APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the 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 S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-D
CAS Numbers: 94-75-7
Date: July 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: An acute-duration inhalation MRL was not derived for 2,4-D.

Rationale for Not Deriving an MRL: No acute-duration inhalation data were available for review.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-D
CAS Numbers: 94-75-7
Date: July 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: An intermediate-duration inhalation MRL was not derived for 2,4-D.

Rationale for Not Deriving an MRL: Only one inhalation study in animals was available for review. In that study, male and female rats were exposed nose-only 6 hours/day, 5 days/week for 28 days to 2,4-D dusts in target concentrations of 0, 50, 100, 300, and 1,000 mg/m^3 (EPA 2008). After termination of exposure, controls and rats from the highest exposure concentration group were kept for a 4-week recovery period to assess reversibility of the effects. A significant reduction in reticulocytes occurred in males and females at 2,4-D exposure concentrations ≥300 mg/m^3 and a significant increase in serum alkaline phosphatase was reported in females at ≥300 mg/m^3. Histopathologic examination of a comprehensive set of organs and tissues revealed no sign of 2,4-D exposure-related systemic effects. The most salient effect was the occurrence of squamous/squamoid epithelial metaplasia with hyperkeratosis in the larynx of all exposed groups, with increasing severity as the exposure concentration increased. The lesions persisted during the recovery period, but with reduced severity. Therefore, the exposure concentration of 50 mg/m^3 represents the study LOAEL, a portal-of-entry LOAEL. Although this is a well-conducted study that examined a comprehensive number of end points, the database is insufficient for MRL derivation. It would be important to determine a NOAEL for the portal-of-entry effects.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-D
CAS Numbers: 94-75-7
Date: July 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: A chronic-duration inhalation MRL was not derived for 2,4-D

Rationale for Not Deriving an MRL: No chronic-duration inhalation data were available for review.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-D
CAS Numbers: 94-75-7
Date: July 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: An acute-duration oral MRL was not derived for 2,4-D.

Rationale for Not Deriving an MRL: No adequate acute-duration human data were located. Information regarding health effects in humans following acute-duration exposure to 2,4-D is limited to case reports of intentional or accidental ingestion of herbicide formulations containing 2,4-D. Effects that have been reported following oral exposure to high amounts of 2,4-D include tachypnea, tachycardia, vomiting, leukocytosis, liver and kidney congestion in fatal cases, metabolic acidosis, and death (Dudley et al. 1972; Durakovic et al. 1992; Keller et al. 1994; Nielsen et al. 1965; Smith and Lewis 1987). While some of these studies provided estimates of amounts of 2,4-D ingested, the reported effects represent the result of exposure to a chemical mixture consisting of 2,4-D and other substances present in the commercial formulations (i.e., solvents, other herbicides), which is the exposure that most humans experience. Yet, the common exposure reported across studies was to 2,4-D. In two studies designed to evaluate the pharmacokinetics of 2,4-D in volunteers, administration of 5 mg 2,4-D/kg once in a gelatin capsule resulted in no ill effects during 144–168 hours post-dosing (Kohli et al. 1974; Sauerhoff et al. 1977). The information available in humans is inadequate for MRL derivation.

Two animal studies defined LOAELs of 50 mg/kg/day. In one of these studies, doses of 50 mg/kg/day (lowest dose tested) induced significant weight loss in pregnant Wistar rats when administered by gavage in water on GDs 6–15 (Fofana et al. 2000). It is not totally clear, however, whether the investigators meant that the final weight was lower than the starting weight or whether treated rats just gained less weight than control rats. In another developmental study, administration of 2,4-D at 50 mg/kg/day by gavage in corn oil to pregnant Sprague-Dawley rats, also on GDs 6–15, did not affect maternal weight (terminal weight similar in treated and controls), but induced a statistically significant reduction in fetal weight (approximately 7%) measured on GD 20 and increased the incidence of some soft-tissue anomalies and skeletal malformations; the NOAEL was 25 mg/kg/day (Schwetz et al. 1971). Long-term oral studies suggest that the kidney is a target for 2,4-D toxicity; however, only one acute-duration study conducted microscopic examinations of the kidneys. The paucity of information regarding the effects of acute-duration oral exposure to 2,4-D in experimental animals precludes deriving an acute-duration oral MRL for 2,4-D.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-D
CAS Numbers: 94-75-7
Date: July 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.2 mg/kg/day
Critical Effect: Increased kidney weight, histopathologic kidney lesions
Reference: Marty et al. 2013
Point of Departure: 16.6 mg/kg/day (NOAEL)
Uncertainty Factor: 100
LSE Graph Key: 33
Species: Rat

MRL Summary: An MRL of 0.2 mg/kg/day has been derived for intermediate-duration oral exposure to 2,4-D based on a NOAEL of 16.6 mg/kg/day and a LOAEL of 45.3 mg/kg/day for increased kidney weight and slight proximal tubule degeneration in the kidney of male Sprague-Dawley rats receiving 2,4-D from food for up to 11 weeks (Marty et al. 2013).

Selection of the Critical Effect: No human data were located. Available animal data identify the kidney and developmental endpoints as most sensitive to 2,4-D toxicity. Available results from intermediate-duration oral treatment of dogs were not considered an appropriate basis for MRL derivation because dogs appear to be more sensitive than rodents or humans due to a significantly lower capacity to eliminate 2,4-D via the kidneys (Timchalk 2004). Table A-1 summarizes study results for renal effects and for developmental effects considered potential points of departure for deriving an intermediate-duration oral MRL for 2,4-D.

Table A-1. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for 2,4-D

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Renal effects					
F344 rat	13 weeks (F)	1	5	Increased homogeneity and altered tinctorial properties in cytoplasm; fine vacuolization of cytoplasm in renal cortex	EPA 1984
B6C3F1 mouse	13 weeks (F)	5	15	M, F: Increased homogeneity, altered tinctorial properties in cytoplasm or renal cortex; M: decreased vacuolization in renal cortex	EPA 1984
B6C3F1 mouse	52 weeks (F)	1 M 45 F	15 M	Increased cytoplasmic homogeneity of renal tubular epithelium due to reduction of cytoplasmic vacuoles	EPA 1987a
F344 rat	40 weeks (F)	5 M	20 M	Increased incidence and severity of fine vacuolization in cytoplasm of renal cortex	EPA 1987b

Table A-1. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for 2,4-D

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
F344 rat	52 weeks (F)	15 F	45 F	F: Increased incidence and severity of fine vacuolization in cytoplasm of renal cortex	EPA 1985
Crl:CD(SD) rat	M: 11–13 weeks F: 10–12 weeks (F)	16.6 M 45.2[a] F	45.3 M	Increased relative kidney weight, increased incidence of multifocal slight degeneration of proximal convoluted tubules in outer stripe of outer zone of medulla	Marty et al. 2013
Crl:CD(SD) rat	PPDs 21–70[b] (F)	28.4 M 28.8 F	76.6 M 57.9 F	F1 parental males and females: kidney lesions similar to those of P1 males	Marty et al. 2013
F344 rat	13 weeks (F)	15	60	M: Increased epithelial cytoplasmic homogeneity, multifocal slight degeneration in descending proximal tubules F: Increased cytoplasmic vacuolization in proximal convoluted tubules	Gorzinski et al. 1987
B6C3F1 mouse	12 months (F)	5 M	62.5 M	5% increased kidney weight; degeneration/regeneration in descending limb of proximal tubules; vacuolation of proximal tubules	Charles et al. 1996a; EPA 1996b
F344 rat	52 weeks (F)	5	75	Degeneration of proximal convoluted tubules	Charles et al. 1996a; EPA 1996a
Crl:CD(SD) rat	M: 71 days F: 96 days (F)	50 M	75 M	Slight multifocal degeneration of proximal convoluted tubules in outer stripe of outer zone of medulla of males	Saghir et al. 2013a
F344 rat	13 weeks (F)	15	100	21 and 12% increased relative kidney weight in males and females, respectively	Charles et al. 1996b
Developmental effects					
Crl:CD(SD) rat	42 days (GD 1–LD 21 (F)	24.7 F	49.4 F	9% depressed PPD 22 F1a male pup body weight (based on estimated TWA parental female dose for GD 0–LD 14)	Marty et al. 2013
Crl:CD(SD) rat	M: 80 days F: 95 days (F)	25	50	13–23% depressed pup weight during PPDs 14–21	Saghir et al. 2013a, 2013b

Table A-1. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for 2,4-D

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
F344 rat	40 weeks (F)	32	110	24% depressed PPD 21 pup body weight	EPA 1986

[a]The P1 female dose is a TWA dose calculated from reported dose estimates for three separate time periods (29 days premating, 21 days of gestation, and the first 14 days of lactation).
[b]Rats had been exposed via their mothers during gestation and lactation as well.

F = female(s); (F) = food; GD = gestation day; LD = lactation day; LOAEL = lowest observed adverse effect level; M = male(s); NOAEL = no-observed-adverse-effect level; PPD = postparturition day; TWA = time-weighted average

Selection of the Principal Study: Available Data Evaluation Records (DERs) from early studies submitted to EPA (EPA 1984, 1985, 1987a, 1987b) provide inadequate descriptions of the kidney lesions reported. Thus, the degenerative nature of the described lesions is in question. Therefore, these studies were not considered as candidate principal studies for deriving an intermediate-duration oral MRL for 2,4-D.

Three studies provide corroborative evidence of degenerative changes in renal proximal tubules within the outer stripe of the outer zone of the medulla of rats (Gorzinski et al. 1987; Marty et al. 2013; Saghir et al. 2013a). Each of these studies described similar histologic changes that included shrinking, crowding and basophilic staining of epithelial cells, and basement membrane thickening.

> Marty et al. (2013, and as more fully described in MRID4792101): "This degenerative lesion involving the proximal convoluted tubules in the outer strip of the outer zone of the medulla, was multifocal in distribution and slight in degree. This lesion was primarily characterized by tubular epithelial cells, which were basophilic staining and had nuclei that were crowded together due to a decrease in the amount of cytoplasm (eosinophilic staining). Pyknotic nuclei were also occasionally noted in these tubules. Remaining portions of these tubular profiles appeared normal. **Affected tubules also had focally thickened basement membranes**, adjacent interstitial fibrous connective tissue proliferation and a mononuclear inflammatory cell infiltrate".

> Saghir et al. (2013a, study submitted to EPA as MRID47417901): "This was a degenerative multifocal lesion involving the proximal convoluted tubules in the outer strip of the outer zone of the medulla and was very slight or slight in degree of severity. This lesion was primarily characterized by tubular epithelial cells, which were basophilic staining and had nuclei that were crowded together due to a decrease in the amount of cytoplasm (eosinophilic staining). Pyknotic nuclei were also occasionally noted in these tubules. Remaining portions of these tubular profiles appeared normal. **Affected tubules also had focally thickened basement membranes**, adjacent interstitial fibrous connective tissue proliferation and a mononuclear inflammatory cell infiltrate".

> Gorzinski et al. (1987): "…multifocal degeneration in the descending part of the proximal tubules...basophilic epithelial cells that were crowded because of decreased cytoplasm...**accompanied with thickened basement membranes** and interstitial fibrosis".

None of the above studies found evidence of cell death or tubule destruction (e.g., apoptosis, necrosis), even at the highest dose, and no studies found evidence of renal functional impairment. Therefore, the

histological changes observed can be considered to be minimally severe (pre-clinical) indications of degenerative changes that might become more severe at higher doses and/or longer exposure durations.

Two-year oral studies in rats (Charles et al. 1996a; EPA 1996b) and mice (Charles et al. 1996a; EPA 1996a) included histopathological evaluations at 1-year interim sacrifice. The rat study identified a NOAEL of 5 mg/kg/day and a LOAEL of 75 mg/kg/day for degeneration in proximal tubules. The mouse study identified a NOAEL of 5 mg/kg/day and a LOAEL of 62.5 mg/kg/day for degeneration/ regeneration in descending limb of proximal tubules in the male mice. There was no mention of basement membrane thickening in the publicly-available summaries of these studies or the unpublished MRID studies. Therefore, these studies were not considered as candidate principal studies for MRL derivation.

Kidney results for male rats from the studies of Gorzinski et al. (1987), Saghir et al. (2013a), and Marty et al. (2013) are summarized in Tables A-2, A-3, and A-4, respectively. Gorzinski et al. (1987) identified a NOAEL of 15 mg/kg/day and La OAEL of 60 mg/kg/day for multifocal degeneration of the descending proximal tubule. The severity of the lesions was graded as slight at 60 mg/kg/day and moderate at ≥100 mg/kg/day. The Saghir et al. (2013a) and Marty et al. (2013) studies reported very slight multifocal degeneration of the convoluted tubules in male rats at low dose levels. The very slight generation was not considered adverse because it was not associated with alterations in kidney weight or evidence of renal impairment. Additionally, a high incidence (9/10) of very slight degeneration was observed in the control group of the Marty et al. (2013) study. The slight degeneration observed at higher doses was considered adverse. The NOAEL and LOAEL values were 50 and 75 mg/kg/day, respectively, in the Saghir et al. (2013a) study and 16.6 and 45.3 mg/kg/day, respectively, in the Marty et al. (2013) study.

