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.

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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*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
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: No intermediate-duration inhalation studies were identified for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
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: No chronic-duration inhalation studies were identified for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: No acute-duration oral MRL was derived for mirex because serious effects (arrhythmias in neonatal pups from maternal exposure during gestation) were observed at the lowest dose tested (0.1 mg/kg/day) (Grabowski 1983). ATSDR does not derive MRLs based on serious effects in the absence of identified NOAEL values.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: Intermediate-duration oral studies in humans are lacking for mirex. The most suitable animal study provides a LOAEL of 0.67 mg/kg/day for endocrine effects (dilation of rough endoplasmic reticulum cisternae of the thyroid) in weanling Sprague-Dawley rats (Singh et al. 1985). Application of a total uncertainty factor of 1,000 (10 for extrapolation from a NOAEL to a LOAEL, 10 for animal to human extrapolation, and 10 for human variability)and a modifying factor of 3 to be protective of mirex-induced developmental toxicity, including arrhythmias in neonatal pups following maternal exposure during gestation at a dose level as low as 0.1 mg/kg/day in the absence of an identified NOAEL (Grabowski 1983) would yield an intermediate-duration oral MRL of 0.0001 mg/kg/day. This potential MRL is lower than the chronic-duration oral MRL of 0.0003 mg/kg/day derived from an NTP (1990) study in rats (see chronic-duration oral MRL). Another candidate study for derivation of an intermediate-duration oral MRL for mirex identifies a LOAEL of 0.49 mg/kg/day for cataracts in female rat pups (4/10 versus 0/14 controls) (Chu et al. 1981b). The parental rats had been administered mirex in the diet for 91 days prior to mating and during mating (males and females) and throughout gestation and lactation (females). This LOAEL of 0.49 mg/kg/day is considered a serious LOAEL and the study did not identify a NOAEL. Therefore, no intermediate-duration oral MRL was developed for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.0003 mg/kg/day
Critical Effect: Histopathologic liver lesions
Reference: NTP 1990
Point of Departure: NOAEL of 0.075 mg/kg/day
Uncertainty Factor: 100
Modifying Factor: 3
LSE Graph Key: 79
Species: Rat

MRL Summary: An MRL of 0.0003 mg/kg/day has been derived for chronic-duration oral exposure to mirex based on dose-related hepatic changes from a 2-year oral study of male and female F344/N rats (NTP 1990). The NOAEL of 0.075 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) and a modifying factor of 3 (to protect for developmental toxicity).

Selection of the Critical Effect: Available animal data identify the liver and kidney as critical targets of mirex toxicity following chronic-duration oral exposure. Potential candidate studies for deriving a chronic-duration oral MRL for mirex are summarized in Table A-1; the lowest LOAEL is 0.75 mg/kg/day for hepatic effects and the corresponding NOAEL is 0.075 mg/kg/day.

Table A-1. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Mirex

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	11% lower mean body weight in female rats treated for 2 years	1.95	3.85	NTP 1990
Body weight	No effect in rats treated for 21 months	0.37		Chu et al. 1981c
Hepatic	No effect in rats treated for 21 months	0.37		Chu et al. 1981c
Hepatic	Focal and centrilobular necrosis; fatty metamorphosis; dilation of sinusoids in rats treated for 2 years	0.075	0.75	NTP 1990
Hepatic	Megalocytosis in rats treated for 18 months followed by 6 months of recovery		3.6	Ulland et al. 1977
Renal	Increased severity of nephrotoxicity in rats treated for 2 years	0.75	1.95	NTP 1990

Table A-1. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Mirex

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Renal	Increased incidence of epithelial hyperplasia of the renal pelvis in rats treated for 2 years	0.075	0.75	NTP 1990

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: NTP (1990) was selected as the principal study for deriving a chronic-duration oral MRL for mirex because it identified the lowest reliable LOAEL for liver effects, a clearly sensitive effect of mirex toxicity.

Summary of the Principal Study:

NTP. 1990. Toxicology and carcinogenesis studies of mirex (CAS No. 2385-85-5) in F344/N rats (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 313.

Groups of male and female F344/N rats (52/sex/group; approximately 7–8 weeks of age) were administered mirex (95% purity) in the diet at 0, 0.1, 1.0, 10, 25, or 50 ppm for 104 weeks (first study). During the first 6 months of the study, additional groups of groups of female rats were started on 0, 50, or 100 ppm mirex in the diet (second study), based on the lack of observable toxic effects in the initial groups of female rats. Based on body weight and food consumption data, the study authors estimated average mirex doses to 0.1, 1, 10, 25, and 50 ppm groups from the first study at 0.007, 0.07, 0.7, 1.8, and 3.8 mg/kg/day, respectively, for the males and 0.007, 0.08, 0.7, 2.0, and 3.9 mg/kg/day, respectively, for the females (for the combined sexes, the author estimated doses at 0.007, 0.075, 0.75, 1.95, and 3.85 mg/kg/day, respectively). Estimated doses to the 50 and 100 ppm groups of females from the second study were 3.9 and 7.7 mg/kg/day, respectively. Animals were monitored for survival, clinical signs, body weight, and food intake. All rats were subjected to gross pathologic examination and all major organs and tissues were processed for histopathologic examination.

Survival of 1.95 and 3.85 mg/kg/day male rats was significantly less than that of controls (19/52 and 15/52, respectively, compared to 44/52 controls), most deaths occurred after treatment weeks 86–87. Survival was not affected in mirex-dosed females. By week 100, mean body weights of 1.95 and 3.85 mg/kg/day surviving males were 11–18% less than that of controls and mean body weights of 3.9 and 7.7 mg/kg/day females were 12–18% less than that of controls. The most notable compound-related histopathologic lesions were observed in the liver of male and female rats and included dose-related increased incidence of fatty metamorphosis, cytomegaly, angiectasis (males only), and necrosis. The NOAEL for liver effects was 0.075 mg/kg/day and the LOAEL was 0.75 mg/kg/day for focal and centrilobular necrosis, fatty metamorphosis, and dilation of sinusoids. Incidences of nephropathy occurred at similar frequency in controls and mirex-dosed groups; however, the severity was judged to be greater in the 1.95, 3.9, and 7.7 mg/kg/day groups. Hyperplasia of the renal pelvis epithelium occurred at significantly increased incidence in male rats of the 10, 25, and 50 ppm groups (5/52, 14/51, and 9/52, respectively, versus 0/51 among controls). Incidences of neoplastic nodules in the liver were significantly greater in 0.75, 1.95, and 3.85 mg/kg/day groups of males than controls (14/52, 15/52, and 26/52, respectively, versus 3/52 in control males). Incidences of neoplastic liver nodules in the female rats of the first study were not significantly different from that of controls. However, the incidence among control

