APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 8 ppm
Critical Effect: Altered auditory tone discrimination and neurobehavioral effects
Reference: Dick et al. 1989
Point of Departure: Minimal LOAEL of 237 ppm
Uncertainty Factor: 30
LSE Graph Key: 1
Species: Human

MRL Summary: The acute-duration inhalation MRL of 8 ppm is based on a minimal LOAEL of 237 ppm for neurobehavioral effects (altered auditory tone discrimination and neurobehavioral effects) in humans exposed for 4 hours (Dick et al. 1989). An uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability) was applied.

Selection of the Critical Effect: Numerous studies have evaluated the neurological effects of acetone. Neurological effects in humans exposed to acetone range from dizziness and headaches (Pomerantz 1950; Raleigh and McGee 1972) to dulling of reflexes (Chen et al. 2002; Haggard et al. 1944) and unconsciousness (Ross 1973). Narcotic effects were found in animals exposed to high doses of acetone (NTP 1988; Specht et al. 1939). These effects are found after both inhalation and oral exposures of varying durations. Table A-1 summarizes relevant NOAEL and LOAEL values following acute inhalation exposures to acetone.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Duration Inhalation Exposure to Acetone

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Human	4 hours	None	237	Altered auditory tone discrimination; increases in anger and hostility	Dick et al. 1989
Human	4.5 hours	247	None	Tests of reaction time and vigilance	Muttray et al. 2005
Human	Two 3-hour sessions with 45-minute interval break	100	250	Self-reports of weakness, tension, lack of energy	Matsushita et al. 1969a
Human	6 hours/day 6 days	None	250	Decreased reaction time; self-reports of weakness, tension, lack of energy	Matsushita et al. 1969b

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Duration Inhalation Exposure to Acetone

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory irritation					
Human	Two 3-hour sessions with 45-minute interval break	None	100	Self-report of irritation of the mucous membrane (nose, throat and trachea)	Matsushita et al. 1969a
Human	6 hours/day 6 days	250	500	Self-report of irritation of the mucous membrane (nose, throat, and trachea)	Matsushita et al. 1969b
Human	3–5 minutes	200	500	Irritation in the majority of subjects (n≈10)	Nelson et al. 1943

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

Neurobehavioral effects were observed in humans exposed to acetone at 237 ppm for 4 hours (Dick et al. 1989). Similar effects have also been observed in humans exposed to 250 ppm acetone for 6 hours or repeatedly for 6 hours/day for 6 days (Matsushita et al. 1969a, 1969b). Effects included lack of energy, general weakness, delayed visual reaction time, and headache. Although irritation of the nose, throat, and trachea was reported in one of five subjects exposed to 100 ppm for two 3-hour exposures (with 45-minute interval break) (Matsushita et al. 1969a), other studies in humans reported respiratory irritation only at higher levels (>250 ppm) for longer durations (Matsushita et al. 1969b; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1973). Furthermore, the reporting of these irritating effects was subjective, and only five volunteers were exposed to 100 ppm (Matsushita et al. 1969a). Therefore, neurological effects were preferentially selected as the critical effect.

Selection of the Principal Study: Matsushita et al. (1969a) reported a NOAEL of 100 ppm and in a subsequent study, Matsushita et al. (1969b) observed neurological effects including lack of energy, weakness, headache, and delayed reaction times after exposure in volunteers to 250 ppm of acetone for 6 hours/day for 6 days. The effects observed in Dick et al. (1989) occurred at a slightly lower concentration of acetone (237 ppm) with a shorter exposure duration of 4 hours. Another study by Muttray et al. (2005) examined the neurological effects of acetone exposures in male volunteers at 247 ppm for 4.5 hours. However, this study involved co-exposure to toluene at 25 ppm. Due to study quality (i.e., small sample size) of Matsushita et al. (1969a) and given the other relevant acute inhalation studies under consideration, Dick et al. (1989) was selected as the key study for its sensitive endpoint (i.e., minimal LOAEL).

Summary of the Principal Study: Dick RB, Setzer JV, Taylor BJ, et al. 1989. Neurobehavioural effects of short duration exposures to acetone and methyl ethyl ketone. Occup Environ Med 46(2):111-121.