Table A-2. Selected Kidney Results from Male F344 Rats Receiving 2,4-D from the Diet for 11 Weeks

Reported 2,4-D dose (mg/kg/day)	0	15	60	100	150
Degeneration descending proximal tubule					
Slight multifocal degeneration	0/10	2/10	8/10[a]	1/10	0/10
Moderate multifocal degeneration	0/10	0/10	2/10	9/10[a]	10/10[a]

[a]Statistically different from control mean by Fischer's exact test ($p<0.01$) performed by ATSDR.

Source: Gorzinski et al. 1987

Table A-3. Selected Kidney Results from Male Crl:CD(SD) Rats Receiving 2,4-D from the Diet for 11 Weeks

Dietary concentration (ppm)	0	100	400	1,000/800	2,000/1,200	1,600
Estimated dose (mg/kg/day)[a]	0	6	25	50	75	100
Kidney weight (g/100 g body weight)	0.68	0.72	0.71	0.74	0.75	0.81[b]
Degeneration proximal convoluted tubule						
Very slight multifocal degeneration	1/10	1/10	6/10[c]	8/10[c]	4/10[d]	7/10[c]
Slight multifocal degeneration	0/10	0/10	0/10	0/10	4/10[c]	1/10

[a]Estimated dose for prebreeding period only.
[b]Statistically different from control mean by Dunnett's test (α=0.05).
[c]Statistically different from control mean by Fischer's exact test (p<0.01) performed by ATSDR.
[d]Statistically different from control mean by Fischer's exact test (p<0.05) performed by ATSDR.

Source: Saghir et al. 2013a

Table A-4. Selected Kidney Results from Male Crl:CD(SD) Rats Receiving Technical Grade 2,4-D from the Diet up to 13 Weeks

Dietary concentration (ppm)	0	100	300	800
Estimated dose (mg/kg/day)	0	5.51	16.6	45.3
Degeneration proximal convoluted tubule				
Very slight multifocal degeneration	9/10	4/10	6/10	3/11
Slight multifocal degeneration	1/10	0/10	1/10	8/11[a]
Kidney weight (g/100 g body weight)	0.662	0.686	0.685	0.734[b]

[a]Statistically different from control mean by Fisher's exact test (p<0.01)
[b]Statistically different from control mean by Dunnett's test (α=0.05).

Source: Marty et al. 2013

Collectively, the studies of Gorzinski et al. (1987), Marty et al. (2013), and Saghir et al. (2013a) support a LOAEL range of 45–75 mg/kg/day for slight degenerative changes in the renal proximal tubule, and a NOAEL range of 6–16.6 mg/kg/day. Among the three studies providing adequate description of degenerative changes in the renal proximal tubule (Gorzinski et al. 1987; Marty et al. 2013; Saghir et al. 2013a), the study of Marty et al. (2013) identified the lowest LOAEL (45.3 mg/kg/day) for increased kidney weight and slight degeneration of the proximal tubule in the parental male rats administered 2,4-D in the diet for up to 13 weeks; the corresponding NOAEL for this effect was 16.6 mg/kg/day. Therefore, the Marty et al. (2013) study was selected as the principal study for deriving an intermediate-duration oral MRL for 2,4-D.

Summary of the Principal Study:

Marty MS, Neal BH, Zablotny CL, et al. 2013. An F1-extended one-generation reproductive toxicity study in Crl:CD(SD) rats with 2,4-dichlorophenoxyacetic acid. Toxicol Sci 136(2):527-547. 10.1093/toxsci/kft213.

In the principal study, male Sprague-Dawley rats (27/group) were fed a diet containing 0, 100, 300, or 800 ppm 2,4-D (97.85% pure) for 4 weeks premating, up to 2 weeks of mating, and up to 7 weeks postmating. This diet provided estimated 2,4-D doses of 0, 5.5, 16.6, and 45.3 mg/kg/day, respectively, to the parental males. Female rats (27/group) were fed a diet containing 0, 100, 300, or 600 ppm 2,4-D for 29 days premating and through gestation (21 days) and lactation (21 days). Estimated 2,4-D doses to the parental females in the 0, 100, 300, and 800 ppm dietary groups were:

- 0, 6.97, 20.6, and 40.2 mg/kg/day during premating;
- 0, 7.37, 21.9, and 43.7 mg/kg/day for GDs 0–20;
- 0, 10.7, 32.4, and 64.5 g/kg/day for LDs 1–7; and
- 0, 8.4, 25.5, and 51.5 mg/kg/day for LDs 7–14.

The P1 generation was evaluated for systemic toxicity as well as reproductive toxicity.

Body weight was reduced in high-dose parental females during lactation, but no data were shown. Exposure to 2,4-D increased absolute and relative kidney weight (11–13%) in high-dose parental males and increased relative kidney weight (11%) in one set of F1 high-dose females. Renal lesions consisting of very slight to slight degeneration of the proximal convoluted tubules in the outer zone of the medulla were seen in high-dose parental males and in two sets of adult F1 females. There were no treatment-related lesions in other tissues (tissues not specified in paper). Renal lesions appeared more severe in males than in females. Nonsignificant decreased T4 and T3 and increased TSH were seen in high-dose satellite females on GD 17. Three out of 12 females had histological alterations consisting of smaller thyroid follicles with small vacuoles in the colloid suggesting colloid resorption. There were no adverse pathological alterations or changes in LD 21 dams, suggesting that the changes were transient and were therefore considered adaptive, although the changes were considered exposure-related.

The kidney effects in the parental male rats (increased incidence of slight degeneration in proximal tubules and increased kidney weight at 45.3 mg/kg/day) in the study of Marty et al. (2013) represent the most sensitive endpoint of intermediate-duration oral exposure to 2,4-D.

Selection of the Point of Departure for the MRL: A benchmark dose (BMD) approach was initially considered to derive an intermediate-duration oral MRL for 2,4-D based on incidences of kidney lesions (slight multifocal degeneration in the proximal convoluted tubule) in the male rats of Marty et al. (2013). However, as shown in Table A-4, an increased incidence of slight degeneration in the proximal tubules of the male rats was only observed in the high-dose group (incidence of 8/11 at 45.3 mg/kg/day versus 1/10, 0/10, and 1/10 for controls, 5.51, and 16.6 mg/kg/day groups, respectively). A dataset exhibiting a response only at the highest dose level would likely provide limited information regarding the shape of a dose-response curve. Therefore, the NOAEL of 16.6 mg/kg/day was considered the most appropriate potential point of departure for the male rat kidney lesion data from Marty et al. (2013).

Relative kidney weight in the male rats of Marty et al. (2013) was amenable to BMD analysis using the mean (and standard deviation) kidney weight data reported in an unpublished version of this study (MRID4792101). All continuous variable models in the benchmark dose software (BMDS) Version 3.1 were fit to the mean relative kidney weight data using a benchmark response (BMR) of one standard deviation from control in the absence of a rationale for using an alternative BMR.

The resulting potential point of departure ($BMDL_{1SD}$ of 34.12 mg/kg/day from the best-fitting model) was higher than the point of departure using a NOAEL/LOAEL approach (NOAEL of 16.6 mg/kg/day). Therefore, the NOAEL/LOAEL approach was taken to derive an intermediate-duration oral MRL.

Calculations

Intermittent Exposure: Not applicable.

Uncertainty Factor: The NOAEL of 16.6 mg/kg/day was divided by a total uncertainty factor of 100:

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

MRL = NOAEL ÷ uncertainty factors
MRL = 16.6 mg/kg/day ÷ (10 x 10) = 0.2 mg/kg/day.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Kidney lesions (degeneration of the descending portion of proximal convoluted tubules) were reported in male and female rats receiving 2,4-D from food at 75 mg/kg/day for 12 months (interim sacrifice in a 2-year study); the NOAEL was 5 mg/kg/day (Charles et al. 1996a; EPA 1996a). Both 12-month interim and 2-year terminal sacrifices of male B6C3F1 mice revealed degenerative kidney lesions in the descending portion of proximal convoluted at a 2,4-D dose level of 62.5 mg/kg/day (Charles et al. 1996a; EPA 1996b). The NOAEL in the mouse study was 5 mg/kg/day.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-D
CAS Numbers: 94-75-7
Date: July 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.2 mg/kg/day
Critical Effect: Proximal tubule degeneration/regeneration in kidney
Reference: Charles et al. 1996a; EPA 1996b
Point of Departure: 16.66 mg/kg/day ($BMDL_{10}$)
Uncertainty Factor: 100
LSE Graph Key: 59
Species: Mouse

MRL Summary: An MRL of 0.2 mg/kg/day has been derived for chronic-duration oral exposure to 2,4-D based on a $BMDL_{10}$ of 16.66 mg/kg/day for proximal tubule degeneration/regeneration in the kidney of male B6C3F1 mice receiving 2,4-D from food for up to 2 years (Charles et al. 1996a; EPA 1996b).

Selection of the Critical Effect: Table A-5 summarizes the potential candidate critical effects for deriving a chronic-duration oral MRL for 2,4-D.

Table A-5. Summary of Potential Candidate Critical Effects for Deriving a Chronic-Duration Oral MRL for 2,4-D

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
F344 rat	2 years (F)	5	75	19% depressed weight gain in females	Charles et al. 1996a; EPA 1996a
Hematological effects					
F344 rat	2 years (F)	5	75	M: decreased platelets F: decreases in platelets, RBC count, hematocrit	Charles et al. 1996a; EPA 1996a
Renal effects					
B6C3F1 mouse	2 years (F)	5 M 5 F	62.5 M 150 F	Proximal tubule degeneration/regeneration	Charles et al. 1996a; EPA 1996b
Endocrine effects					
F344 rat	2 years (F)	5	75	M, F: decreased serum T4 F: increased thyroid weight	Charles et al. 1996a; EPA 1996b

(F) = food; F = female(s); LOAEL = lowest observed adverse effect level; M = male(s); NOAEL = no-observed-adverse-effect level; RBC = red blood cell; T4 = thyroxine

Selection of the Principal Study: No adequate human data were located. Chronic-duration oral studies in rats (Charles et al. 1996a; EPA 1996a; Hansen et al. 1971), mice (Charles et al. 1996a; EPA 1987a, 1996b), and dogs (Hansen et al. 1971) were available for review. In the dog study (Hansen et al. 1971),

no adverse effects were observed at the highest 2,4-D dose level tested (10 mg/kg/day). Furthermore, as previously stated, dogs appear to be more sensitive to 2,4-D toxicity than other species (including humans) due to a significantly lower capacity to eliminate 2,4-D via the kidneys (Timchalk 2004). Therefore, the dog study was not considered as a potential principal study for deriving a chronic-duration oral MRL for 2,4-D.

A 2-year bioassay in F-344 rats defined an overall NOAEL of 5 mg 2,4-D/kg/day for organs and tissue histopathology and hematological and clinical chemistry parameters (Charles et al. 1996a; EPA 1996a). An oral dose level of 75 mg/kg/day resulted in decreased platelet and erythrocyte counts and hematocrit in female rats (data not shown), increased serum ALT in male rats, and decreased serum T4 in both sexes. Histological alterations were noted at 150 mg/kg/day and consisted of a nonsignificant increase in parafollicular cell nodular hyperplasia in the thyroid from females and minimal panlobular tinctorial properties in the liver from males and females. No clear treatment-related histological alterations were observed in the kidneys at 2,4-D doses of 5, 75, or 150 mg/kg/day. An earlier study did not report treatment-related alterations in organs and tissues from Osborne-Mendel rats receiving 2,4-D from food for 2 years at approximately 92 mg/kg/day (Hansen et al. 1971).

In a 2-year mouse study submitted to EPA, male B6C3F1 mice receiving 2,4-D from food for 2 years at 15 mg/kg/day exhibited significantly increased incidence of cytoplasmic homogeneity in the renal tubular epithelium; this was attributed to a reduction of cytoplasmic vacuoles normally present in the cytoplasm of epithelial cells. No significant increase was seen at 1 mg/kg/day. The available DER from the study (EPA 1987a) provides an inadequate description of the kidney lesions reported. Thus, the degenerative nature of the described lesions is in question. Therefore, this study was not considered as a candidate for deriving a chronic-duration oral MRL for 2,4-D.