females (10/52 or 19%) was significantly greater than the historical control incidence (2.8%). In the second study that included 0, 3.9, and 7.7 mg/kg/day groups of female rats, incidences of neoplastic liver nodules (usually consisting of enlarged hepatocytes with eosinophilic or clear cytoplasm arranged in irregular distorted cords one or two cell layers thick, but some consisting of cells with basophilic cytoplasm) were 23/52 (44%), and 30/52 (58%), respectively, versus 2/52 (4%) within a concurrent control group. Incidences of transitional cell papillomas of the renal pelvis of male rats occurred with a positive trend ($p<0.02$). The incidence in the 3.85 mg/kg/day males was 3/52 (6%) compared to 0/51 (0%) among controls and was noted to be higher than the highest incidence previously observed in controls (1/48 or 2%). Incidences of pheochromocytomas of the adrenal gland occurred with a positive trend and the incidences in 1.95 and 3.85 mg/kg/day male rats were significantly greater than that of controls. Incidences of mononuclear cell leukemia in analysis of all female rats in the first and second studies (combined) were significantly increased in the 0.75, 1.95, 3.9, and 7.7 mg/kg/day groups (14/52 or 27%, 18/52 or 35%, 27/104 or 26%, and 14/52 or 27%) versus 14/104 (13%) among controls.

Selection of the Point of Departure: The treatment-related increased incidence of renal pelvis hyperplasia identified in the 2-year dietary study of rats (NTP 1990) was not considered an appropriate basis for deriving a chronic-duration oral MRL for mirex because the hyperplasia was observed in areas of the kidney that also exhibited tumors. Therefore, the hyperplasia may represent a preneoplastic lesion. However, the liver lesions (focal and centrilobular necrosis, fatty metamorphosis, dilation of sinusoids) identified in the same study (NTP 1990) are nonneoplastic effects that were selected as the critical effects for deriving a chronic-duration oral MRL. The NOAEL of 0.075 mg/kg/day for liver effects was selected as the point of departure for deriving a chronic-duration oral MRL for mirex.

Uncertainty Factor: The NOAEL of 0.075 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Modifying Factor: A modifying factor of 3 was applied to be protective of mirex-induced developmental toxicity (see Section 2.17), including arrhythmias in neonatal pups following maternal exposure during gestation at a dose level as low as 0.1 mg/kg/day in the absence of an identified NOAEL (Grabowski 1983).

Other Additional Studies or Pertinent Information that Lend Support: Adverse hepatic effects were reported in a number of intermediate- or chronic-duration animal studies that employed oral exposure to mirex (Bell and Mehendale 1985; Chu et al. 1980c, 1981a, 1981b; Curtis and Hoyt 1984; Dai et al. 2001; Davison et al. 1976; Gaines and Kimbrough 1970; Larson et al. 1979a; Mehendale 1981; Ulland et al. 1977).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified for chlordecone.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
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: No intermediate-duration inhalation studies were identified for chlordecone.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
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: No chronic-duration inhalation studies were identified for chlordecone.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordecone
CAS Numbers:	143-50-0
Date:	October 2020
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL	0.01 mg/kg/day
Critical Effect:	Neurological effects
Reference:	EPA 1986a
Point of Departure:	NOAEL of 1.25 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	12
Species:	Rat

MRL Summary: An acute-duration oral MRL of 0.01 mg/kg/day was derived for chlordecone based on neurological effects (increased startle response) observed in young adult male Fischer 344 rats in a 10-day gavage study conducted by EPA (1986a). The MRL is based on a NOAEL of 1.25 mg/kg/day and a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Numerous studies have evaluated the toxicity of chlordecone following acute-duration oral exposure. Many studies reported treatment-related neurological effects or developmental effects. Other studies collectively identified the following targets: body weight, cardiovascular system, hematological system, musculoskeletal system, liver, renal system, endocrine system, immunological system, and female reproductive system.

Recent reports evaluated development of the reproductive system following gavage treatment of pregnant mice with chlordecone at 0.1 mg/kg/day during gestation days 6.5–15.5. Gely-Pernot et al. (2018) reported significantly decreased numbers of spermatozoa in adult F1 and F3 mice (note only the parental [F0] dams were administered chlordecone). Legoff et al. (2019) reported delayed vaginal opening and adverse ovarian follicular effects in F1 mice. Both studies only tested a single dose; thus, dose-response relationships cannot be evaluated. The lack of dose-response data along with weaknesses in the reporting of the study design and results preclude using either study as the basis of an MRL. Study weaknesses include the lack of examination for potential maternal toxicity, although the study authors stated that the selected dose level (0.1 mg/kg/day) "has no effect on murine health;" lack of information regarding numbers of pregnant mice/group, numbers of litters produced, numbers of litters contributing to the quantitative data reported; and use of only four progeny/group in some of the analyses.

A summary of the lowest reliable LOAELs for each endpoint is presented in Table A-2. A comparison of the LOAEL values across endpoints supports the identification of the nervous system as the most sensitive target of toxicity.

Table A-2. Lowest LOAELs Identified in Acute-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	15% depressed maternal body weight gain in rats gavaged daily on gestation days 7–16		2	Chernoff and Rogers 1976
Hematological	Decreased neutrophils in rats exposed for 10 days	5	10	Smialowicz et al. 1985
Hepatic	Increased serum alkaline phosphatase, ALT, gamma-glutamyl transferase in rats gavaged daily for 10 days	5	10	EPA 1986a
Renal	Increased blood urea nitrogen in rats gavaged daily for 10 days	5	10	EPA 1986a
Endocrine	Depletion of epinephrine in adrenal medulla of rats treated for 8 days in diet		17	Baggett et al. 1980
Immunological	Decreases in spleen and thymus weights, leukocyte counts, natural killer cell activity, Concanavalin A responsiveness in rats gavaged daily for 10 days	5	10	EPA 1986a
Neurological	Increased startle response in young adult male rats gavaged daily for 10 days	1.25	2.5	EPA 1986a
Reproductive	Persistent estrus in rats gavaged once		35	Swanson and Woolley 1982
	Induction of persistent vaginal estrus in mice repeatedly gavaged for 4 or 6 weeks		2	Swartz et al. 1988
Developmental	86% decreased postnatal day 3 pup survival following daily gavage treatment of maternal rats during gestation days 7–16		10	EPA 1986a

ALT = alanine aminotransferase; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The lowest reliable LOAEL values were identified for body weight, neurological effects, and effects on the female reproductive system. Chernoff and Rogers (1976) reported decreases in maternal body weight gain in rat dams administered 2 mg/kg/day chlordecone on gestation days 7–16. Swartz et al. (1988) reported the induction of persistent vaginal estrus in sexually mature mice administered chlordecone by gavage at 2 mg/kg/day, 5 days/week for 2 weeks. EPA (1986a) reported increased startle response in young adult male rats administered 2.5 mg/kg/day chlordecone for 10 days. These comparable LOAELs are at least 4 times lower than the LOAELs for hematological, hepatic, renal, immunological, and developmental effects. The EPA (1986a) study was selected as the principal study for deriving an acute-duration oral MRL for chlordecone because it identified a NOAEL (1.25 mg/kg/day).