Dick et al. (1989) exposed 11 male and 11 female volunteers to a concentration of 237 ppm of acetone (note: the target concentration for participants was 250 ppm acetone, but monitoring of acetone concentrations during the 4-hour exposures indicated a mean concentration of 237 ppm). Additional participants were exposed to either methyl ethyl ketone (MEK) at a target concentration of 200 ppm, a combination of acetone at 125 ppm and MEK at 100 ppm, or ethanol solution. Two control groups were also examined. Participants were aged 18–32 years old and did not have pre-existing medical conditions or substance use disorders. Neurobehavioral testing occurred during six test sessions: one session on the

day before the exposures occurred, four sessions on the day of exposure, and one final session on the day after exposure. Psychomotor, sensorimotor, and psychological tests were administered to participants to assess a variety of neurobehavioral tasks.

Participants exposed to acetone at a mean concentration of 237 ppm showed significant differences on two neurobehavioral tasks as compared to controls. Acetone-exposed participants showed significant increases in response time ($p < 0.05$) and significantly greater false alarm percentages ($p < 0.005$) on the auditory tone discrimination task compared to controls. The changes in performance on this task were persistent and mirrored the measured blood concentrations of acetone, indicating that tolerance to acetone did not occur. In addition, significant increases in measures of anger and hostility were observed in males, but not females, exposed to acetone ($p < 0.001$). However, the study authors noted that this finding may be due to chance, given the small sample size and absence of any other significant changes in tests of mood.

Selection of the Point of Departure for the MRL: The MRL was derived from the minimal LOAEL of 237 ppm for neurological effects (auditory tone discrimination task and neurobehavioral effects) in humans exposed to acetone for 4 hours (Dick et al. 1989). Benchmark dose (BMD) modeling could not be performed as only one dose of exposure to acetone alone was examined.

Adjustment for Intermittent Exposure: Because acetone is evenly distributed in blood after absorption, an adjustment for intermittent to continuous exposure was deemed not necessary. Henry's law indicates that acetone has a high blood to air partition coefficient and will therefore dissolve in blood upon pulmonary gas exchange.

Adjustments for Animal to Human Exposure: Not applicable.

Uncertainty Factor (UF): The LOAEL of 237 was divided by a total uncertainty factor of 30.

- 3 for use of a minimal LOAEL
- 10 for human variability

MRL = LOAEL ÷ UF = 237 ppm ÷ 30 = 8 ppm

Other Additional Studies or Pertinent Information that Lend Support: A second minimal LOAEL of 250 ppm for neurobehavioral effects (Matsushita et al. 1969b) was considered for derivation of an acute inhalation MRL. Using an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability), the resulting MRL would be 8 ppm, which is equivalent to the proposed MRL.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL due to extremely high exposure levels and limitations in study design. Table A-2 indicates the breadth of the data available.

Table A-2. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Inhalation Exposure to Acetone

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Human	1, 3, or 7.5 hours/day, 4 days/week, 6 weeks	1,000	1,250	Significantly increased amplitude of the visual evoked response	Stewart et al. 1975
Rat (Sprague-Dawley)	3 hours/day, 5 days/week, 8 weeks	None	19,000	Significant decreases in brain weight	Bruckner and Peterson 1981b
Rat (Crl:CD BR)	6 hours/day, 5 days/week, 13 weeks	4,000	None	Schedule-controlled operant conditioning	Christoph et al. 2003