In another 2-year mouse study (Charles et al. 1996a; EPA 1996b), a significant increase in minimal degeneration with regeneration of the descending portion of the proximal tubules was reported for male B6C3F1 mice receiving 2,4-D from food at ≥62.5 mg/kg/day; the NOAEL was 5 mg/kg/day. Reduced vacuolization of the cytoplasm in tubular cells of the male mice dosed at ≥62.5 mg/kg/day was noted as well. Because of the unclear biological significance of the reduced vacuolization of the cytoplasm in tubular cells, the degeneration/regeneration change in the proximal tubule of the male mice represents a more toxicologically relevant endpoint for MRL derivation. No other treatment-related histological alterations in organs or tissues or in hematology tests were reported in mice.

The 2-year mouse study (Charles et al. 1996a; EPA 1996b) was selected as the principal study for deriving a chronic-duration oral MRL for 2,4-D because it identified the lowest reliable LOAEL for kidney effects that represent the most sensitive target of 2,4-D toxicity.

Summary of the Principal Study:

Charles JM, Bond DM, Jeffries TK, et al. 1996a. Chronic dietary toxicity/oncogenicity studies on 2,4-dichlorophenoxyacetic acid in rodents. Fundam Appl Toxicol 33(2):166-172.

EPA. 1996b. Data Evaluation Record. Carcinogenicity study – mice. 2,4-Dichlorophenoxyacetic acid (2,4-D) [MRIDs evaluated: 43879801 & 43597201]

Groups of B6C3F1 mice (60/sex/group) were fed a diet for 2 years that provided 2,4-D at 0, 5, 62.5, and 125 mg/kg/day for males and 0, 5, 150, and 300 mg/kg/day for females (Charles et al. 1996a; EPA 1996b). Ten mice per group were killed at 1 year for examination. Endpoints monitored included overt toxicity, morbidity, and lethality at least twice weekly. Body weight, clinical signs, and food consumption were determined weekly for the first 13 weeks and monthly thereafter. Ophthalmoscopic

examination was performed at the beginning and at the end of the study. Hematology testing was conducted during weeks 52, 78, and 104. All survivors were subjected to necropsy after 52 or 104 weeks of treatment. Major organ weights were recorded; all major organs and tissues were examined microscopically.

Dosing with 2,4-D did not significantly affect survival rate. There were no treatment-related changes in clinical appearance or behavior. Body weight gain was not significantly affected by dosing with 2,4-D. Results from hematological tests were unremarkable. Ophthalmology tests did not show treatment-related alterations. Significant changes in organ weights were limited to an increase in relative kidney weight in males and females at 125 mg/kg/day. Treatment-related histological alterations were restricted to the kidneys and consisted of a significant increase in the incidence of degeneration/regeneration in the descending limb of the proximal tubule of the kidneys in males and females at 62.5 and 125 mg/kg/day and increased incidence of vacuolization of the proximal tubule in males at 62.5 and 125 mg/kg/day.

Selection of the Point of Departure for the MRL: The incidence data for degeneration with regeneration of the descending portion of the proximal tubules in the male mice (Table A-6) were analyzed using all available dichotomous models in the EPA BMDS (version 3.1), the extra risk option, and a BMR of 10% change from controls.

Table A-6. Incidence of Degeneration/Regeneration in the Descending Limb of the Proximal Tubules of Male B6C3F1 Mice Administered 2,4-D in the Food for 2 Years

Dose (mg/kg/day)	Mice/group	Incidence
0	50	0
5	50	0
62.5	50	25[a]
125	50	48[a]

[a]$p \leq 0.05$.

Sources: Charles et al. 1996a; EPA 1996b

Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the point of departure when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. As shown in Table A-7, all models except the Multistage (1-degree) and Dichotomous Hill models provided an adequate fit to the dataset.

Table A-7. Model Predictions for Incidence of Degeneration/Regeneration in the Descending Limb of the Proximal Tubules of Male Mice Administered 2,4-D in the Food for 2 Years

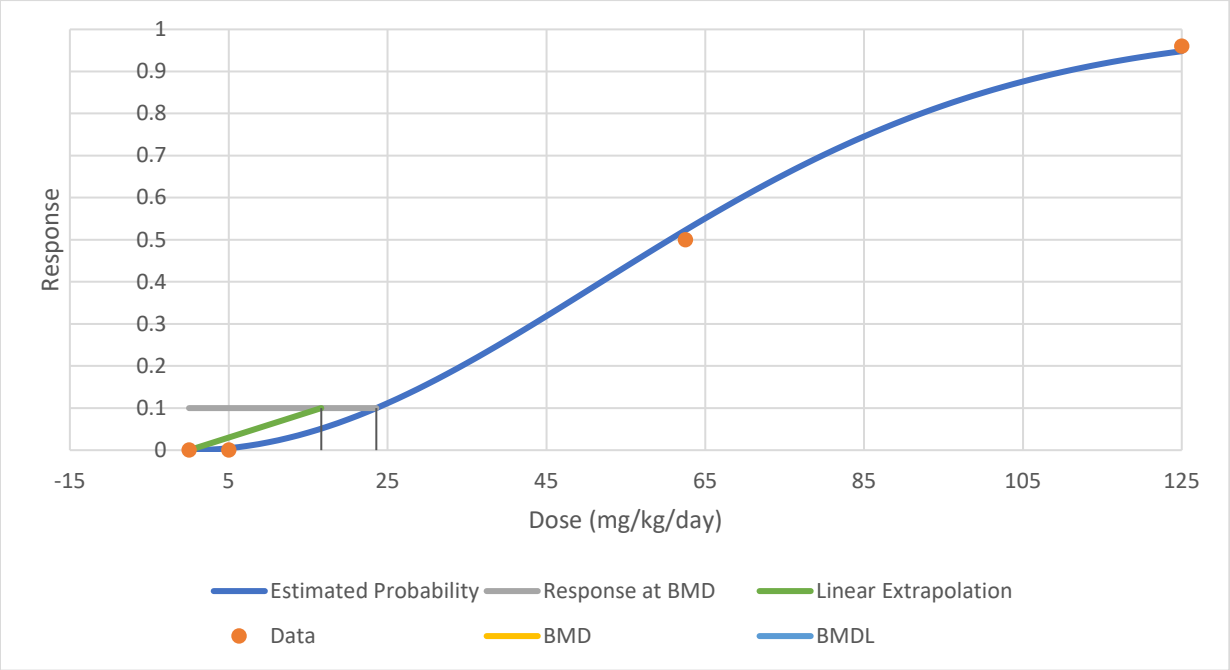
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg/d)	$BMDL_{10}$ (mg/kg/d)
Gamma[c]	1	0.0014	0.97	-0.0368	0.0035	-0.0368	92.112	33.25	20.70
LogLogistic	1	0.0005	0.98	-0.0216	0.0006	-0.0216	92.110	38.71	27.32
Multistage (3-degree)[d]	1	0.1893	0.66	-0.423	0.0859	-0.423	92.477	26.11	16.00
Multistage (2-degree)[d,e]	**3**	**0.4844**	**0.92**	**-0.487**	**-0.323**	**-0.487**	**88.841**	**23.59**	**16.66**
Multistage (1-degree)[d]	3	11.342	0.01						
Weibull[c]	**1**	0.1275	0.72	-0.001	0.047	0.047	92.345	27.53	17.95
Dichotomous Hill[f]	0	0.0005	ND						
Logistic	2	3.7024	0.16	-0.8699	0.7077	-1.382	94.514	35.19	27.68
LogProbit[g]	1	1.5×10^{-6}	1.00	-0.0009	8.9×10^{-6}	8.9×10^{-6}	92.109	37.63	26.33
Probit	2	3.1532	0.21	-0.8026	0.9576	-1.093	94.007	32.63	25.34

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Slope restricted to ≥1.
[d]Power restricted to ≥1.
[e]Among models providing adequate fit to the data, $BMDL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (2-degree Multistage).
[f]Invalid degrees of freedom and χ^2 values.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with 10% extra risk); DF = degrees of freedom; ND = not determined (degrees of freedom = 0; model saturated; goodness-of-fit not calculated)

The model providing the best fit (lowest AIC) is the Multistage (2-degree) model, which defined a BMD_{10} of 23.59 mg 2,4-D/kg/day and a $BMDL_{10}$ of 16.66 mg 2,4-D/kg/day. The fit of the multistage (2-degree) model is presented in Figure A-1.

Figure A-1. Fit of Multistage (2-Degree) Model for Degeneration/Regeneration in Descending Limb of Proximal Tubules of Male B6C3F1 Mice Administered 2,4-D in the Food for 2 Years



Calculations

Intermittent Exposure: Not applicable

Uncertainty Factor: The $BMDL_{10}$ of 16.66 mg/kg/day was divided by a total uncertainty factor of 100:

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

MRL = $BMDL_{10}$ ÷ uncertainty factors
MRL = 16.66 mg/kg/day ÷ (10 x 10) = 0.2 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Kidney lesions (degeneration of the descending portion of proximal convoluted tubules) were reported in male and female rats receiving 2,4-D from food at 75 mg/kg/day for 12 months (interim sacrifice in a 2-year study); the NOAEL was 5 mg/kg/day (Charles et al. 1996a; EPA 1996a). Both 12-month interim and 2-year terminal sacrifice among male and female B6C3F1 mice revealed kidney lesions in the descending portion of proximal convoluted tubules (degeneration in males and hypercellularity in females) at a dose level of 62.5 and 150 mg/kg/day for males and females, respectively, at both 12-month interim and 2-year terminal sacrifice (Charles et al. 1996a; EPA 1996b). The NOAEL in the mouse study was 5 mg/kg/day for both sexes. Increased relative kidney weight and increased incidence of slight degeneration of proximal tubules in outer zone of medulla were reported among male Sprague-Dawley rats receiving 2,4-D from food for up to 12 weeks at 45.3 mg/kg/day; the corresponding NOAEL was 16.6 mg/kg/day (Marty et al. 2013).

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 2,4-D

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 2,4-D.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 2,4-D. 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 2,4-D 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 2,4-D are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 2,4-D released for public comment in 2017; thus, the literature search was restricted to studies published between February 2014 and January 2018. The following main databases were searched in January 2018:

- 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, Medical Subject Headings (MeSH) headings, and keywords for 2,4-D. 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 2,4-D 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	
01/2018	(("2,4-Dichlorophenoxyacetic Acid"[mh] OR 94-75-7[rn] OR 14214-89-2[rn] OR 2307-55-3[rn] OR 2702-72-9[rn] OR 3766-27-6[rn]) AND (2014/02/01 : 3000[dp] OR 2015/02/01 : 3000[mhda])) OR ((("(2,4-Dichlorophenoxy)acetic acid"[tw] OR "(2,4-dichlorophenoxy)-Acetic acid "[tw] OR "(2,4-Dichlorophenyloxy)acetic acid"[tw] OR "2-(2,4-Dichlorophenoxy)acetic acid"[tw] OR "2-(2,4-dichlorophenoxy)-Acetic acid"[tw] OR "2,4-D"[tw] OR "2,4-Dichlorophenoxyacetic acid"[tw] OR "2,4-dichloro-Phenoxyacetic acid"[tw] OR "2,4-Dichlorophenoxyethanoic acid"[tw] OR "2,4-PA"[tw] OR "Acme LV 4"[tw] OR "Acme LV 6"[tw] OR "Agricorn D"[tw] OR "Agrion"[tw] OR "Agrotect"[tw] OR "Aminopielik 50SL"[tw] OR "Aminopielik 720"[tw] OR "Ammonium 2,4-dichlorophenoxyacetate"[tw] OR "Amoxone"[tw] OR "Basalcoat"[tw] OR "BH 2,4-D"[tw] OR "Brush-rhap"[tw] OR "B-Selektonon"[tw] OR "Butoxy-D 3: 1 Liquid emulsifiable Brushkiller LV96"[tw] OR "Chipco turf herbicide D"[tw] OR "Chloroxone"[tw] OR "Citrus fix"[tw] OR "Crop rider"[tw] OR "Croprider"[tw] OR "Debroussaillant 600"[tw] OR "Ded-Weed LV-69"[tw] OR "Deherban"[tw] OR "De-Pester Ded-Weed LV-2"[tw] OR "Desormone"[tw] OR "Dezormon"[tw] OR "Dichlordon sodium"[tw] OR "Dichlorophenoxyacetic acid"[tw] OR "Diclordon"[tw] OR "Diconirt"[tw] OR "Diconirt D"[tw] OR "Dicopur"[tw] OR "Dikonirt"[tw] OR "Dikonirt D"[tw] OR "Dormon"[tw] OR "Dormone"[tw] OR "Emulsamine"[tw] OR "ENT 8,538"[tw] OR "Envert DT"[tw] OR "Esteron 44 weed killer"[tw] OR "Esteron 76 BE"[tw] OR "Estone"[tw] OR "Fernesta"[tw] OR "Fernimine"[tw] OR "Fernoxene"[tw] OR "Fernoxone"[tw] OR "Ferxone"[tw] OR "Foredex 75"[tw] OR "Green Cross Weed-No-More 80"[tw] OR "Herbidal"[tw] OR "Hivol-44"[tw] OR "HM 2010"[tw] OR "Hormit"[tw] OR "Huragan"[tw] OR "Invesamina 480SL"[tw] OR "Ipaner"[tw] OR "Isadiamineyeom"[tw] OR "Kar D"[tw] OR "Lawn-keep"[tw] OR "Lithium 2,4-dichlorophenoxyacetate"[tw] OR "Macondray"[tw] OR "Macrondray"[tw] OR "Monosan"[tw] OR "Monosan herbi"[tw] OR "Mota Maskros"[tw] OR "Moxone"[tw] OR "Netagrone"[tw] OR "Netagrone 600"[tw] OR "NSC 2925"[tw] OR "Pennamine D"[tw] OR "Pielik"[tw] OR "Pielik E"[tw] OR "Planotox"[tw] OR "Plantgard"[tw] OR "Potassium (2,4-dichlorophenoxy)acetate"[tw] OR "Potassium 2,4-dichlorophenoxyacetate"[tw] OR "Profiamina"[tw] OR "Red Devil Dry Weed Killer"[tw] OR "R-H Weed Rhap 20"[tw] OR "Scott's 4-XD Weed Control"[tw] OR "Silvaprop 1"[tw] OR "Sodium (2,4-dichlorophenoxy)acetate"[tw] OR "Sodium 2,4-dichlorophenoxyacetate"[tw] OR "Sodium diclordon"[tw] OR "Solushan"[tw] OR "Spray-hormite"[tw] OR "Spritz-hormit"[tw] OR "Superormone concentre"[tw] OR "Taficide"[tw] OR "Tiller S"[tw] OR "Tornado DF"[tw] OR "Tributon"[tw] OR "U 46D"[tw] OR "U 46DP"[tw] OR "U-46-D-Fluid"[tw] OR "U-5043"[tw] OR "Vergemaster"[tw] OR "Verton 2D"[tw] OR "Verton 38"[tw] OR "Vidon 638"[tw] OR "Visko-rhap low drift herbicides"[tw] OR "Visko-rhap low volatile 4l"[tw] OR "Weed TOX"[tw] OR "Weed-Ag-Bar"[tw] OR "Weedatul"[tw] OR "Weed-B-gon"[tw] OR "Weedez Wonder BAR"[tw] OR "Weedone"[tw] OR "Weed-rhap"[tw] OR "Weed-Rhap A-4"[tw] OR "Weed-Rhap B-266"[tw] OR "Weed-Rhap B-4"[tw] OR "Weed-

Table B-2. Database Query Strings

Database search date	Query string
	Rhap I-3.34"[tw] OR "Weed-Rhap LV-4-0"[tw] OR "Weedtrol"[tw]) AND (2014/02/01 : 3000[dp] OR 2015/02/01 : 3000[crdat] OR 2015/02/01 : 3000[edat])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] 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 (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR "toxicokinetics"[mh:noexp])) OR ((("(2,4-Dichlorophenoxy)acetic acid"[tw] OR "(2,4-dichlorophenoxy)-Acetic acid "[tw] OR "(2,4-Dichlorophenyloxy)acetic acid"[tw] OR "2-(2,4-Dichlorophenoxy)acetic acid"[tw] OR "2-(2,4-dichlorophenoxy)-Acetic acid"[tw] OR "2,4-D"[tw] OR "2,4-Dichlorophenoxyacetic acid"[tw] OR "2,4-dichloro-Phenoxyacetic acid"[tw] OR "2,4-Dichlorophenoxyethanoic acid"[tw] OR "2,4-PA"[tw] OR "Acme LV 4"[tw] OR "Acme LV 6"[tw] OR "Agricorn D"[tw] OR "Agrion"[tw] OR "Agrotect"[tw] OR "Aminopielik 50SL"[tw] OR "Aminopielik 720"[tw] OR "Ammonium 2,4-dichlorophenoxyacetate"[tw] OR "Amoxone"[tw] OR "Basalcoat"[tw] OR "BH 2,4-D"[tw] OR "Brush-rhap"[tw] OR "B-Selektonon"[tw] OR "Butoxy-D 3: 1 Liquid emulsifiable Brushkiller LV96"[tw] OR "Chipco turf herbicide D"[tw] OR "Chloroxone"[tw] OR "Citrus fix"[tw] OR "Crop rider"[tw] OR "Croprider"[tw] OR "Debroussaillant 600"[tw] OR "Ded-Weed LV-69"[tw] OR "Deherban"[tw] OR "De-Pester Ded-Weed LV-2"[tw] OR "Desormone"[tw] OR "Dezormon"[tw] OR "Dichlordon sodium"[tw] OR "Dichlorophenoxyacetic acid"[tw] OR "Diclordon"[tw] OR "Diconirt"[tw] OR "Diconirt D"[tw] OR "Dicopur"[tw] OR "Dikonirt"[tw] OR "Dikonirt D"[tw] OR "Dormon"[tw] OR "Dormone"[tw] OR "Emulsamine"[tw] OR "ENT 8,538"[tw] OR "Envert DT"[tw] OR "Esteron 44 weed killer"[tw] OR "Esteron 76 BE"[tw] OR "Estone"[tw] OR "Fernesta"[tw] OR "Fernimine"[tw] OR "Fernoxene"[tw] OR "Fernoxone"[tw] OR "Ferxone"[tw] OR "Foredex 75"[tw] OR "Green Cross Weed-No-More 80"[tw] OR "Herbidal"[tw] OR "Hivol-44"[tw] OR "HM 2010"[tw] OR "Hormit"[tw] OR "Huragan"[tw] OR "Invesamina 480SL"[tw] OR "Ipaner"[tw] OR "Isadiamineyeom"[tw] OR "Kar D"[tw] OR "Lawn-keep"[tw] OR "Lithium 2,4-dichlorophenoxyacetate"[tw] OR "Macondray"[tw] OR "Macrondray"[tw] OR "Monosan"[tw] OR "Monosan herbi"[tw] OR "Mota Maskros"[tw] OR "Moxone"[tw] OR "Netagrone"[tw] OR "Netagrone 600"[tw] OR "NSC 2925"[tw] OR "Pennamine D"[tw] OR "Pielik"[tw] OR "Pielik E"[tw] OR "Planotox"[tw] OR "Plantgard"[tw] OR "Potassium (2,4-dichlorophenoxy)acetate"[tw] OR "Potassium 2,4-dichlorophenoxyacetate"[tw] OR "Profiamina"[tw] OR "Red Devil Dry Weed Killer"[tw] OR "R-H Weed Rhap 20"[tw] OR "Scott's 4-XD Weed Control"[tw] OR "Silvaprop 1"[tw] OR "Sodium (2,4-dichlorophenoxy)acetate"[tw] OR "Sodium 2,4-dichlorophenoxyacetate"[tw] OR "Sodium diclordon"[tw] OR "Solushan"[tw] OR "Spray-hormite"[tw] OR "Spritz-hormit"[tw] OR "Superormone concentre"[tw] OR "Taficide"[tw] OR "Tiller S"[tw] OR "Tornado DF"[tw] OR "Tributon"[tw] OR "U 46D"[tw] OR "U 46DP"[tw] OR "U-46-D-Fluid"[tw] OR "U-5043"[tw] OR "Vergemaster"[tw] OR "Verton 2D"[tw] OR "Verton 38"[tw] OR "Vidon 638"[tw] OR "Visko-rhap low drift herbicides"[tw] OR "Visko-rhap low volatile 4l"[tw] OR "Weed TOX"[tw] OR "Weed-Ag-Bar"[tw] OR "Weedatul"[tw] OR "Weed-B-

Table B-2. Database Query Strings

Database search date	Query string
	gon"[tw] OR "Weedez Wonder BAR"[tw] OR "Weedone"[tw] OR "Weed-rhap"[tw] OR "Weed-Rhap A-4"[tw] OR "Weed-Rhap B-266"[tw] OR "Weed-Rhap B-4"[tw] OR "Weed-Rhap I-3.34"[tw] OR "Weed-Rhap LV-4-0"[tw] OR "Weedtrol"[tw]) AND (2014/02/01 : 3000[dp] OR 2015/02/01 : 3000[crdat] OR 2015/02/01 : 3000[edat])) NOT medline[sb])
	"2,4-Dichlorophenoxyacetic Acid"[mh] AND "Adverse Outcome Pathways"[mh]
	("5742-19-8"[rn] OR "2008-39-1"[rn] OR "5742-17-6"[rn] OR "18584-79-7"[rn] OR "1929-73-3"[rn] OR "1928-43-4"[rn] OR "94-11-1"[rn] OR "2,4-D amine"[nm] OR "butoxyethanol ester of 2,4-dichlorophenoxyacetic acid"[nm] OR "2-ethylhexyl 2,4-dichlorophenoxyacetate"[nm]) OR "2,4-D Bis(2-hydroxyethyl)ammonium"[tw] OR "2,4-D Diethanolamine"[tw] OR "2,4-D Diethanolamine salt"[tw] OR "2,4-D-Bis(2-hydroxyethyl)ammonium"[tw] OR "2,4-D-diolamine"[tw] OR "2,4-Dichlorophenoxyacetic acid diethanolamine salt"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2,2'-iminobis(ethanol) (1:1)"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, diethanolamine salt"[tw] OR "Bis(2-hydroxyethyl)ammonium 2,4-dichlorophenoxyacetate"[tw] OR "Diethanolamine 2,4-dichlorophenoxyacetate"[tw] OR "Diethanolamine salt of 2,4-dichlorophenoxyacetic acid solution"[tw] OR "(2,4-Dichlorophenoxy)acetic acid compd. with isopropylamine"[tw] OR "(2,4-Dichlorophenoxy)acetic acid isopropylamine salt"[tw] OR "2,4-D isopropylamine"[tw] OR "2,4-D isopropylamine salt"[tw] OR "2,4-D-isopropylammonium"[tw] OR "2-Propanamine, (2,4-dichlorophenoxy)acetate"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2-propanamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with isopropylamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropylamine salt"[tw] OR "Isopropylamine 2,4-dichlorophenoxyacetate"[tw] OR "Isopropylamine, compd. with (2,4-dichlorophenoxy)acetic acid"[tw] OR "(2,4-Dichlorophenoxy)acetic acid compd. with 1,1',1-nitrilotris[2-propanol]"[tw] OR "2,4-D Triisopropanolamine"[tw] OR "2,4-D triisopropanolamine salt"[tw] OR "2,4-D triisopropanolamine sodium salt"[tw] OR "2,4-D triisopropanolammonium salt"[tw] OR "2,4-D, triisopropanolamine salt"[tw] OR "2,4-D-tris(2-hydroxypropyl)ammonium"[tw] OR "2,4-D-Trisopropyl salt"[tw] OR "2,4-Dichlorophenoxyacetic acid triisopropanolamine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid, triisopropanolamine salt solution"[tw] OR "2-Propanol, 1,1',1"-nitrilotri-, (2,4-dichlorophenoxy)acetate (salt)"[tw] OR "2-Propanol, 1,1',1"-nitrilotris-, (2,4-dichlorophenoxy)acetate (salt)"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1"-nitrilotri-2-propanol"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1"-nitrilotris(2-propanol)"[tw] OR "Triisopropanolamine 2,4-dichlorophenoxyacetate"[tw] OR "(2,4-Dichlorophenoxy)acetic acid, 1-methylethyl ester"[tw] OR "2,4-D ester"[tw] OR "2,4-D esters"[tw] OR "2,4-D Isopropyl ester"[tw] OR "2,4-D, isopropyl ester"[tw] OR "2,4-D-ester"[tw] OR "2,4-D-Isopropyl"[tw] OR "2,4-Dichlorophenoxyacetic acid ester"[tw] OR "2,4-Dichlorophenoxyacetic acid, 1-methylethyl ester"[tw] OR "2,4-Dichlorophenoxyacetic acid, isopropyl ester"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, 1-methylethyl ester"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropyl ester"[tw] OR "Amchem Weed Killer 650"[tw] OR "Barber's Weed Killer (Ester Formulation)"[tw] OR "Bridgeport Spot Weed Killer"[tw] OR "Chemical Insecticide's Isopropyl Ester of 2,4-D Liquid Concentrate"[tw] OR "Crop Rider 3-34D-2"[tw] OR "Crop Rider 3.34D"[tw] OR "Esteron 44"[tw] OR "Isopropyl (2,4-dichlorophenoxy)acetate"[tw] OR "Isopropyl 2,4-D ester"[tw] OR "Isopropyl 2,4-dichlorophenoxyacetate"[tw] OR "Isopropylester kyseliny 2,4-dichlorfenoxyoctove"[tw] OR "Isopropylester kyseliny 2,4-dichlorfenoxyoctove [Czech]"[tw] OR "Monsanto 2,4-D Isopropyl Ester"[tw] OR "Niagara Estasol"[tw] OR "Parsons 2,4-D Weed Killer Isopropyl Ester"[tw] OR "Swift's Gold Bear 44 Ester"[tw] OR "Weedone 128"[tw]
	("(2,4-Dichlorophenoxy)acetic acid dimethylamine"[tw] OR "(2,4-Dichlorophenoxy)acetic acid dimethylamine salt"[tw] OR "2,4-D amine"[tw] OR "2,4-D amine salt"[tw] OR "2,4-D

