APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chloromethane
CAS Numbers:	74-87-3
Date:	September 2023
Profile Status:	Final
Route:	Inhalation
Duration:	Acute
MRL:	0.5 ppm (1 mg/m^3)
Critical Effect:	Degenerative changes in the cerebellum granule cells
Reference:	Landry et al. (1985)
Point of Departure:	NOAEL of 50 ppm ($NOAEL_{HEC}$ of 46 ppm)
Uncertainty Factor:	30
Modifying Factor:	3
LSE Graph Key:	26
Species:	Mouse

MRL Summary: An acute-duration inhalation MRL of 0.5 ppm was derived for chloromethane based on neurological effects including moderate degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis in female C57BL/6 mice following exposure to chloromethane for 22 hours/day for 11 days (Landry et al. 1985). The MRL is based on a NOAEL of 50 ppm, which was adjusted to a human equivalent concentration ($NOAEL_{HEC}$) of 46 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) and a modifying factor of 3 to account for the steepness of the dose-response curve.

Selection of the Critical Effect: Based on systematic review (see Appendix C), it was determined that hepatic, neurological, and male reproductive effects were presumed health effects associated with inhalation exposure. These presumed health effects were subsequently the focus of the acute-duration MRL evaluation.

For presumed health effects, the lowest reported LOAELs and serious LOAELs from acute-duration inhalation studies were reviewed to determine the most sensitive effects (Table A-1). Since studies used a variety of exposure paradigms, ranging from intermittent exposure (5.5 or 6 hours/day) to continuous or near-continuous exposure (22–24 hours/day), LOAELs and serious LOAELs were adjusted for continuous exposure. The lowest reported duration-adjusted LOAELs and serious LOAELs were 92 and 486 ppm, respectively, for neurological effects; 92 and 375 ppm, respectively, for hepatic effects; and 501 and 500 ppm, respectively, for male reproductive effects. Based on duration-adjusted values, the lowest LOAELs are comparable for neurological and hepatic effects, and the severity of effects show a comparable dose-response curve. Therefore, both the nervous and hepatic systems are considered sensitive targets of chloromethane toxicity. However, the human evidence (predominantly from case reports) shows that neurological effects are the main observed adverse outcome after accidental acute-duration exposure to chloromethane (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Minami 1998; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). Therefore, neurological effects are selected as the critical effect for the acute-duration inhalation MRL.

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

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Neurological effects					
C57BL/6 mouse	11 days 22 hours/day	50 (46)	100 (92)	Slight cerebellar granule cell degeneration	Landry et al. 1985
C57BL/6 mouse	11 days 5.5 hours/day	150 (34)	400 (92)	Slight cerebellar granule cell degeneration	Landry et al. 1985
Beagle dog	3 days 23.5 hours/day	197 (193)	496 (486) (SLOAEL)	Severe clinical signs of neurotoxicity; lesions in brain and spinal cord; axonal loss	McKenna et al. 1981a
Swiss, Strain A, C3H mouse	2 weeks 6 hours/day 6 days/week	300 (64)	500 (107) (SLOAEL)	Neuromuscular abnormalities, impaired gait, hindlimb drag	Smith and von Oettingen 1947b
Dog (NS)	2 weeks 6 hours/day 6 days/week	300 (64)	500 (107) (SLOAEL)	Tremors, spasticity, impaired gait	Smith and von Oettingen 1947b
C57BL/6 mouse	12 days 6 hours/day GDs 6–17	251 (63)	502 (126) (SLOAEL)	Ataxia in dams	Wolkowski-Tyl et al. 1981b, 1983b
Hepatic effects					
C57BL/6 mouse	11 days 22 hours/day	50 (46)	100 (92)	Decreased hepatocyte size; glycogen depletion	Landry et al. 1985
C57BL/6 mouse	11 days 5.5 hours/day	150 (34)	400 (92)	Decreased hepatocyte size; glycogen depletion	Landry et al. 1985
C57BL/6 or C3H mouse	12 days 6 hours/day	ND	500 (125)	Minimal hepatocellular degeneration	Morgan et al. 1982
Sprague-Dawley rat	48 hours continuous	ND	196 (196)	Decreased liver weight	Burek et al. 1981
Sprague-Dawley rat	72 hours continuous	ND	198 (198)	Decreased absolute and relative liver weight and altered tinctorial[a] appearance in males, lipid accumulation in females	Burek et al. 1981
Guinea pig	6 days 6 hours/day	500	1,000 (250)	Fatty metamorphosis	Dunn and Smith 1947
B6C3F1 mouse	6 hours	ND	1,500 (375) (SLOAEL)	Hepatocellular necrosis and cytoplasmic vacuolization; increased serum ALT	Chellman et al. 1986b
Male reproductive effects					
Sprague-Dawley rat	48 hours continuous	196 (196)	501 (501)	Testicular lesions, decreased sperm in the lumen	Burek et al. 1981
Sprague-Dawley rat	72 hours continuous	198 (198)	504 (504)	Testicular lesions, decreased sperm in the lumen	Burek et al. 1981