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

Rationale for Not Deriving an MRL: Bruckner and Peterson (1981b) only examined high-dose acetone exposure (19,000 ppm). This exposure level resulted in a serious LOAEL for significant decreases in brain weights of rats; therefore, it is not appropriate for derivation of an MRL. Christoph et al. (2003) observed that exposure of male rats to acetone vapor concentrations as high as 4,000 ppm for 6 hours/day, 5 days/week for 13 weeks did not cause lasting effects on schedule-controlled operant performance. The study authors noted that their study design was not intended to investigate the operant processes that have been associated with occupational exposures to acetone in humans (e.g., decreased digit-span retention); conclusions of the study only "serve to increase confidence that prolonged exposures within specified limits are unlikely to have enduring effects on the expression of previously well-learned behaviors" (p. 797). Therefore, other unmeasured neurological effects may have occurred at the concentrations examined and the study is not appropriate for derivation of the MRL. Stewart et al. (1975) examined adults exposed to varying durations of acetone at concentrations of 0, 200, 1,000, and 1,250 ppm. No significant neurological effects were observed, apart from increases in visual evoked response in two of four males exposed to 1,250 ppm. However, multiple studies of acute exposure suggest that acetone causes neurological effects in humans at levels around 250 ppm (Dick et al. 1989; Matsushita et al. 1969a, 1969b). Additionally, the Stewart et al. (1975) study only examined a maximum of four participants per dosage and contains poor reporting of methodology and results; it was not considered to be of sufficient quality for derivation of an MRL.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration inhalation MRL was not derived for acetone because a suitable NOAEL or LOAEL for a sensitive endpoint was not sufficiently characterized. The only studies located were three epidemiological studies. Ott et al. (1983a, 1983c) observed no hematological or hepatic effects in workers exposed 5 days/week, 8 hours/day to up to 1,070 ppm for months to years. However, the study did not monitor all endpoints that are known to be sensitive endpoints of acetone exposure, such as neurological effects; other endpoints may have been affected at this exposure level. Additionally, this study has significant limitations: there was no true reference group for the acetone-exposed workers and high potential for misclassification of exposure. Two occupational studies found evidence of neurological and behavioral effects (lack of energy, general weakness, delayed visual reaction time, and headache) associated with exposures to acetone (Mitran et al. 1997; Satoh et al. 1996). Mitran et al. (1997) examined 71 workers at a coin printing factory who were exposed to TWA concentrations of acetone ranging from 416 to 980 ppm for a mean duration of 14 years. Acetone-exposed workers showed significant decreases in measures of attention and delays in tests of nerve conduction velocity and visual reaction time relative to controls. In addition to neurological effects, the workers self-reported a higher prevalence of respiratory irritation, eye irritation, and gastrointestinal symptoms relative to matched controls. Satoh et al. (1996) reported symptoms of heavy, vague, or faint feelings in the head, along with impaired neurobehavioral responses, in a group of 110 male workers at an acetate fiber manufacturing plant where acetone was used for production. Controls consisted of 67 unexposed workers at the same facility. Acetone levels at the end of the work shift measured 5–1,212 ppm in the breathing zone (mean of 361.4 ppm). It is difficult to establish a NOAEL and LOAEL for effects observed in the occupational studies by Mitran et al. (1997) and Satoh et al. (1996), as the occupational exposures observed varied widely in concentration and duration. Therefore, these studies were deemed inappropriate for derivation of an MRL for chronic inhalation exposures to acetone.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: An acute-duration oral MRL was not derived for acetone because a suitable NOAEL or LOAEL for a sensitive endpoint was not sufficiently characterized. Brown and Hewitt (1984) found a renal LOAEL of 871 mg/kg/day in rats; however, this study was a one-time gavage exposure and is therefore not considered to be applicable to human exposure scenarios. Additionally, other studies failed to find renal effects in rats following 2 days of gavage exposure to 1,766 mg/kg/day acetone (Valentovic et al. 1992) or 14 days of drinking water exposure at concentrations of 8,560 mg/kg/day (Dietz et al. 1991; NTP 1991). Mice also tolerated doses up to 12,725 mg/kg/day without renal effect (Dietz et al. 1991; NTP 1991). Similarly, Ross et al. (1995) found increased liver weights in eight rats administered 90 mg/kg/day of acetone in drinking water for 14 days. However, other studies have only observed these effects at higher levels of exposure. Moreover, available evidence from epidemiological and human controlled studies suggests that acetone is not associated with hepatic endpoints in humans.

The other acute studies located showed effects above 2,241 mg/kg/day, which is a serious effect level for neurological and metabolic effects for human exposures (Gitelson et al. 1966). Therefore, these studies cannot be used as they would not be the most sensitive endpoint nor species in the current dataset.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.6 mg/kg/day
Critical Effect: Anemia with decreased reticulocyte count
Reference: Dietz et al. (1991); NTP (1991)
Point of Departure: $BMDL_{1SD}$ of 57.0 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 22
Species: Rat

MRL Summary: The intermediate-duration oral MRL of 0.6 mg/kg/day is based on a $BMDL_{1SD}$ of 57.0 mg/kg/day for anemia with decreased reticulocyte count in rats treated with acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991). An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) was applied.

