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*:** Hexachlorobutadiene
CAS Numbers: 87-68-3
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: The acute-duration inhalation database was not considered suitable for derivation of an MRL due to the lack of a repeated exposure study which examined the kidney and serious body weight effects at the lowest concentration (10 ppm) tested in a 5-day study.

Five studies have evaluated the acute toxicity of inhaled hexachlorobutadiene in rats or mice and reported respiratory tract, kidney, body weight, eye, adrenal gland, and nervous system effects; the results of these studies are summarized in Table A-1. In addition to these effects, NIOSH (1981) reported 100% mortality in mice exposed to 50 ppm hexachlorobutadiene for 5 days (7 hours/day).

Table A-1. Summary of Effects Resulting from Acute-Duration Inhalation Exposure to Hexachlorobutadiene

Species	Exposure	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects					
Mouse 6 M	15 minutes		155	Decreased respiratory rate	de Ceaurriz et al. 1988
Rat 4 M, 4 F	4 hours/day 2 days		250	Nose irritation and respiratory difficulty	Gage 1970
Renal effects					
Mouse NS M	4 hours		2.75	Histochemical evidence of damaged proximal tubules	de Ceaurriz et al. 1988
Rat 4 M, 4 F	4 hours/day 2 days		250	Degeneration of proximal tubules	Gage 1970
Body weight effects					
Rat 10 M	7 hours/day 5 days		10*	57% decrease body weight gain	NIOSH 1981
Mouse 10 M	7 hours/day 5 days		10*	Weight loss (4.6% loss between days 1 and 2)	NIOSH 1981
Ocular effects					
Rat 4 M, 4 F	4 hours/day 2 days		250	Eye irritation	Gage 1970
Endocrine effects					
Rat 4 M, 4 F	4 hours/day 2 days		250	Degeneration in adrenal cortex	Gage 1970

Table A-1. Summary of Effects Resulting from Acute-Duration Inhalation Exposure to Hexachlorobutadiene

Species	Exposure	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Rat 10 M	7 hours/day 5 days	10	50	Animals appeared subdued and showed little response to audio stimuli	NIOSH 1981
Death					
Mouse 10 M	7 hours/day 5 days		50 (serious LOAEL)	100% mortality	NIOSH 1981

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = males(s); NOAEL = no-observed-adverse-effect level

The lowest LOAEL identified in the available studies is 2.75 ppm for histochemical evidence of proximal tubule damage in mice (de Ceaurriz et al. 1988). This study is not suitable as the basis of an MRL because it involved a single 4-hour exposure to hexachlorobutadiene and there is considerable uncertainty that the value would be protective of continuous exposure for 14 days. The lowest LOAEL in repeated exposure studies is 10 ppm in rats and mice exposed 7 hours/day for 5 days (NIOSH 1981). However, 10 ppm was categorized as a serious LOAEL for large decreases in body weight gain in rats and weight loss in mice. Additionally, this study did not evaluate the kidney, which is the presumed most sensitive target of toxicity. Given the uncertainty in using a single exposure study and the lack of a repeated exposure study that examined the kidney and identified a NOAEL or less serious LOAEL, the acute-inhalation database was not considered suitable for derivation of an MRL.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorobutadiene
CAS Numbers: 87-68-3
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: The intermediate-duration inhalation database was not considered suitable for derivation of an MRL due to the limited number of endpoints examined in the two available studies and the lack of study details reported in the general toxicity study.