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

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Fischer-344 rat	9 days 6 hours/day	ND	2,000 (500) (SLOAEL)	Reduced sperm, immature sperm in lumen, testicular lesions	Morgan et al. 1982

[a]Altered staining properties of hepatocyte.

ADJ = adjusted for continuous exposure; ALT = alanine aminotransferase; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: The 11-day mouse study (Landry et al. 1985) was selected as the principal study because it provides the highest NOAEL below the lowest LOAEL for the critical effect (neurotoxicity).

Summary of the Principal Study:

Landry TD, Quast JF, Gushow TS, et al. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female c57bl/6 mice. Fundam Appl Toxicol 5(1):87-98.

Landry et al. (1985) evaluated the neurological effects of chloromethane following nearly continuous exposure versus intermittent exposure in female C57BL/6 mice. This species, strain, and sex were chosen due to their high sensitivity to chloromethane-associated neurological effects. Groups of 12 mice each were exposed to chloromethane in whole-body inhalation chambers for 11 days for either 22 hours/day (referred to as "continuous" by the study authors) or 5.5 hours/day (referred to as intermittent by the study authors). Each duration protocol had two distinct experiments, each with their own concurrent control. For the continuous exposure, the first experiment exposed mice to 0, 15, 50, or 150 ppm and the second experiment exposed mice to 0, 100, 200, or 400 ppm. For the intermittent exposure, the first experiment exposed mice to 0, 150, or 2,400 ppm and the second experiment exposed mice to 0, 400, 800, or 1,600 ppm. Mice were evaluated twice daily for clinical signs of toxicity. Motor coordination was evaluated using a rotarod (ability to stay on a rotating 4-cm diameter rod) on exposure days 4, 8, and 11. Mice were weighed prior to exposure, on exposure days 4 and 8, and at necropsy. Animals were sacrificed after exposure, and the following tissues were collected, weighed, and prepared for histological evaluation in six mice/group: brain (cerebellum, cerebrum, and brain stem), sciatic nerve, vertebral bone with spinal cord, liver, kidneys, and thymus.

All mice exposed continuously to ≥150 ppm and intermittently to 2,400 ppm died or were sacrificed moribund prior to scheduled sacrifice. Prior to death/moribund sacrifice, mice displayed inanition (exhaustion caused by lack of nourishment) associated with decreased food consumption. Hematuria was observed in mice exposed to 2,400 ppm. Consistent with this, body weights were decreased by >10% at both continuous and intermittent exposure levels associated with decreased survival. Mice continuously exposed to ≥200 ppm showed ataxia and prostration by day 3; therefore, they were not assessed on the rotarod. In other continuously exposed groups, performance on a rotating rod was significantly decreased following exposure to 150 ppm starting on day 4, with severity of impairment increasing in a duration-related manner; no changes in motor coordination were observed at ≤100 ppm. In mice exposed

intermittently, sedation and hind-limb rigidity were observed in some mice at ≥1,600 ppm. Transient decreases in motor coordination on the rotarod were observed in mice exposed to 800 or 1,600 ppm on day 4; however, decreases were not observed on days 8 or 11. In mice intermittently exposed to 2,400 ppm, motor activity decreased in a duration-related manner starting on day 4.

