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

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

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

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

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

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

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

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

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

N = number; SD = standard deviation

Source: Kavlock et al. 1981

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

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

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

Source: Kavlock et al. 1981

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

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

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

Source: Kavlock et al. 1981

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

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

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

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

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

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

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

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

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

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

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

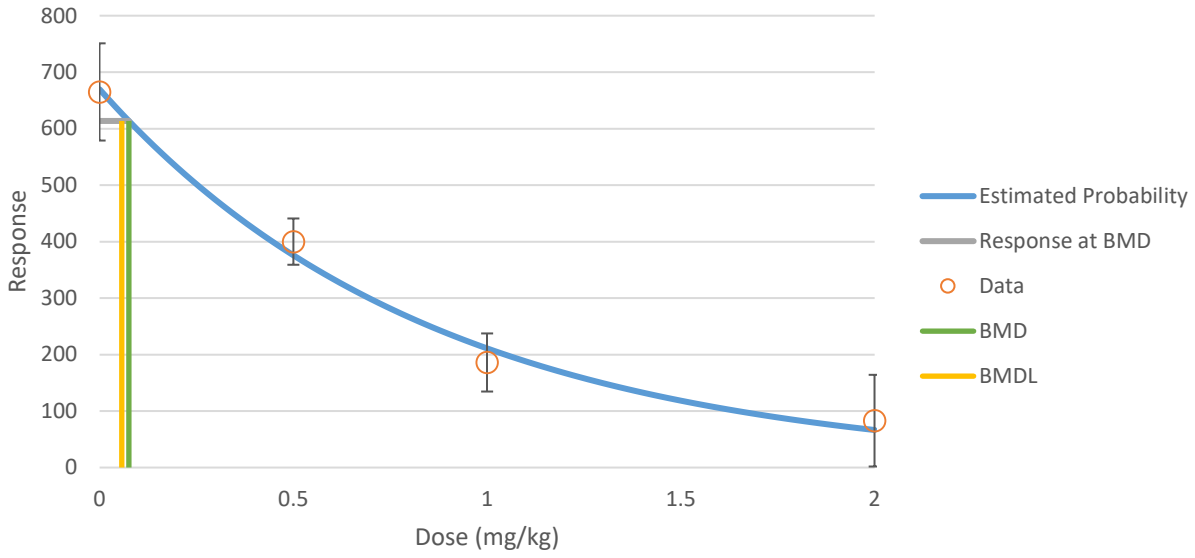
Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Decreased locomotor activity on day 1 in rats (Kavlock et al. 1981)	ND	0.5	0.075 (BMD_{1SD})	0.057[a] ($BMDL_{1SD}$)
Increased relative liver weight in mouse dams (Kavlock et al. 1981)	ND	0.5	0.82 (BMD_{RD10})	0.642 ($BMDL_{RD10}$)

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

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

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

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



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

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

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

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

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

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

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

[a]Selected POD.

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

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

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

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

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

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

Source: Gray et al. 1981

Agency Contacts (Chemical Manager): Susan Zells Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

[a]Selected POD.

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

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

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

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

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

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

MRL = NOAEL ÷ uncertainty factors

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

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

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

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ENDRIN

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

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

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

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

B.1.1 Literature Search

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

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

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

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to endrin were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2020	("Endrin"[mh] OR 72-20-8[rn] OR 7421-93-4[rn] OR 53494-70-5[rn] OR "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "(1R,4S,4aS,5S,6S,7R,8R,8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-1R,4S,4aS,5S,6,7R,8R,8aR-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene"[tw] OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo,endo-1,4 5,8-dimethanonaphthalene"[tw] OR "3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "3,4,5,6,9,9-Hexachloro-1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aR,2R,2aR,3R,6S,6aS,7S,7aS)-rel-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene"[tw] OR "Compound 269"[tw] OR "Endrex"[tw] OR "Endricol"[tw] OR "endrin"[tw] OR "Experimental Insecticide 269"[tw] OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene"[tw] OR "Hexadrin"[tw] OR "Mendrin"[tw] OR "Nendrin"[tw] OR "Oktanex"[tw] OR "SD 3419"[tw] OR "Stardrin"[tw] OR "1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-"[tw] OR "SD 7442"[tw] OR "delta-Keto 153"[tw] OR "delta-Ketoendrin"[tw] OR "SD 2614"[tw] OR "(2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one"[tw] OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one"[tw]) AND (2017/04/01:3000[mhda] OR 2017/04/01:3000[crdt] OR 2017/04/01:3000[edat] OR 2016/04/01:3000[dp]) "Compd. 269"[tw] OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene"[tw] OR "(1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde"[tw] OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,7.beta.,7a.alpha.)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octa-hydro-2,7 3,6-Dimethanonaphth[2,3-b]oxirene"[tw] OR "(1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene"[tw] OR "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene"[tw] OR "(1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde"[tw] OR "(1aR,2R,2aR,3R,6S,6aS,7S,7aS)-rel-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-Dimethanonaphth[2,3-b]oxirene"[tw] OR