Table B-2. Database Query Strings

Database search date	Query string
	dimethylamine"[tw] OR "2,4-D dimethylamine salt"[tw] OR "2,4-D DMA"[tw] OR "2,4-D N,N-dimethylamine"[tw] OR "2,4-D, alkanolamine salt"[tw] OR "2,4-D-dimethylammonium"[tw] OR "2,4-Diamin SL"[tw] OR "2,4-Dichlorophenoxy)acetic acid compd. with N-methylmethanamine"[tw] OR "2,4-Dichlorophenoxy)acetic acid dimethylamine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid dimethylamine"[tw] OR "2,4-Dichlorophenoxyacetic acid dimethylamine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid, dimethyl amine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid, dimethylamine salt solution"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with dimethylamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with N-methylmethanamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with dimethylamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with N-methylmethanamine"[tw] OR "Dimethylamine 2,4-dichlorophenoxyacetate"[tw] OR "Dimethylamine salt of 2,4-dichlorophenoxyacetic acid solution"[tw] OR "Dimethylamine, (2,4-dichlorophenoxy)acetate"[tw] OR "Dimethylammonium 2,4-dichlorophenoxyacetate"[tw] OR "Methanamine, N-methyl-, (2,4-dichlorophenoxy)acetate"[tw] OR "N-Methylmethanamine (2,4-dichlorophenoxy)acetate"[tw] OR "N-Methylmethanamine 2,4-dichlorophenoxyacetate"[tw] OR "Alkano amine salt of 2,4-D"[tw] OR "Amicide"[tw] OR "Amine-2,4-D"[tw] OR "Aminol"[tw] OR "Aminopielek 720"[tw] OR "Aminopielik 600SL"[tw] OR "Aminoprelik 39"[tw] OR "Amisol"[tw] OR "Banvel 3 Liquid Herbicide"[tw] OR "Banvel-720"[tw] OR "Barber's Weed Killer"[tw] OR "Best 4 Servis Brand Lawn Weed Killer"[tw] OR "Bladex G"[tw] OR "Blitz 64"[tw] OR "Brabant 2,4-D amine"[tw] OR "Chipman 2,4-D Amine No. 4"[tw] OR "Chipman Lawn Weedkiller"[tw] OR "Chipman's 2,4-D amine No. 4"[tw] OR "Clean Crop 2,4-D Amine 500"[tw] OR "Co-op Premium Lawn Weed Killer"[tw] OR "D 50 (pesticide)"[tw] OR "Ded-Weed Sulv"[tw] OR "Desormone"[tw] OR "Diamond Shamrock Amine 6D"[tw] OR "Dikamin D"[tw] OR "DMA 4"[tw] OR "DMA 6"[tw] OR "DMA-2,4-D"[tw] OR "Dma-4"[tw] OR "Dow DMA-4"[tw] OR "Dow Formula 40"[tw] OR "Du Pont Lawn Weed Killer"[tw] OR "Du Pont Turf Food With Weed Killer"[tw] OR "Du Pont Weed Killer No. 2"[tw] OR "Farmco D 50"[tw] OR "Farmco D-50"[tw] OR "Floro Tox 2,4-D Amine Weed Killer"[tw] OR "Formula 40"[tw] OR "FS Amine 400 Weed Killer"[tw] OR "Green Cross Killex Spot Weeder Pressurized Spray"[tw] OR "Green Cross Poison Ivy Killer"[tw] OR "Herbitex"[tw] OR "Hormin"[tw] OR "Liquid Clearit Vegetation Killer"[tw] OR "Liquid Wonder Weeder"[tw] OR "Manco Kill-Weed"[tw] OR "Marquette Herbitex Plus"[tw] OR "Mecoturf Plus 2,4-D Liquid Weedkiller"[tw] OR "Monosan"[tw] OR "Monsanto 2,4-D Amine"[tw] OR "Morselect"[tw] OR "Norkem 40t"[tw] OR "Ortho Super Weed-B-Gon Spray"[tw] OR "Pacific Cooperatives P 2,4-D Amine Weed Killer"[tw] OR "Parsons 2,4-D Weed Killer"[tw] OR "Parsons 2,4-D Weed Killer No. 40"[tw] OR "Phordene"[tw] OR "Reed amine 400"[tw] OR "Shirweed 500"[tw] OR "Spraygraze"[tw] OR "Spritz-Hormin"[tw] OR "Sure Death 2,4-D Amine Weedkiller"[tw] OR "Techne 2,4-D Amine Weed Killer"[tw] OR "U 46D Fluid"[tw] OR "U-46 D-Fluid"[tw] OR "Vigoro Dandelions Killer"[tw] OR "Weed-Rhap A-4D"[tw] OR "Weedar 64"[tw] OR "Weedar 96"[tw] OR "Weedkiller D"[tw] OR "Wilbur-Ellis 2,4-D Amine 500"[tw] OR "Wilson's Multi-Weeder"[tw] OR "Zehrung 2,4-D Selective Amine Weed Killer"[tw] OR "(2,4-Dichlorophenoxy)acetic acid butoxyethyl ester"[tw] OR "(2,4-Dichlorophenoxy)acetic acid, 2-butoxyethyl ester"[tw] OR "2,4-D (BEE)"[tw] OR "2,4-D (BOEE)"[tw] OR "2,4-D 2-butoxyethyl ester"[tw] OR "2,4-D butoxyethanol"[tw] OR "2,4-D butoxyethanol ester"[tw] OR "2,4-D butoxyethyl ester"[tw] OR "2,4-D esters"[tw] OR "2,4-D isobutoxyethanol"[tw] OR "2,4-D, BEE"[tw] OR "2,4-D, butoxyethanol ester"[tw] OR "2,4-D, butoxyethyl ester"[tw] OR "2,4-D-(2-Butoxyethyl)"[tw] OR "2,4-D-BEE"[tw] OR "2,4-D-butotyl"[tw] OR "2,4-DBE"[tw] OR "2,4-DBEE"[tw] OR "2,4-Dichlorophenoxyacetic acid 2-Butoxyethyl ester"[tw] OR "2,4-Dichlorophenoxyacetic acid butoxyethanol ester"[tw] OR "2,4-Dichlorophenoxyacetic acid ethylene glycol butyl ether ester"[tw] OR "2,4-

Table B-2. Database Query Strings

Database search date	Query string
	Dichlorophenoxyacetic acid, butoxyethyl ester"[tw] OR "2,4-Dichlorophenoxyacetic acids"[tw] OR "2-Butoxyethyl 2,4-dichlorophenoxyacetate"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-butoxyethyl ester"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, butoxyethyl ester"[tw] OR "Aqua-Kleen"[tw] OR "BEE 2,4-D"[tw] OR "Bladex-B"[tw] OR "Brush killer 64"[tw] OR "Butoxy-D 3"[tw] OR "Butoxyethanol ester of (2,4-dichlorophenoxy)acetic acid"[tw] OR "Butoxyethanol ester of 2,4-dichlorophenoxyacetic acid"[tw] OR "Butoxyethyl 2,4-dichlorophenoxyacetate"[tw] OR "Butoxyethyl ester of 2,4-dichlorophenoxy acetic acid"[tw] OR "Esteron 99 Concentrate"[tw] OR "Lo-Estasol"[tw] OR "Planotox"[tw] OR "Silvaprop 1"[tw] OR "Weed-Rhap LV-4D"[tw] OR "Weedone 100 Emulsifiable"[tw] OR "Weedone 638"[tw] OR "Weedone LV 4"[tw] OR "Weedone LV-6"[tw] OR "Weedone LV4"[tw] OR "(2,4-Dichlorophenoxy)acetic acid 2-ethylhexyl ester"[tw] OR "2,4-D 2-Ethylhexyl ester"[tw] OR "2,4-D Ethylhexyl ester"[tw] OR "2,4-D-2-ethylhexyl"[tw] OR "2-Ethylhexyl (2,4-dichlorophenoxy)acetate"[tw] OR "2-Ethylhexyl 2,4-dichlorophenoxyacetate"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-ethylhexyl ester"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] 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 (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR "toxicokinetics"[mh:noexp])
	("(2,4-Dichlorophenoxy)acetic acid dimethylamine"[tw] OR "(2,4-Dichlorophenoxy)acetic acid dimethylamine salt"[tw] OR "2,4-D amine"[tw] OR "2,4-D amine salt"[tw] OR "2,4-D dimethylamine"[tw] OR "2,4-D dimethylamine salt"[tw] OR "2,4-D DMA"[tw] OR "2,4-D N,N-dimethylamine"[tw] OR "2,4-D, alkanolamine salt"[tw] OR "2,4-D-dimethylammonium"[tw] OR "2,4-Diamin SL"[tw] OR "2,4-Dichlorophenoxy)acetic acid compd. with N-methylmethanamine"[tw] OR "2,4-Dichlorophenoxy)acetic acid dimethylamine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid dimethylamine"[tw] OR "2,4-Dichlorophenoxyacetic acid dimethylamine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid, dimethyl amine salt"[tw] OR "2,4-Dichlorophenoxyacetic acid, dimethylamine salt solution"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with dimethylamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with N-methylmethanamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with dimethylamine"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with N-methylmethanamine"[tw] OR "Dimethylamine 2,4-dichlorophenoxyacetate"[tw] OR "Dimethylamine salt of 2,4-dichlorophenoxyacetic acid solution"[tw] OR "Dimethylamine, (2,4-dichlorophenoxy)acetate"[tw] OR "Dimethylammonium 2,4-dichlorophenoxyacetate"[tw] OR "Methanamine, N-methyl-, (2,4-dichlorophenoxy)acetate"[tw] OR "N-Methylmethanamine (2,4-dichlorophenoxy)acetate"[tw] OR "N-Methylmethanamine 2,4-dichlorophenoxyacetate"[tw] OR "Alkano amine salt of 2,4-D"[tw] OR "Amicide"[tw] OR "Amine-2,4-D"[tw] OR "Aminol"[tw] OR "Aminopielek 720"[tw] OR "Aminopielik 600SL"[tw] OR "Aminoprelik 39"[tw] OR "Amisol"[tw] OR "Banvel 3 Liquid Herbicide"[tw] OR "Banvel-720"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Barber's Weed Killer"[tw] OR "Best 4 Servis Brand Lawn Weed Killer"[tw] OR "Bladex G"[tw] OR "Blitz 64"[tw] OR "Brabant 2,4-D amine"[tw] OR "Chipman 2,4-D Amine No. 4"[tw] OR "Chipman Lawn Weedkiller"[tw] OR "Chipman's 2,4-D amine No. 4"[tw] OR "Clean Crop 2,4-D Amine 500"[tw] OR "Co-op Premium Lawn Weed Killer"[tw] OR "D 50 (pesticide)"[tw] OR "Ded-Weed Sulv"[tw] OR "Desormone"[tw] OR "Diamond Shamrock Amine 6D"[tw] OR "Dikamin D"[tw] OR "DMA 4"[tw] OR "DMA 6"[tw] OR "DMA-2,4-D"[tw] OR "Dma-4"[tw] OR "Dow DMA-4"[tw] OR "Dow Formula 40"[tw] OR "Du Pont Lawn Weed Killer"[tw] OR "Du Pont Turf Food With Weed Killer"[tw] OR "Du Pont Weed Killer No. 2"[tw] OR "Farmco D 50"[tw] OR "Farmco D-50"[tw] OR "Floro Tox 2,4-D Amine Weed Killer"[tw] OR "Formula 40"[tw] OR "FS Amine 400 Weed Killer"[tw] OR "Green Cross Killex Spot Weeder Pressurized Spray"[tw] OR "Green Cross Poison Ivy Killer"[tw] OR "Herbitex"[tw] OR "Hormin"[tw] OR "Liquid Clearit Vegetation Killer"[tw] OR "Liquid Wonder Weeder"[tw] OR "Manco Kill-Weed"[tw] OR "Marquette Herbitex Plus"[tw] OR "Mecoturf Plus 2,4-D Liquid Weedkiller"[tw] OR "Monosan"[tw] OR "Monsanto 2,4-D Amine"[tw] OR "Morselect"[tw] OR "Norkem 40t"[tw] OR "Ortho Super Weed-B-Gon Spray"[tw] OR "Pacific Cooperatives P 2,4-D Amine Weed Killer"[tw] OR "Parsons 2,4-D Weed Killer"[tw] OR "Parsons 2,4-D Weed Killer No. 40"[tw] OR "Phordene"[tw] OR "Reed amine 400"[tw] OR "Shirweed 500"[tw] OR "Spraygraze"[tw] OR "Spritz-Hormin"[tw] OR "Sure Death 2,4-D Amine Weedkiller"[tw] OR "Techne 2,4-D Amine Weed Killer"[tw] OR "U 46D Fluid"[tw] OR "U-46 D-Fluid"[tw] OR "Vigoro Dandelions Killer"[tw] OR "Weed-Rhap A-4D"[tw] OR "Weedar 64"[tw] OR "Weedar 96"[tw] OR "Weedkiller D"[tw] OR "Wilbur-Ellis 2,4-D Amine 500"[tw] OR "Wilson's Multi-Weeder"[tw] OR "Zehrung 2,4-D Selective Amine Weed Killer"[tw] OR "(2,4-Dichlorophenoxy)acetic acid butoxyethyl ester"[tw] OR "(2,4-Dichlorophenoxy)acetic acid, 2-butoxyethyl ester"[tw] OR "2,4-D (BEE)"[tw] OR "2,4-D (BOEE)"[tw] OR "2,4-D 2-butoxyethyl ester"[tw] OR "2,4-D butoxyethanol"[tw] OR "2,4-D butoxyethanol ester"[tw] OR "2,4-D butoxyethyl ester"[tw] OR "2,4-D esters"[tw] OR "2,4-D isobutoxyethanol"[tw] OR "2,4-D, BEE"[tw] OR "2,4-D, butoxyethanol ester"[tw] OR "2,4-D, butoxyethyl ester"[tw] OR "2,4-D-(2-Butoxyethyl)"[tw] OR "2,4-D-BEE"[tw] OR "2,4-D-butotyl"[tw] OR "2,4-DBE"[tw] OR "2,4-DBEE"[tw] OR "2,4-Dichlorophenoxyacetic acid 2-Butoxyethyl ester"[tw] OR "2,4-Dichlorophenoxyacetic acid butoxyethanol ester"[tw] OR "2,4-Dichlorophenoxyacetic acid ethylene glycol butyl ether ester"[tw] OR "2,4-Dichlorophenoxyacetic acid, butoxyethyl ester"[tw] OR "2,4-Dichlorophenoxyacetic acids"[tw] OR "2-Butoxyethyl 2,4-dichlorophenoxyacetate"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-butoxyethyl ester"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, butoxyethyl ester"[tw] OR "Aqua-Kleen"[tw] OR "BEE 2,4-D"[tw] OR "Bladex-B"[tw] OR "Brush killer 64"[tw] OR "Butoxy-D 3"[tw] OR "Butoxyethanol ester of (2,4-dichlorophenoxy)acetic acid"[tw] OR "Butoxyethanol ester of 2,4-dichlorophenoxyacetic acid"[tw] OR "Butoxyethyl 2,4-dichlorophenoxyacetate"[tw] OR "Butoxyethyl ester of 2,4-dichlorophenoxy acetic acid"[tw] OR "Esteron 99 Concentrate"[tw] OR "Lo-Estasol"[tw] OR "Planotox"[tw] OR "Silvaprop 1"[tw] OR "Weed-Rhap LV-4D"[tw] OR "Weedone 100 Emulsifiable"[tw] OR "Weedone 638"[tw] OR "Weedone LV 4"[tw] OR "Weedone LV-6"[tw] OR "Weedone LV4"[tw] OR "(2,4-Dichlorophenoxy)acetic acid 2-ethylhexyl ester"[tw] OR "2,4-D 2-Ethylhexyl ester"[tw] OR "2,4-D Ethylhexyl ester"[tw] OR "2,4-D-2-ethylhexyl"[tw] OR "2-Ethylhexyl (2,4-dichlorophenoxy)acetate"[tw] OR "2-Ethylhexyl 2,4-dichlorophenoxyacetate"[tw] OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-ethylhexyl ester"[tw]) NOT medline[sb]
Toxline	
01/2018	Limited 2014-present: "(2,4-Dichlorophenoxy)acetic acid" OR "(2,4-dichlorophenoxy)-Acetic acid " OR "(2,4-Dichlorophenyloxy)acetic acid" OR "2-(2,4-Dichlorophenoxy)acetic acid" OR "2-(2,4-

