+	+	+	+	+	First
Bandyopadhyay et al. 1982b rat	+	+	+	+	+	+	+	+	+	First
Shakoori et al. 1982 rat	+	+	+	+	+	+	+	+	+	First
Stevenson et al. 1995 mouse	+	+	+	+	+	+	+	+	+	First
Treon et al. 1951a rat	+	+	+	+	+	+	+	+	+	First
Treon et al. 1951b dog	+	+	+	+	+	+	+	+	+	First
Treon et al. 1953a rat	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Deichmann et al. 1970 rat	+	+	+	+	+	+	+	+	+	First
Fitzhugh et al. 1964 rat	+	+	+	+	+	+	+	+	+	First
Fitzhugh et al. 1964 dog	+	+	+	+	+	+	+	+	+	First
Harr et al. 1970 rat	+	+	+	+	+	+	+	+	+	First

Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Kitselman 1953 dog	+	+	+	+	+	+	+	+	+	First
NCI 1978a rat	+	+	+	+	+	+	+	+	+	First
NCI 1978a mouse	+	+	+	+	+	+	+	+	+	First
Walker et al. 1973 rat	+	+	+	+	+	+	+	+	+	First
Walker et al. 1973 dog	+	+	+	+	+	+	+	+	+	First
Outcome: Neurological effects										
Oral acute exposure										
Burt 1975 rat (16.7 mg/kg)	+	+	+	+	+	+	+	+	+	First
Burt 1975 rat (2.5, 5 mg/kg)	+	+	+	+	+	+	+	+	+	First
Burt 1975 rat (8.4, 16.7 mg/kg)	+	+	+	+	+	+	+	+	+	First
Foster et al. 2008 mouse	+	+	+	+	+	+	+	+	+	First
Foster et al. 2008 mouse rep	+	+	+	+	+	+	+	+	+	First
Mehrotra et al. 1989 rat	+	+	+	+	+	+	+	+	+	First
Sandler et al. 1969 sheep	+	+	+	+	+	+	+	+	+	First
Woolley et al. 1985 rat	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure										
Burt 1975 rat	+	+	+	+	+	+	+	+	+	First
NCI 1978b rat	+	+	+	+	+	+	+	+	+	First
Smith et al. 1976 monkey	+	+	+	+	–	+	+	+	+	First

Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in the exposure characterization?	Detection bias: **Confidence in the outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Other bias: Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Treon et al. 1951b dog	+	+	+	+	+	+	+	+	+	First
Van Gelder 1975 sheep	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Khairy 1960 rat	+	+	+	+	+	+	+	+	+	First
Kitselman 1953 dog	+	+	+	+	+	+	+	+	+	First
NCI 1978a mouse	+	+	+	+	+	+	+	+	+	First
NCI 1978b rat	+	+	+	+	+	+	+	+	+	First
Walker et al. 1969 rat	++	+	+	+	+	+	+	+	+	First
Walker et al. 1969 dog	++	+	+	+	+	+	+	+	+	First
Walker et al. 1973 mouse 128 weeks	++	+	+	+	+	+	+	+	+	First
Dermal acute exposure										
Treon et al. 1953b rabbit	+	+	+	+	+	+	+	+	+	First
Outcome: Reproductive effects										
Oral intermediate exposure										
Good and Ware 1969 mouse	+	+	+	+	+	+	+	+	+	First
Treon et al. 1954a rat	+	+	+	+	+	+	+	+	+	First
Virgo and Bellward 1975 mouse	+	+	+	+	+	+	+	+	+	First
Outcome: Developmental effects										

Table C-24. Summary of Risk of Bias Assessment for Dieldrin—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in the exposure characterization?	Detection bias: **Confidence in the outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Other bias: Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Oral acute exposure										
Carlson and Rosellini 1987 rat	+	+	+	+	+	+	+	+	+	First
Chernoff et al. 1975 mouse	+	+	+	+	+	+	+	+	+	First
Dix et al. 1977 mouse	+	+	+	+	+	+	+	+	+	First
Ottolenghi et al. 1974 mouse	+	+	+	+	+	+	+	+	+	First
Ottolenghi et al. 1974 hamster	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure										
Harr et al. 1970 rat	+	+	+	+	+	+	+	+	+	First
Treon et al. 1954a rat	+	+	+	+	+	+	+	+	+	First
Virgo and Bellward 1975 mouse	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure										
Kitselman 1953 dog	+	+	+	+	+	+	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.11 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME— DIELDRIN

As discussed in greater detail in Section C.6, confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.11.1 Initial Confidence Rating—Dieldrin

As discussed in greater detail in Section C.6.1, the body of evidence for an association (or no association) between exposure to dieldrin and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. Refer to Tables C-10, C-11, and C-12, respectively, for the key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies.

