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 Division of Toxicology and Human Health Sciences, 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 Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordane
CAS Numbers: 12789-03-6 (chlordane technical)
Date: May 1994
April 2017-Updated literature search
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: An MRL has not been derived for acute-duration inhalation exposure to chlordane. Only one acute inhalation study (Khasawinah et al. 1989; Velsicol Chemical Co. 1984) was located, and this study did not sufficiently identify target organs, and serious effects (death, convulsions) occurred at the lowest concentration tested.

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017—Updated literature search
Profile Status:	Final
Route:	Inhalation
Duration:	Intermediate
MRL	0.0002 mg/m^3
Critical Effect:	Hepatocellular hypertrophy
Reference:	Khasawinah et al. 1989; Velsicol Chemical Co. 1984
Point of Departure:	$NOAEL_{ADJ}$ of 0.024 mg/m^3
Uncertainty Factor:	100
LSE Graph Key:	3
Species:	Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.0002 mg/m^3 was derived for chlordane technical. The MRL is based on a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy in rats exposed to chlordane technical for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). The NOAEL was adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Intermediate-duration inhalation exposure data in rats have identified the hematological system, liver, central nervous system, thyroid, and possibly the thymus in female rats, as the target organs (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). A NOAEL of 5.8 mg/m^3 was associated with a LOAEL of 28.2 mg/m^3 for hypersensitivity to touch and decreased thymus weight in female rats and hepatocellular hypertrophy in male and female rats exposed to chlordane technical by inhalation for 8 hours/day, 5 days/week, for 28 days. A 90-day repeated exposure study (8 hours/day, 5 days/week) identified a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy, increased leukocytes, and decreased platelets in female rats. Altered follicular cell structure was noted in male rats exposed at 10 mg/m^3. Among available intermediate-duration inhalation studies for chlordane technical, hepatocellular hypertrophy was the most common effect and occurred in male and female rats at the lowest LOAEL (1.0 mg/m^3) and was therefore selected as the critical effect for deriving an intermediate-duration inhalation MRL for chlordane technical.

Selection of the Principal Study: No adverse effects were observed among monkeys following inhalation exposure to chlordane technical at 10 mg/m^3 for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). Two rat studies (a 28-day study and a 90-day study) evaluated the effects of repeated inhalation exposure to chlordane technical. The 90-day study identified the lowest LOAEL for liver effects and was selected as the principal study for deriving an intermediate-duration inhalation MRL for chlordane (Khasawinah et al. 1989; Velsicol Chemical Co. 1984).

Summary of the Principal Study:

Khasawinah AM, Hardy CJ, Clark GC. 1989. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J Toxicol Environ Health 28:327-347.

Velsicol Chemical Co. 1984. Chlordane: A 90-day inhalation toxicity study in the rat and monkey. Unpublished study No. VCL28 conducted by Huntingdon Research Centre. (cited in EPA 1987f).

Groups of Wistar rats (35–47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/m^3 technical chlordane for 8 hours/day, 5 days/week for 13 weeks, followed by a 13-week recovery period. Blood chemistry and urinalysis were performed prior to the beginning of exposure and at exposure weeks 5 and 13. Rats were sacrificed at 9 weeks (5/sex/group) and 13 weeks (15/sex/group). The remaining rats were sacrificed following 13 weeks of recovery. There were no exposure-related effects on mortality, clinical signs (with the exception of sensitivity to touch at the highest exposure level), food consumption, body weight, ophthalmoscopy, rectal temperature, or urinalysis. Exposure-related hematological changes (e.g., increases in total white blood cells, lymphocytes, neutrophils; decreases in hemoglobin and platelets) were of relatively small magnitude, occurred primarily in female rats, and values were within normal ranges for rats; therefore, these changes are not considered adverse. Exposure-related changes indicative of liver effects were observed at 1 mg/m^3 and included increases serum P-450 activity, globulins, total protein, and cholesterol; and decreased albumin and albumin/globulin ratio. Histopathologic examinations revealed hepatocellular hypertrophy in all rats of the 10 mg/m^3 exposure group and 5/15 males and 5/15 females of the 1 mg/m^3 exposure group (compared to 0/15/sex/group at 0 or 0.1 mg/m^3).

Selection of the Point of Departure for the MRL: The NOAEL of 0.1 mg/m^3 was selected as the basis for the MRL.

Intermittent Exposure: The NOAEL was adjusted from intermittent exposure (8 hours/day, 5 days/week) to account for continuous exposure according to the following equation:

$NOAEL_{ADJ}$ = NOAEL (0.1 mg/m^3) x 8 hours/24 hours x 5 days/7days = 0.024 mg/m^3.

Human Equivalent Concentration: The duration-adjusted $NOAEL_{ADJ}$ of 0.024 mg/m^3 was converted to a human equivalent concentration (HEC) according to the equation used to calculate a HEC for extrarespiratory effects of a Category 3 gas (EPA 1994): $NOAEL_{HEC}$ (mg/m^3) = $NOAEL_{ADJ}$ (mg/m^3) x $(H_{b/g})A/(H_{b/g})H$ (i.e., the ratio of the blood:gas [air] partition coefficient of the chemical for the laboratory animal species to the human value; the value of 1.0 is used when measured values are not available).

$NOAEL_{HEC}$ = 0.024 mg/m^3 x 1 = 0.024 mg/m^3.

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 100:

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

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Liver effects were observed in the 28-day and 90-day rat studies (Khasawinah et al. 1989; Velsicol Chemical Co. 1984).