Selection of the Critical Effect: Table A-3 summarizes relevant NOAEL and LOAEL values following intermediate oral exposures to acetone. The available data indicate that hematological effects are the most sensitive endpoint associated with intermediate duration oral exposure to acetone. Additionally, there is evidence of the hematological effects of acetone from human and animal studies. Hematological effects have been observed in humans exposed by inhalation to acetone (Matsushita et al. 1969a, 1969b), in rats exposed to 200 mg/kg/day in the drinking water for 14 days (Dietz et al. 1991; NTP 1991), and in rats treated by gavage with 2,500 mg/kg/day for 93–95 days (American Biogenics Corp. 1986).

Table A-3. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Oral Exposure to Acetone

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Rat	6 weeks	None	650	Decreased motor nerve conduction velocity	Ladefoged et al. 1989
Hematological effects					
Rat (F344/N)	13 weeks	200	400	Anemia with decreased reticulocyte counts	Dietz et al. 1991; NTP 1991
Rat (Crl:CD BR)	93–95 days, 1 time/day	500	2,500	Increased hemoglobin, hematocrit, mean cell hemoglobin, mean cell volume, decreased platelets	American Biogenics Corp. 1986

Table A-3. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Oral Exposure to Acetone

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Reproductive effects					
Rat (F344/N)	13 weeks	200	3,400	11.7% decreased sperm motility	Dietz et al. 1991; NTP 1991[a]

[a]Dietz et al. (1991) and NTP (1991) refer to the same study.

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

The critical hematological effect observed by Dietz et al. (1991) and NTP (1991) is anemia with decreased reticulocyte count (Table A-3). Reticulocytes are necessary for bone marrow to regenerate in response to anemia. The absence of reticulocytes in an anemic subject indicates that the bone marrow is not regenerating in response to the anemia, a condition known as non-regenerative anemia. Dietz et al. (1991) and NTP (1991) also observed statistically significantly increased relative kidney weight in female rats, along with decreased sperm motility and increased mean corpuscular hemoglobin in male rats. However, each of these results was not consistent as doses increased. Further, Dietz et al. (1991) and NTP (1991) observed kidney nephropathy in male rats exposed to doses as low as 200 mg/kg/day, with increasing incidence and severity as doses increased up to 3,400 mg/kg/day; however, the male control group developed minimal and mild severity kidney nephropathy similar to the 200 mg/kg/day dose group, and no similar kidney nephropathy effects were observed in the female rats. American Biogenics Corp. (1986) also observed severe kidney nephropathy in male rats at doses of 500 and 2,500 mg/kg/day via oral gavage, in addition to an accentuation of hyaline droplet accumulation, with no observed kidney effects in female rats. It is widely known that male rats have a high likelihood of developing chronic progressive kidney nephropathy as a part of their natural aging process, which often confounds intermediate and chronic studies of kidney nephropathy in these animals (Hard and Khan 2004; Hard et al. 2009). The accentuation of hyaline droplet accumulation observed in the American Biogenics Corp. (1986) study is often a biomarker of one mechanism of this kidney nephropathy that is not considered relevant for extrapolation to humans, specifically pointing to α2-μglobulin induced renal pathology (ATSDR 2018). Additionally, chronic progressive nephropathy that only occurs in male rats and not female rats, as was the case in Dietz et al. (1991) and NTP (1991), is generally considered to be age-related, even if the test chemical is shown to potentially exacerbate this age-related effect (ATSDR 2018). ATSDR does not use lesions of chronic progressive nephropathy where there was no concurrent enhancement in females as endpoints in MRL derivation (ATSDR 2018).

Selection of the Principal Study: Hematological effects are considered to be a sensitive endpoint associated with acetone exposure. Of the two intermediate-duration studies identified (American Biogenics Corp. 1986; Dietz et al. 1991; NTP 1991), the study published by Dietz et al. (1991) and NTP (1991) had the lowest NOAEL and LOAEL identified.

Summary of the Principal Study:

Dietz DD, Leininger JR, Rauckman EJ, et al. 1991. Toxicity studies of acetone administered in the drinking water of rodents. Toxicol Sci 17(2):347-360. https://doi.org/10.1093/toxsci/17.2.34.

NTP. 1991. National Toxicology Program - technical report no. 3. Toxicity studies of acetone in F344/N rats and B6C3F, mice (drinking water studies). U.S. Department of Health and Human Services, Public Health Service, National Institute of Health. NIH publication no. 91-3122.