The presence or absence of the key features and the initial confidence levels for studies examining hepatic and neurological outcomes observed in the observational epidemiology studies; human controlled-exposure studies; and hepatic, neurological, reproductive, and developmental outcomes in animal experimental studies are presented in Tables C-25, C-26, and C-27, respectively.

Table C-25. Presence of Key Features of Study Design for Dieldrin—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Hepatic effects					
Cohort					
de Jong 1991	No	Yes	Yes	Yes	Moderate
Hoogendam et al. 1965	No	Yes	Yes	No	Low
Hunter et al. 1972	No	Yes	Yes	Yes	Moderate
Jager 1970	No	Yes	Yes	Yes	Moderate
Morgan and Lin 1978	No	Yes	Yes	No	Low
Morgan and Roan 1974	No	Yes	Yes	Yes	Moderate
van Sittert and de Jong 1987	No	Yes	Yes	Yes	Moderate
Warnick and Carter 1972	No	Yes	Yes	Yes	Moderate
Case series					
Black 1974	No	Yes	Yes	NA	Low
Garrettson and Curley 1969	No	Yes	Yes	NA	Low
Radomski et al. 1968	No	Yes	Yes	Yes	Moderate

Table C-25. Presence of Key Features of Study Design for Dieldrin—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Neurological effects					
Cohort					
de Jong 1991	No	Yes	Yes	Yes	Moderate
Hoogendam et al. 1962	No	Yes	Yes	No	Low
Hoogendam et al. 1965	No	Yes	Yes	No	Low
Case-control					
Sandifer et al. 1981	No	Yes	Yes	Yes	Moderate
Weisskopf et al. 2010	No	Yes	Yes	Yes	Moderate
Case series					
Black 1974	No	Yes	Yes	NA	Low
Garrettson and Curley 1969	No	Yes	Yes	NA	Low
Patel and Rao 1958	No	Yes	Yes	NA	Low
Pennell et al. 2006	No	Yes	Yes	NA	Low
Outcome: Developmental effects					
Cohort					
Beranger et al. 2020	No	Yes	Yes	NA	Low
Yamazaki et al. 2020	No	Yes	Yes	NA	Low
Cross-sectional					
Abdel Hamid et al. 2020	No	Yes	Yes	NA	Low
Dwivedi et al. 2021	No	Yes	Yes	NA	Low
Kao et al. 2019a	No	Yes	Yes	NA	Low

Table C-26. Presence of Key Features of Study Design for Dieldrin—Human Controlled-Exposure Studies

Reference	Key features: Comparison group or subjects as own controls	Sufficient number of subjects	Appropriate methods to measure outcomes	Appropriate statistics or adequate data for independent statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Oral chronic exposure					
Hunter and Robinson 1967	Yes	No	No	No	Very low
Outcome: Neurological effects					
Oral chronic exposure					
Hunter and Robinson 1967	Yes	No	No	No	Very low

Table C-27. Presence of Key Features of Study Design for Dieldrin—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Oral acute exposure					
Chernoff et al. 1975 rat	Yes	Yes	No	Yes	Moderate
Chernoff et al. 1975 mouse	Yes	Yes	No	Yes	Moderate
Goel et al. 1988 rat	Yes	No	No	Yes	Low
Kohli et al. 1977 rat	Yes	Yes	No	Yes	Moderate
Wright et al. 1972 mouse	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Ahmed et al. 1986 rat	Yes	Yes	No	Yes	Moderate
Bandyopadhyay et al. 1982b rat	Yes	Yes	No	Yes	Moderate
Shakoori et al. 1982 rat	Yes	Yes	No	Yes	Moderate
Stevenson et al. 1995 mouse					
Treon et al. 1951a rat	Yes	Yes	Yes	No	Moderate
Treon et al. 1951b dog	Yes	No	No	No	Very low
Treon et al. 1953a rat	Yes	Yes	Yes	Yes	High