Two studies have examined the toxicity of hexachlorobutadiene following intermediate-duration inhalation exposure. In rats exposed to hexachlorobutadiene 6 hours/day, 5 days/week for 15 exposures, Gage (1970) reported decreases in body weight gain at 10 ppm and respiratory difficulty and histological alterations in the renal proximal tubules at 25 ppm. At 100 ppm (animals only exposed 12 times), 50% of the female rats died and anemia and degeneration of the renal cortical tubules were observed. No adverse effects were observed at 5 ppm. The second study is a developmental toxicity study that found decreases in maternal weight gain at ≥5 ppm and decreases in fetal body weight at 15 ppm; no other developmental effects were observed (Saillenfait et al. 1989). The intermediate-duration database was not considered suitable for derivation of an MRL because the two available studies examined a limited number of endpoints; additionally, the general toxicity study (Gage 1970) did not provide information on the magnitude of the body weight changes, description of the renal lesions observed at 25 ppm, incidence data, or statistical analyses.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorobutadiene
CAS Numbers: 87-68-3
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic duration inhalation studies were identified for hexachlorobutadiene.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorobutadiene
CAS Numbers: 87-68-3
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.006 mg/kg/day
Critical Effect: Renal proximal tubular degeneration
Reference: Harleman and Seinen 1979
Point of Departure: LOAEL of 5.9 mg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 2
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.006 mg/kg/day was derived for hexachlorobutadiene based on an increased incidence of renal proximal tubule degeneration in rats exposed to hexachlorobutadiene in the diet for 14 days (Harleman and Seinen 1979). The MRL is based on a LOAEL of 5.9 mg/kg/day and a total uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Three studies have evaluated the acute oral toxicity of hexachlorobutadiene. Two studies involved a single gavage dose of hexachlorobutadiene, which resulted in necrosis in the renal proximal tubules in rats exposed to ≥100 mg/kg (Birner et al. 1995; Jonker et al. 1993a); at 200 mg/kg, there was evidence of impaired renal function (increases in blood urea nitrogen, urine volume, urinary protein, and urinary glucose levels) (Jonker et al. 1983a). The third study was a range-finding study that found renal proximal tubule degeneration in male and female rats exposed to 5.9 or 6.2 mg/kg/day, respectively, hexachlorobutadiene in the diet for 14 days (Harleman and Seinen 1979). Decreases in body weight gain (9.5%) were also observed in the female rats exposed to 6.2 mg/kg/day and the male rats exposed to 19 mg/kg/day (21%). The study did not find any histological alterations in the liver of rats exposed to doses as high as 59 or 62 mg/kg/day.

The available acute oral studies identify the kidney as the most sensitive target of hexachlorobutadiene toxicity. Although the studies examined a limited number of potential endpoints, more extensive intermediate-duration studies confirm that the kidney is the most sensitive target of toxicity (Harleman and Seinen 1979; Kociba et al. 1971; NTP 1991; Schwetz et al. 1977).

Selection of the Principal Study: The Harleman and Seinen (1979) study identified the lowest LOAEL for renal effects and was selected as the principal study for the MRL.

Summary of the Principal Study:

Harleman JH, Seinen W. 1979. Short-term toxicity and reproduction studies in rats with hexachloro-(1,3)-butadiene. Toxicol Appl Pharmacol 47:1-14.

Groups of six male and six female Wistar rats were exposed to 0, 50, 150, or 450 ppm hexachlorobutadiene in the diet for 2 weeks. Doses of 0, 5.9, 19, and 59 mg/kg/day for males and 0, 6.2, 20, and 62 mg/kg/day for females were estimated using reported body weights and EPA's allometric equation to calculate food intake. Parameters used to assess toxicity included body weight, food consumption, liver and kidney weights, and histopathological examination of the liver and kidney.

Significant decreases in body weight gain were observed in males at 19 and 62 mg/kg/day (21 and 31% of controls, respectively) and in females at 6.2, 20, and 62 mg/kg/day (9.5, 26, and 33% of controls, respectively). Decreases in food intake were also observed; however, decreases in food efficiency (growth/food intake) were only observed at the highest dose. Significant increases in relative kidney weight were observed in the males and females at ≥19 and 20 mg/kg/day; no alterations in relative liver weight were observed. Degeneration of the proximal tubular epithelial cells was observed at all hexachlorobutadiene exposure levels; no alterations were observed in the liver. Although incidence data were not provided, the investigators noted that histological changes were observed in the kidneys of all animals exposed to hexachlorobutadiene.

Selection of the Point of Departure: The lowest LOAEL value of 5.9 mg/kg/day identified for renal effects in males was selected as the point of departure for the MRL; the study did not identify a NOAEL value. The lack of incidence data precluded using benchmark dose modeling to calculate a point of departure.