Dietz et al. (1991) and NTP (1991) examined exposures to acetone in the drinking water of F344/N rats and B6C3F1 mice (10 males and 10 females per dose per species). In the 13-week study, rats and female mice were continuously exposed to acetone in drinking water at 0, 2,500, 5,000, 10,000, 20,000 or 50,000 ppm. Concentrations examined in male mice were 0, 1,250, 2,500, 5,000, 10,000 or 20,000 ppm of acetone. The authors calculated TWA doses (mg/kg/day) associated with each concentration.

Clinical examinations of exposed animals occurred twice daily throughout the 13-week exposure period. At the end of the exposure period, animals were sacrificed, and histopathological and hematological examinations were conducted.

No hematological effects or histologically observable lesions in hematopoietic tissues were found in male or female mice (Dietz et al. 1991; NTP 1991). In contrast to the mouse data, Dietz et al. (1991) and NTP (1991) found evidence of macrocytic anemia in male, but not female, rats exposed to acetone in drinking water for 13 weeks. This evidence consisted of significantly ($p<0.05$ or $p<0.01$) decreased hemoglobin concentration, increased mean corpuscular hemoglobin and mean corpuscular volume, decreased erythrocyte counts, decreased reticulocyte counts and platelets, and splenic hemosiderosis. The LOAEL for these effects was 400 mg/kg/day, and the NOAEL was 200 mg/kg/day. The number of affected parameters increased as the dose increased. Table A-4 displays results for the most sensitive hematological effect observed: decreased reticulocyte counts in male rats. The data were amenable to BMD modeling and were fit to the continuous models in EPA's Benchmark Dose Modeling Software (BMDS; version 3.1.2).

Table A-4. Reticulocyte Counts in Male Rats Administered Acetone via Drinking Water for 13 Weeks (Dietz et al. 1991; NTP 1991)

Dose (mg/kg/day)	Reticulocyte count mean (10^6/µL)	Reticulocyte count standard deviation
0	225	34.8
200	195	46.5
400	171[a]	47.1
900	179[b]	47.4
1,700	168[a]	34.8
3,400	152[a]	29.4

[a]$p \leq 0.01$.
[b]$p \leq 0.05$.

Selection of the Point of Departure for the MRL: BMD modeling was conducted to identify a point of departure (POD) using the data from Dietz et al. (1991) and NTP (1991) displayed in Table A-4. The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a benchmark response (BMR) of 10% extra risk and the default settings for the application of restrictions. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest $BMDL_{1SD}$ was selected as the POD when the difference between the BMDLs estimated from these models was >3 fold; otherwise, the $BMDL_{1SD}$ from the model with the lowest

Akaike's Information Criterion (AIC) was chosen. Table A-5 presents only those BMD/BMDL values considered for MRL derivation. The MRL was based on a $BMDL_{1SD}$ of 57.0 mg/kg/day for a decrease in reticulocytes in rats treated with acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991).

Table A-5. Results from BMD Analysis of Decreased Reticulocyte Counts in Sprague-Dawley Rats After Intermediate Oral Exposure via Drinking Water for 13 Weeks (Dietz et al. 1991; NTP 1991)

					Scaled residuals[c]	
Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	P Value[b]	AIC	Dose below BMD	Dose above BMD
Exponential (2-degree)[d]	2,422.23	1,495.34	0.12	621.93	-0.20	1.90
Exponential (3-degree)[d]	2,419.46	1,495.34	0.12	621.93	-0.20	1.90
Exponential (5-degree)[d]	281.18	119.84	0.48	619.01	0.16	0.01
Hill[e,f]	**263.80**	**57.02**	**0.60**	**618.41**	**0.11**	**-0.21**

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. The exponential and Hill models provided adequate fit to the data. BMDLs for models providing adequate fit differed by >3-fold; therefore, the model with the lowest $BMDL_{1SD}$ was selected (Hill).

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = dose associated with 1 standard deviation from the mean); DF = degree of freedom

Adjustment for Intermittent Exposure: Because acetone is evenly distributed in blood after absorption, an adjustment for intermittent to continuous exposure was deemed not necessary. Henry's law indicates that acetone has a high blood to air partition coefficient and therefore will dissolve in blood upon pulmonary gas exchange.

