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. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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 S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
MRL: 13 ppm (provisional) (34 mg/m^3)
Critical Effect: Increased incidence of DFFC of skull bones
Reference: Scortichini et al. 1986
Point of Departure: NOAEL of 1,504 ppm ($NOAEL_{HEC}$ of 376 ppm)
Uncertainty Factor: 30
LSE Graph Key: 13
Species: Mouse

MRL Summary: A provisional acute-duration MRL of 13 ppm was derived for chloroethane based on a NOAEL of 1,504 ppm for developmental effects (increased incidence of DFFC of skull bones) in mouse fetuses exposed for 6 hours/day on GDs 6–15 (Scortichini et al. 1986). The NOAEL was adjusted for continuous exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 376.0 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Developmental and neurological effects were observed at approximately 5,000 ppm following acute-duration inhalation exposure of chloroethane in animals (Table A-1). Two studies looked at developmental effects of chloroethane. In pregnant mice exposed to chloroethane for 6 hours/day on GDs 6–15, an increase in incidence of DFFC of the skull bones (a developmental delay of ossification of small centers of unossified bone of the skull) was seen in the fetuses at 4,946 ppm (Scortichini et al. 1986). Incidence based on number of fetuses affected was significant for dose-response trend, but not in a pairwise comparison to the control group. Incidence data for number of litters affected were not statistically different from controls (by pairwise or trend tests); however, this effect was considered biologically relevant. The second developmental study reported that mouse fetuses exposed to 15,000 ppm for 6 hours/day on GDs 6–15 appeared normal; however, fetuses were not examined for skeletal or visceral alterations (Dow 1985). This study was not included in Table A-1 because no developmental effects occurred in the only treatment group.

Neurological effects have been reported in humans and several animal species. These effects consisted of a feeling of dizziness and intoxication in humans, hyperactivity in mice and dogs, lethargy in rats, and unsteadiness in guinea pigs; however, the study with the lowest LOAEL for neurological effects (Dow 1985) did not report a NOAEL value. Developmental toxicity (increased incidence of DFFC of the skull in fetuses) was selected as the critical effect because Scortichini et al. (1986) provided the lowest LOAEL with an accompanying NOAEL value.

Table A-1. Selected NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Chloroethane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Developmental effects					
Mouse (CF-1)	10 days 6 hours/day GDs 6–15	1,504	4,946	Increased incidence of delayed fetal foramina closure (DFFC) of the skull bones (developmental delay of ossification of bones of the skull of fetuses)	Scortichini et al. 1986
Neurological effects					
Human	Up to 22 minutes	ND	13,000	LOAEL: subjective feeling of intoxication, increased reaction times	Davidson 1925
Fisher-344 rat	2 weeks 5 days/week 6 hours/day	3,980	9,980	Slight lethargy	Landry et al. 1982
CD-1 mouse	10 days 6 hours/day GDs 6–15	ND	5,000	Increased activity and stereotypic behavior (highly repetitive running patterns) in dams	Dow 1985
Beagle dog	2 weeks 5 days/week 6 hours/day	3,980	9,980	Hyperactivity during exposure in 1/2 dogs	Landry et al. 1982

[a]Selected study/endpoint for derivation of acute-duration inhalation MRL.

LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: Of the two developmental studies, Scortichini et al. (1986) was selected as the principal study because visceral and skeletal examinations were performed. In addition, this study provided a LOAEL with an accompanying NOAEL value.

Summary of the Principal Study:

Scortichini BH, Johnson KA, Momany-Pfruenderd JJ, et al. 1986. Ethyl chloride: Inhalation teratology study in CF-1 mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA section FYI. OTS0001135. FYI-OTS-0794-1135. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0001135.xhtml. April 12, 2023.

Pregnant CF-1 mice (23–26/group) were exposed to 99.9% pure chloroethane at 0, 491, 1,504, or 4,946 ppm 6 hours/day on GDs 6–15. Body weights were recorded on GDs 6, 9, 12, 15, and 18, and food and water intakes were measured. The animals were sacrificed on GD 18 and the following data were recorded: maternal liver weight; number and position of fetuses *in utero*; number of live and dead fetuses; number and position of resorption sites; weight and sex of each fetus; and gross external alterations. Half of each litter was examined for visceral alterations, and the other half was examined for skeletal alterations.

No maternal toxicity (body weight, food and water intake, liver weight) was observed. There were no effects on pregnancy rate, resorption rate, litter size, sex ratio, or fetal body weight. No changes in gross external or visceral alterations were seen in the exposed fetuses compared to controls. An increase in supernumerary ribs was found, although the effect was not indicated as statistically significant. The incidences of fetuses with supernumerary ribs were 2/257, l/299, 6/311, and 2/242 at 0, 491, 1,504, and 4,946 ppm, respectively. The incidences in litters were 2/22, l/25, 5/26, and 4/22 at 0, 491, 1,504, and 4,946 ppm, respectively.

A small increase in the incidence of DFFC of the skull bones (developmental delay of ossification of small centers of unossified bone of the skull) was observed at the high dose. The incidence data based on number of fetuses affected were 1/126, 1/142, 1/147, and 5/116 at 0, 491, 1,504, and 4,946 ppm, respectively. The study authors indicated that the foramina data were statistically significant. ATSDR's analysis of the data determined that there was a significant trend (p=0.0488) for the fetal data, but no significance in a pairwise comparison to the control group for the fetal data. Incidence data for number of litters affected were 1/22, 1/24, 1/25, and 5/22 at 0, 491, 1,504, and 4,946 ppm, respectively. The study authors indicated that the litter data were not significantly different from control. ATSDR's analysis determined that there were no significant differences in the pairwise comparison to control or trend test for the litter data.