Uncertainty Factor: The LOAEL of 5.9 mg/kg/day is divided by a total uncertainty factor (UF) of 1,000:

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

MRL = LOAEL ÷ UFs
5.9 mg/kg/day ÷ (10 x 10 x 10) = 0.006 mg/kg/day

Other Additional Studies or Pertinent Information: No human studies examining the acute oral toxicity of hexachlorobutadiene were identified. In addition to the previously discussed acute studies, a number of intermediate- and chronic-duration oral studies (Harleman and Seinen 1979; Kociba et al. 1971, 1977; NTP 1991; Schwetz et al. 1977) and acute-duration parenteral studies (Boroushaki 2003; Chiusolo et al. 2008; Cristofori et al. 2013; Kirby and Bach 1995; Maguire et al. 2013; Swain et al. 2011; Zanetti et al. 2010) support the identification of the kidney as the most sensitive target of toxicity for hexachlorobutadiene.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorobutadiene
CAS Numbers: 87-68-3
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.002 mg/kg/day
Critical Effect: Renal proximal tubular regeneration
Reference: NTP 1991
Point of Departure: NOAEL of 0.2 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 13
Species: Mouse

MRL Summary: An intermediate-duration oral MRL of 0.002 mg/kg/day was derived for hexachlorobutadiene based on an increased incidence of renal proximal tubule regeneration in mice exposed to hexachlorobutadiene in the diet for 13 weeks (NTP 1991). The MRL is based on a NOAEL of 0.2 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of hexachlorobutadiene toxicity following intermediate-duration oral exposure. These studies have identified several targets of toxicity including body weight, liver, kidney, nervous system, hematological system, reproductive system, and developing organism. A summary of the lowest LOAEL values for these endpoints is presented in Table A-2. A comparison of the LOAEL values across endpoints supports the identification of the kidney as the most sensitive target of toxicity.

Table A-2. Lowest LOAELs Identified in Intermediate-Duration Oral Studies of Hexachlorobutadiene

Endpoint	Effect	NOAEL[a] (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	9.9% decrease in body weight gain in mice exposed for 13 weeks	1.5	4.9	NTP 1991
Hematological	Increased hemoglobin concentration in rats exposed for 30 days	3	10	Kociba et al. 1971
Hepatic	Increased cytoplasmic basophilia in rats exposed for 13 weeks	6.3	15.6	Harleman and Seinen 1979
Renal	Proximal tubular epithelial regeneration in mice exposed for 13 weeks	0.2	0.5	NTP 1991
Neurological	Lethargy, hunched posture, incoordination in mice exposed to 40 mg/kg/day for 15 days	12	40	NTP 1991
Reproductive	Infertility in female rats exposed for 15 weeks	15	150	Harleman and Seinen 1979

Table A-2. Lowest LOAELs Identified in Intermediate-Duration Oral Studies of Hexachlorobutadiene

Endpoint	Effect	NOAEL[a] (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Developmental	16–19% decrease in pup body weight (rat dams exposed for 18 weeks)		15	Harleman and Seinen 1979

[a]NOAEL identified in the same study as the lowest LOAEL.

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

Selection of the Principal Study: A summary of the NOAEL and LOAEL values for renal effects is presented in Table A-3.

Table A-3. Summary of Renal Effects Observed in Intermediate-Duration Oral Studies of Hexachlorobutadiene

Species	Exposure	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Mouse	13 weeks (F)	0.2 F 1.5 M	0.5 F 4.9 M	Tubular epithelial regeneration	NTP 1991
Rat	147 days (F)	0.2 F 2 M	2 F 20 M	Tubular dilation and hypertrophy with foci of degeneration and regeneration	Schwetz et al. 1977
Rat	13 weeks (GO)	1 F 2.5 M	2.5 F 6.3 M	Enlarged hyperchromatic nuclei in the proximal tubules; decreased urine osmolarity in females	Harleman and Seinen 1979
Rat	4 weeks (F)		2.5 F	Decreased BUN in females	Jonker et al. 1993b
Rat	32 days (GO)	1 F	4 F	Focal tubular vacuolization and increased relative kidney weight	Jonker et al. 1996
Rat	18 weeks (F)		15 F	Proximal tubular degeneration and necrosis	Harleman and Seinen 1979
Rat	30 days (F)	10 F	30 F	Tubular degeneration, necrosis, and regeneration	Kociba et al. 1971
Rat	3 weeks (F)	37 M	190 M	Proximal tubules lined with basophilic epithelium	Nakagawa et al. 1998
Rat	30 weeks (F)	94 M			Nakagawa et al. 1998

BUN = blood urea nitrogen; (F) = feed; F = female(s); (GO) = gavage in oil; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level

In all studies involving exposure of male and female rats or mice, the lower LOAEL values were identified in the females. The lowest LOAEL for renal effects was 0.5 mg/kg/day identified in female mice exposed to hexachlorobutadiene in the diet for 13 weeks (NTP 1991); no effects were observed at 0.2 mg/kg/day. The Schwetz et al. (1977) reproductive/developmental toxicity study also identified a

NOAEL of 0.2 mg/kg/day for kidney effects with a LOAEL of 2 mg/kg/day. The NTP (1991) study was selected as the principal study because it identified the lowest LOAEL for renal effects.