Table B-2. Database Query Strings

Database search date	Query string
	dichlorophenoxy)-Acetic acid" OR "2,4-D" OR "2,4-Dichlorophenoxyacetic acid" OR "2,4-dichloro-Phenoxyacetic acid" OR "2,4-Dichlorophenoxyethanoic acid" OR "2,4-PA" OR "Acme LV 4" OR "Acme LV 6" OR "Agricorn D"
	Limited 2014-present: "Agrion" OR "Agrotect" OR "Aminopielik 50SL" OR "Aminopielik 720" OR "Ammonium 2,4-dichlorophenoxyacetate" OR "Amoxone" OR "Basalcoat" OR "BH 2,4-D" OR "Brush-rhap" OR "B-Selektonon" OR "Butoxy-D 3: 1 Liquid emulsifiable Brushkiller LV96" OR "Chipco turf herbicide D" OR "Chloroxone" OR "Citrus fix" OR "Crop rider" OR "Croprider" OR "Debroussaillant 600"
	Limited 2014-present: "Ded-Weed LV-69" OR "Deherban" OR "De-Pester Ded-Weed LV-2" OR "Desormone" OR "Dezormon" OR "Dichlordon sodium" OR "Dichlorophenoxyacetic acid" OR "Diclordon" OR "Diconirt" OR "Diconirt D" OR "Dicopur" OR "Dikonirt" OR "Dikonirt D" OR "Dormon" OR "Dormone" OR "Emulsamine" OR "ENT 8,538" OR "Envert DT" OR "Esteron 44 weed killer" OR "Esteron 76 BE" OR "Estone" OR "Fernesta"
	Limited 2014-present: "Fernimine" OR "Fernoxene" OR "Fernoxone" OR "Ferxone" OR "Foredex 75" OR "Green Cross Weed-No-More 80" OR "Herbidal" OR "Hivol-44" OR "HM 2010" OR "Hormit" OR "Huragan" OR "Invesamina 480SL" OR "Ipaner" OR "Isadiamineyeom" OR "Kar D" OR "Lawn-keep" OR "Lithium 2,4-dichlorophenoxyacetate" OR "Macondray" OR "Macrondray" OR "Monosan" OR "Monosan herbi"
	Limited 2014-present: "Mota Maskros" OR "Moxone" OR "Netagrone" OR "Netagrone 600" OR "NSC 2925" OR "Pennamine D" OR "Pielik" OR "Pielik E" OR "Planotox" OR "Plantgard" OR "Potassium (2,4-dichlorophenoxy)acetate" OR "Potassium 2,4-dichlorophenoxyacetate" OR "Profiamina" OR "Red Devil Dry Weed Killer" OR "R-H Weed Rhap 20" OR "Scott's 4-XD Weed Control" OR "Silvaprop 1"
	Limited 2014-present: "Sodium (2,4-dichlorophenoxy)acetate" OR "Sodium 2,4-dichlorophenoxyacetate" OR "Sodium diclordon" OR "Solushan" OR "Spray-hormite" OR "Spritz-hormit" OR "Superormone concentre" OR "Taficide" OR "Tiller S" OR "Tornado DF" OR "Tributon" OR "U 46D" OR "U 46DP" OR "U-46-D-Fluid" OR "U-5043" OR "Vergemaster" OR "Verton 2D" OR "Verton 38" OR "Vidon 638"
	Limited 2014-present: "Visko-rhap low drift herbicides" OR "Visko-rhap low volatile 4l" OR "Weed TOX" OR "Weed-Ag-Bar" OR "Weedatul" OR "Weed-B-gon" OR "Weedez Wonder BAR" OR "Weedone" OR "Weed-rhap" OR "Weed-Rhap A-4" OR "Weed-Rhap B-266" OR "Weed-Rhap B-4" OR "Weed-Rhap I-3.34" OR "Weed-Rhap LV-4-0" OR "Weedtrol" OR 94-75-7[rn] OR 14214-89-2[rn] OR 2307-55-3[rn] OR 2702-72-9[rn] OR 3766-27-6[rn]
	"Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2,2'-iminobis(ethanol) (1:1)" OR "Acetic acid, (2,4-dichlorophenoxy)-, diethanolamine salt" OR "Bis(2-hydroxyethyl)ammonium 2,4-dichlorophenoxyacetate" OR "Diethanolamine 2,4-dichlorophenoxyacetate" OR "2,4-Diamin SL" OR "2,4-Dichlorophenoxy)acetic acid compd. with N-methylmethanamine" OR "2,4-Dichlorophenoxy)acetic acid dimethylamine salt"
	"Acetic acid, (2,4-dichlorophenoxy)-, cmpd with dimethylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with N-methylmethanamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with dimethylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-,

Table B-2. Database Query Strings

Database search date	Query string
	compd. with N-methylmethanamine" OR "Dimethylamine 2,4-dichlorophenoxyacetate" OR "Dimethylamine, (2,4-dichlorophenoxy)acetate"
	"Dimethylammonium 2,4-dichlorophenoxyacetate" OR "Methanamine, N-methyl-, (2,4-dichlorophenoxy)acetate" OR "N-Methylmethanamine (2,4-dichlorophenoxy)acetate" OR "N-Methylmethanamine 2,4-dichlorophenoxyacetate" OR "Alkano amine salt of 2,4-D" OR "Amicide" OR "Amine-2,4-D" OR "Aminol" OR "Aminopielek 720" OR "Aminopielik 600SL" OR "Aminoprelik 39"
	"Amisol" OR "Banvel 3 Liquid Herbicide" OR "Banvel-720" OR "Barber's Weed Killer" OR "Best 4 Servis Brand Lawn Weed Killer" OR "Bladex G" OR "Blitz 64" OR "Chipman Lawn Weedkiller" OR "Co-op Premium Lawn Weed Killer" OR "D 50 pesticide" OR "Ded-Weed Sulv" OR "Desormone" OR "Diamond Shamrock Amine 6D" OR "Dikamin D" OR "DMA 4" OR "DMA 6" OR "DMA-2,4-D" OR "Dma-4" OR "Dow DMA-4"
	"Dow Formula 40" OR "Du Pont Lawn Weed Killer" OR "Du Pont Turf Food With Weed Killer" OR "Du Pont Weed Killer No. 2" OR "Farmco D 50" OR "Farmco D-50" OR "Formula 40" OR "FS Amine 400 Weed Killer" OR "Green Cross Killex Spot Weeder Pressurized Spray" OR "Green Cross Poison Ivy Killer" OR "Herbitex" OR "Hormin" OR "Liquid Clearit Vegetation Killer" OR "Liquid Wonder Weeder" OR "Manco Kill-Weed"
	"Marquette Herbitex Plus" OR "Monosan" OR "Morselect" OR "Norkem 40t" OR "Ortho Super Weed-B-Gon Spray" OR "Phordene" OR "Reed amine 400" OR "Shirweed 500" OR "Spraygraze" OR "Spritz-Hormin" OR "Vigoro Dandelions Killer" OR "Weed-Rhap A-4D" OR "Weedar 64" OR "Weedar 96" OR "Weedkiller D" OR "Wilson's Multi-Weeder" OR "2-Propanamine, (2,4-dichlorophenoxy)acetate"
	"Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2-propanamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with isopropylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropylamine salt" OR "Isopropylamine 2,4-dichlorophenoxyacetate" OR "2-Propanol, 1,1',1"-nitrilotri-, (2,4-dichlorophenoxy)acetate (salt)" OR "2-Propanol, 1,1',1"-nitrilotris-, (2,4-dichlorophenoxy)acetate (salt)"
	"Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1"-nitrilotri-2-propanol" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1"-nitrilotris(2-propanol)" OR "Triisopropanolamine 2,4-dichlorophenoxyacetate" OR "2,4-DBE" OR "2,4-DBEE" OR "2,4-Dichlorophenoxyacetic acids" OR "2-Butoxyethyl 2,4-dichlorophenoxyacetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-butoxyethyl ester"
	"Acetic acid, (2,4-dichlorophenoxy)-, butoxyethyl ester" OR "Aqua-Kleen" OR "BEE 2,4-D" OR "Bladex-B" OR "Brush killer 64" OR "Butoxy-D 3" OR "Butoxyethyl 2,4-dichlorophenoxyacetate" OR "Butoxyethyl ester of 2,4-dichlorophenoxy acetic acid" OR "Esteron 99 Concentrate" OR "Lo-Estasol" OR "Planotox" OR "Silvaprop 1" OR "Weed-Rhap LV-4D" OR "Weedone 100 Emulsifiable" OR "Weedone 638"
	"Weedone LV 4" OR "Weedone LV-6" OR "Weedone LV4" OR "2-Ethylhexyl (2,4-dichlorophenoxy)acetate" OR "2-Ethylhexyl 2,4-dichlorophenoxyacetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-ethylhexyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, 1-methylethyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropyl ester" OR "Amchem Weed Killer 650"
	"Barber's Weed Killer (Ester Formulation)" OR "Bridgeport Spot Weed Killer" OR "Crop Rider 3-34D-2" OR "Crop Rider 3.34D" OR "Esteron 44" OR "Isopropyl (2,4-dichlorophenoxy)acetate" OR "Isopropyl 2,4-dichlorophenoxyacetate" OR "Niagara Estasol" OR "Swift's Gold Bear 44 Ester" OR "Weedone 128" OR 5742-19-8[rn] OR 2008-39-1[rn] OR 5742-17-6[rn] OR 18584-79-7[rn] OR 1929-73-3[rn] OR 1928-43-4[rn] OR 94-11-1[rn]