Selection of the Point of Departure for the MRL: The NOAEL of 1,504 ppm for developmental effects (increased incidence of DFFC of the skull) in fetuses exposed 6 hours/day on GDs 6–15 (Scortichini et al. 1986) was selected as the point of departure (POD). Benchmark dose (BMD) modeling was not done on litter data due to lack of statistical significance by both pairwise comparison and for trend.

Adjustment for Intermittent Exposure: The intermittent NOAEL of 1,504 ppm was adjusted to a 24-hour continuous exposure using the following equation:

$$NOAEL_{ADJ} = NOAEL \times \frac{6\ hours}{24\ hours} = 1{,}504\ ppm \times \frac{6\ hours}{24\ hours} = 376.0\ ppm$$

Human Equivalent Concentration: The HEC was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of the chloroethane air:blood partition coefficient for humans and mice. The reported blood:gas (air) partition coefficient ($H_{b/g}$) values for chloroethane are 5.1 for mice and 1.9 or 2.69 for humans (Gargas et al. 1989, 2008; Morgan et al. 1970). Since the ratio of mouse to human blood:gas (air) partition coefficient is >1, a default value of 1 was used. The duration-adjusted $LOAEL_{HEC}$ was 1,237 ppm.

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(H_{b/g})_A}{(H_{b/g})_H} = 376.0\ ppm \times 1 = 376.0\ ppm$$

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

$$MRL = NOAEL_{HEC} \div UFs$$
$$376.0\ ppm \div 30 = 12.53\ ppm \approx 13\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No supporting studies or pertinent information were available.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL: 13 ppm (34 mg/m^3) (provisional)
Critical Effect: Increased estrous cycle length in mice
Reference: Bucher et al. 1995
Point of Departure: LOAEL of 15,000 ppm ($LOAEL_{HEC}$ of 3,750 ppm)
Uncertainty Factor: 300
LSE Graph Key: 18
Species: Mouse

MRL Summary: A provisional intermediate-duration inhalation MRL of 13 ppm was derived for chloroethane based on a LOAEL of 15,000 ppm for reproductive effects (increased estrous cycle length) in mice exposed 6 hours/day for 21 days (Bucher et al. 1995). The LOAEL was adjusted to continuous-duration exposure and converted to a human equivalent concentration ($LOAEL_{HEC}$) of 3,750 ppm and divided by a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans after dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: The only adverse effect identified in intermediate-duration inhalation studies is related to the estrous cycle. The average duration of the estrous cycle increased significantly by 7% from 5.15 to 5.52 days in mice exposed to 15,000 ppm (only concentration tested) for 21 days, although no consistent effects on estradiol or progesterone were noted (Bucher et al. 1995). Breslin et al. (1988) also studied the length of the estrous cycle in mice after 14 days of exposure to 14,955 ppm for 6 hours/day. No significant increase in the estrous cycle length was seen during exposure compared to pre-exposure (5.0±0.7 days pre-exposure versus 5.6±0.8 days during exposure). The discrepancy between the two studies regarding increased estrous cycle length may be due to duration of exposure (14 versus 21 days) or number of animals studied. Bucher et al. (1995) studied 30 females/group, whereas Breslin et al. (1988) studied 10 females/group. The larger sample size would lend itself to greater statistical power to distinguish differences. In 13-week inhalation studies, no adverse effects (including histopathology on a complete panel of tissues) were observed in rats or mice exposed up to 19,000 ppm (NTP 1989). No adverse effects were observed in rats or rabbits exposed to 10,000 ppm (only concentration tested) for 6.5 months (Dow 1941).

Selection of the Principal Study: The intermediate-duration inhalation study investigating estrous cycle length was selected as the principal study (Bucher et al. 1995). No other intermediate-duration study reported a toxicologically relevant adverse effect.

Summary of the Principal Study:

Bucher JR, Morgan DL, Adkins B, et al. 1995. Early changes in sex hormones are not evident in mice exposed to the uterine carcinogens chloroethane or bromoethane. Toxicol Appl Pharmacol 130:169-173. http://doi.org/10.1006/taap.1995.1022.

Female B6C3F1 mice (30/group) were exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 21 days. Before the exposures, all the mice were sham-exposed for 21 days, and vaginal cytology studies were completed daily during the sham exposures and during the 21-day exposure period. Body weights

were measured at least weekly. At necropsy, blood was drawn for measurement of serum estradiol and progesterone. The liver and uterus were weighed. The liver, uterus, pituitary gland, adrenal glands, and ovaries were examined microscopically.

No clinical signs of toxicity were observed. Body weights were not different from control (data not shown). In the exposed group, mean estrous cycle length significantly increased from 5.15±0.15 days prior to exposure to 5.52±0.19 days during exposure (a 7% increase). In the control group, mean estrous cycle length was not different between the pre-exposure period and exposure period (5.02±0.2 versus 5.0±0.2, pre-exposure and exposure, respectively). The proportion of time spent in the stages of the cycle during exposure was significantly different compared to pre-exposure in both the exposed and control group. Mice spent shorter time in metestrus and longer time in the other stages. No significant difference in serum estradiol or progesterone were seen at the end of the exposure. No significant differences in weights of liver, uterus, or ovary were seen compared to control (data not shown). No histological changes were observed in the ovaries, pituitary, uterus, or adrenal glands.

Selection of the Point of Departure for the MRL: The LOAEL of 15,000 ppm for reproductive effects (increased duration of estrous cycle) in mice exposed 6 hours/day for 21 days (Bucher et al. 1995) was selected as the POD.