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Inhalation
Duration:	Chronic
MRL	0.00002 mg/m^3
Critical Effect:	Hepatocellular hypertrophy
Reference:	Khasawinah et al. 1989; Velsicol Chemical Co. 1984
Point of Departure:	NOAEL of 0.1 mg/m^3
Uncertainty Factor:	1,000
LSE Graph Key:	3
Species:	Rat

MRL Summary: A chronic-duration inhalation MRL of 0.00002 mg/m^3 (0.02 $\mu g/m^3$) was derived for chlordane technical. The MRL is based on a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy in rats exposed to chlordane technical for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). The NOAEL was adjusted for intermittent exposure and converted to a human equivalent concentration (NOAEL_HEC) of 0.024 mg/m^3 and was divided by an uncertainty factor of 1,000 (10 for extrapolation from intermediate to chronic duration, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Intermediate-duration inhalation exposure data in rats have identified the hematological system, liver, central nervous system, thyroid, and possibly the thymus in female rats, as the target organs (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). A NOAEL of 5.8 mg/m^3 was associated with a LOAEL of 28.2 mg/m^3 for hypersensitivity to touch and decreased thymus weight in female rats and hepatocellular hypertrophy in male and female rats exposed to chlordane technical by inhalation for 8 hours/day, 5 days/week, for 28 days. A 90-day repeated exposure study (8 hours/day, 5 days/week) identified a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy, increased leukocytes, and decreased platelets in female rats. Altered follicular cell structure was noted in male rats exposed at 10 mg/m^3. Among available intermediate-duration inhalation studies for chlordane technical, hepatocellular hypertrophy was the most common effect and occurred in male and female rats at the lowest LOAEL (1.0 mg/m^3) and was therefore selected as the critical effect for deriving an intermediate-duration inhalation MRL for chlordane technical.

Selection of the Principal Study: No adverse effects were observed among monkeys following inhalation exposure to chlordane technical at 10 mg/m^3 for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). Two rat studies (a 28-day study and a 90-day study) evaluated the effects of repeated inhalation exposure to chlordane technical. The 90-day study identified the lowest LOAEL for liver effects and was selected as the principal study for deriving an intermediate-duration inhalation MRL for chlordane (Khasawinah et al. 1989; Velsicol Chemical Co. 1984).

Summary of the Principal Study:

Khasawinah AM, Hardy CJ, Clark GC. 1989. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J Toxicol Environ Health 28:327-347.

Velsicol Chemical Co. 1984. Chlordane: A 90-day inhalation toxicity study in the rat and monkey. Unpublished study No. VCL28 conducted by Huntingdon Research Centre. (cited in EPA 1987f).

Groups of Wistar rats (35–47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/m^3 technical chlordane for 8 hours/day, 5 days/week for 13 weeks, followed by a 13-week recovery period. Blood chemistry and urinalysis were performed prior to the beginning of exposure and at exposure weeks 5 and 13. Rats were sacrificed at 9 weeks (5/sex/group) and 13 weeks (15/sex/group). The remaining rats were sacrificed following 13 weeks of recovery. There were no exposure-related effects on mortality, clinical signs (with the exception of sensitivity to touch at the highest exposure level), food consumption, body weight, ophthalmoscopy, rectal temperature, or urinalysis. Exposure-related hematological changes (e.g., increases in total white blood cells, lymphocytes, neutrophils; decreases in hemoglobin and platelets) were of relatively small magnitude, occurred primarily in female rats, and values were within normal ranges for rats; therefore, these changes are not considered adverse. Exposure-related changes indicative of liver effects were observed at 1 mg/m^3 and included increases serum P-450 activity, globulins, total protein, and cholesterol; and decreased albumin and albumin/globulin ratio. Histopathologic examinations revealed hepatocellular hypertrophy in all rats of the 10 mg/m^3 exposure group and 5/15 males and 5/15 females of the 1 mg/m^3 exposure group (compared to 0/15/sex/group at 0 or 0.1 mg/m^3).

Selection of the Point of Departure for the MRL: The NOAEL of 0.1 mg/m^3 was selected as the basis for the MRL.

Intermittent Exposure: The NOAEL was adjusted from intermittent exposure (8 hours/day, 5 days/week) to account for continuous exposure according to the following equation:

$NOAEL_{ADJ}$ = NOAEL (0.1 mg/m^3) x 8 hours/24 hours x 5 days/7days = 0.024 mg/m^3.

Human Equivalent Concentration: The duration-adjusted $NOAEL_{ADJ}$ of 0.024 mg/m^3 was converted to a human equivalent concentration (HEC) according to the equation used to calculate a HEC for extrarespiratory effects of a Category 3 gas (EPA 1994): $NOAEL_{HEC}$ (mg/m^3) = $NOAEL_{ADJ}$ (mg/m^3) x $(H_{b/g})A/(H_{b/g})H$ (i.e., the ratio of the blood:gas [air] partition coefficient of the chemical for the laboratory animal species to the human value; the value of 1.0 is used when measured values are not available).

$NOAEL_{HEC}$ = 0.024 mg/m^3 x 1 = 0.024 mg/m^3.

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 1000:

- 10 for extrapolation from intermediate-duration to chronic-duration exposure
- 10 for extrapolation from animals to humans
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Liver effects were observed in the 28-day and 90-day rat studies (Khasawinah et al. 1989; Velsicol Chemical Co. 1984)

Agency Contact (Chemical Manager): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL	0.001 mg/kg/day
Critical Effect:	Developmental effects
Reference:	Al-Hachim and Al-Baker 1973
Point of Departure:	LOAEL of 1 mg/kg/day
Uncertainty Factor:	1,000
LSE Graph Key:	17
Species:	Mouse

MRL Summary: An acute-duration oral MRL of 0.001 mg/kg/day was derived for chlordane technical. The MRL is based on a LOAEL of 1 mg/kg/day for developmental effects (depressed conditioned avoidance response acquisition, increased exploratory activity in open field testing, and increased seizure threshold) in offspring of mice exposed to chlordane during the third trimester of gestation (7 days) (Al-Hachim and Al-Baker 1973). The LOAEL divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Acute oral data have identified the liver and the central nervous system as target organs in rats and mice; LOAELs range from 50 to 200 mg/kg/day (Ambrose et al. 1953a; Hrdina et al. 1974; Ogata and Izushi 1991; Truhaut et al. 1974, 1975). One oral study in mice identified the lowest LOAEL (1 mg/kg/day for developmental effects) associated with acute-duration oral exposure to chlordane technical (Al-Hachim and Al-Baker 1973). This study identified the lowest LOAEL; therefore, it serves as the critical effect for deriving an acute-duration oral MRL for chlordane technical.