Summary of the Principal Study:

NTP. 1991. National Toxicology Program. Toxicity studies of hexachloro-1,3-butadiene in B6C3F1 mice (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH publication no. 91-3120.

Groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 1, 10, 30, or 100 ppm hexachlorobutadiene in the diet for 13 weeks; the investigators estimated the doses to be 0, 0.1, 0.4, 1.5, 4.9, and 16.8 mg/kg/day in males and 0, 0.2, 0.5, 1.8, 4.5, and 19.2 mg/kg/day in the females. The following parameters were used to assess toxicity: body weight, food intake (measured weekly), organ weight (brain, heart, kidney, liver, spleen, testis), gross necropsy, histopathological examination of major tissues and organs in the controls and high-dose animals and all animals dying early; histopathology of kidneys in all groups; sperm morphology; and vaginal cytology.

One male in the 0.1 mg/kg/day group died early. No overt clinical signs were observed in exposed mice. Decreases in body weight gain were observed in males at 4.9 and 16.8 mg/kg/day (9.9 and 15.8%, respectively) and in females at 19.2 mg/kg/day (15%); no alterations in feed intake were noted. Significant decreases in absolute and relative kidney weights were observed at ≥4.9 mg/kg/day in males; relative kidney weight was also decreased in males at 1.5 mg/kg/day. In females, the only significant alteration in kidney weight was a decrease in absolute weight at 19.2 mg/kg/day. The investigators noted that a decrease in absolute heart weight in males at 16.8 mg/kg/day may be clinically relevant; however, no histological alterations were observed in the heart. Renal tubular epithelial regeneration, prominent in the outer stripe of the outer medullary rays (pars recta) was observed in 0/10, 0/10, 0/10, 0/9, 10/10, and 10/10 males at 0, 0.1, 0.4, 1.5, 4.9, and 16.8 mg/kg/day, respectively, and in 0/10, 1/10, 9/10, 10/10, 10/10, and 10/10 females at 0, 0.2, 0.5, 1.8, 4.5, and 19.2 mg/kg/day, respectively. A significant decrease in sperm motility was observed at 1.5, 4.9, and 16.8 mg/kg/day, but the magnitude of the decrease was not dose-related. No significant alterations in sperm count, incidence of abnormal sperm, estrual cyclicity, or average estrous cycle length were observed.

Selection of the Point of Departure: The NOAEL of 0.2 mg/kg/day identified in female mice was selected as the point of departure for the MRL. The incidence data for renal tubular regeneration was not considered suitable for benchmark dose modeling due to the lack of dose-response data between the extremes in the incidence in the control and lowest dose groups and the incidences in higher dose groups.

Uncertainty Factor: The NOAEL of 0.2 mg/kg/day is divided by a total uncertainty factor (UF) of 100:

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

MRL = LOAEL ÷ UFs
0.2 mg/kg/day ÷ (10 x 10) = 0.002 mg/kg/day

Other Additional Studies or Pertinent Information: No human studies examining the toxicity of hexachlorobutadiene following intermediate-duration oral exposure were identified. The identification of the kidney as the most sensitive target of toxicity is supported by a number of intermediate-duration oral studies and a chronic-duration oral study.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorobutadiene
CAS Numbers: 87-68-3
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: One study has evaluated the chronic oral toxicity of hexachlorobutadiene (Kociba et al. 1977). In this study, an increase in the incidence of tubular epithelial hyperplasia was observed at 20 mg/kg/day. The investigators also noted that there was a possible increase in incidence of hyperplasia at 2 mg/kg/day; however, no incidence data were provided. An increase in the incidence of total number of renal tubular neoplasms were observed at 20 mg/kg/day. The Kociba et al. (1977) study was not considered suitable for derivation of an MRL because incidence data were not provided to allow for an independent assessment of whether there was a significant increase in the incidence of hyperplasia at 2 mg/kg/day.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR HEXACHLOROBUTADIENE

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 hexachlorobutadiene.