Summary of the Principal Study:

EPA. 1986a. Final report on the evaluation of four toxic chemicals in an '*in vivo/in vitro'* toxicological screen: Acrylamide, chlordecone, cyclophosphamide, and diethylstilbestrol. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory. EPA600186002.

Groups of young adult male Fischer 344 rats (10/group) were administered chlordecone (in corn oil vehicle) by gavage for 10 days at 0, 0.625, 1.25, 2.5, 5.0, or 10.0 mg/kg/day. Animals were monitored for survival and body weight. Motor activity (performance in a figure 8 maze) and acoustic startle response were evaluated at 1 day following the final dose treatment. Urine was collected for urinalysis and blood was drawn for serum chemistry. At sacrifice, selected organ weights were determined. At ≥2.5 mg/kg/day, the amplitude of the acoustic startle response was significantly increased. At the other two doses, the amplitude was increased with all decibel stimuli. Motor activity in a figure-8 maze was decreased at the highest dose tested. Terminal body weight was depressed by 12% at 10 mg/kg/day. Relative liver weight was significantly increased at 5 and 10 mg/kg/day (15–16% higher than controls). Selected serum chemistry parameters were statistically significantly different from controls only in the high-dose group.

Selection of the Point of Departure: The NOAEL of 1.25 mg/kg/day was selected as the point of departure for deriving an acute-duration oral MRL for chlordecone.

Uncertainty Factor: The NOAEL of 1.25 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support: As stated above, numerous animal studies reported neurological effects associated with acute-duration oral exposure to chlordecone (Albertson et al. 1985; Aldous et al. 1984; Baggett et al. 1980; Chang-Tsui and Ho 1979; Desaiah et al. 1980a; Egle et al. 1979; End et al. 1981; Fujimori et al. 1982a; Hoskins and Ho 1982; Huang et al. 1980; Jordan et al. 1981; Klingensmith and Mehendale 1982a; Mactutus et al. 1984; Mishra et al. 1980; Smialowicz et al. 1985; Swanson and Wooley 1982; Tilson et al. 1985).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.003 mg/kg/day
Critical Effect: Neurological and male reproductive effects
Reference: Linder et al. 1983
Point of Departure: NOAEL of 0.26 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 57
Species: Rat

MRL Summary: An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure to chlordecone based on neurological and male reproductive effects from a 90-day oral study of male Sprague-Dawley rats (Linder et al. 1983). The NOAEL of 0.26 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Studies that evaluated chlordecone toxicity in humans did not include dose-response data; therefore, human data were not considered for MRL derivation. Treatment-related effects on the liver, nervous system, body weight, cardiovascular system, endocrine system, reproductive system, and development have been consistently associated with intermediate-duration oral exposure of laboratory animals to chlordecone. A summary of the lowest LOAELs for each endpoint is presented in Table A-3.

Table A-3. Lowest LOAELs Identified in Intermediate-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	13% decreased body weight gain in rats treated for 3 months in diet		1.17	Cannon and Kimbrough 1979
Hepatic	Focal necrosis in rats treated for 3 months in diet		1.17	Cannon and Kimbrough 1979
Endocrine	Reversible hyperplasia of adrenal cortex in rats treated for 3 months in diet		1.17	Cannon and Kimbrough 1979
Neurological	Hyperexcitability, mild tremors in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983
Reproductive	46–48% decreased sperm motility and viability; 19% decreased epididymal sperm concentration in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983

Table A-3. Lowest LOAELs Identified in Intermediate-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Developmental	Decreased postnatal survival in pups from parental mice treated for up to 130 days in diet	1.9	7	Huber 1965

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

A comparison of the LOAEL values across endpoints supports the identification of the nervous system and male reproductive system as the most sensitive targets of toxicity. The identification of the neurotoxicity and reproductive toxicity as sensitive endpoints for chlordecone is supported by several other intermediate-duration studies, which are summarized in Tables A-4 and A-5, respectively.

Table A-4. Selected LOAELs for Neurological Effects Identified in Intermediate-Duration Oral Studies of Chlordecone

Species (strain)	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat (Sprague-Dawley)	Tremors in rats treated for 15 days in diet		4.7	Agarwal and Mehendale 1984a
Rat (Sherman)	Tremors, hyperexcitability, exaggerated startle response in rats treated for 3 months in diet		1.17 M 1.62 F	Cannon and Kimbrough 1979
Rat (Zivac-Miller)	Tremors, decreased operant behavior in rats repeatedly gavaged for 90 days		1	Dietz and McMillan 1979
Rat (Wistar)	Tremors (dose-related earlier onset and increased severity) in rats treated for up to 6 months in diet		2.1 M 2.4 F	Larson et all 1979b
Rat (Sprague-Dawley)	Hyperexcitability, mild tremors in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983
Rat (Sprague-Dawley)	Tremors, hypersensitivity to noise and stress in rats treated for 16 days in diet		3.95	Mehendale et al. 1978
Rat (Fischer 344)	Increased startle response in rats repeatedly gavaged for 15 weeks	2.8	4.1	Pryor et al. 1983
Rat (Fischer 344)	Exaggerated startle response in rats treated for 90 days in diet		1.0	Squibb and Tilson 1982a
Mouse (BALB/c)	Tremor in mice treated for 2–12 months in diet	1.9	5.6	Huber 1965

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Table A-5. Lowest LOAELs for Reproductive Effects Identified in Intermediate-Duration Oral Studies of Chlordecone

Species (strain)	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat (Sherman)	Decreased number of litters born to control males mated to females treated for 3 months in diet		1.62	Cannon and Kimbrough 1979
Rat (Wistar)	Testicular atrophy in 4/5 males treated for 3 months in diet		2.1	Larson et al. 1979b
Rat (Sprague-Dawley)	46–48% decreased sperm motility and viability; 19% decreased epididymal sperm concentration in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983
Mouse (BALB/c)	36% decrease in second litters in mice treated for 5 months (including 1 month premating) in diet		0.94	Good et al. 1965
Mouse (BALB/c)	8% decrease in litter size and 19% increase in pair-days to litter among mice treated for 130 days (1 month premating) in diet		1.9	Huber 1965
Mouse (CD-1)	Increased ovulation, persistent vaginal estrus in mice gavaged for 4 or 6 weeks (5 days/week)		2	Swartz et al. 1988

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The study of Linder et al. (1983) identified the lowest LOAEL (0.83 mg/kg/day) for both tremors and impaired sperm parameters; the NOAEL was 0.26 mg/kg/day. This multiple dose study was selected as the principal study for derivation of an intermediate-duration oral MRL for chlordecone.