Adjustment for Intermittent Exposure: The intermittent 6 hours/day LOAEL of 15,000 ppm was adjusted to a 24-hour continuous exposure using the following equation:

$$LOAEL_{ADJ} = LOAEL \times \frac{6\ hours}{24\ hours} = 15{,}000\ ppm \times \frac{6\ hours}{24\ hours} = 3{,}750\ ppm$$

Human Equivalent Concentration: The HEC was calculated by multiplying the $LOAEL_{ADJ}$ by the ratio of the chloroethane air:blood partition coefficient for humans and mice. The reported blood:gas (air) partition coefficient ($H_{b/g}$) values for chloroethane are 5.1 for mouse and 1.9 or 2.69 for humans (Gargas et al. 1989, 2008; Morgan et al. 1970). Since the ratio of mouse to human blood:gas (air) partition coefficient is >1, a default value of 1 was used.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times \frac{(H_{b/g})_A}{(H_{b/g})_H} = 3{,}750\ ppm \times 1 = 3{,}750\ ppm$$

Uncertainty Factor: The $LOAEL_{HEC}$ was divided by a total uncertainty factor of 300:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

$$MRL = LOAEL_{HEC} \div UFs$$
$$3{,}750\ ppm \div 300 = 12.5\ ppm \approx 13\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No supporting studies or pertinent information were available.

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: Renal and neurological effects were observed in female mice exposed to 15,000 ppm chloroethane for 100 weeks (only concentration tested) (NTP 1989). However, this study also reported decreased survival in these exposed mice, attributed to carcinomas of the uterus. An MRL for renal and/or neurological effects was not derived since serious health effects were seen at the concentration level studied.

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: The database was not considered adequate for derivation of an acute-duration oral MRL for chloroethane.

Rationale for Not Deriving an MRL: No acute-duration oral MRL was derived due to lack of adequate data regarding the potential effects of chloroethane. No toxicologically relevant effects were seen in rats exposed to chloroethane in drinking water at doses ranging from 297 to 662 mg/kg/day for 7 or 14 days (Dow 1995).

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: The database was not considered adequate for derivation of an intermediate-duration oral MRL for chloroethane.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies were located that met ATSDR quality inclusion criteria; therefore, no MRL could be derived.

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: The database was not considered adequate for derivation of a chronic-duration oral MRL for chloroethane.

Rationale for Not Deriving an MRL: No studies were located that describe the effects of chronic-duration oral exposure to chloroethane in humans or animals.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROETHANE

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 chloroethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were 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 chloroethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of chloroethane 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 chloroethane 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

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

Developmental effects
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

B.1.1 Literature Search

The current literature search was intended to update the 1998 Toxicological Profile for Chloroethane; thus, the literature search was restricted to studies published between January 1996 and May 2022. The following main databases were searched in May 2022:

- 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 chloroethane. 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 chloroethane 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	
05/2022	("Ethyl Chloride"[mh] OR 75-00-3[rn] OR "Chloroethane"[tw] OR "Ethane, chloro-"[tw] OR "Ethyl chloride"[tw] OR "ethylchloride"[tw] OR "Freon 160"[tw] OR "Monochlorethane"[tw] OR "Monochloroethane"[tw] OR "chlorethane"[tw] OR "Aethylis"[tw] OR "Anodynon"[tw] OR "Chlorethan"[tw] OR "Chloryl anesthetic"[tw] OR "Chloryle anesthetic"[tw] OR "Cloretilo"[tw] OR "Dublofix"[tw] OR "Ether chloratus"[tw] OR "Ether chloridum"[tw] OR "Ether hydrochloric"[tw] OR "Ether muriatic"[tw] OR "Hydrochloric ether"[tw] OR "Kelene"[tw] OR "Muriatic ether"[tw] OR "Narcotile"[tw] OR "Chelen"[tw] OR "Chlorene"[tw] OR "Chloridum"[tw] OR "Chloryl"[tw] OR "Chlorethyl"[tw]) AND 1996:3000[dp]
NTRL	
05/2022	"Chloroethane" OR "Ethane, chloro-" OR "Ethyl chloride" OR "ethylchloride" OR "Freon 160" OR "Monochlorethane" OR "Monochloroethane" OR "chlorethane" OR "Aethylis" OR "Anodynon" OR "Chlorethan" OR "Chloryl anesthetic" OR "Chloryle anesthetic" OR "Cloretilo" OR "Dublofix" OR "Ether chloratus" OR "Ether chloridum" OR "Ether hydrochloric" OR "Ether muriatic" OR "Hydrochloric ether" OR "Kelene" OR "Muriatic ether" OR "Narcotile" OR "Chelen" OR "Chlorene" OR "Chloridum" OR "Chloryl" OR "Chlorethyl" Limited to 1996-2022
Toxcenter	
05/2022	FILE 'TOXCENTER' ENTERED AT 16:55:39 ON 16 MAY 2022 CHARGED TO COST=EH038.15.03.LB.04 L1 2227 SEA FILE=TOXCENTER 75-00-3 L2 2132 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 1807 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 1040 SEA FILE=TOXCENTER L3 AND PY>1995 ACTIVATE TOXQUERY/Q --------- 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?)