Uncertainty Factor (UF): The $BMDL_{1SD}$ of 57.0 mg/kg/day was divided by a total uncertainty factor of 100.

- 10 for interspecies extrapolation
- 10 for human variability

$$MRL = BMDL_{1SD} \div UF = 57.0 \text{ mg/kg/day} \div 100 = 0.6 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Not applicable.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration oral MRL was not derived for acetone because no chronic-duration oral exposure studies were identified.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ACETONE

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 acetone.

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 acetone. 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 acetone 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 acetone 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 acetone released for public comment in 2021; thus, the literature search was restricted to studies published between March 2019 and November 2021. The following main databases were searched in November 2021:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for acetone. 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 acetone 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	
11/2021	("acetone"[MeSH Terms] OR (("2-Propanone"[tw] OR "acetona"[tw] OR "Acetone"[tw] OR "beta-Ketopropane"[tw] OR "Dimethyl ketone"[tw] OR "Dimethylformaldehyde"[tw] OR "Dimethylketal"[tw] OR "Dimethylketone"[tw] OR "Ketone propane"[tw] OR "Ketone, dimethyl"[tw] OR "Methyl ketone"[tw] OR "Propan-2-one"[tw] OR "Propanone"[tw] OR "Pyroacetic acid"[tw] OR "Pyroacetic ether"[tw] OR "β-Ketopropane"[tw]) NOT medline[sb])) AND (2018/01/01:3000[dp] OR 2019/01/01:3000[mhda] OR 2019/01/01:3000[crdat] OR 2019/01/01:3000[edat])
NTRL	
11/2021	"2-Propanone" OR "acetona" OR "Acetone" OR "beta-Ketopropane" OR "Dimethyl ketone" OR "Dimethylformaldehyde" OR "Dimethylketal" OR "Dimethylketone" OR "Ketone propane" OR "Ketone, dimethyl" OR "Methyl ketone" OR "Propan-2-one" OR "Propanone" OR "Pyroacetic acid" OR "Pyroacetic ether" OR "β-Ketopropane"
Toxcenter	
11/2021	FILE 'TOXCENTER' ENTERED AT 16:32:34 ON 18 NOV 2021 CHARGED TO COST=EH038.13.01.LB.04 ACT ACETONE/A --------- L1 (47903)SEA FILE=TOXCENTER 67-64-1 L2 (47712)SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 (28488)SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 (22419)SEA FILE=TOXCENTER L3 AND PY>1991 L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))

Table B-2. Database Query Strings

Database search date	Query string
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 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?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L35 QUE L33 OR L34 L36 (9567)SEA FILE=TOXCENTER L4 AND L35 L37 (2307)SEA FILE=TOXCENTER L36 AND PY>2017 L38 (79)SEA FILE=TOXCENTER L37 AND MEDLINE/FS L39 (2228)SEA FILE=TOXCENTER L37 NOT MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L40 (2232)DUP REM L38 L39 (75 DUPLICATES REMOVED) L41 (79)SEA FILE=TOXCENTER L40 L42 (2153)SEA FILE=TOXCENTER L40 L43 2153 SEA FILE=TOXCENTER (L41 OR L42) NOT MEDLINE/FS --------- D SCAN L43

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2021	Compound searched: 67-64-1
NTP	
11/2021	Limited to 2018-present 67-64-1 "Acetone" "Propanone" "Dimethyl Ketone" "Methyl Ketone" "2-Propanone" "Pyroacetic Acid" "Pyroacetic Ether" "Dimethylformaldehyde" "Beta-ketopropane" "Dimethyl Formaldehyde" "Ketone Propane"
Regulations.gov	
11/2021	Limited to 2018-present in dockets, documents, EPA notices 67-64-1 Acetone "Dimethyl Ketone" "Methyl Ketone" "2-Propanone" "Pyroacetic Acid" "Pyroacetic Ether" "Dimethylformaldehyde" "Beta-ketopropane" "Dimethyl Formaldehyde" "Ketone Propane" "Propanone"
NIH RePORTER	
12/2021	Search Criteria Fiscal Year: Active ProjectsText Search: "2-Propanone" OR "acetona" OR "Acetone" OR "beta-Ketopropane" OR "Dimethyl ketone" OR "Dimethylformaldehyde" OR "Dimethylketal" OR "Dimethylketone" OR "Ketone propane" OR "Ketone, dimethyl" OR "Methyl ketone" OR "Propan-2-one" OR "Propanone" OR "Pyroacetic acid" OR "Pyroacetic ether" OR "β-Ketopropane" (advanced)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 4,590
- Number of records identified from other strategies: 10
- Total number of records to undergo literature screening: 4,600