Summary of the Principal Study:

Linder RE, Scotti TM, McElroy WK, et al. 1983. Spermotoxicity and tissue accumulation of chlordecone (Kepone) in male rats. J Toxicol Environ Health 12:183-192.

Groups of 20 adult male Sprague-Dawley rats were administered technical grade chlordecone (purity not specified) in the diet at 0, 5, 15, or 30 ppm for 90 days. Rats were monitored for clinical signs, body weight, and food intake. The study authors estimated chlordecone doses to the 5, 15, and 30 ppm groups to have been 0.26, 0.83, and 1.67 mg/kg/day, respectively. After the 90-day treatment period, 10 rats/group were sacrificed; testes, epididymides, prostate, and seminal vesicles were weighed; epididymal fluid was extracted for evaluation of spermatozoal motility and viability. Reproductive tissues were then processed for histologic examination. The other 10 rats/group were returned to normal diet and each bred to two untreated virgin females during a 14-day posttreatment period. Mated females were sacrificed on gestation day 20 and fetal weights, fetal viability, and total implants were determined. Male rats used for breeding were sacrificed at 4.5 months after cessation of treatment for evaluation of recovery from chlordecone treatment.

One 0.83 mg/kg/day rat died on treatment day 84; one rat each in the 0.26 and 1.67 mg/kg/day groups died during the recovery period (recovery days 64 and 30, respectively). Clinical signs of neurotoxicity, including hyperexcitability and mild tremors, were observed in rats of the 0.83 and 1.67 mg/kg/day groups (incidences not included in the study report). The 1.67 mg/kg/day group sacrificed at 90 days exhibited approximately 7% lower mean final body weight than controls (not considered an adverse effect because the decrease was <10%). The 1.67 mg/kg/day group of rats exhibited significantly lower absolute weights of seminal vesicles and prostate (12 and 24%, respectively, less than controls). Sperm concentration (sperm count) and incidences and type of morphologically abnormal spermatozoa were similar between controls and all chlordecone-treated groups. However, within the 0.83 and 1.67 mg/kg/day groups, decreases in sperm motility (48 and 39%, respectively, less than controls), sperm viability (46 and 33%, respectively, less than controls), and epididymal concentration (19% less than controls for both 0.83 and 1.67 mg/kg/day groups) were observed. There were no chlordecone treatment-related effects on reproductive performance (number of males siring litters, live litters, average litter size, average number of implants, percent resorptions, or fetal weight). At the end of the recovery period, sperm parameters and reproductive organ weights were similar to those of controls. The study identified a NOAEL of 0.26 mg/kg/day and a LOAEL of 0.83 mg/kg/day for clinical signs of neurotoxicity (tremors) and effects on sperm parameters. The LOAEL for effects on sperm parameters is not considered a serious LOAEL due to the lack of effects on reproductive performance.

Selection of the Point of Departure: The NOAEL of 0.26 mg/kg/day was selected as the point of departure for deriving an intermediate-duration oral MRL for chlordecone.

Benchmark dose (BMD) analysis of the neurological effects in the principal study (Linder et al. 1983) was precluded by lack of incidence data for the treatment-related tremors. BMD analysis was conducted on the datasets for sperm motility and sperm viability (Table A-6) to identify potential points of departure for deriving an intermediate-duration oral MRL for chlordecone.

Table A-6. Sperm Motility and Viability Data for Sprague-Dawley rats Administered Chlordecone in the Diet for 90 Days

Dose (mg/kg/day)	0	0.26	0.83	1.67
Number of rats	10	10	10	10
Percent motile sperm[a]	37.0±3.9	33.2±3.8	19.2±4.4[b]	22.6±5.5[b]
Percent live sperm[a]	46.0±4.7	36.2±3.3	25.0±3.3[b]	30.9±4.8[b]

[a]Mean ± standard error of the mean (SEM).
[b]Significantly different from control ($p<0.05$).

Source: Linder et al. 1983

The data for sperm motility and for sperm viability were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2). The following procedure for fitting continuous data was used: the simplest model (linear) was first applied to the data while assuming constant variance; if the data were consistent with the assumption of constant variance ($p\geq0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by four criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR), and BMDL that was not 10 times lower than the lowest non-zero dose. Among all models providing adequate fit to the data, the lowest BMDL (the lower limit of a one-sided 95% confidence interval [CI] on the BMD) was selected as a reasonably conservative

point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was chosen. For both datasets, a BMR of 1 standard deviation (SD) change from the control was used.

Table A-7 presents the results of the BMD modeling with constant variance of the sperm motility data. Although most models provided adequate statistical fit, visual inspection of the plotted data indicated a poor fit of the estimated mean values to the measured mean values for the two dose levels closest to the BMD and BMDL.

Table A-7. Results of BMD Analysis (with Constant Variance) of Percent Motile Sperm in Rats Exposed to Chlordecone in the Diet for 90 Days (Linder et al. 1983)

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]	1.27	0.63	0.185	330.23	0.95	0.34
Exponential 3[d]	1.27	0.63	0.185	330.23	0.94	0.34
Exponential 4[d]	0.65	0.20	0.209	330.44	-0.90	-0.25
Exponential 5			NA	331.19	0.00	0.00
Hill[d,e]			0.564	329.19	0.00	0.01
Polynomial Degree 3[d]	1.55	0.93	0.124	331.03	0.80	0.61
Polynomial Degree 2[d]	1.55	0.93	0.124	331.03	0.80	0.61
Power[d]	1.55	0.93	0.124	331.03	0.80	0.61
Linear	1.55	0.93	0.124	331.03	0.80	0.61

[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 at doses immediately below and above the BMD.
[d]Restricted model.
[e]The Hill model was not considered adequate since less than five dose groups were used.