Table C-27. Presence of Key Features of Study Design for Dieldrin—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral chronic exposure					
Deichmann et al. 1970 rat	Yes	Yes	Yes	Yes	High
Fitzhugh et al. 1964 rat	Yes	Yes	Yes	Yes	High
Fitzhugh et al. 1964 dog	Yes	No	Yes	Yes	Moderate
Harr et al. 1970 rat	Yes	No	Yes	Yes	Moderate
Kitselman 1953 dog	Yes	No	No	No	Very low
NCI 1978a rat	Yes	Yes	Yes	Yes	High
NCI 1978a mouse	Yes	Yes	Yes	Yes	High
Walker et al. 1969 rat	Yes	Yes	Yes	Yes	High
Walker et al. 1969 dog	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Oral acute exposure					
Burt 1975 rat (16.7 mg/kg)	Yes	Yes	No	Yes	Moderate
Burt 1975 rat (2.5, 5 mg/kg)	Yes	Yes	No	Yes	Moderate
Burt 1975 rat (8.4, 16.7 mg/kg)	Yes	Yes	No	Yes	Moderate
Foster et al. 2008 mouse	Yes	Yes	No	No	Low
Foster et al. 2008 mouse rep	Yes	Yes	No	No	Low
Mehrotra et al. 1989 rat	Yes	No	Yes	Yes	Moderate
Sandler et al. 1969 sheep	No	No	No	No	Very low
Woolley et al. 1985 rat	No	No	No	No	Very low
Oral intermediate exposure					
Burt 1975 rat	Yes	Yes	No	Yes	Moderate
NCI 1978b rat	Yes	Yes	No	No	Low
Smith et al. 1976 monkey	Yes	No	Yes	No	Low
Treon et al. 1951b dog	Yes	No	No	No	Very low
Van Gelder 1975 sheep					
Oral chronic exposure					
Khairy 1960 rat	Yes	No	No	No	Very low
Kitselman 1953 dog	Yes	No	No	No	Very low
NCI 1978a rat	Yes	Yes	Yes	No	Moderate
NCI 1978a mouse	Yes	Yes	Yes	No	Moderate
NCI 1978b rat	Yes	Yes	Yes	No	Moderate
Walker et al. 1969 rat	Yes	Yes	Yes	No	Moderate
Walker et al. 1969 dog	Yes	Yes	Yes	No	Moderate

Table C-27. Presence of Key Features of Study Design for Dieldrin—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Walker et al. 1973 mouse 128 weeks	Yes	Yes	Yes	No	Moderate
Dermal acute exposure					
Treon et al. 1953b rabbit					
Outcome: Reproductive effects					
Oral intermediate exposure					
Good and Ware 1969 mouse	Yes	Yes	Yes	Yes	High
Treon et al. 1954a rat	Yes	Yes	Yes	Yes	High
Virgo and Bellward 1975 mouse	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Oral acute exposure					
Carlson and Rosellini 1987 rat					
Chernoff et al. 1975 rat	Yes	Yes	Yes	Yes	High
Chernoff et al. 1975 mouse	Yes	Yes	Yes	Yes	High
Dix et al. 1977 mouse					
Ottolenghi et al. 1974 mouse	Yes	No	Yes	Yes	Moderate
Ottolenghi et al. 1974 hamster	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Harr et al. 1970 rat	Yes	No	Yes	Yes	Moderate
Treon et al. 1954a rat	Yes	Yes	Yes	Yes	High
Virgo and Bellward 1975 mouse	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Kitselman 1953 dog	Yes	No	No	No	Very low

A summary of the initial confidence ratings for each outcome is presented in Table C-28. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-28.

Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hepatic effects		
Inhalation chronic exposure		
Human studies		
de Jong 1991	Moderate	Moderate
Hoogendam et al. 1965	Low	
Hunter et al. 1972	Moderate	
Jager 1970	Moderate	
Morgan and Lin 1978	Low	
Morgan and Roan 1974	Moderate	
van Sittert and de Jong 1987	Moderate	
Warnick and Carter 1972	Moderate	
Oral acute exposure		
Human studies		
Black 1974	Low	Low
Garrettson and Curley 1969	Low	
Animal studies		
Chernoff et al. 1975 rat	Moderate	Moderate
Chernoff et al. 1975 mouse	Moderate	
Goel et al. 1988 rat	Low	
Kohli et al. 1977 rat	Moderate	
Wright et al. 1972 mouse	Moderate	
Oral intermediate exposure		
Animal studies		
Ahmed et al. 1986 rat	Moderate	High
Bandyopadhyay et al. 1982b rat	Moderate	
Shakoori et al. 1982 rat	Moderate	
Stevenson et al. 1995 mouse		
Treon et al. 1951a rat	Moderate	
Treon et al. 1951b dog	Very low	
Treon et al. 1953a rat	High	
Oral chronic exposure		
Human studies		
Radomski et al. 1968	Moderate	Moderate
Animal studies		
Deichmann et al. 1970 rat	High	High
Fitzhugh et al. 1964 rat	Moderate	
Fitzhugh et al. 1964 dog	Moderate	
Harr et al. 1970 rat	Moderate	
Kitselman 1953 dog	Very low	
NCI 1978a rat	High	
NCI 1978a mouse	High	
Walker et al. 1969 rat	High	
Walker et al. 1969 dog	High	

Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Neurological effects		
Inhalation acute exposure		
Human studies		
Patel and Rao 1958	Low	Low
Inhalation chronic exposure		
Human studies		
de Jong 1991	Moderate	Moderate
Hoogendam et al. 1962	Low	
Hoogendam et al. 1965	Low	
Sandifer et al. 1981	Moderate	
Oral acute exposure		
Human studies		
Black 1974	Low	Low
Garrettson and Curley 1969	Low	
Animal studies		
Burt 1975 rat (16.7 mg/kg)	Moderate	Moderate
Burt 1975 rat (2.5, 5 mg/kg)	Moderate	
Burt 1975 rat (8.4, 16.7 mg/kg)	Moderate	
Foster et al. 2008 mouse	Low	
Foster et al. 2008 mouse rep	Low	
Mehrotra et al. 1989 rat	Moderate	
Sandler et al. 1969 sheep	Very low	
Woolley et al. 1985 rat	Very low	
Oral intermediate exposure		
Animal studies		
Burt 1975 rat	Moderate	Moderate
NCI 1978b rat	Low	
Smith et al. 1976 monkey	Low	
Treon et al. 1951b dog	Very low	
Van Gelder 1975 sheep		
Oral chronic exposure		
Human studies		
Pennell et al. 2006	Low	Moderate
Weisskopf et al. 2010	Moderate	
Animal studies		
Khairy 1960 rat	Very low	Moderate
Kitselman 1953 dog	Very low	
NCI 1978a rat	Moderate	
NCI 1978a mouse	Moderate	
NCI 1978b rat	Moderate	
Walker et al. 1969 rat	Moderate	
Walker et al. 1969 dog	Moderate	
Walker et al. 1973 mouse 128 weeks	Moderate	
Dermal acute exposure		

Table C-28. Initial Confidence Rating for Dieldrin Health Effects Studies

	Initial study confidence	Initial confidence rating
Animal studies		
Treon et al. 1953b rabbit		
Outcome: Reproductive effects		
Oral intermediate exposure		
Animal studies		
Good and Ware 1969 mouse	High	
Treon et al. 1954a rat	High	High
Virgo and Bellward 1975 mouse	High	
Outcome: Developmental effects		
Oral acute exposure		
Animal studies		
Carlson and Rosellini 1987 rat		
Chernoff et al. 1975 rat	High	
Chernoff et al. 1975 mouse	High	
Dix et al. 1977 mouse		
Ottolenghi et al. 1974 mouse	Moderate	
Ottolenghi et al. 1974 hamster	Moderate	High
Oral intermediate exposure		
Animal studies		
Harr et al. 1970 rat	Moderate	
Treon et al. 1954a rat	High	High
Virgo and Bellward 1975 mouse	High	
Oral chronic exposure		
Human Studies		
Abdel Hamid et al. 2020	Low	
Beranger et al. 2020	Low	
Dwivedi et al. 2021	Low	Low
Kao et al. 2019a	Low	
Yamazaki et al. 2020	Low	
Animal studies		
Kitselman 1953 dog	Very low	Very low

C.11.2 Adjustment of the Confidence Rating—Dieldrin

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The five properties of the body of evidence that were considered to determine whether the confidence rating should be downgraded and the four properties of the body of evidence that were considered to determine whether the confidence rating should be upgraded are described above in Section C.6.2. The summaries of the assessment of the confidence in the body of evidence for hepatic effects, neurological effects, reproductive effects, and developmental effects are presented in Table C-29. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with dieldrin exposure is presented in Table C-30.