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 hexachlorobutadiene. 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 hexachlorobutadiene 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 hexachlorobutadiene 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

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

Other noncancer effects
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

A.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for hexachlorobutadiene released for public comment in 2019; thus, the literature search was restricted to studies published between March 2016 and May 2020. The following main databases were searched in May 2020:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for hexachlorobutadiene. 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 hexachlorobutadiene 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	
05/2020	(87-68-3[rn] OR "1,1,2,3,4,4-Hexachloro-1,3-butadiene"[tw] OR "1,3-Hexachlorobutadiene"[tw] OR "Dolen-pur"[tw] OR "HCBD"[tw] OR "Hexachloro-1,3-butadiene"[tw] OR "Hexachlorobuta-1,3-diene"[tw] OR "Hexachlorobutadiene"[tw] OR "Perchlorobutadiene"[tw] OR "1,3-Butadiene, 1,1,2,3,4,4-hexachloro-"[tw] OR "1,3-Butadiene, hexachloro-"[tw] OR "BUTADIENE, HEXACHLORO-"[tw] OR "D033"[tw] OR "GP-40-66:120"[tw] OR "Perchloro-1,3-butadiene"[tw]) AND (2017/03/01 : 3000[mhda] OR 2017/03/01 : 3000[crdt] OR 2017/03/01 : 3000[edat] OR 2016/03/01 : 3000[dp])
NTRL	
05/2020	"87-68-3" OR "1,1,2,3,4,4-Hexachloro-1,3-butadiene" OR "1,3-Hexachlorobutadiene" OR "Dolen-pur" OR "HCBD" OR "Hexachloro-1,3-butadiene" OR "Hexachlorobuta-1,3-diene" OR "Hexachlorobutadiene" OR "Perchlorobutadiene" OR "1,3-Butadiene, 1,1,2,3,4,4-hexachloro-" OR "1,3-Butadiene, hexachloro-" OR "BUTADIENE, HEXACHLORO-" OR "D033" OR "GP-40-66 120" OR "Perchloro-1,3-butadiene"
Toxcenter	
05/2020	FILE 'TOXCENTER' ENTERED AT 15:05:56 ON 22 MAY 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 2478 SEA FILE=TOXCENTER 87-68-3 L2 2356 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 110 SEA FILE=TOXCENTER L2 AND ED>=20170301 L4 147 SEA FILE=TOXCENTER L2 AND PY>2015 L5 158 SEA FILE=TOXCENTER L3 OR L4 ACT TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR

Table B-2. Database Query Strings

Database search date	Query string
	DIETARY OR DRINKING(W)WATER?)
	L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR
	OVUM?)
	L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR
	TERATOGEN?)
	L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE 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 OR L30
	L32 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?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L36 QUE L34 OR L35

Table B-2. Database Query Strings

Database search date	Query string

	L38 71 SEA FILE=TOXCENTER L5 AND L36
	L39 6 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
	L40 65 SEA FILE=TOXCENTER L38 NOT L39
	L41 65 DUP REM L39 L40 (6 DUPLICATES REMOVED)
	ANSWERS '1-65' FROM FILE TOXCENTER
	L*** DEL 6 S L38 AND MEDLINE/FS
	L*** DEL 6 S L38 AND MEDLINE/FS
	L42 6 SEA FILE=TOXCENTER L41
	L*** DEL 65 S L38 NOT L39
	L*** DEL 65 S L38 NOT L39
	L43 59 SEA FILE=TOXCENTER L41
	L44 59 SEA FILE=TOXCENTER (L42 OR L43) NOT MEDLINE/FS
	D SCAN L44

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
05/2020	Compounds searched: 87-68-3
NTP	
05/2020	87-68-3 "1,1,2,3,4,4-Hexachloro-1,3-butadiene" "1,3-Hexachlorobutadiene" "Dolen-pur" "HCBD" "Hexachloro-1,3-butadiene" "Hexachlorobuta-1,3-diene" "Hexachlorobutadiene" "Perchlorobutadiene" "1,3-Butadiene, 1,1,2,3,4,4-hexachloro-" "1,3-Butadiene, hexachloro-" "BUTADIENE, HEXACHLORO-" "D033" "GP-40-66 120" "Perchloro-1,3-butadiene"
Regulations.gov	
05/2020	Compounds searched: 87-68-3
NIH RePORTER	
08/2020	Text Search: "1,1,2,3,4,4-Hexachloro-1,3-butadiene" OR "1,3-Hexachlorobutadiene" OR "Dolen-pur" OR "HCBD" OR "Hexachloro-1,3-butadiene" OR "Hexachlorobuta-1,3-diene" OR "Hexachlorobutadiene" OR "Perchlorobutadiene" OR "1,3-Butadiene, 1,1,2,3,4,4-hexachloro-" OR "1,3-Butadiene, hexachloro-" OR "BUTADIENE, HEXACHLORO-" OR "D033" OR "GP-40-66:120" OR "Perchloro-1,3-butadiene" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 85
- Number of records identified from other strategies: 55
- Total number of records to undergo literature screening: 140

A.1.2 Literature Screening

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

- 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.