Selection of the Principal Study: The study of Al-Hachim and Al-Baker (1973) was selected as the principal study because it provided the lowest LOAEL (1 mg/kg/day for developmental effects) among candidate acute-duration oral toxicity studies.

Summary of the Principal Study:

Al-Hachim GM, Al-Baker A. 1973. Effects of chlordane on conditioned avoidance response, brain seizure threshold and open-field performance of prentally-reated mice. Br J Pharmacol 49:311-315.

Groups of pregnant albino mice (6/group) were administered technical-grade chlordane by gavage (in olive oil) for 7 days during the third trimester) at 0, 1, or 2.5 mg/kg/day. Ten mice/litter were tested for conditioned avoidance response during postnatal days 30–37. Electroshock seizure threshold was measured at 38 days of age, and open field testing was performed during postnatal weeks 6 and 7. Offspring exhibited significantly depressed conditioned avoidance response acquisition, increased exploratory activity in open field testing, and increased seizure threshold at the lowest maternal dose level (1 mg/kg/day).

Selection of the Point of Departure for the MRL: The LOAEL of 1 mg/kg/day was selected as the basis for the MRL.

Intermittent Exposure: Not applicable.

Human Equivalent Concentration: Not applicable.

Uncertainty Factor: The LOAEL was divided by a total uncertainty factor of 1,000:

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

MRL = LOAEL ÷ UFs
1 mg/kg/day ÷ 1,000 = 0.001 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No supporting study results.

Agency Contact (Chemical Manager): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
MRL	0.0006 mg/kg/day
Critical Effect:	Liver effects
Reference:	EPA 1985a; Khasawinah and Grutsch 1989a
Point of Departure:	NOAEL of 0.055 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	47
Species:	Rat

MRL Summary: The chronic-duration oral MRL for chlordane technical was adopted as the intermediate-duration oral MRL as well. See the MRL Worksheet for the chronic-duration oral MRL for details regarding selection of the critical effect and principal study, summary of the principal study, selection of the point of departure for the MRL, and uncertainty factors.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Centrilobular hypertrophy was also observed in rats receiving chlordane technical from the diet for up to 9 months at an estimated dose of 0.125 mg/kg/day, the lowest dose tested (Ortega et al. 1957).

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Chronic
MRL	0.0006 mg/kg/day
Critical Effect:	Hepatocellular hypertrophy
Reference:	EPA 1985a; Khasawinah and Grutsch 1989a
Point of Departure:	NOAEL of 0.055 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	47
Species:	Rat

MRL Summary: A chronic-duration oral MRL of 0.0006 mg/kg/day was derived for chlordane technical. The MRL is based on a NOAEL of 0.055 mg/kg/day and a LOAEL of 0.237 mg/kg/day for hepatocellular hypertrophy in female rats administered chlordane technical in the diet for 30 months (EPA 1985a; Khasawinah and Grutsch 1989a). The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Among available chronic-duration oral animal studies for chlordane technical, targets of toxicity include the liver and body weight (Ambrose et al. 1953; EPA 1985a; Khasawinah and Grutsch 1989a). Body weight effects were observed at 16 mg/kg/day (Ambrose et al. 1953), whereas hepatocellular hypertrophy was noted in rats at doses as low as 0.273 mg/kg/day in one rat study (EPA 1985a; Khasawinah and Grutsch 1989a) and 4 mg/kg/day in another rat study (Ambrose et al. 1953). Hepatocellular hypertrophy was also noted in male and female mice at 0.47 mg/kg/day, with a corresponding NOAEL of 0.1 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989a). NCI (1977) reported neurological effects in rats and mice administered analytical-grade chlordane in the diet at estimated doses of 7.3–12.1 mg/kg/day (corresponding NOAELs were 3.9 and 6.0 mg/kg/day for rats and mice, respectively). Among available chronic-duration oral animal data, the most sensitive effect is hepatocellular hypertrophy, which was selected as the critical effect for deriving a chronic-duration oral MRL for chlordane technical.

Selection of the Principal Study: Treatment-related liver effects were associated with chronic-duration oral exposure to chlordane technical in rats (Ambrose et al. 1953; Khasawinah and Grutsch 1989a) and mice (Khasawinah and Grutsch 1989a). The study reports that reported the lowest LOAEL for liver effects (0.273 mg/kg/day in female rats) and corresponding NOAEL (0.055 mg/kg/day in female rats) were selected to represent the principal study for deriving a chronic-duration oral MRL for chlordane technical.

Summary of the Principal Study:

EPA. 1985a. Memorandum. 6(a)(2) Data on chlordane. Chronic mouse and rat studies for oncogenicity testing. Act. Nos. 252267, 254665, 251815, Review No. 004635. Office of Pesticides and Toxic Substances, Washington, DC.

Khasawinah AM, Grutsch JF. 1989a. Chlordane thirty-month tumorigenicity and chronic toxicity test in rats. Regul Toxicol Pharmacol 10:95-109.

Groups of Fischer 344 rats (80/sex/group) were administered chlordane technical in the diet for up to 30 months at 0, 1, 5, or 25 ppm (author-calculated doses of 0, 0.045, 0.229, and 1.175 mg/kg/day, respectively, for males and 0, 0.055, 0.273, and 1.409 mg/kg/day, respectively, for females). The only reported treatment-related nonneoplastic effect was that of hepatocellular hypertrophy in females at 0.273 mg/kg/day. There were no apparent treatment-related effects on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or renal systems, or dermal/ocular or body weight effects at the highest dose tested (1.175 and 1.409 mg/kg/day for males and females, respectively).