Table B-2. Database Query Strings

Database search date	Query string
Toxcenter	
01/2018	FILE 'TOXCENTER' ENTERED AT 10:27:31 ON 29 JAN 2018 CHARGED TO COST=EH011.05.LB.02.05 L1 14208 SEA FILE=TOXCENTER 94-75-7 OR 14214-89-2 OR 2307-55-3 OR 2702-72-9 OR 3766-27-6 L2 12917 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 12905 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 630 SEA FILE=TOXCENTER L3 AND ED>=20150201 L5 759 SEA FILE=TOXCENTER 5742-19-8 OR 2008-39-1 OR 5742-17-6 OR 18584-79-7 OR 1929-73-3 OR 1928-43-4 OR 94-11-1 L6 674 SEA FILE=TOXCENTER L5 NOT PATENT/DT L7 674 SEA FILE=TOXCENTER L6 NOT TSCATS/FS L8 431 SEA FILE=TOXCENTER L7 NOT L1 ACT TOXQUERY/Q --------- L9 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L10 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L11 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L12 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L13 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L14 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L15 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L16 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L17 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L18 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L19 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L20 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L21 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L22 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L23 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L24 QUE (ENDOCRIN? AND DISRUPT?) L25 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L26 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)

Table B-2. Database Query Strings

Database search date	Query string
	L27 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L28 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L29 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L30 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L31 QUE (NEPHROTOX? OR HEPATOTOX?) L32 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L33 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L34 QUE 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 OR L33 L35 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?) L36 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L37 QUE L34 OR L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 --------- L40 355 SEA FILE=TOXCENTER L4 AND L39 L41 324 SEA FILE=TOXCENTER L7 AND L39 L42 186 SEA FILE=TOXCENTER L41 NOT L1 L43 321 SEA FILE=TOXCENTER L41 NOT L40 D SCAN L40 D SCAN L43

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
01/2018	Compounds searched: 94-75-7; 14214-89-2; 2307-55-3; 2702-72-9; 3766-27-6; 5742-19-8; 2008-39-1; 5742-17-6; 18584-79-7; 1929-73-3; 1928-43-4; 94-11-1
NTP	
01/2018	Limited to dates 2014-1/2018 or not dated and Reports & Publications only. Terms searched: "94-75-7" OR "14214-89-2" OR "2307-55-3" OR "2702-72-9" OR "3766-27-6" "5742-19-8" OR "2008-39-1" OR "5742-17-6" OR "18584-79-7" OR "1929-73-3" OR "1928-43-4" OR "94-11-1"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"(2,4-Dichlorophenoxy)acetic acid" OR "(2,4-dichlorophenoxy)-Acetic acid " OR "(2,4-Dichlorophenyloxy)acetic acid" OR "2-(2,4-Dichlorophenoxy)acetic acid" OR "2-(2,4-dichlorophenoxy)-Acetic acid" OR "2,4-D" OR "2,4-Dichlorophenoxyacetic acid" OR "2,4-dichloro-Phenoxyacetic acid" OR "2,4-Dichlorophenoxyethanoic acid" OR "2,4-PA" OR "Acme LV 4" OR "Acme LV 6" OR "Agricorn D" OR "Agrion" OR "Agrotect" OR "Aminopielik 50SL" OR "Aminopielik 720" OR "Ammonium 2,4-dichlorophenoxyacetate" OR "Amoxone" OR "Basalcoat" OR "BH 2,4-D" OR "Brush-rhap" OR "B-Selektonon" OR "Butoxy-D 3: 1 Liquid emulsifiable Brushkiller LV96" OR "Chipco turf herbicide D" OR "Chloroxone" OR "Citrus fix" OR "Crop rider" OR "Croprider" OR "Debroussaillant 600" OR "Ded-Weed LV-69" OR "Deherban" OR "De-Pester Ded-Weed LV-2" OR "Desormone" OR "Dezormon" OR "Dichlordon sodium" OR "Dichlorophenoxyacetic acid" OR "Diclordon" OR "Diconirt" OR "Diconirt D" OR "Dicopur" OR "Dikonirt" OR "Dikonirt D" OR "Dormon" OR "Dormone" OR "Emulsamine" OR "ENT 8,538" OR "Envert DT" OR "Esteron 44 weed killer" OR "Esteron 76 BE" OR "Estone" OR "Fernesta" OR "Fernimine" OR "Fernoxene" OR "Fernoxone" OR "Ferxone" OR "Foredex 75" OR "Green Cross Weed-No-More 80" OR "Herbidal" OR "Hivol-44" OR "HM 2010"
	"Hormit" OR "Huragan" OR "Invesamina 480SL" OR "Ipaner" OR "Isadiamineyeom" OR "Kar D" OR "Lawn-keep" OR "Lithium 2,4-dichlorophenoxyacetate" OR "Macondray" OR "Macrondray" OR "Monosan" OR "Monosan herbi" OR "Mota Maskros" OR "Moxone" OR "Netagrone" OR "Netagrone 600" OR "NSC 2925" OR "Pennamine D" OR "Pielik" OR "Pielik E" OR "Planotox" OR "Plantgard" OR "Potassium (2,4-dichlorophenoxy)acetate" OR "Potassium 2,4-dichlorophenoxyacetate" OR "Profiamina" OR "Red Devil Dry Weed Killer" OR "R-H Weed Rhap 20" OR "Scott's 4-XD Weed Control" OR "Silvaprop 1" OR "Sodium (2,4-dichlorophenoxy)acetate" OR "Sodium 2,4-dichlorophenoxyacetate" OR "Sodium diclordon" OR "Solushan" OR "Spray-hormite" OR "Spritz-hormit" OR "Superormone concentre" OR "Taficide" OR "Tiller S" OR "Tornado DF" OR "Tributon" OR "U 46D" OR "U 46DP" OR "U-46-D-Fluid" OR "U-5043" OR "Vergemaster" OR "Verton 2D" OR "Verton 38" OR "Vidon 638" OR "Visko-rhap low drift herbicides" OR "Visko-rhap low volatile 4l" OR "Weed TOX" OR "Weed-Ag-Bar" OR "Weedatul" OR "Weed-B-gon" OR "Weedez Wonder BAR" OR "Weedone" OR "Weed-rhap" OR "Weed-Rhap A-4" OR "Weed-Rhap B-266" OR "Weed-Rhap B-4" OR "Weed-Rhap I-3.34" OR "Weed-Rhap LV-4-0" OR "Weedtrol"
	"Bis(2-hydroxyethyl)ammonium 2,4-dichlorophenoxyacetate" OR "Diethanolamine 2,4-dichlorophenoxyacetate" OR "2,4-Diamin SL" OR "2,4-Dichlorophenoxy)acetic acid compd. with N-methylmethanamine" OR "2,4-Dichlorophenoxy)acetic acid dimethylamine salt" OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with dimethylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with N-methylmethanamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with dimethylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with N-methylmethanamine" OR "Dimethylamine 2,4-dichlorophenoxyacetate" OR "Dimethylamine, (2,4-dichlorophenoxy)acetate" OR "Dimethylammonium 2,4-dichlorophenoxyacetate" OR "Methanamine, N-methyl-, (2,4-dichlorophenoxy)acetate" OR "N-Methylmethanamine (2,4-dichlorophenoxy)acetate" OR "N-Methylmethanamine 2,4-dichlorophenoxyacetate" OR "Alkano amine salt of 2,4-D" OR "Amicide" OR "Amine-2,4-D" OR "Aminol" OR "Aminopielek 720" OR "Aminopielik 600SL" OR "Aminoprelik 39"
	"Amisol" OR "Banvel 3 Liquid Herbicide" OR "Banvel-720" OR "Barber's Weed Killer" OR "Best 4 Servis Brand Lawn Weed Killer" OR "Bladex G" OR "Blitz 64" OR "Chipman Lawn Weedkiller" OR "Co-op Premium Lawn Weed Killer" OR "D 50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	(pesticide)" OR "Ded-Weed Sulv" OR "Desormone" OR "Diamond Shamrock Amine 6D" OR "Dikamin D" OR "DMA 4" OR "DMA 6" OR "DMA-2,4-D" OR "Dma-4" OR "Dow DMA-4" OR "Dow Formula 40" OR "Du Pont Lawn Weed Killer" OR "Du Pont Turf Food With Weed Killer" OR "Du Pont Weed Killer No. 2" OR "Farmco D 50" OR "Farmco D-50" OR "FS Amine 400 Weed Killer" OR "Green Cross Killex Spot Weeder Pressurized Spray" OR "Green Cross Poison Ivy Killer" OR "Herbitex" OR "Hormin" OR "Liquid Clearit Vegetation Killer" OR "Liquid Wonder Weeder" OR "Manco Kill-Weed" OR "Marquette Herbitex Plus" OR "Monosan" OR "Morselect" OR "Norkem 40t" OR "Ortho Super Weed-B-Gon Spray" OR "Phordene" OR "Reed amine 400" OR "Shirweed 500" OR "Spraygraze" OR "Spritz-Hormin" OR "Vigoro Dandelions Killer" OR "Weed-Rhap A-4D" OR "Weedar 64" OR "Weedar 96" OR "Weedkiller D" OR "Wilson's Multi-Weeder" OR "2-Propanamine, (2,4-dichlorophenoxy)acetate"
	"Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2-propanamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with isopropylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropylamine salt" OR "Isopropylamine 2,4-dichlorophenoxyacetate" OR "2-Propanol, 1,1',1"-nitrilotri-, (2,4-dichlorophenoxy)acetate (salt)" OR "2-Propanol, 1,1',1"-nitrilotris-, (2,4-dichlorophenoxy)acetate (salt)" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1"-nitrilotri-2-propanol" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1"-nitrilotris(2-propanol)" OR "Triisopropanolamine 2,4-dichlorophenoxyacetate" OR "2,4-DBE" OR "2,4-DBEE" OR "2,4-Dichlorophenoxyacetic acids" OR "2-Butoxyethyl 2,4-dichlorophenoxyacetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-butoxyethyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, butoxyethyl ester" OR "Aqua-Kleen" OR "BEE 2,4-D" OR "Bladex-B" OR "Brush killer 64" OR "Butoxy-D 3" OR "Butoxyethyl 2,4-dichlorophenoxyacetate" OR "Butoxyethyl ester of 2,4-dichlorophenoxy acetic acid" OR "Esteron 99 Concentrate" OR "Lo-Estasol" OR "Planotox" OR "Silvaprop 1" OR "Weed-Rhap LV-4D" OR "Weedone 100 Emulsifiable" OR "Weedone 638"
	"Weedone LV 4" OR "Weedone LV-6" OR "Weedone LV4" OR "2-Ethylhexyl (2,4-dichlorophenoxy)acetate" OR "2-Ethylhexyl 2,4-dichlorophenoxyacetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-ethylhexyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, 1-methylethyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropyl ester" OR "Amchem Weed Killer 650" OR "Barber's Weed Killer (Ester Formulation)" OR "Bridgeport Spot Weed Killer" OR "Crop Rider 3-34D-2" OR "Crop Rider 3.34D" OR "Esteron 44" OR "Isopropyl (2,4-dichlorophenoxy)acetate" OR "Isopropyl 2,4-dichlorophenoxyacetate" OR "Niagara Estasol" OR "Swift's Gold Bear 44 Ester" OR "Weedone 128" OR "Acetic acid, (2,4-dichlorophenoxy)-, diethanolamine salt" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2,2'-iminobis(ethanol)"
NPIRS	
01/2018	Limited 2015-present. CASRNs searched: 94-75-7 OR 14214-89-2 OR 2307-55-3 OR 2702-72-9 OR 3766-27-6
Regulations.gov	
01/2018	CASRNs searched: 94-75-7; 14214-89-2; 2307-55-3; 2702-72-9; 3766-27-6; 5742-19-8; 2008-39-1; 5742-17-6; 18584-79-7; 1929-73-3; 1928-43-4; 94-11-1