Table B-2. Database Query Strings

Database search date	Query string
	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))
	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 (NONHUMAN MAMMALS)/ORGN

Table B-2. Database Query Strings

Database search date	Query string
	L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 414 SEA FILE=TOXCENTER L4 AND L37 L39 52 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L41 362 SEA FILE=TOXCENTER L38 NOT MEDLINE/FS L42 393 DUP REM L39 L41 (21 DUPLICATES REMOVED) L*** DEL 52 S L38 AND MEDLINE/FS L*** DEL 52 S L38 AND MEDLINE/FS L43 52 SEA FILE=TOXCENTER L42 L*** DEL 362 S L38 NOT MEDLINE/FS L*** DEL 362 S L38 NOT MEDLINE/FS L44 341 SEA FILE=TOXCENTER L42 L45 341 SEA FILE=TOXCENTER (L43 OR L44) NOT MEDLINE/FS D SCAN L45

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
05/2022	Compounds searched: 75-00-3
NTP	
05/2022	75-00-3 chloroethane "ethyl chloride"
Regulations.gov	
05/2022	chloroethane 75-00-3 "ethyl chloride" Limited to EPA docket or notices
NIH RePORTER	
03/2023	Search Criteria Fiscal Year: Active Projects Text Search: "Chloroethane" OR "Ethane, chloro-" OR "Ethyl chloride" OR "ethylchloride" OR "Freon 160" OR "Monochlorethane" OR "Monochloroethane" OR "chlorethane" OR "Aethylis" OR "Anodynon" OR "Chlorethan" OR "Chloryl anesthetic" OR "Chloryle anesthetic" OR "Cloretilo" OR "Dublofix" OR "Ether chloratus" OR "Ether chloridum" OR "Ether hydrochloric" OR "Ether muriatic" OR "Hydrochloric ether" OR "Kelene" OR "Muriatic ether" OR "Narcotile" OR "Chelen" OR "Chlorene" OR "Chloryl" OR "Chlorethyl" (advanced)Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active Projects Text Search: "Chloridum" (advanced)Limit to: Project

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 688
- Number of records identified from other strategies: 74
- Total number of records to undergo literature screening: 762

B.1.2 Literature Screening

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

- 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.

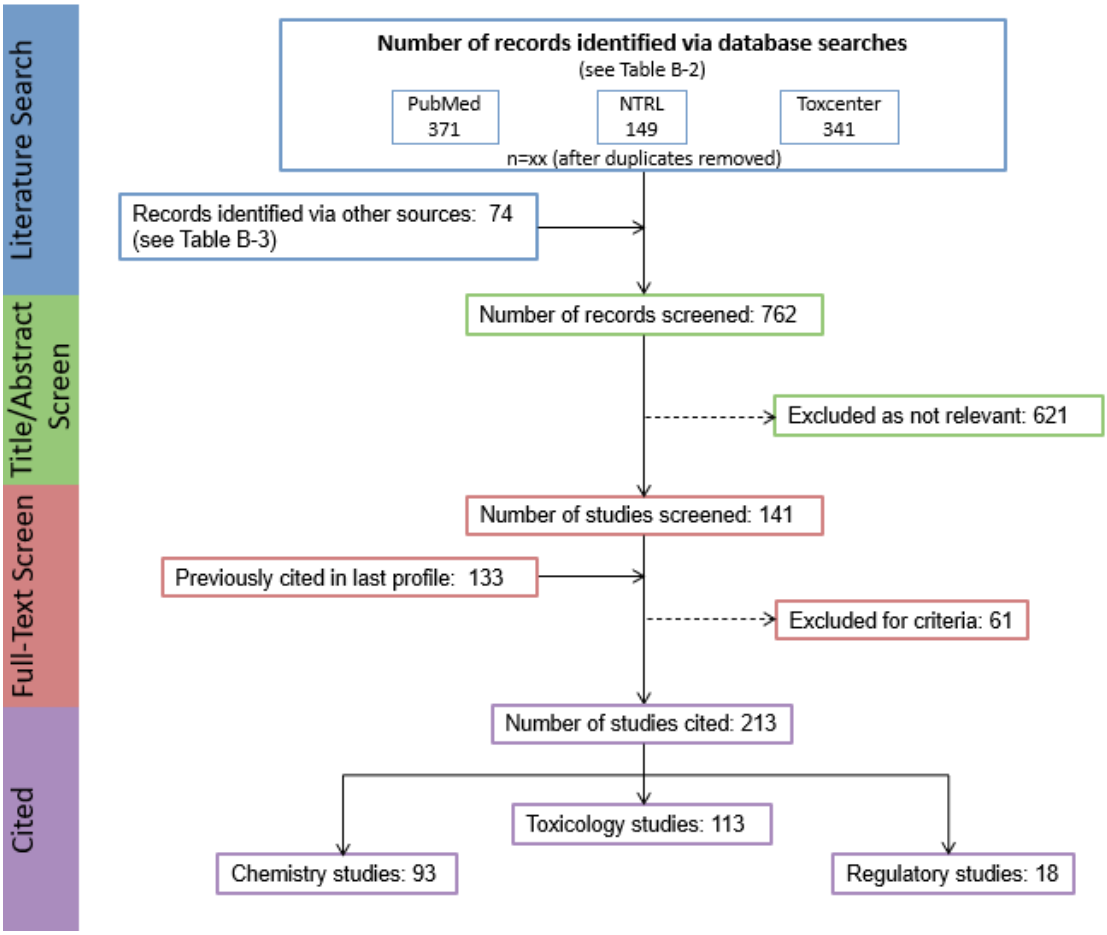
- Number of titles and abstracts screened: 762
- Number of studies considered relevant and moved to the next step: 141

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: 141
- Number of studies cited in the previous toxicological profile: 133
- Total number of studies cited in the profile: 213

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

Figure B-1. May 2022 Literature Search Results and Screen for Chloroethane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR CHLOROETHANE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to chloroethane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to chloroethane:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to chloroethane. The inclusion criteria used to identify relevant studies examining the health effects of chloroethane are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

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

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of chloroethane. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 1998 toxicological profile for chloroethane; thus, the literature search was restricted to studies published between January 1996 and May 2022. See Appendix B for the databases searched and the search strategy.

See Appendix B for the databases searched and the search strategy.