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

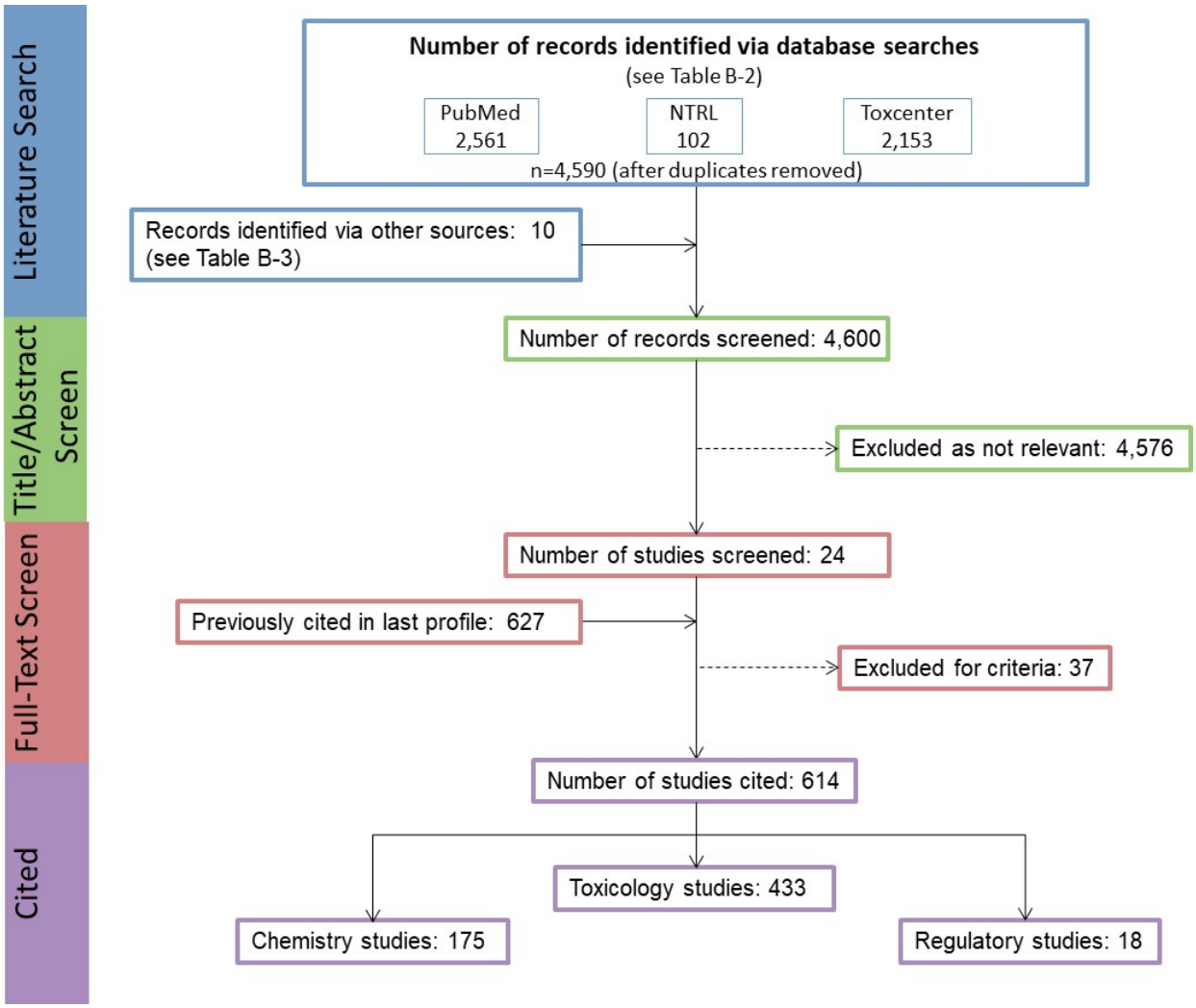
- Number of titles and abstracts screened: 4,600
- Number of studies considered relevant and moved to the next step: 24

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: 24
- Number of studies cited in the pre-public draft of the toxicological profile: 627
- Total number of studies cited in the profile: 614

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

Figure B-1. November 2021 Literature Search Results and Screen for Acetone



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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page 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.