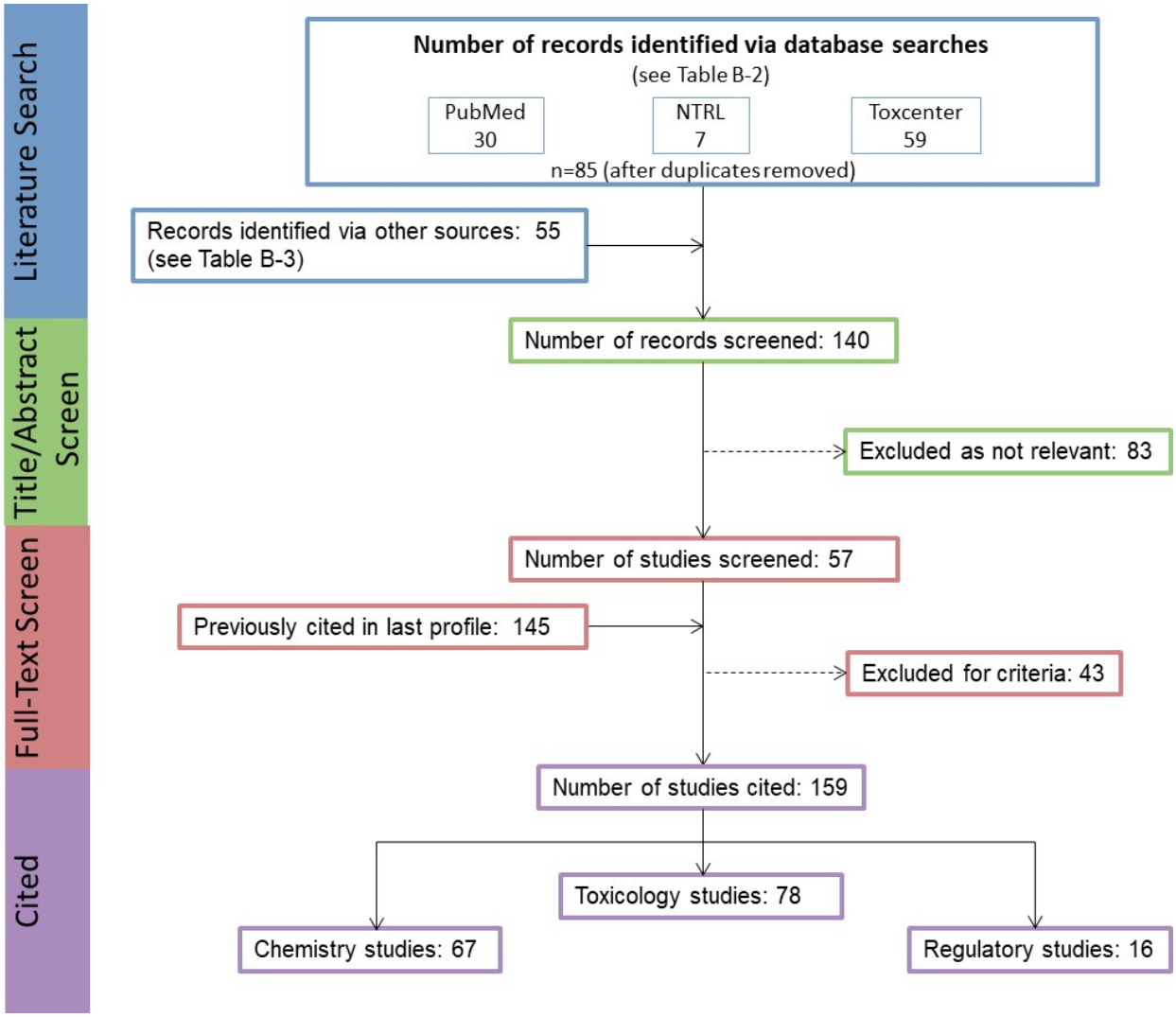
- Number of titles and abstracts screened: 140
- Number of studies considered relevant and moved to the next step: 57