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of chloroethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 761 records were reviewed; 30 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 62 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 62 documents (79 studies), 20 documents (33 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted from Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Chloroethane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for chloroethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Human inhalation studies examined a limited number of health outcomes, whereas animal inhalation and oral studies examined a comprehensive set of endpoints. Dermal exposure studies in humans were primarily interested in analgesic effects of chloroethane (discussed in Section 2.11). Both human and animal studies suggest the nervous system is the primary target of chloroethane exposure. Additionally, animal studies suggest the reproductive and developmental effects may also be sensitive targets. Although there are several case reports evaluating neurological effects in humans following inhalation, these studies were not included in this systematic review due to either a lack of estimated exposure or a comparison group (discussed in Section 2.15). The

remaining human (inhalation) and animal (inhalation and oral) studies related to neurological, reproductive and developmental outcomes were carried through to Steps 4–8 of the systematic review. There were 33 studies (published in 20 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

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Table C-3. Overview of the Health Outcomes for Chloroethane Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort																	
Case control																	
Population												1 1	1 1				
Case series		3 3	2 1	2 2	1 0		2 2						8 8				
Human controlled			1 1							1 1			3 3				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series									3 1	1 1		3 3					
Human controlled									18 0				1 1				
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

APPENDIX C

Table C-4. Overview of the Health Outcomes for Chloroethane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	11 0	12 1	13 6	6 1	3 0	3 0	12 2	10 1	5 0	3 0	7 0	8 1	15 10	10 1	2 0		
Intermediate-duration	6 1	5 1	3 1	2 0			7 2	5 1	2 0	1 0	5 0	6 2	4 2	4 2			
Chronic-duration	2 0	2 0	2 0	2 0		2 0	2 0	2 1	2 0		2 0	2 0	2 1	2 0			2 2
Oral studies																	
Acute-duration	2 0		1 0		1 0		1 0	1 0			1 0	1 0	3 1	1 0			
Intermediate-duration	1 0																
Chronic-duration																	
Dermal studies																	
Acute-duration						1 1			1 1				1 1				
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of chloroethane health effects studies (human-controlled exposure and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for Chloroethane – Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							Risk of bias tier
	Selection bias		Performance bias	Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	
Outcome: Neurological effects								
Inhalation acute exposure								
USBM 1929	–	+	–	–	–	–	–	Third
Davidson 1925	–	+	–	+	–	+	–	Second
Bush et al. 1952	–	+	+	–	–	+	–	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is the confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Neurological Effects									
Inhalation acute exposure									
Bush et al. 1952	–	+	–	+	–	– –	–	–	Third
Dow 1941 (monkey)	–	+	–	+	+	–	+	+	Second
Dow 1992 (mouse)	++	+	++	+	+	++	+	+	First
Dow 1992 (rat, ^{14}C-chloroethane)	++	+	++	+	+	++	+	+	First
Dow 1992 (mouse, ^{14}C-chloroethane)	++	+	++	+	+	++	+	+	First
Dow 1985	++	+	+	+	+	–	++	+	First
Gohlke and Schmidt 1972; Schmidt et al. 1972	–	+	–	+	–	–	+	+	Second
Landry et al. 1982 (rat)	++	+	+	+	+	++	+	+	First
Landry et al. 1982 (dog)	++	+	+	+	+	++	+	+	First
Landry et al. 1987, 1989	++	+	+	+	++	++	+	++	First
Lazarew 1929	–	+	–	+	–	–	+	+	Second
NTP 1989 (mouse, 2 weeks)	++	+	+	+	+	+	–	+	Second
NTP 1989 (rat, 2 weeks)	++	+	+	+	+	+	–	+	Second
Morris et al. 1953	–	+	–	+	+	– –	+	–	Second
USBM 1929 (810 minutes)	–	+	–	+	++	–	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is the confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate exposure									
NTP 1989 (rat, 13 weeks)	++	+	+	+	++	+	+	+	First
NTP 1989 (mouse, 13 weeks)	++	+	+	+	++	+	+	+	First
Inhalation chronic exposure									
NTP 1989 (rat, 102 weeks)	++	+	+	+	++	+	+	+	First
NTP 1989 (mouse, 100 weeks)	++	+	+	+	++	+	+	+	First
Oral acute exposure									
Dow 1992 (mouse non-labelled)	++	+	–	+	+	++	+	+	First
Dow 1992 (rat, ^{14}C-chloroethane)	++	+	–	+	+	++	+	+	First
Dow 1992 (mouse, ^{14}C-chloroethane)	++	+	–	+	+	++	+	+	First
Dow 1995	++	+	+	+	++	++	+	++	First
Outcome: Reproductive Effects									
Inhalation acute exposure									
Breslin et al. 1988	++	+	+	+	+	+	+	+	First
Fedtke et al. 1994a, 1994b (rat)	–	+	–	+	+	+	+	–	First
Fedtke et al. 1994a, 1994b (mouse)	–	+	–	+	+	+	+	–	First

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Table C-9. Summary of Risk of Bias Assessment for Chloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is the confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Gohlke and Schmidt 1972; Schmidt et al. 1972	–	+	–	+	–	–	+	+	Second
Landry et al. 1982 (rat)	++	+	+	+	+	++	+	+	First
Landry et al. 1982 (dog)	++	+	+	+	+	++	+	+	First
Landry et al. 1987, 1989	++	+	+	+	++	++	+	++	First
NTP 1989 (mouse, 2 weeks)	++	+	+	+	+	+	–	+	Second
NTP 1989 (rat, 2 weeks)	++	+	+	+	+	+	–	+	Second
van Liere et al. 1966	–	+	–	+	–	– –	+	–	Second
Inhalation intermediate exposure									
Bucher et al. 1995	+	+	+	+	++	+	+	+	First
NTP 1989 (rat, 13 weeks)	++	+	+	+	++	+	+	+	First
NTP 1989 (mouse, 13 weeks)	++	+	+	+	++	+	+	+	First
Inhalation chronic exposure									
NTP 1989 (rat, 102 weeks)	++	+	+	+	++	+	+	++	First
NTP 1989 (mouse, 100 weeks)	++	+	+	+	++	+	+	++	First
Oral acute exposure									
Dow 1995	++	+	+	+	++	++	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is the confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Developmental Effects									
Inhalation acute exposure									
Dow 1985	++	+	+	+	+	–	+	+	First
Scortichini et al. 1986	++	+	+	+	+	++	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to chloroethane and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to chloroethane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining neurological and reproductive outcomes observed in the human-controlled exposure and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Chloroethane—Human-Controlled Exposure