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

Database search date	Query string
	(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha)-" OR "2,7 3,6-Dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aR,2R,2aR,3R,6S,6aS,7S,7aS)-rel-" "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha., 6a.beta.,7.beta.,7a.alpha.)-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aR,2R,2aR,3R,6S,6aS,7S,7aS)-rel-" OR "2,7 3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-" OR "3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-[2,7 3,6-dimethanonaphth[2,3-b]oxirene,[1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.]" OR "endo,endo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4 5,8-Dimethanonaphthalene"
Toxcenter	
06/2020	FILE 'TOXCENTER' ENTERED AT 18:13:03 ON 14 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 7788 SEA FILE=TOXCENTER 72-20-8 OR 7421-93-4 OR 53494-70-5 L2 7648 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 532 SEA FILE=TOXCENTER L2 AND ED>=2016 ACT TOXQUERY/Q --------- L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28
	L30 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L32 QUE L29 OR L30 OR L31
	L33 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L34 QUE L32 OR L33

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

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2020	Compounds searched: 72-20-8; 7421-93-4; 53494-70-5
NTP	
06/2020	72-20-8 7421-93-4 53494-70-5 "Compound 269" "Endrex" "Endricol" "endrin" "Experimental Insecticide 269" "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene" "Hexadrin" "Mendrin" "Nendrin" "Oktanex" "SD 3419" "Stardrin" "Compd. 269" "delta-Keto 153" "delta-Ketoendrin" "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene" "SD 2614" "SD 7442"
Regulations.gov	
06/2020	Compounds searched: 72-20-8; 7421-93-4; 53494-70-5
NIH RePORTER	
08/2020	Text Search: "Compound 269" OR "Endrex" OR "Endricol" OR "endrin" OR "Experimental Insecticide 269" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene" OR "Hexadrin" OR "Mendrin" OR "Nendrin" OR "Oktanex" OR "SD 3419" OR "Stardrin" OR "1,2,4-Methenocyclopenta(cd)pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-, (1alpha,2beta,2abeta,4beta,4abeta,5beta,6abeta,6bbeta,7R)-" OR "SD 7442" OR "delta-Keto 153" OR "delta-Ketoendrin" OR "SD 2614" OR "(2-alpha,3a-beta,3b-beta,4-beta,5-beta,6a-beta,7-alpha,7a-beta,8R)-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one" OR "(2R,3aR,3bS,4R,5R,6aS,7S,7aR,8R)-rel-3b,4,5,6,6,6a-hexachlorodecahydro-2,5,7-Metheno-3H-cyclopenta(a)pentalen-3-one" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1R,4S,4aS,5S,6S,7R,8R,8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1R,4S,4aS,5S,6,7R,8R,8aR-octahydro-6,7-epoxy-1,4 5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo,endo-1,4 5,8-dimethanonaphthalene" OR "3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "3,4,5,6,9,9-Hexachloro-1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha-octahydro-2,7 3,6-dimethanonaphth(2,3-b)oxirene" OR "(1aR,2R,2aR,3R,6S,6aS,7S,7aS)-rel-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7 3,6-Dimethanonaphth(2,3-b)oxirene" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "Compd. 269" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonapthalene" OR "(1.alpha.,2.beta.,2a.beta.,4.beta.,4a.beta.,5.beta.,6a.beta.,6b.beta.,7R)-2,2a,3,3,4,7-hexachlorodecahydro-1,2,4-Methenocyclopenta[cd]pentalene-5-