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: 145
- Total number of studies cited in the profile: 159

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

Figure B-1. May 2020 Literature Search Results and Screen for Hexachlorobutadiene



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

APPENDIX C

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

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

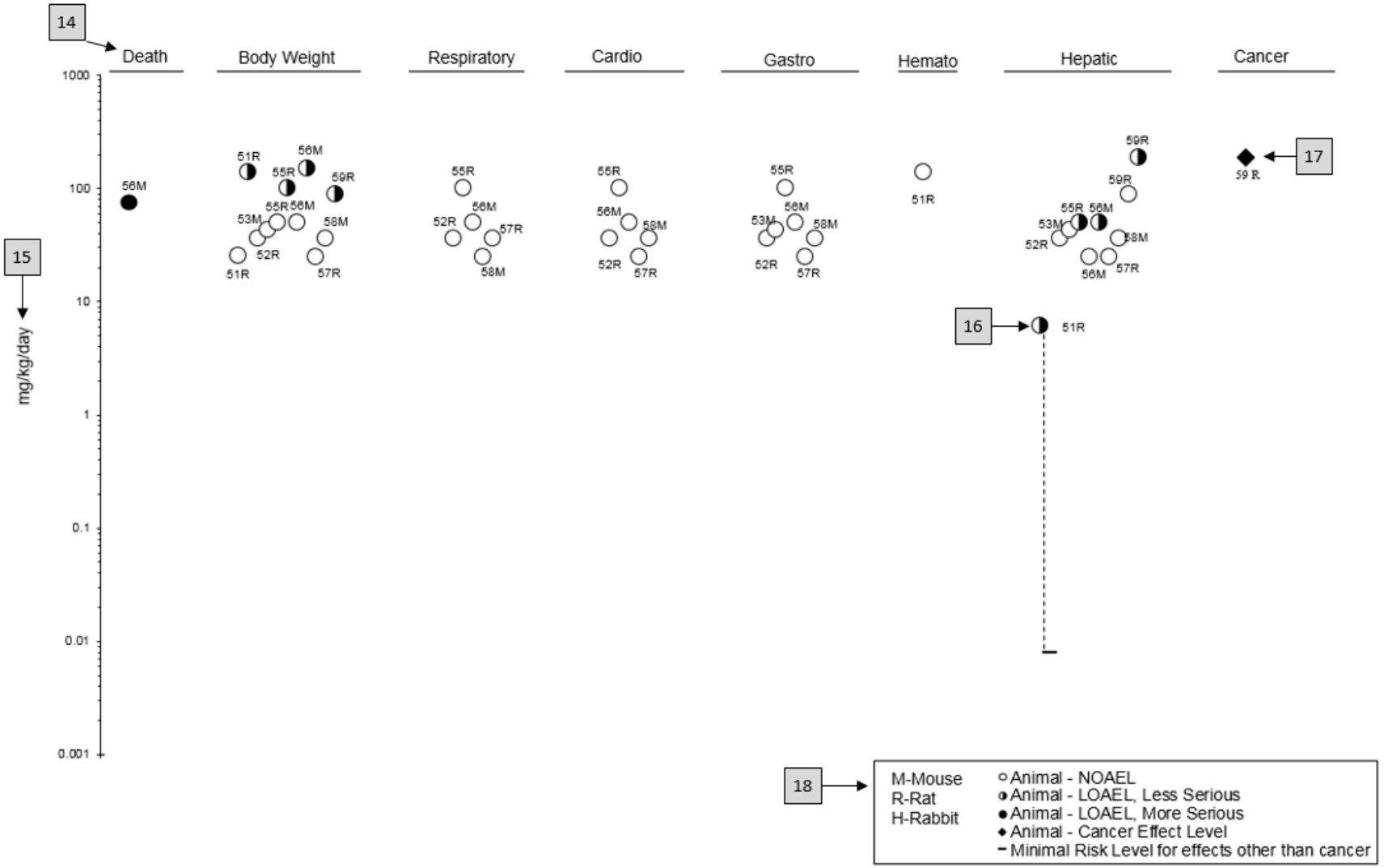
[a]The number corresponds to entries in Figure 2-x.

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

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

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

13 → Chronic (≥365 days)



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PEHSU	Pediatric Environmental Health Specialty Unit
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