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
05/2019	Limited to Active projects. Terms searched: "94-75-7" OR "14214-89-2" OR "2307-55-3" OR "2702-72-9" OR "3766-27-6" OR "(2,4-Dichlorophenoxy)acetic acid" OR "(2,4-dichlorophenoxy)-Acetic acid " OR "(2,4-Dichlorophenyloxy)acetic acid" OR "2-(2,4-Dichlorophenoxy)acetic acid" OR "2-(2,4-dichlorophenoxy)-Acetic acid" OR "2,4-Dichlorophenoxyacetic acid" OR "2,4-dichloro-Phenoxyacetic acid" OR "2,4-Dichlorophenoxyethanoic acid" OR "2,4-PA" OR "Ammonium 2,4-dichlorophenoxyacetate" OR "Dichlorophenoxyacetic acid" OR "Lithium 2,4-dichlorophenoxyacetate" OR "Potassium (2,4-dichlorophenoxy)acetate" OR "Potassium 2,4-dichlorophenoxyacetate" OR "Sodium (2,4-dichlorophenoxy)acetate" OR "Sodium 2,4-dichlorophenoxyacetate" "5742-19-8" OR "2008-39-1" OR "5742-17-6" OR "18584-79-7" OR "1929-73-3" OR "1928-43-4" OR "94-11-1" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2,2'-iminobis(ethanol) (1:1)" OR "Acetic acid, (2,4-dichlorophenoxy)-, diethanolamine salt" OR "Bis(2-hydroxyethyl)ammonium 2,4-dichlorophenoxyacetate" OR "Diethanolamine 2,4-dichlorophenoxyacetate" OR "2,4-Dichlorophenoxy)acetic acid compd. with N-methylmethanamine" OR "2,4-Dichlorophenoxy)acetic acid dimethylamine salt" OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with dimethylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, cmpd with N-methylmethanamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with dimethylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with N-methylmethanamine" OR "Dimethylamine 2,4-dichlorophenoxyacetate" OR "Dimethylamine, (2,4-dichlorophenoxy)acetate" OR "Dimethylammonium 2,4-dichlorophenoxyacetate" OR "Methanamine, N-methyl-, (2,4-dichlorophenoxy)acetate" OR "N-Methylmethanamine (2,4-dichlorophenoxy)acetate" OR "N-Methylmethanamine 2,4-dichlorophenoxyacetate" OR "2-Propanamine, (2,4-dichlorophenoxy)acetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 2-propanamine" "Acetic acid, (2,4-dichlorophenoxy)-, compd. with isopropylamine" OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropylamine salt" OR "Isopropylamine 2,4-dichlorophenoxyacetate" OR "2-Propanol, 1,1',1''-nitrilotri-, (2,4-dichlorophenoxy)acetate (salt)" OR "2-Propanol, 1,1',1''-nitrilotris-, (2,4-dichlorophenoxy)acetate (salt)" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1''-nitrilotri-2-propanol" OR "Acetic acid, (2,4-dichlorophenoxy)-, compd. with 1,1',1''-nitrilotris(2-propanol)" OR "Triisopropanolamine 2,4-dichlorophenoxyacetate" OR "2,4-DBE" OR "2,4-DBEE" OR "2,4-Dichlorophenoxyacetic acids" OR "2-Butoxyethyl 2,4-dichlorophenoxyacetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-butoxyethyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, butoxyethyl ester" OR "Butoxyethyl 2,4-dichlorophenoxyacetate" OR "Butoxyethyl ester of 2,4-dichlorophenoxy acetic acid" OR "2-Ethylhexyl (2,4-dichlorophenoxy)acetate" OR "2-Ethylhexyl 2,4-dichlorophenoxyacetate" OR "Acetic acid, (2,4-dichlorophenoxy)-, 2-ethylhexyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, 1-methylethyl ester" OR "Acetic acid, (2,4-dichlorophenoxy)-, isopropyl ester" OR "Isopropyl (2,4-dichlorophenoxy)acetate" OR "Isopropyl 2,4-dichlorophenoxyacetate"
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 2018 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 794
- Number of records identified from other strategies: 36
- Total number of records to undergo literature screening: 830

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 2,4-D:

- 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.

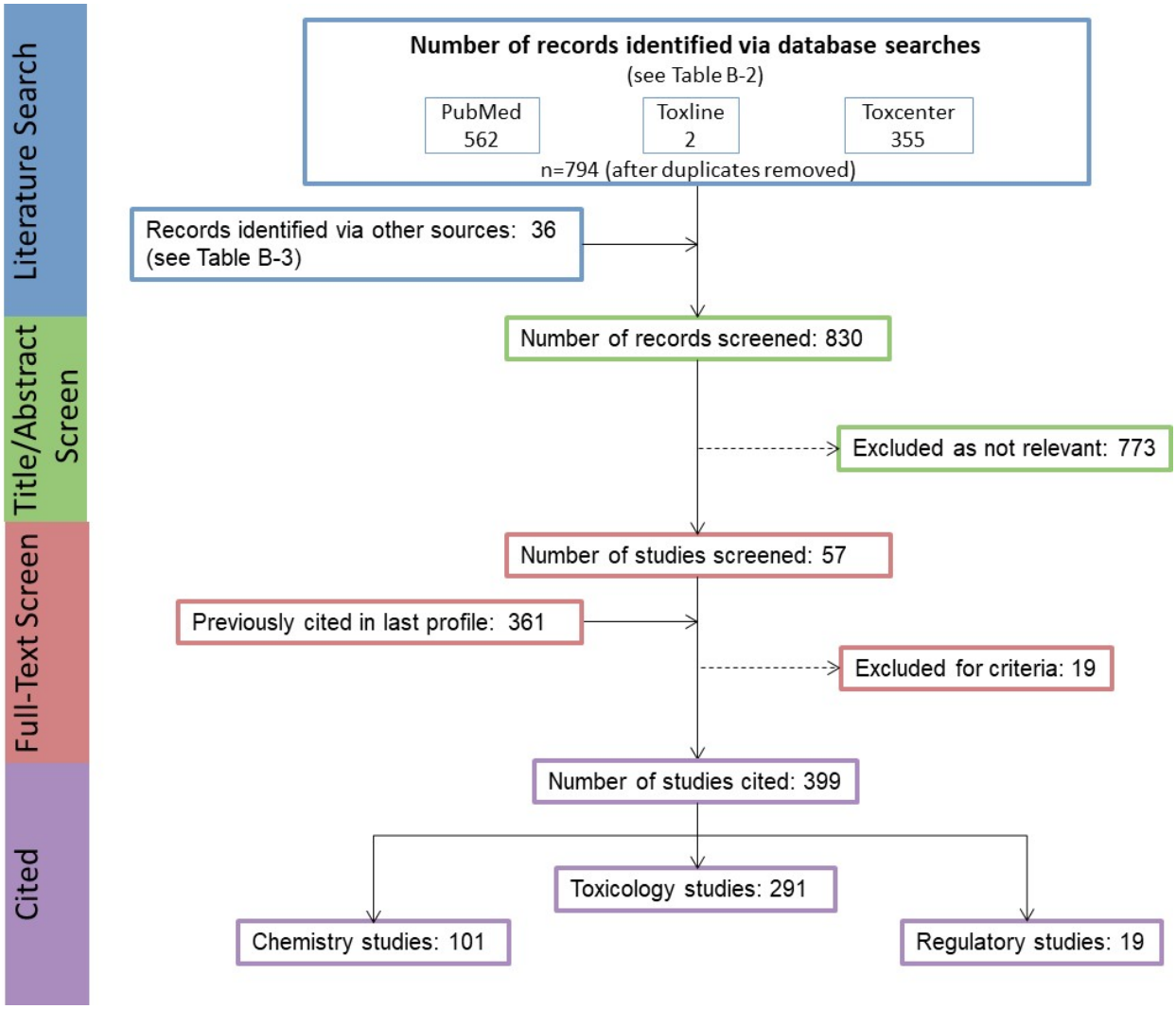
- Number of titles and abstracts screened: 830
- Number of studies considered relevant and moved to the next step: 57

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: 57
- Number of studies cited in the pre-public draft of the toxicological profile: 361
- Total number of studies cited in the profile: 399

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

Figure B-1. January 2018 Literature Search Results and Screen for 2,4-D



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

APPENDIX C

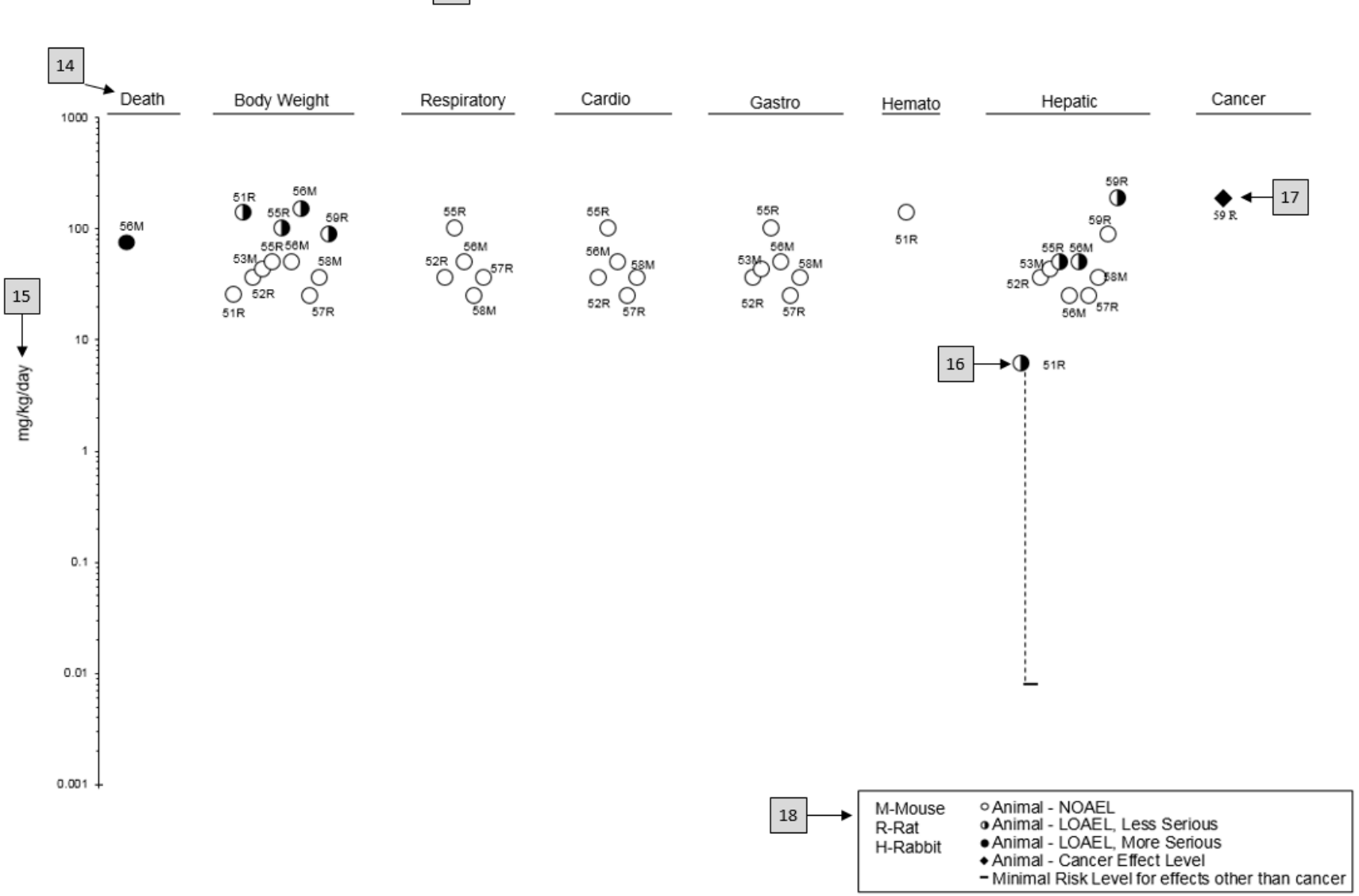
Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
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									
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.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

The following additional materials are available online:

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

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AHS	Agricultural Health Study
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