Reference	Key Features				
	Comparison group or served as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Appropriate statistical analysis	Initial study confidence
Outcome: Neurological Effects					
Inhalation acute exposure					
USBM 1929	No	No	No	No	Very Low
Davidson 1925	No	No	Yes	No	Very Low
Bush et al. 1952	No	Yes	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Chloroethane—Experimental Animal Studies

Reference	Key features				
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Neurological Effects					
Inhalation acute exposure					
Bush et al. 1952	No	Yes	Yes	No	Low
Dow 1941 (monkey)	No	No	No	No	Low
Dow 1992 (mouse)	Yes	No	Yes	No	Low
Dow 1992 (rat, ^{14}C-chloroethane)	No	Yes	Yes	Yes	Moderate
Dow 1992 (mouse, ^{14}C-chloroethane)	No	Yes	Yes	No	Low
Dow 1985 (10 days)	Yes	Yes	Yes	No	Moderate
Gohlke and Schmidt 1972; Schmidt et al. 1972	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (rat)	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (dog)	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for Chloroethane—Experimental Animal Studies

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Landry et al. 1987, 1989	Yes	Yes	Yes	Yes	High
Lazarew 1929	No	No	Yes	No	Very Low
NTP 1989 (mouse, 2 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (rat, 2 weeks)	Yes	Yes	Yes	Yes	High
Morris et al. 1953	No	Yes	Yes	No	Low
USBM 1929 (540 minutes)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
NTP 1989 (rat, 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 13 weeks)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1989 (rat, 102 weeks)	Yes	Yes	Yes	No	Moderate
NTP 1989 (mouse, 100 weeks)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Dow 1992 (mouse)	No	No	Yes	Yes	Low
Dow 1992 (rat, ^{14}C-chloroethane)	No	Yes	Yes	Yes	Moderate
Dow 1992 (mouse, ^{14}C-chloroethane)	No	Yes	Yes	Yes	Moderate
Dow 1995	Yes	Yes	Yes	Yes	High
Outcome: Reproductive Effects					
Inhalation acute exposure					
Breslin et al. 1988	Yes	Yes	Yes	Yes	High
Fedtke et al. 1994a (rat)	Yes	Yes	No	No	Low
Fedtke et al. 1994a (mouse)	Yes	Yes	No	No	Low
Gohlke and Schmidt 1972; Schmidt et al. 1972	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (rat)	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (dog)	Yes	Yes	Yes	No	Moderate
Landry et al. 1987, 1989	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 2 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (rat, 2 weeks)	Yes	Yes	Yes	Yes	High
van Liere et al. 1966	No	Yes	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Chloroethane—Experimental Animal Studies

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Bucher et al. 1995	Yes	Yes	Yes	Yes	High
NTP 1989 (rat, 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 13 weeks)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1989 (rat, 102 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 100 weeks)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Dow 1995	Yes	Yes	No	Yes	Moderate
Outcome: Developmental Effects					
Inhalation acute exposure					
Dow 1985	Yes	Yes	Yes	No	Moderate
Scortichini et al. 1986	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Chloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Neurological Effects		
Inhalation acute exposure		
Human studies		
USBM 1929	Very Low	Low
Davidson 1925	Very Low	
Bush et al. 1952	Low	
Animal studies		
Bush et al. 1952	Low	
Dow 1941 (monkey)	Low	

Table C-15. Initial Confidence Rating for Chloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Dow 1992 (mouse)	Low	High
Dow 1992 (rat, ^{14}C-chloroethane)	Moderate	
Dow 1992 (mouse, ^{14}C-chloroethane)	Low	
Dow 1985 (10 days)	Moderate	
Gohlke and Schmidt 1972; Schmidt et al. 1972	Moderate	
Landry et al. 1982 (rat)	Moderate	
Landry et al. 1982 (dog)	Moderate	
Landry et al. 1987, 1989	High	
Lazarew 1929	Very Low	
NTP 1989 (mouse, 2 weeks)	High	
NTP 1989 (rat, 2 weeks)	High	
Morris et al. 1953	Low	
USBM 1929 (540 minutes)	Moderate	
Inhalation intermediate exposure		
Animal studies		
NTP 1989 (rat, 13 weeks)	High	High
NTP 1989 (mouse, 13 weeks)	High	
Inhalation chronic exposure		
Animal studies		
NTP 1989 (rat, 102 weeks)	Moderate	Moderate
NTP 1989 (mouse, 100 weeks)	Moderate	
Oral acute exposure		
Animal studies		
Dow 1992 (mouse)	Low	High
Dow 1992 (rat, ^{14}C-chloroethane)	Moderate	
Dow 1992 (mouse, ^{14}C-chloroethane)	Moderate	
Dow 1995	High	
Outcome: Reproductive Effects		
Inhalation acute exposure		
Animal studies		
Breslin et al. 1988	High	High
Fedtke et al. 1994a, 1994b (rat)	Low	
Fedtke et al. 1994a, 1994b (mouse)	Low	
Gohlke and Schmidt 1972; Schmidt et al. 1972	Moderate	
Landry et al. 1982 (rat)	Moderate	
Landry et al. 1982 (dog)	Moderate	
Landry et al. 1987, 1989	High	
NTP 1989 (mouse, 2 weeks	High	
NTP 1989 (rat, 2 weeks)	High	
van Liere et al. 1966	Low	High