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

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

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

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

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

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

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

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

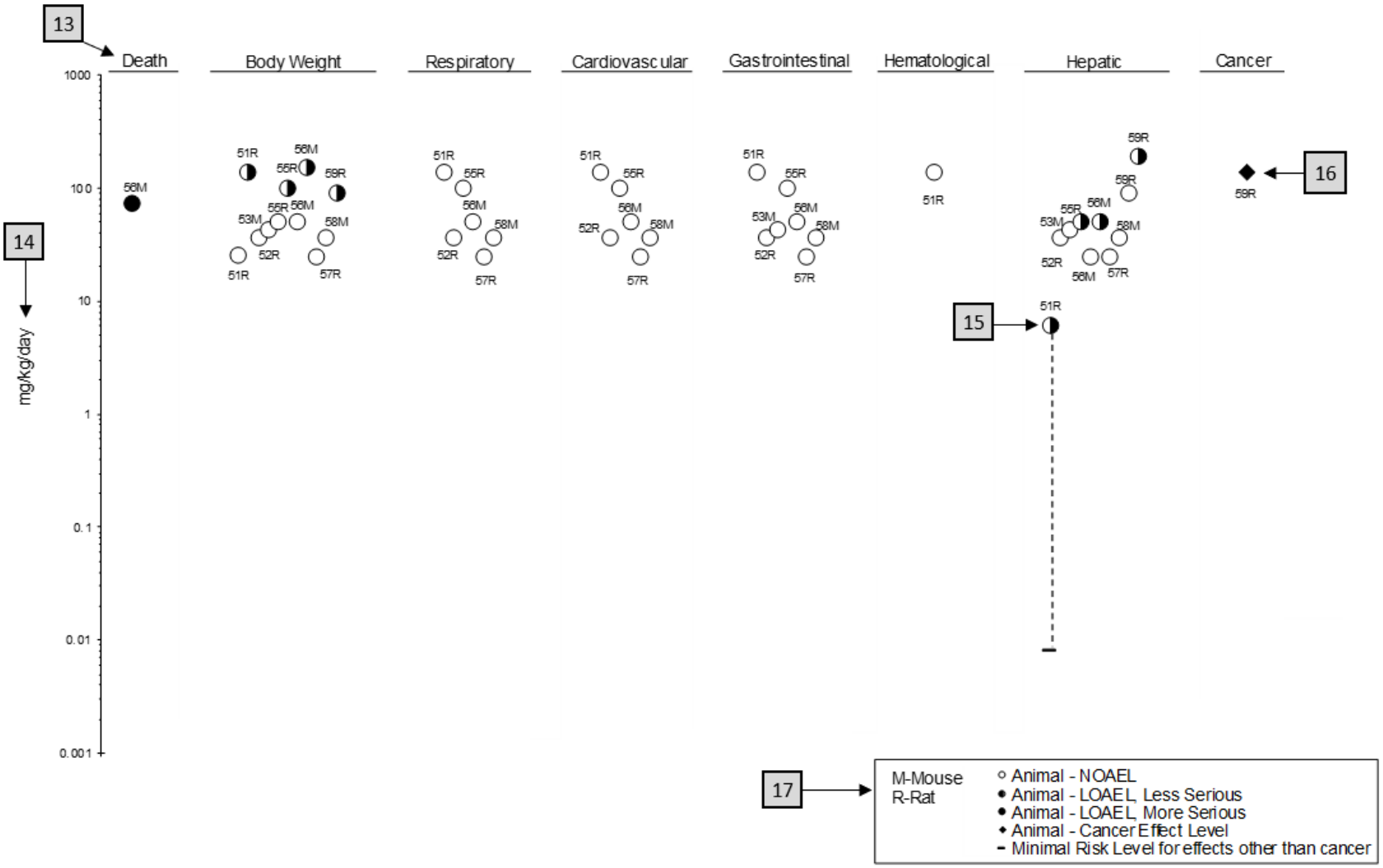
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX 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

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

https://www.atsdr.cdc.gov/emes/health_professionals/index.html for more information on resources for clinicians.

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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