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., $_{1SD}$ = exposure dose associated with a 10% relative deviation from control)

The results of BMD analysis of sperm viability are presented in Table A-8. For the sperm viability data, the Exponential Model 4 was the only model to provide adequate statistical fit to the mean data. However, visual inspection of the plotted data from Exponential Model 4 indicated a poor fit of the estimated mean values to the measured mean values for sperm viability. Therefore, the BMDL estimated from this model was not considered suitable as the basis of the MRL.

Table A-8. Results of BMD Analysis (with Constant Variance) of Percent Sperm Viability in Rats Exposed to Chlordecone in the Diet for 90 Days (Linder et al. 1983)

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]			0.0331	326.91	1.25	1.11
Exponential 3[d]			0.0331	326.91	1.25	1.11
Exponential 4[d]			0.2064	323.68	0.33	-0.08
Exponential 5	0.32	0.10	NA	325.23	0.00	0.05
Hill[d]			0.2857	323.23	0.00	0.00
Polynomial Degree 3[d]			0.0218	327.73	1.04	1.36
Polynomial Degree 2[d]			0.0218	327.73	1.04	1.36
Power[d]			0.0218	327.73	1.04	1.36
Linear			0.0218	327.73	1.04	1.36

[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 at doses immediately below and above the BMD.
[d]Restricted model.

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., $_{1SD}$ = exposure dose associated with a 10% relative deviation from control)

A NOAEL/LOAEL approach to deriving an intermediate-duration oral MRL for chlordecone was applied because a BMD approach was precluded by lack of adequate modeling results.

Uncertainty Factor: The NOAEL of 0.26 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support: Squibb and Tilson (1982a) reported chlordecone-induced exaggerated startle response in male rats administered chlordecone in the diet for 90 days at 1.0 mg/kg/day). Cannon and Kimbrough (1979) reported tremors, hyperactivity, and exaggerated startle response among male and female rats receiving chlordecone from the diet for 3 months at 1.17 and 1.62 mg/kg/day, respectively (lowest exposure level tested). Good et al. (1965) reported decreased numbers of second litters produced by mice at a chlordecone dose level as low as 0.94 mg/kg/day. Cannon and Kimbrough (1979) reported decreased number of litters born to control males mated to chlordecone-treated females dosed at 1.62 mg/kg/day. Larson et al. (1979b) reported testicular atrophy in male rats administered chlordecone for 3 months at 2.1 mg/kg/day.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.0009 mg/kg/day
Critical Effect: Renal effects
Reference: Larson et al. 1979b
Point of Departure: NOAEL of 0.089 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 75
Species: Rat

MRL Summary: An MRL of 0.0009 mg/kg/day was derived for chronic-duration oral exposure to chlordecone based on renal effects in rats administered chlordecone in the diet for up to 2 years (Larson et al. 1979b). The NOAEL of 0.089 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Treatment-related effects on body weight, hematological system, liver, renal system, and nervous system, and dermal irritation have been associated with chronic-duration oral exposure of laboratory animals to chlordecone. A summary of the lowest LOAELs for each endpoint is presented in Table A-9. A comparison of the LOAEL values across endpoints supports the identification of the renal system as the most sensitive target of toxicity.

Table A-9. Lowest LOAELs Identified in Chronic-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	>10% depressed body weight in rats treated for 1 or 2 years in diet	0.89	2.2	Larson et al. 1979b
Hematological	Anemia in male rats treated for 80 weeks in diet		0.56	NCI 1976
Hepatic	Fatty infiltration and degeneration in male rats treated for 80 weeks in diet		0.56	NCI 1976
Renal	Proteinuria and increased severity of glomerulosclerosis in rats treated for up to 2 years in diet	0.089	0.45	Larson et al. 1979b
Dermal	Dermatitis in rats treated for 80 weeks in diet		0.56	NCI 1976
Neurological	Tremors in rats treated for 80 weeks in diet		0.56	NCI 1976

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Results from several studies were considered in the selection of the critical effect for derivation of a chronic-duration oral MRL for chlordecone. Larson et al. (1979b) administered chlordecone in the diet to rats for up to 2 years and reported depressed body weight gain, decreased hematocrit levels, and tremors at 2.2 mg/kg/day; fatty changes in the liver at 0.89 mg/kg/day; and proteinuria and increased severity of glomerulosclerosis in the kidney at 0.45 mg/kg/day. In an 80-week study of rats administered chlordecone in the diet (NCI 1976), adverse dermal, hepatic, hematological, and neurological effects were observed at the lowest dose tested (0.56 and 1.4 mg/kg/day for males and females, respectively). Similarly-treated mice exhibited adverse hepatic and neurological effects at the lowest dose tested (3.4 and 3.5 mg/kg/day for males and females, respectively). Larson et al. (1979b) also treated dogs for up to 128 weeks at doses up to 1.2 mg/kg/day and observed no neurological effects. Chu et al. (1981c) reported histopathological thyroid lesions in male Sprague-Dawley rats treated with chlordecone in the diet for 21 months at 0.07 mg/kg/day. However, the study report indicated that 4/10 control rats exhibited thyroid lesions (mild degenerative and proliferative changes in follicular epithelium without alteration in colloid density) and that 4/6 chlordecone-treated rats exhibited mild histological changes that may have included decreased colloid density. Thus, it is not clear whether a significant difference existed between controls and chlordecone-treated rats regarding thyroid lesions. Therefore, the thyroid lesion data were not considered for MRL derivation.

Selection of the Principal Study: Larson et al. (1979b) was selected as the principal study for deriving a chronic-duration oral MRL for chlordecone because it identified a NOAEL (0.089 mg/kg/day) associated with the lowest LOAEL (0.45 mg/kg/day for renal effects). The kidney effect observed in rats treated for up to 2 years represents the lowest reliable LOAEL (0.45 mg/kg/day) among the candidate treatment-related adverse effects from chronic-duration oral exposure to chlordecone, and was therefore selected as the critical effect for deriving a chronic-duration oral MRL for chlordecone.

Summary of the Principal Study:

Larson PS, Egle JL Jr, Hennigar CR, et al. 1979b. Acute, subchronic, and chronic toxicity of chlordecone. Toxicol Appl Pharmacol 48:29-41.