Selection of the Point of Departure for the MRL: The NOAEL of 0.055 mg/kg/day for female rats was selected as the basis for the MRL.

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

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

MRL = NOAEL ÷ UFs
0.055 mg/kg/day ÷ 100 = 0.0006 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Hepatocellular hypertrophy was also observed in male and female mice orally exposed to chlordane technical for 24 months at 0.47 mg/kg/day; the corresponding NOAEL was 0.10 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989a).

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLORDANE

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 chlordane.

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 chlordane. 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 chlordane 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 chlordane 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
Cancer

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

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 health effects sections of the existing toxicological profile for chlordane (ATSDR 1994), thus, the literature search was restricted to studies published between January 1990 to April 2017. The following main databases were searched in April 2017:

- 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 chlordane. 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 chlordane 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	
04/2017	((("Chlordan"[mh]) OR ("nonachlor"[nm])) AND (1992/01/01 : 3000[mhda] OR 1992/01/01 : 3000[dp])) OR (((("1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane"[tw] "1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-

Table B-2. Database Query Strings

Database search date	Query string
	methanoindene"[tw] OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a, 4,7,7a-tetrahydroindane"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano [Italian]"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoinden, 1,2,4,5,6,7,8,9-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "Aspon-chlordane"[tw] OR "Chlor Kil"[tw] OR "Chlordan"[tw] OR "Chlordane"[tw] OR "Chlordane, technical"[tw] OR "Chlordane-technical"[tw] OR "Chlorindan"[tw] OR "Chlorotox"[tw] OR "Clordano"[tw] OR "Corodane"[tw] OR "Cortilan-neu"[tw] OR "Dichlorochlordene"[tw] OR "Dowchlor"[tw] OR "HCS 3260"[tw] OR "Intox"[tw] OR "Kilex lindane"[tw] OR "Kypchlor"[tw] OR "Octa-klor"[tw] OR "Octachlor"[tw] OR "Octachlordane"[tw] OR "Octachloro-4,7-methanotetrahydroindane"[tw] OR "Octachlorodihydrodicyclopentadiene"[tw] OR "Oktaterr"[tw] OR "OMS 1437"[tw] OR "Ortho-Klor"[tw] OR "SD 5532"[tw] OR "Shell SD-5532"[tw] OR "Starchlor"[tw] OR "Sydane"[tw] OR "Synklor"[tw] OR "TAT chlor 4"[tw] OR "Termex"[tw] OR "Termi-ded"[tw] OR "Topichlor 20"[tw] OR "Topiclor"[tw] OR "Toxichlor"[tw] OR "Unexan-Koeder"[tw] OR "Velsicol 1068"[tw] OR "(1alpha, 2alpha, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "(1alpha, 2beta, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1-alpha, 3a-alpha, 4-beta, 5-alpha, 6a-alpha)-"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1R, 3aS, 4S, 5S, 6aS)-rel-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1-alpha, 3a-beta, 6-alpha, 7a-beta, 8R*)-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1R, 3aR, 6S, 7aR, 8R)-rel-"[tw] OR "1-exo, 2-endo, 4,5,6,7,8,8-Octachloro-2,3-exo-epoxy-2,3,3a, 4,7,7a-hexahydro-4,7-methanoindene"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-,(1aR, 1bS, 2R, 5S, 5aR, 6S, 6aS)-rel-"[tw] OR "3a, 4,7,7a-Tetrahydro-1,2-epoxy-4,5,6,7,8,8-hexachloro-4,7-methanoindan"[tw] OR "4,5,6,7,8,8-Hexachlor-delta(sup 1,5)-tetrahydro-4,7-methanoinden"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methano-1H-indene"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methanoindene"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachlor-2,3,3a, 4,7,7a-hexahydro-,(1-alpha, 2-beta, 3-alpha, 3a-alpha, 4-beta, 7-beta, 7a-alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha, 3aalpha, 4beta, 7beta, 7aalph"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3alpha, 3aalpha, 4beta, 7beta,"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2R, 3aS, 4S, 7R, 7aS)-rel-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2S, 3aS, 4S, 7R, 7aS)-rel"[tw] OR "4,7-Methano-1H-indene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3-epoxy-3a, 4,7,7a-tetrahydro-, exo, endo-"[tw] OR "4,7-Methanoindan, 1-alpha, 2-alpha, 4-beta, 5,6,7-beta, 8,8-octachloro-3a-alpha, 4,7,7a-alpha-tetrahydro-"[tw] OR "4,7-Methanoindan, 3a, 4,7,7a-tetrahydro-2,3-epoxy-1,2,4,5,6,7,8,8-octachloro-, exo,