Table C-29. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Hepatic effects			
Human studies	Moderate	Downgrade one confidence level; most studies in risk of bias second tier	Low
Animal studies	High	No adjustments	High
Outcome: Neurological effects			
Human studies	Moderate	Downgrade one confidence level; most studies in risk of bias second tier	Low
Animal studies	Moderate	No adjustments	Moderate
Outcome: Reproductive effects			
Animal studies	High	No adjustments	High
Outcome: Developmental effects			
Human studies	Low	Downgrade one confidence level; studies in risk of bias second tier	Very low
Animal studies	High	No adjustments	High

Table C-30. Confidence in the Body of Evidence for Dieldrin

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic effects	Low	High
Neurological effects	Low	Moderate
Reproductive effects		High
Developmental effects	Low	High

C.12 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—DIELDRIN

As described in Section C.7, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted.

A summary of the level of evidence of health effects for dieldrin is presented in Table C-31.

Table C-31. Level of Evidence of Health Effects for Dieldrin

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	Low	Health effect	Moderate
Neurological effects	Low	Health effect	Moderate
Developmental effects	Very low	Heath effect	Low
Animal studies			
Hepatic effects	High	Health effect	High
Neurological effects	Moderate	Health effect	Moderate
Reproductive effects	High	Health effect	High
Developmental effects	High	Health effect	High

C.13 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—DIELDRIN

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. Refer to Section C.8 for the four hazard identification conclusion categories for health effects, the hazard characterization scheme (see Figure C-1), and the hazard identification conclusion categories.

The hazard identification conclusions for dieldrin are listed below and summarized in Table C-32.

Presumed Health Effects

- Hepatic effects
  - Human studies evaluating hepatic endpoints have not provided convincing evidence of aldrin-induced liver effects.
  - Increased liver weight and histopathologic hepatic changes have been observed in laboratory animals following chronic-duration oral exposure to dieldrin (Ahmed et al. 1986; Fitzhugh et al. 1964; Harr et al. 1970; Kitselman 1953; Shakoori et al. 1982; Thorpe and Walker 1973; Treon et al. 1951a; Walker et al. 1969).

- Neurological effects
  - Various clinical signs and abnormal EEGs have been observed among workers involved in the production of dieldrin or its use as an insecticide (Avar and Czegledi-Janko 1970; Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). Neurological effects were observed in individuals inadvertently or intentionally ingesting dieldrin-containing solutions (Black 1974; Garrettson and Curley 1969).
  - Oral dosing of laboratory animals with dieldrin has resulted in neurological effects such as increased locomotor activity, impaired operant behavior, impaired learning, convulsions, tremors, and neuronal degeneration (Burt 1975; Carlson and Rosellini 1987; Kitselman 1953; Mehrotra et al. 1989; NCI 1978a; Sandler et al. 1969; Smith et al. 1976; Van Gelder 1975; Wagner and Greene 1978; Woolley et al. 1985).

- Reproductive effects
  - No human studies evaluated reproductive endpoints.
  - Decreased fertility was observed in studies of laboratory animals administered dieldrin orally (Keplinger et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975).

- Developmental effects
  - Studies evaluating birth outcomes found an inverse association between maternal blood dieldrin and birth weight (Dwivedi et al. 2021), a positive association between maternal hair dieldrin and birth length (Beranger et al. 2020) and no association between maternal blood dieldrin and infant gender (Abdel Hamid et al. 2020). A neurodevelopmental study found that higher infant language scores were associated with higher breast milk levels of dieldrin (Kao et al. 2019a). No associations were observed between maternal serum levels and infant thyroid hormone levels (Yamazaki et al. 2020).
  - Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975). Aldrin or dieldrin exposure during gestation has resulted in some evidence of external malformations or skeletal anomalies in animals (Chernoff et al. 1975; Ottolenghi et al. 1974).