Groups of Wistar rats (40/sex/group) were administered chlordecone in the diet for up to 2 years at 0, 5, 10, 25, 50, or 80 ppm. Other groups of male and female Wistar rats (40/sex/group) were administered chlordecone in the diet for up to 2 years at 0 or 1 ppm (estimated chlordecone doses of 0 and 0.089 mg/kg/day, respectively) and similarly evaluated. Estimated chlordecone doses of 0, 0.089, 0.45, 0.89, 2.2, 4.5, and 7.1 mg/kg/day were calculated for the 1, 5, 10, 25, 50, and 80 ppm dietary concentrations, respectively, using a time-weighted average (TWA) of reported body weights (0.254 kg) and a food consumption rate (0.0226 kg/day) calculated using EPA's (1988) allometric equation. After 1 year, five rats/sex/dose group were sacrificed. All rats in the 4.5 and 7.1 mg/kg/day groups died by week 25. Proteinuria was noted in all 0.45, 0.89, and 2.2 mg/kg/day groups at all intervals after 3 months except in males at 21 and 24 months when control levels were elevated, and in females at 24 months when the levels in only the 0.89 and 2.2 mg/kg/day were elevated. There was no indication of proteinuria in the 0.089 mg/kg/day of male or female rats. The severity of observed glomerulosclerosis was increased in both males and females at ≥0.45 mg/kg/day. Non-statistically significantly increased kidney weight relative to body weight was reported. The NOAEL for kidney effects was 0.089 mg/kg/day. At 1- and 2-year sacrifice, NOAELs of 0.45 and 0.89 mg/kg/day and their respective LOAELs (0.89 mg/kg/day for fatty changes in the liver and 2.2 mg/kg/day for depressed hematocrit levels) were identified.

Selection of the Point of Departure for the MRL: The NOAEL of 0.089 mg/kg/day was selected as the point of departure for deriving a chronic-duration oral MRL for chlordecone. The proteinuria and

glomerulosclerosis severity data were not amenable to BMD modeling because standard deviations were not reported.

Uncertainty Factor: The NOAEL of 0.089 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Although other available chronic-duration oral studies did not identify renal effects in chlordecone-treated animals, adverse dermal, hepatic, hematological, and/or neurological effects were observed at doses in the range of 0.4–2.6 mg/kg/day.

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MIREX AND CHLORDECONE

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 mirex and chlordecone.

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, and chemical interactions data for mirex and chlordecone. 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 mirex and chlordecone 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 mirex and chlordecone 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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for mirex and chlordecone released for public comment in May 2019. The following main databases were searched in October 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for mirex and chlordecone. 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 mirex and chlordecone were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2019	("Mirex"[mh] OR 2385-85-5[rn] OR "Chlordecone"[mh] OR 143-50-0[rn] OR "1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene"[tw] OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene dimer"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-"[tw] OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, dodecachlorooctahydro-"[tw] OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-, dimer"[tw] OR "Bichlorendo"[tw] OR "CG-1283"[tw] OR "Cyclopentadiene, hexachloro-, dimer"[tw] OR "Dechlorane"[tw] OR "Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene"[tw] OR "Dodecachloropentacyclo(3.2.2.0(sup 2,6),0(sup 3,9),0(sup 5,10))decane"[tw] OR "Dodecachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane"[tw] OR "Dodecachloropentacyclo(5.2.1.02,6.03,9.05,8)decane"[tw] OR "Dodecachloropentacyclodecane"[tw] OR "Dodecaclor"[tw] OR "Ferriamicide"[tw] OR "Fire Ant Bait"[tw] OR "GC 1283"[tw] OR "Hexachlorocyclopentadiene dimer"[tw] OR "HRS 1276"[tw] OR "HRS l276"[tw] OR "Mirex"[tw] OR "Paramex"[tw] OR "Pentacyclodecane, dodecachloro-"[tw] OR "Perchlordecone"[tw] OR "Perchlorodihomocubane"[tw] OR "Perchloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane"[tw] OR "Perchloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decane"[tw] OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decane"[tw] OR "Perchloropentacyclodecane"[tw] OR "1,1a,3,3a,4,5,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "1,2,3,4,5,5,6,7,8,9,10,10-Dodecachlorooctahydro-1,3,4-metheno-2-cyclobuta(c,d)pentalone"[tw] OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-"[tw] OR "2,3,3a,4,5,6,7,7a,8,8a-Decachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one"[tw] OR "Chlordecone"[tw] OR "Ciba 8514"[tw] OR "Clordecone"[tw] OR "Compound 1189"[tw] OR "Decachloro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "Decachloroketone"[tw] OR "Decachlorooctahydro-1,3,4-methano-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "Decachlorotetracyclodecanone"[tw] OR "Decachlorotetrahydro-4,7-methanoindeneone"[tw] OR "GC 1189"[tw] OR "General chemicals 1189"[tw] OR "Kepone"[tw] OR "Kepone-2-one, decachlorooctahydro-"[tw] OR "Merex"[tw] OR "1,2,3,5,6,7,8,9,10,10-Decachloro(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decano-4-one"[tw] OR "Decachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5),(8))decan-4-one"[tw] OR "Decachloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decan-4-one"[tw] OR "Decachloropentacyclo(5.3.0.0(sup 2,6).0(sup 4,10).0(sup 5,9))decan-3-one"[tw] OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decan-5-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])
	("1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachloroactahydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene"[tw] OR "Dodecachlor"[tw] OR "Dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalene"[tw] OR "Dodecachloropentacyclo[5.3.0.0(2.6).0(3.9).0(4.8)]decane"[tw] OR "Perchloropentacyclo[5.2.1.02,6.03,9.05,8]decane"[tw] OR "Perchloropentacyclo[5.3.0.02,6.03,9.04,8]decane"[tw] OR "1,1a,3,3a,4,5,5,5a,5b,6-Decachloro-octahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "1,1a,3,3a,4,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta [cd]pentalen-2-one"[tw] OR "1,3,4-Metheno-2H-cyclobuta[cd]pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobuta[cd]pentalen-2-one, 1,1a,3,3a,4,5,5a,5b,6-decachlorooctahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobuta[cd]pentalen-2-one, decachlorooctahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobutal [cd]pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloro-octahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobutal[cd]pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloroctahydro-"[tw] OR "Decachloroctalhydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Decachloropentacyclo[5.2.1.02,6.03,9.05,8]decan-4-one"[tw]) AND (1993:3000[dp] OR 1993:3000[mhda] OR 1993:3000[edat] OR 1993:3000[crdat]))
Toxline	
10/2019	"Mirex" OR 2385-85-5[rn] OR "Chlordecone" OR 143-50-0[rn] Year of Publication 2016 through 2019
	"1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene" OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene dimer" OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-" OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, dodecachlorooctahydro-" OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-, dimer" OR "Bichlorendo" OR "CG-1283" OR "Cyclopentadiene, hexachloro-, dimer" OR "Dechlorane" OR "Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene" Year of Publication 2016 through 2019
	"Dodecachloropentacyclo(3.2.2.0(sup 2,6),0(sup 3,9),0(sup 5,10))decane" OR "Dodecachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane" OR "Dodecachloropentacyclo(5.2.1.02,6.03,9.05,8)decane" OR "Dodecachloropentacyclodecane" OR "Dodecaclor" OR "Ferriamicide" OR "Fire Ant Bait" OR "GC 1283" OR "Hexachlorocyclopentadiene dimer" OR "HRS 1276" OR "HRS l276" OR "Mirex" OR "Paramex" OR "Pentacyclodecane, dodecachloro-" Year of Publication 2016 through 2019
	"Perchlordecone" OR "Perchlorodihomocubane" OR "Perchloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane" OR "Perchloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decane" OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decane" OR "Perchloropentacyclodecane" OR "1,1a,3,3a,4,5,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "1,2,3,4,5,5,6,7,8,9,10,10-Dodecachlorooctahydro-1,3,4-metheno-2-cyclobuta(c,d)pentalone" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-" Year of Publication 2016 through 2019
	"2,3,3a,4,5,6,7,7a,8,8a-Decachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one" OR "Chlordecone" OR "Ciba 8514" OR "Clordecone" OR "Compound 1189" OR "Decachloro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "Decachloroketone" OR "Decachlorooctahydro-1,3,4-methano-2H-cyclobuta(cd)pentalen-2-one" OR "Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "Decachlorotetracyclodecanone" OR "Decachlorotetrahydro-4,7-methanoindeneone" OR "GC 1189" OR "General chemicals 1189" Year of Publication 2016 through 2019
	"Kepone" OR "Kepone-2-one, decachlorooctahydro-" OR "Merex" OR "1,2,3,5,6,7,8,9,10,10-Decachloro(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decano-4-one" OR "Decachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5),(8))decan-4-one" OR "Decachloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decan-4-one" OR "Decachloropentacyclo(5.3.0.0(sup 2,6).0(sup 4,10).0(sup 5,9))decan-3-one" OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decan-5-one" Year of Publication 2016 through 2019
	"1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachloroactahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene" OR "Dodecachlor" OR "Dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalene" OR "Dodecachloropentacyclo(5.3.0.0(2.6).0(3.9).0(4.8))decane" OR