Table B-2. Database Query Strings

Database search date	Query string
	endo-"[tw] OR "4,7-Methanoindan, 3a-beta, 4,7,7a-beta-tetrahydro-1-beta, 2-alpha, 4-alpha, 5,6,7-alpha, 8,8-octachloro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-delta(sup 1,5)-tetrahydro-"[tw] OR "c-Nonachlor"[tw] OR "Chlordene"[tw] OR "cis-Nonachlor"[tw] OR "gamma-Chlordene"[tw] OR "Nonachlor, cis-"[tw] OR "Nonachlor, trans-"[tw] OR "Oxychlordan"[tw] OR "Oxychlordane"[tw] OR "t-Nonachlor"[tw] OR "trans-Nonachlor"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[sh:noexp] OR "chlordan/antagonists and inhibitors"[Mesh Terms] OR "hydrocarbons, chlorinated/antagonists and inhibitors"[Mesh Terms] OR toxicokinetics[mh:noexp])) OR (("1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane"[tw] OR "1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methanoindene"[tw] OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a, 4,7,7a-tetrahydroindane"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano [Italian]"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoinden, 1,2,4,5,6,7,8,9-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "Aspon-chlordane"[tw] OR "Chlor Kil"[tw] OR "Chlordan"[tw] OR "Chlordane"[tw] OR "Chlordane, technical"[tw] OR "Chlordane-technical"[tw] OR "Chlorindan"[tw] OR "Chlorotox"[tw] OR "Clordano"[tw] OR "Corodane"[tw] OR "Cortilan-neu"[tw] OR "Dichlorochlordene"[tw] OR "Dowchlor"[tw] OR "HCS 3260"[tw] OR "Intox"[tw] OR "Kilex lindane"[tw] OR "Kypchlor"[tw] OR "Octa-klor"[tw] OR "Octachlor"[tw] OR "Octachlordane"[tw] OR "Octachloro-4,7-methanotetrahydroindane"[tw] OR "Octachlorodihydrodicyclopentadiene"[tw] OR "Oktaterr"[tw] OR "OMS 1437"[tw] OR "Ortho-Klor"[tw] OR "SD 5532"[tw] OR "Shell SD-5532"[tw] OR "Starchlor"[tw] OR "Sydane"[tw] OR "Synklor"[tw] OR "TAT chlor 4"[tw] OR "Termex"[tw] OR "Termi-ded"[tw] OR "Topichlor 20"[tw] OR "Topiclor"[tw] OR "Toxichlor"[tw] OR "Unexan-Koeder"[tw] OR "Velsicol 1068"[tw] OR "(1alpha, 2alpha, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "(1alpha, 2beta, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1-alpha, 3a-alpha, 4-beta, 5-alpha, 6a-alpha)-"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1R, 3aS, 4S, 5S, 6aS)-rel-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1-alpha, 3a-beta, 6-alpha, 7a-beta, 8R*)-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1R, 3aR, 6S, 7aR, 8R)-rel-"[tw] OR "1-exo, 2-endo, 4,5,6,7,8,8-

Table B-2. Database Query Strings

Database search date	Query string
	Octachloro-2,3-exo-epoxy-2,3,3a, 4,7,7a-hexahydro-4,7-methanoindene"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-,(1aR, 1bS, 2R, 5S, 5aR, 6S, 6aS)-rel-"[tw] OR "3a, 4,7,7a-Tetrahydro-1,2-epoxy-4,5,6,7,8,8-hexachloro-4,7-methanoindan"[tw] OR "4,5,6,7,8,8-Hexachlor-delta(sup 1,5)-tetrahydro-4,7-methanoinden"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methano-1H-indene"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methanoindene"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachlor-2,3,3a, 4,7,7a-hexahydro-,(1-alpha, 2-beta, 3-alpha, 3a-alpha, 4-beta, 7-beta, 7a-alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha, 3aalpha, 4beta, 7beta, 7aalph"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3alpha, 3aalpha, 4beta, 7beta,"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2R, 3aS, 4S, 7R, 7aS)-rel-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2S, 3aS, 4S, 7R, 7aS)-rel"[tw] OR "4,7-Methano-1H-indene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3-epoxy-3a, 4,7,7a-tetrahydro-, exo, endo-"[tw] OR "4,7-Methanoindan, 1-alpha, 2-alpha, 4-beta, 5,6,7-beta, 8,8-octachloro-3a-alpha, 4,7,7a-alpha-tetrahydro-"[tw] OR "4,7-Methanoindan, 3a, 4,7,7a-tetrahydro-2,3-epoxy-1,2,4,5,6,7,8,8-octachloro-, exo, endo-"[tw] OR "4,7-Methanoindan, 3a-beta, 4,7,7a-beta-tetrahydro-1-beta, 2-alpha, 4-alpha, 5,6,7-alpha, 8,8-octachloro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-delta(sup 1,5)-tetrahydro-"[tw] OR "c-Nonachlor"[tw] OR "Chlordene"[tw] OR "cis-Nonachlor"[tw] OR "gamma-Chlordene"[tw] OR "Nonachlor, cis-"[tw] OR "Nonachlor, trans-"[tw] OR "Oxychlordan"[tw] OR "Oxychlordane"[tw] OR "t-Nonachlor"[tw] OR "trans-Nonachlor"[tw]) NOT medline[sb])) AND (1992/01/01 : 3000[dp] OR 1992/01/01 : 3000[crdt] OR 1992/01/01 : 3000[edat]))
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Table B-2. Database Query Strings

Database search date	Query string
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	("4 7 methanoindan 1 2 4 5 6 7 8 8 octachloro 2 3 3a 4 7 7a hexahydro " OR "4 7 methanoindan 1 2 4 5 6 7 8 8 octachloro 3a 4 7 7a tetrahydro " OR "4 7 methanoinden 1 2 4 5 6 7 8 9 octachloro 3a 4 7 7a tetrahydro " OR "aspon chlordane" OR "chlor kil" OR "chlordan" OR "chlordane") AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("chlordane technical" OR "chlordane technical" OR "chlorindan" OR "chlorotox" OR "clordano" OR "corodane" OR "cortilan neu" OR "dichlorochlordene" OR "dowchlor" OR "hcs 3260" OR "intox" OR "kilex lindane" OR "kypchlor" OR "octa klor" OR "octachlor" OR "octachlordane" OR "octachloro 4 7 methanotetrahydroindane") AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR

Table B-2. Database Query Strings

Database search date	Query string
	RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("c nonachlor" OR "chlordene" OR "cis nonachlor" OR "gamma chlordene" OR "nonachlor cis " OR "nonachlor trans " OR "oxychlordan" OR "oxychlordane" OR "t nonachlor" OR "trans nonachlor") AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
04/2017	(FILE 'HOME' ENTERED AT 13:26:52 ON 06 APR 2017) FILE 'TOXCENTER' ENTERED AT 13:27:06 ON 06 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 5760 SEA FILE=TOXCENTER 12789-03-6 L2 1053 SEA FILE=TOXCENTER 57-74-9 L3 4698 SEA FILE=TOXCENTER 5103-71-9 OR 5103-74-2 OR 27304-13-8 OR 56641-38-4 OR 56534-02-2 OR 39765-80-5 OR 5103-73-1 OR 3734-48-3 L4 10746 SEA FILE=TOXCENTER L1 OR L2 OR L3 L5 10719 SEA FILE=TOXCENTER L4 NOT TSCATS/FS L6 10484 SEA FILE=TOXCENTER L5 NOT PATENT/DT L7 6220 SEA FILE=TOXCENTER L6 AND PY>1991 ACT TOXQUERY/Q --------- L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L23 QUE (ENDOCRIN? AND DISRUPT?) L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L30 QUE (NEPHROTOX? OR HEPATOTOX?) L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L33 QUE L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 L34 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L36 QUE L33 OR L34 OR L35 L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L38 QUE L36 OR L37 --------- L39 3586 SEA FILE=TOXCENTER L7 AND L38 L40 198 SEA FILE=TOXCENTER L39 AND MEDLINE/FS L41 882 SEA FILE=TOXCENTER L39 AND BIOSIS/FS L42 2446 SEA FILE=TOXCENTER L39 AND CAPLUS/FS L43 60 SEA FILE=TOXCENTER L39 NOT (L40 OR L41 OR L42) SAVE TEMP L42 CHLORDANECA CHLORDANECA/A L44 3074 DUP REM L40 L41 L43 L42 (512 DUPLICATES REMOVED) ANSWERS '1-3074' FROM FILE TOXCENTER L*** DEL 198 S L39 AND MEDLINE/FS L*** DEL 198 S L39 AND MEDLINE/FS L45 198 SEA FILE=TOXCENTER L44

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 882 S L39 AND BIOSIS/FS
	L*** DEL 882 S L39 AND BIOSIS/FS
	L46 788 SEA FILE=TOXCENTER L44
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L47 2037 SEA FILE=TOXCENTER L44
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L48 51 SEA FILE=TOXCENTER L44
	L49 788 SEA FILE=TOXCENTER (L45 OR L46 OR L47 OR L48) AND BIOSIS/FS
	L50 643 SEA FILE=TOXCENTER L49 AND PY>1998
	L51 0 SEA FILE=TOXCENTER L49 AND CAPLUS/FS
	L*** DEL 198 S L39 AND MEDLINE/FS
	L*** DEL 198 S L39 AND MEDLINE/FS
	L52 198 SEA FILE=TOXCENTER L44
	L*** DEL 882 S L39 AND BIOSIS/FS
	L*** DEL 882 S L39 AND BIOSIS/FS
	L53 788 SEA FILE=TOXCENTER L44
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L54 2037 SEA FILE=TOXCENTER L44
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L55 51 SEA FILE=TOXCENTER L44
	L56 2037 SEA FILE=TOXCENTER (L52 OR L53 OR L54 OR L55) AND CAPLUS/FS SAVE TEMP L56 CHLORDANECA/A
	L*** DEL 198 S L39 AND MEDLINE/FS
	L*** DEL 198 S L39 AND MEDLINE/FS
	L57 198 SEA FILE=TOXCENTER L44
	L*** DEL 882 S L39 AND BIOSIS/FS
	L*** DEL 882 S L39 AND BIOSIS/FS
	L58 788 SEA FILE=TOXCENTER L44
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L59 2037 SEA FILE=TOXCENTER L44
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L60 51 SEA FILE=TOXCENTER L44
	L61 51 SEA FILE=TOXCENTER (L57 OR L58 OR L59 OR L60) NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L62 694 SEA FILE=TOXCENTER L50 OR L61
	L63 2731 SEA FILE=TOXCENTER L62 OR L56 D SCAN L62 D SCAN L56