Table B-3. Strategies to Augment the Literature Search

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

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	octahydro-[2,7 3,6-dimethanonaphth[2,3-b]oxirene,[1a.alpha.,2.beta.,2a.beta.,3.alpha.,6.alpha.,6a.beta.,7.beta.,7a.alpha.]" OR "endo,endo-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4 5,8-Dimethanonaphthalene" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

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

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

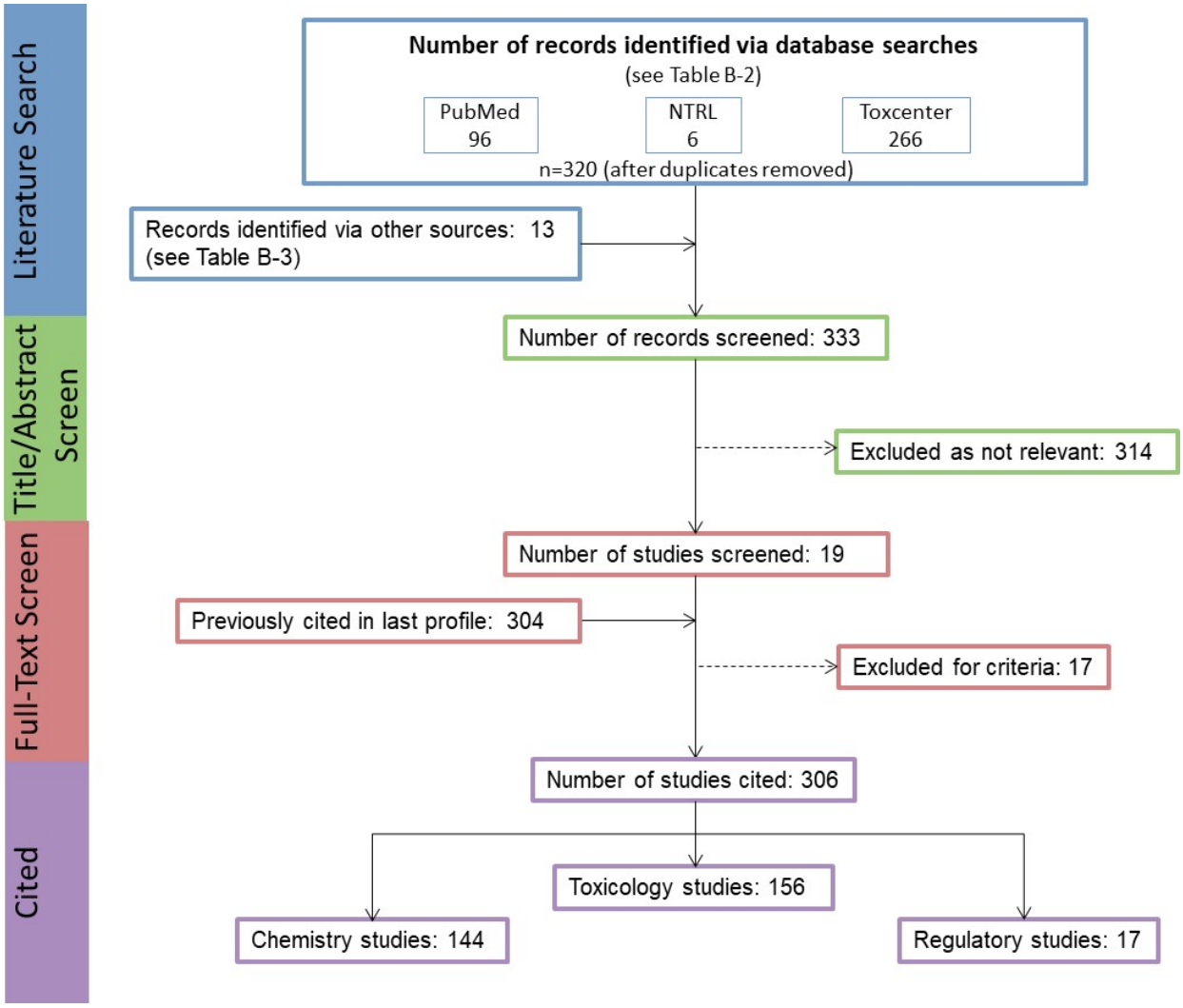
- Number of titles and abstracts screened: 333
- Number of studies considered relevant and moved to the next step: 17