Table B-2. Database Query Strings

Database search date	Query string
	"Perchloropentacyclo(5.2.1.02,6.03,9.05,8)decane" OR "Perchloropentacyclo(5.3.0.02,6.03,9.04,8)decane" Year of Publication 1993 through 2019
	"1,1a,3,3a,4,5,5,5a,5b,6-Decachloro-octahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "1,1a,3,3a,4,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta (cd)pentalen-2-one" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5a,5b,6-decachlorooctahydro-" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, decachlorooctahydro-" Year of Publication 1993 through 2019
	"1,3,4-Metheno-2H-cyclobutal(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloro-octahydro-" OR "1,3,4-Metheno-2H-cyclobutal(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloroctahydro-" OR "Decachloroctalhydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "Decachloropentacyclo(5.2.1.02,6.03,9.05,8)decan-4-one" Year of Publication 1993 through 2019
Toxcenter	
10/2019	FILE 'TOXCENTER' ENTERED AT 11:37:01 ON 08 OCT 2019 CHARGED TO COST=EH038.06.01.LB.02 L1 6689 SEA FILE=TOXCENTER 2385-85-5 OR 143-50-0 L2 6678 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 6545 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 206 SEA FILE=TOXCENTER L3 AND ED>=20170401 L48 36 SEA FILE=TOXCENTER L4 AND MEDLINE/FS L49 170 SEA FILE=TOXCENTER L4 NOT MEDLINE/FS L50 179 DUP REM L48 L49 (27 DUPLICATES REMOVED) ANSWERS '1-179' FROM FILE TOXCENTER L*** DEL 36 S L4 AND MEDLINE/FS L*** DEL 36 S L4 AND MEDLINE/FS L51 36 SEA FILE=TOXCENTER L50 L*** DEL 170 S L4 NOT MEDLINE/FS L*** DEL 170 S L4 NOT MEDLINE/FS L52 143 SEA FILE=TOXCENTER L50 L53 143 SEA FILE=TOXCENTER (L51 OR L52) NOT MEDLINE/FS D SCAN L53

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2019	Compounds searched: 2385-85-5, 143-50-0
NTP	
10/2019	"2385-85-5" "143-50-0" "Mirex" "Chlordecone" "Dechlorane" "Dodecachloropentacyclodecane" "Dodecaclor" "Kepone" "Fire Ant Bait" "Paramex" "Perchloropentacyclodecane" "Decachloroketone" "Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" "Perchlordecone" "Clordecone" "Ferriamicide" "Dodecachlor"
Regulations.gov	
10/2019	Compounds searched: 2385-85-5, 143-50-0
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 331
- Number of records identified from other strategies: 10
- Total number of records to undergo literature screening: 431

B.1.2 Literature Screening

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

- 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.