Table C-32. Hazard Identification Conclusions for Dieldrin

Outcome	Hazard identification
Hepatic effects	Presumed health effect in humans
Neurological effects	Presumed health effect in humans
Reproductive effects	Presumed health effect in humans
Developmental effects	Presumed health effect in humans

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

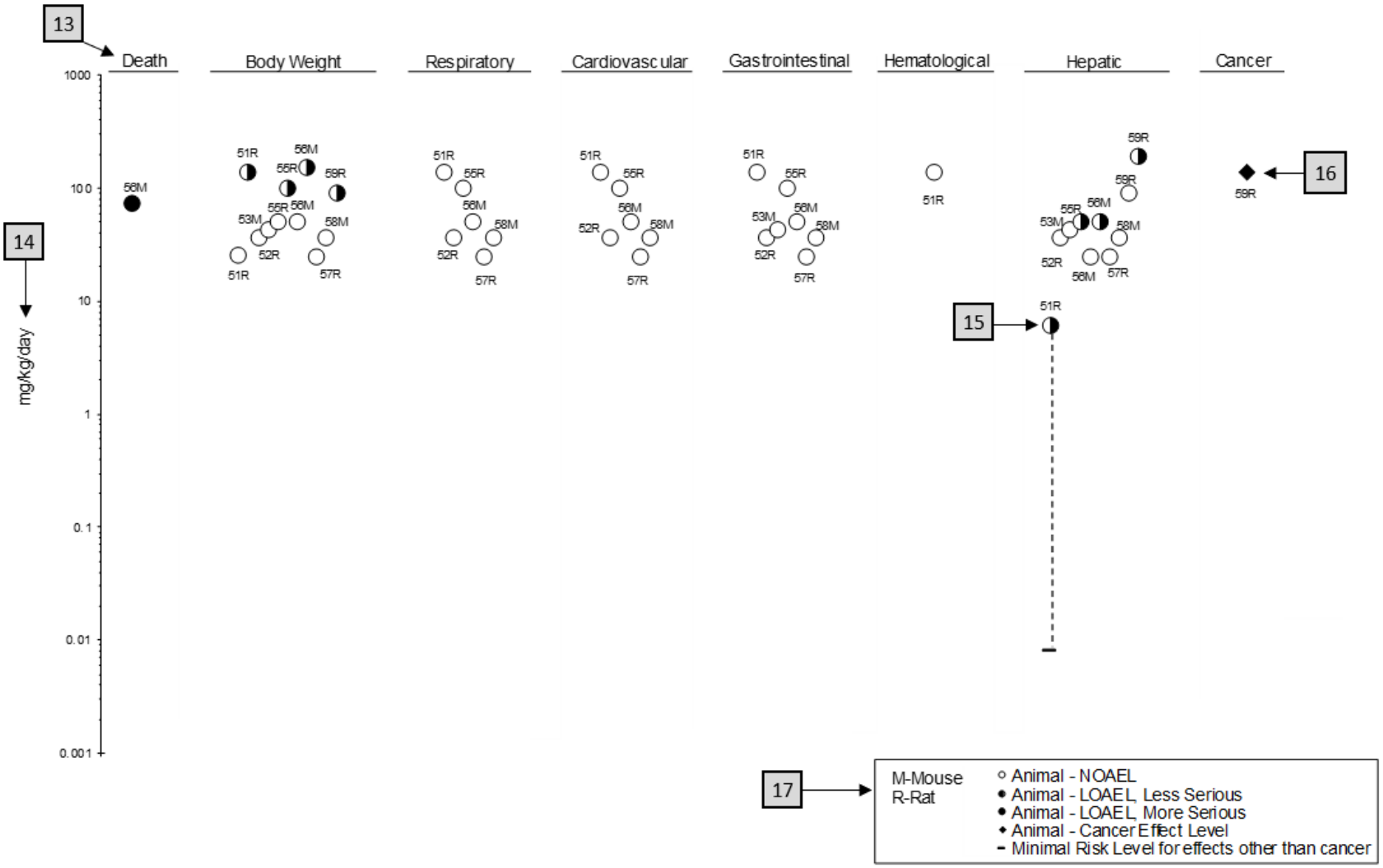
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. Physician Overviews are narrated powerpoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result