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

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

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

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



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

APPENDIX C

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

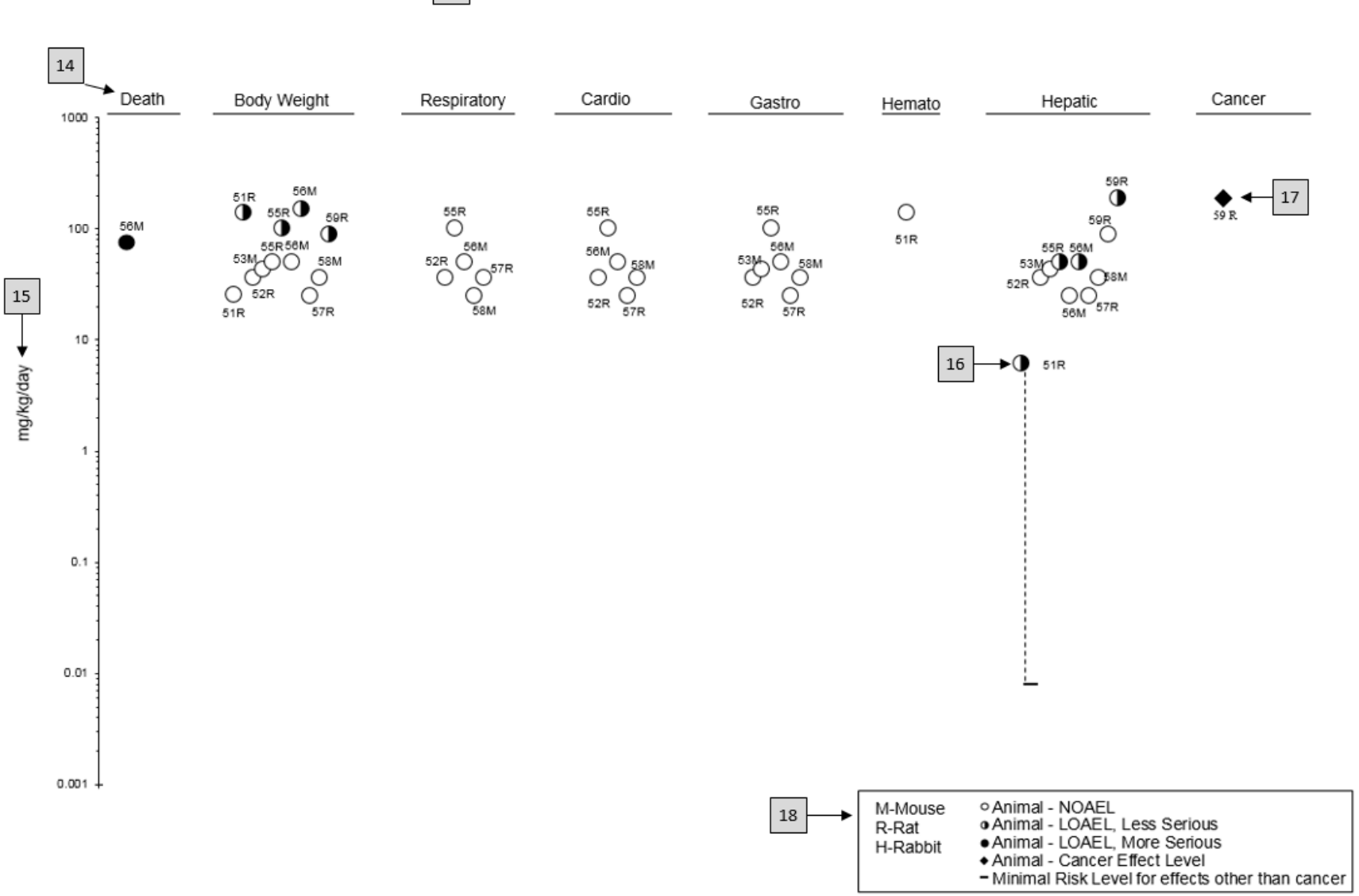
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

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

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

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result