Table C-15. Initial Confidence Rating for Chloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Animal studies		
Bucher et al. 1995	High	High
NTP 1989 (rat, 13 weeks)	High	
NTP 1989 (mouse, 13 weeks)	High	
Inhalation chronic exposure		
Animal studies		
NTP 1989 (rat, 102 weeks)	High	High
NTP 1989 (mouse, 100 weeks)	High	
Oral acute exposure		
Animal studies		
Dow 1995	Moderate	Moderate
Outcome: Developmental Effects		
Inhalation acute exposure		
Animal studies		
Dow 1985	Moderate	High
Scortichini et al. 1986	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for neurological and reproductive effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with chloroethane exposure is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Neurological Effects			
Human studies	Low	-1 risk of bias +1 consistency	Low
Animal studies	High	+1 consistency -1 indirectness	High
Outcome: Reproductive Effects			
Animal studies	High	-1 inconsistency -1 indirectness	Low

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Developmental Effects			
Animal studies	High	-1 inconsistency -1 indirectness -1 imprecision	Low

Table C-17. Confidence in the Body of Evidence for Chloroethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Neurological effects	Low	High
Reproductive effects	No data	Low
Developmental effects	No data	Low

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects

- Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% Cis for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the

null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

- Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for chloroethane, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for chloroethane is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Chloroethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Neurological	Low	Health effect	Low
Animal studies			
Neurological	High	Health effect	High
Reproductive	Low	Health effect	Low
Developmental	Low	Health effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

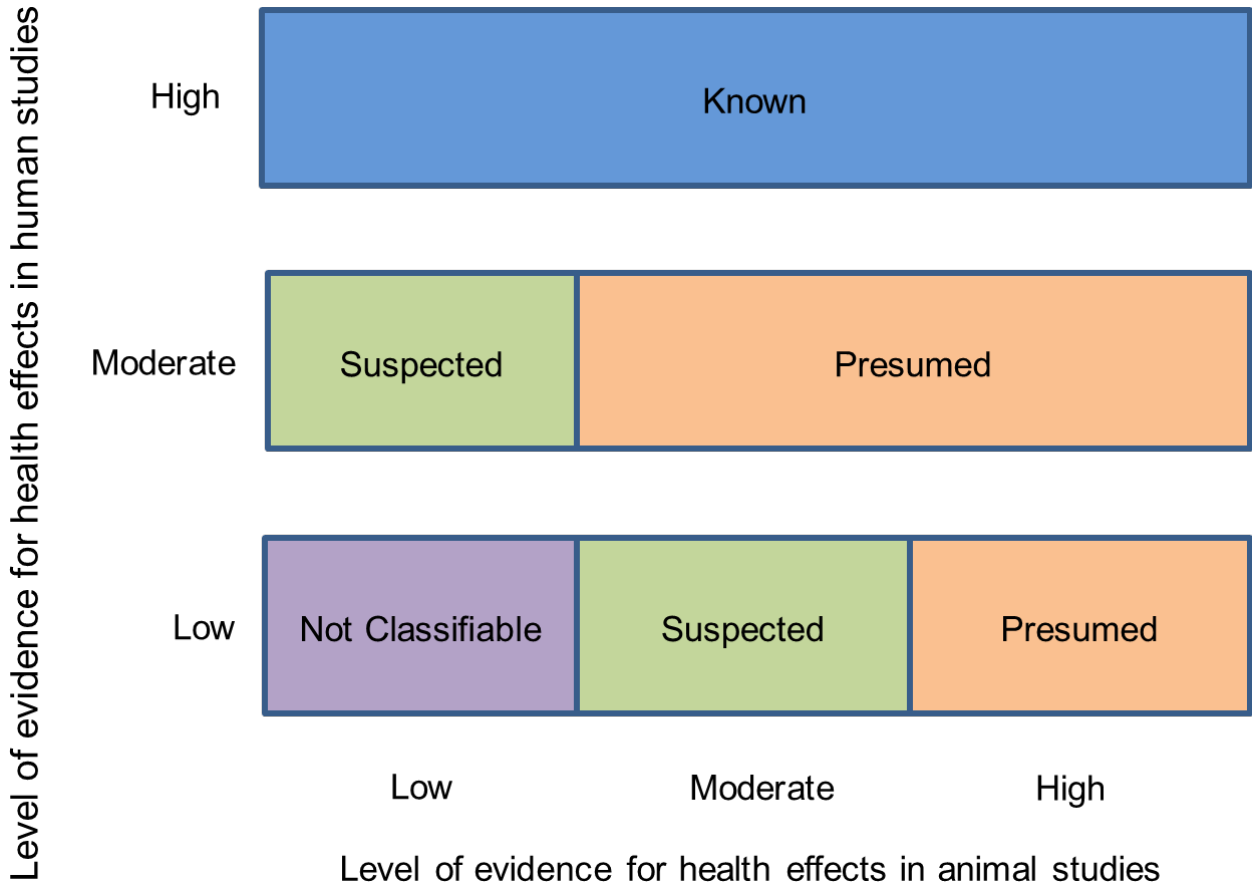
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
    - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
    - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
    - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
    - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
    - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
    - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for chloroethane are listed below and summarized in Table C-19.