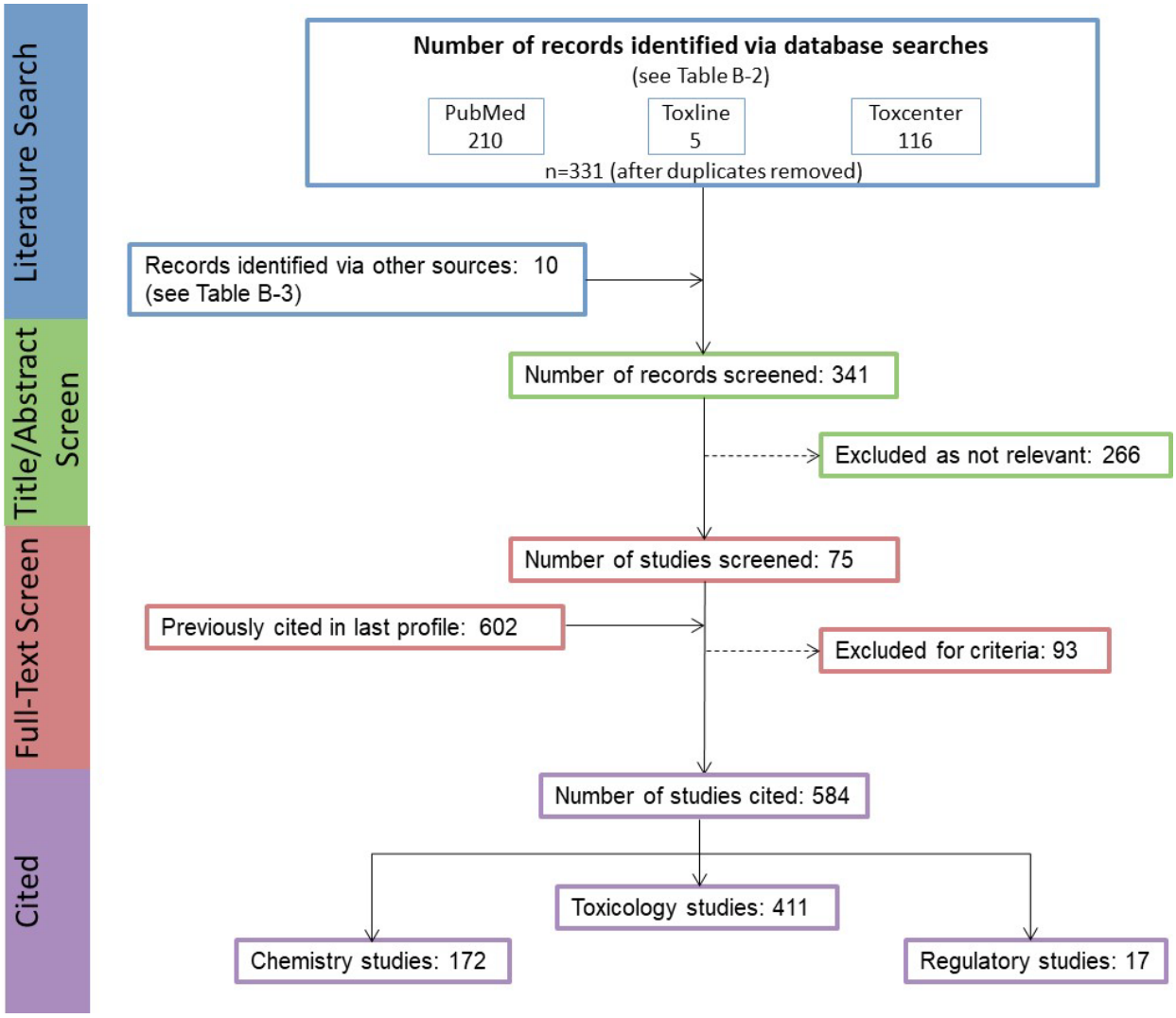
- Number of titles and abstracts screened: 431
- Number of studies considered relevant and moved to the next step: 75

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: 75
- Number of studies cited in the pre-public draft of the toxicological profile: 602
- Total number of studies cited in the profile: 584

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

Figure B-1. October 2019 Literature Search Results and Screen for Mirex and Chlordecone



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.

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

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

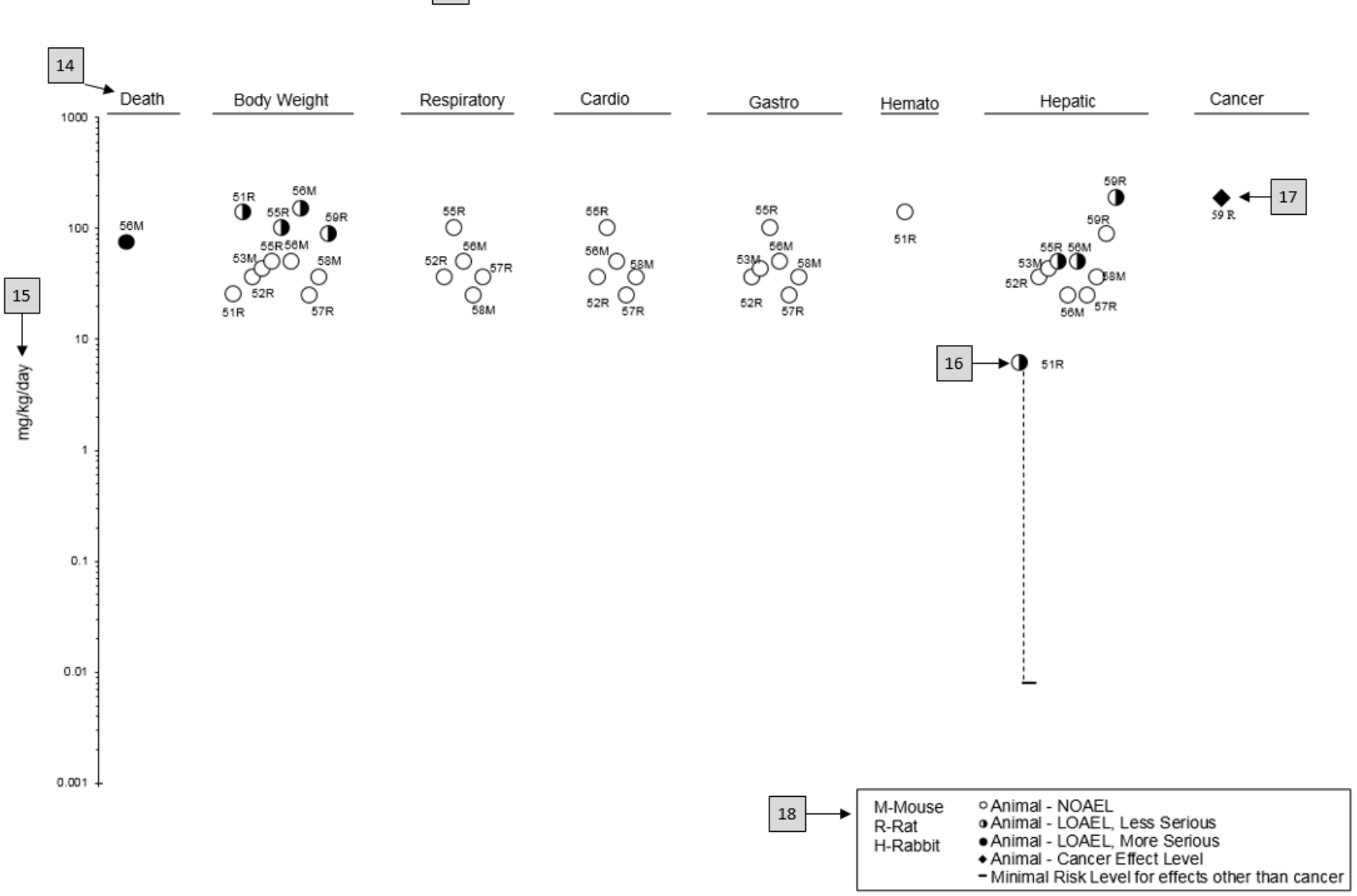
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX C

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 three-volume 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). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

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