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
04/2017	Compound searched: 57-74-9 5103-71-9 5103-74-2 27304-13-8 56641-38-4 12789-03-6 56534-02-2 39765-80-5 5103-73-1 3734-48-3
NTP	
04/2017	57-74-9 5103-71-9 5103-74-2 27304-13-8 56641-38-4 12789-03-6 56534-02-2 39765-80-5 5103-73-1 3734-48-3 chlordan chlordane chlordene oxychlordane cis-Nonachlor trans-Nonachlor
NIH RePORTER	
08/2017	Text Search: "1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane" OR "1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene" OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-" OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-" OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-" OR "4,7-Methanoinden, 1,2,4,5,6,7,8,9-octachloro-3a,4,7,7a-tetrahydro-" OR "Aspon-chlordane" OR "Chlor Kil" OR "Chlordan" OR "Chlordane" OR "Chlordane, technical" OR "Chlordane-technical" OR "Chlorindan" OR "Chlorotox" OR "Clordano" OR "Corodane" OR "Cortilan-neu" OR "Dichlorochlordene" OR "Dowchlor" OR "HCS 3260" OR "Intox" OR "Kilex lindane" OR "Kypchlor" OR "Octa-klor" OR "Octachlor" OR "Octachlordane" OR "Octachloro-4,7-methanotetrahydroindane" OR "Octachlorodihydrodicyclopentadiene" OR "Oktaterr" OR "OMS 1437" OR "Ortho-Klor" OR "SD 5532" OR "Shell SD-5532" OR "Starchlor" OR "Sydane" OR "Synklor" OR "TAT chlor 4" OR "Termex" OR "Termi-ded" OR "Topichlor 20" OR "Topiclor" OR "Toxichlor" OR "Unexan-Koeder" OR "Velsicol 1068" OR "(1alpha,2alpha,3aalpha,4beta,7beta,7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene" OR "(1alpha,2beta,3aalpha,4beta,7beta,7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene" OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	1,3a,4,5,6,6a-hexahydro-, (1-alpha,3a-alpha,4-beta,5-alpha,6a-alpha)-" OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a,4,5,6,6a-hexahydro-, (1R,3aS,4S,5S,6aS)-rel-" OR "1,6-Methano-1H-indene, 2,3,3a,4,5,8-hexachloro-3a,6,7,7a-tetrahydro-, (1-alpha,3a-beta,6-alpha,7a-beta,8R)-" OR "1,6-Methano-1H-indene, 2,3,3a,4,5,8-hexachloro-3a,6,7,7a-tetrahydro-, (1R,3aR,6S,7aR,8R)-rel-" OR "1-exo,2-endo,4,5,6,7,8,8-Octachloro-2,3-exo-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene" OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a,7,7-octachloro-1a,1b,5,5a,6,6a-hexahydro-" OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a,7,7-octachloro-1a,1b,5,5a,6,6a-hexahydro-, (1aR,1bS,2R,5S,5aR,6S,6aS)-rel-" OR "3a,4,7,7a-Tetrahydro-1,2-epoxy-4,5,6,7,8,8-hexachloro-4,7-methanoindan" OR "4,5,6,7,8,8-Hexachlor-delta(sup 1,5)-tetrahydro-4,7-methanoinden" OR "4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene" OR "4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
	Text Search: "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachlor-2,3,3a,4,7,7a-hexahydro-, (1-alpha,2-beta,3-alpha,3a-alpha,4-beta,7-beta,7a-alpha)-" OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2alpha,3alpha)-" OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2alpha,3alpha,3aalpha,4beta,7beta,7aalph" OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2beta,3alpha,3aalpha,4beta,7beta," OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2alpha,3a alpha,4beta,7beta,7a alpha)-" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2beta,3a alpha,4beta,7beta,7a alpha)-" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1R,2R,3aS,4S,7R,7aS)-rel-" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1R,2S,3aS,4S,7R,7aS)-rel" OR "4,7-Methano-1H-indene, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-" OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-, exo,endo-" OR "4,7-Methanoindan, 1-alpha,2-alpha,4-beta,5,6,7-beta,8,8-octachloro-3a-alpha,4,7,7a-alpha-tetrahydro-" OR "4,7-Methanoindan, 3a,4,7,7a-tetrahydro-2,3-epoxy-1,2,4,5,6,7,8,8-octachloro-, exo,endo-" OR "4,7-Methanoindan, 3a-beta,4,7,7a-beta-tetrahydro-1-beta,2-alpha,4-alpha,5,6,7-alpha,8,8-octachloro-" OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-" OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-delta(sup 1,5)-tetrahydro-" OR "c-Nonachlor" OR "Chlordene" OR "cis-Nonachlor" OR "gamma-Chlordene" OR "Nonachlor, cis-" OR "Nonachlor, trans-" OR "Oxychlordan" OR "Oxychlordane" OR "t-Nonachlor" OR "trans-Nonachlor" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 4,696
- Number of records identified from other strategies: 27
- Total number of records to undergo literature screening: 4,723

B.1.2 Literature Screening

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

- 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.

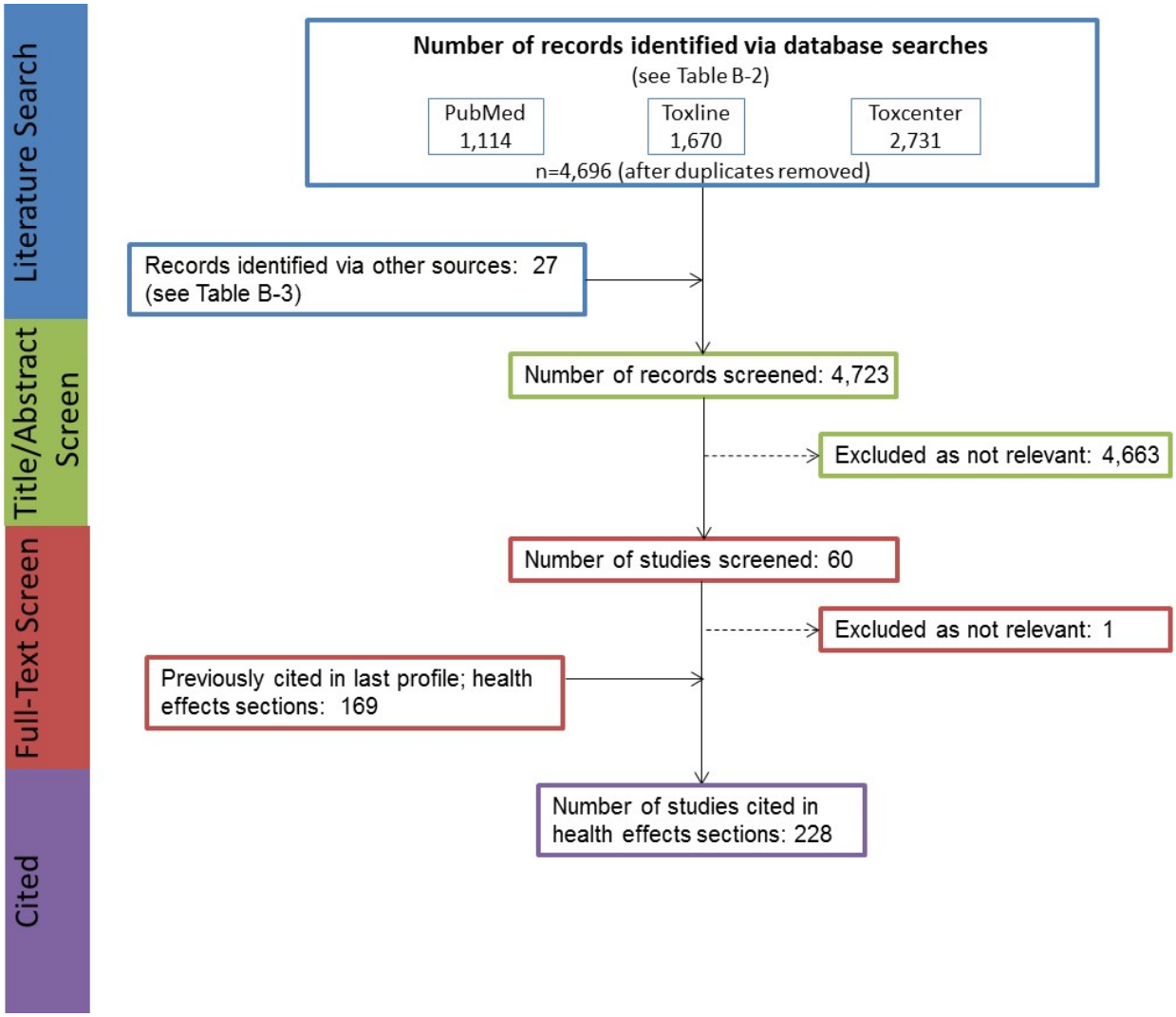
- Number of titles and abstracts screened: 4,723
- Number of studies considered relevant and moved to the next step: 60