Presumed Health Effects

- Neurological
  - Low level of evidence from human studies: several case reports described neurological symptoms after inhaling chloroethane; however, exposure levels are not known (Al-Ajmi et al. 2018; Demarest et al. 2011; Finch and Lobo 2005; Hager et al. 2021; Hes et al. 1979; Kuthiah and Er 2019; Nordin et al. 1988; Senussi and Chalise 2015). Volunteers who inhaled chloroethane reported feeling dizzy and slightly intoxicated and had increased reaction times (Davidson 1925; USBM 1929); however, these studies were poor quality with high risk of bias.
  - High level of evidence from animal studies: neurological effects have been reported in several species following inhalation (Bush et al. 1952; Dow 1985, 1992, 1995; Landry et al. 1982; Lazarew 1929; Morris et al. 1953; NTP 1989; USBM 1929;) and gavage (Dow 1992) exposure.

Not Classifiable Health Effects

- Reproductive
  - Low level of evidence from animal studies: inhalation studies have reported effects on the length of the estrous cycle (Bucher et al. 1995), uterine weight (Fedtke et al. 1994a), and uterine glutathione levels (Fedtke et al. 1994b), although no histopathological and/or hormonal changes have been reported after exposure (Bucher et al. 1995; Landry et al. 1982, 1987, 1989; NTP 1989). Breslin et al. (1988) reported that inhalation did not affect the estrous cycle of mice.
- Developmental
  - Low level of confidence from animal studies: one inhalation study reported increased incidence of delayed fetal foramina closure (DFFC) of the skull bones in pups exposed *in utero* on GDs 6–15 (Scortichini et al. 1986), whereas another study of pups exposed *in utero* on GDs 6–15 did not report any fetal abnormalities (Dow 1985).

Table C-19. Hazard Identification Conclusions for Chloroethane

Outcome	Hazard identification
Neurological	Presumed
Reproductive	Not classifiable
Developmental	Not classifiable

APPENDIX D. 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 D-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 D-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)

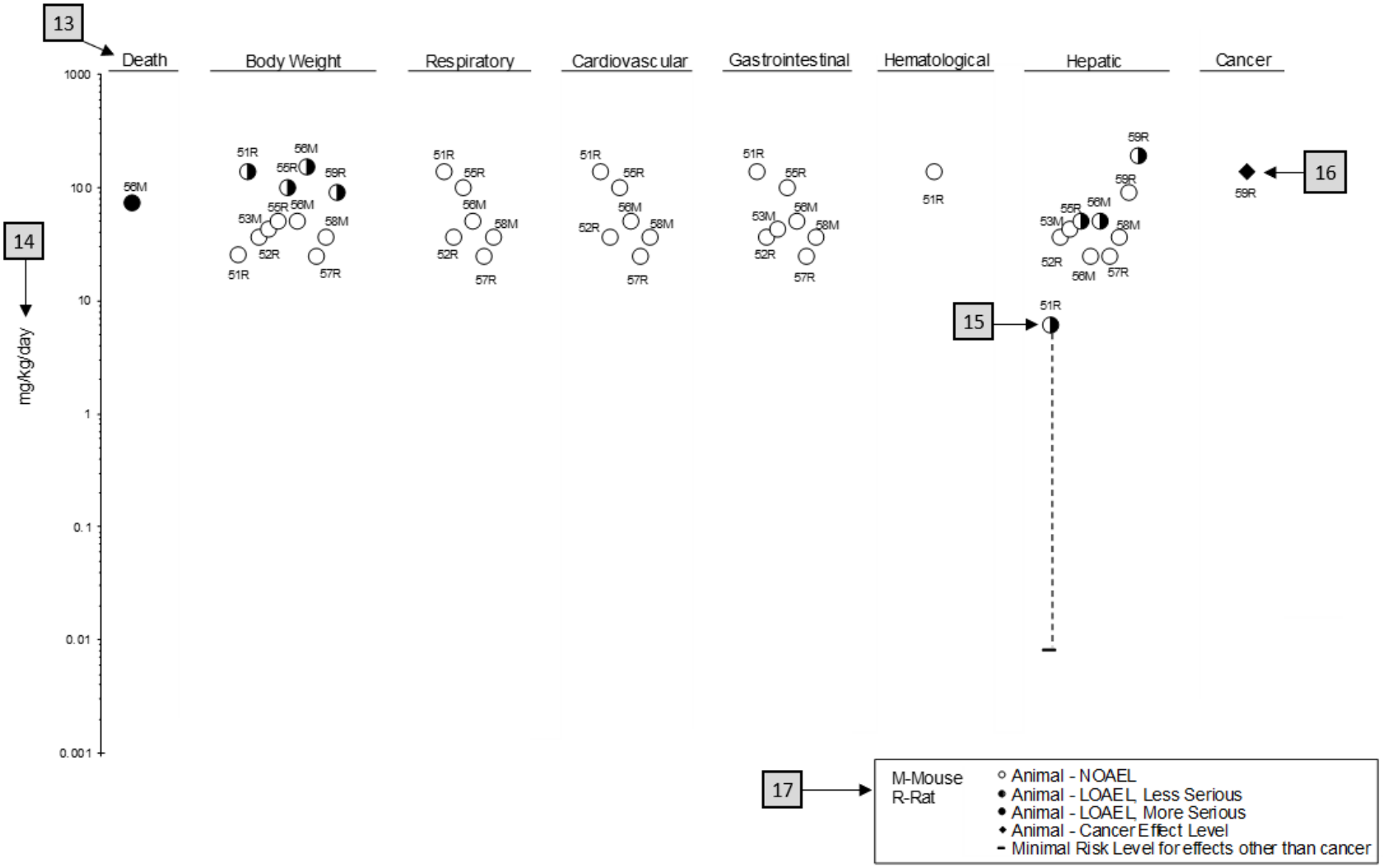
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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).

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



APPENDIX E. 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:

Clinical Briefs and Overview discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

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 F. 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 malignant 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 LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

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 G. 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 Substances 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	lactate 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