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: 60
- Number of studies cited in the health effects sections of the existing toxicological profile (May,1994): 169
- Total number of studies cited in the health effects sections of the updated profile: 228

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

Figure B-1. April 2017 Literature Search Results and Screen for Chlordane



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									

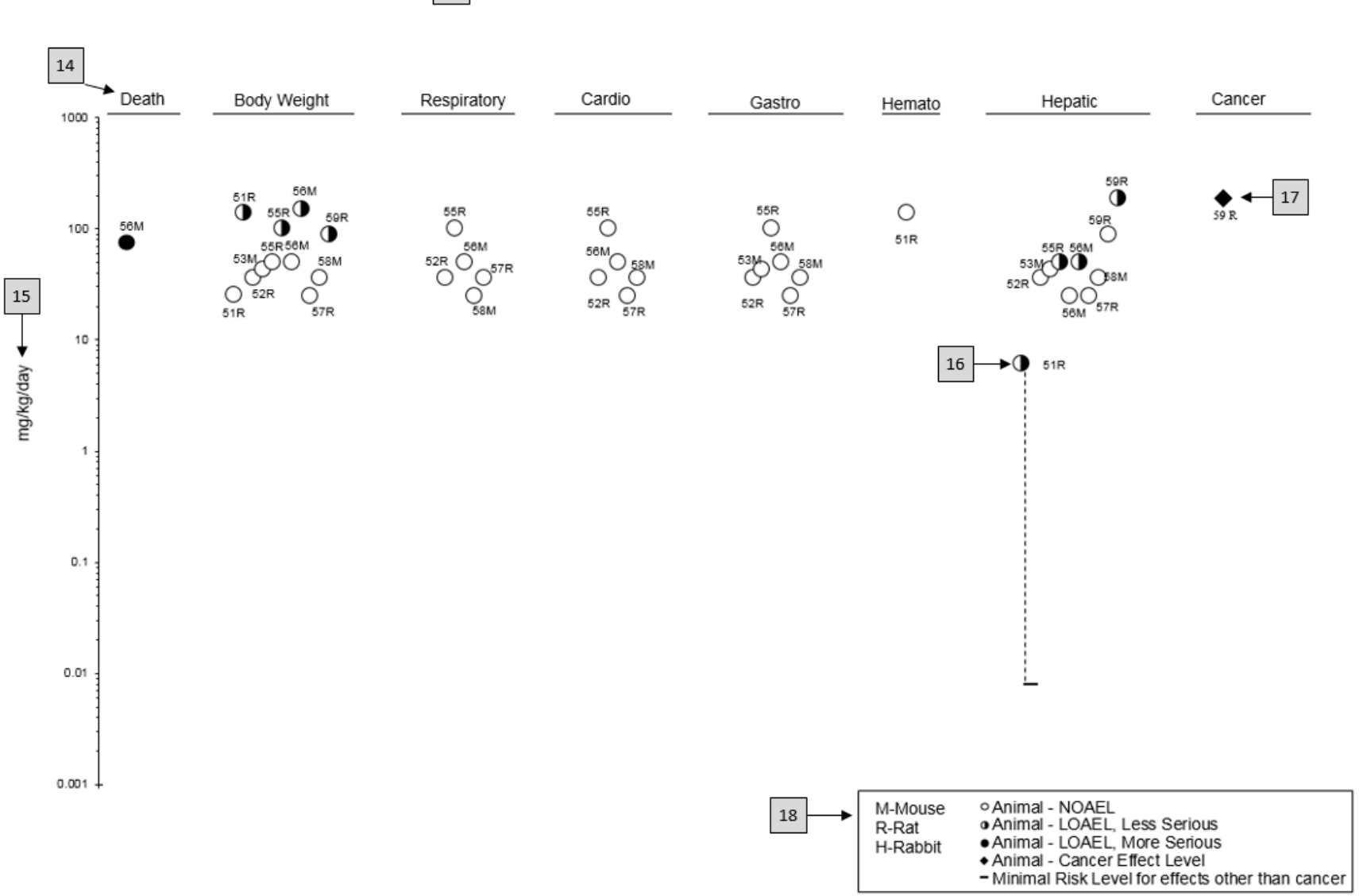
[a]The number corresponds to entries in Figure 2-x.

(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) $\geq$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
DHHS	Department of Health and Human Services
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