At sacrifice, gross necropsy showed thymus atrophy at ≥1,600 ppm and an enlarged spleen at 2,400 ppm in mice exposed intermittently. The enlarged spleen was accompanied by hemoglobinuria, which is suggestive of extramedullary hematopoiesis. Absolute and relative thymus weights were reduced in all exposure groups from the first continuous exposure group (15, 50, and 150 ppm); however, no changes in thymus weights were observed in the second experiment at 100 ppm (thymic weights were not weighed at higher exposure levels due to early death). Therefore, the biological significance of decreased thymus weight at low concentrations is unclear due to lack of clear dose-response. In intermittently exposed mice, absolute and relative thymus weights were reduced at ≥1,600 ppm, and absolute and relative liver weights were increased at 1,600 ppm (but not at 2,400 ppm; this may be due to early sacrifice at this concentration). Other observed organ weight changes, including decreased absolute liver weight and increased relative kidney weight after continuous exposure to 150 ppm, were considered secondary to body weight effects.

Histopathological changes were observed in the brain, liver, and kidney. In the brain, degenerative changes in the cerebellum granule cells were observed in 100% of mice continuously exposed to ≥100 ppm, 33% of mice intermittently exposed to 400 ppm, 65–67% of mice intermittently exposed to 800–1,600 ppm, and 100% of mice intermittently exposed to 2,400 ppm. The changes consisted of nuclear pyknosis, karyorrhexis, and hemorrhaged areas, and the severity of the lesions increased in a concentration- and duration-dependent manner. In the liver, decreased hepatocyte size (attributed to glycogen depletion by the study authors) were also observed in mice continuously exposed to ≥100 ppm or intermittently exposed to ≥400 ppm. The study authors noted focal hepatic necrosis at unspecified "higher concentrations." In the kidney, slight multifocal degeneration of the renal tubules was observed after intermittent exposure to 2,400 ppm. Incidence data were not provided for hepatic or renal lesions.

Selection of the Point of Departure for the MRL: In order to select the POD based on neurological effects observed by Landry et al. (1985), data from experiments with the same daily duration were combined for dose-response analysis, and duration adjustments were made to compare across continuous and intermittent exposure scenarios (Table A-2). While the adjusted LOAEL concentrations are comparable across exposure scenarios, the continuous exposure scenario provides the highest NOAEL below the lowest LOAEL; therefore, the continuous exposure scenario was selected for derivation of the acute-duration inhalation MRL. Additionally, due to the steep dose-response curve (cerebellar lesion incidence of 0% at NOAEL and 100% at LOAEL), benchmark dose (BMD) modeling was not conducted to develop the MRL. Subsequently, the NOAEL of 50 ppm ($NOAEL_{ADJ}$ of 46 ppm) was used in derivation of the MRL.

Table A-2. Summary of Neurological Effects Observed in Mice Exposed to Chloromethane for 11 Days via Inhalation

Continuous exposure (22 hours/day)		Intermittent exposure (5.5 hours/day)	
Concentration (adjusted[a]) (ppm)	Effect	Concentration (adjusted[a]) (ppm)	Effect
15 (14)	No neurological effects		
50 (46)	No neurological effects	150 (34)	No neurological effects
100 (92)	Slight degenerative changes in the cerebellum granule cells (100% incidence)	400 (92)	Slight degenerative changes in the cerebellum granule cells (33% incidence)
150 (138)	Moderate cerebellar lesions (100% incidence); impaired motor coordination		
200 (183)	Incapacitated after 4 days, severe cerebellar lesions (100% incidence)	800 (183)	Slight degenerative changes in the cerebellum granule cells (67% incidence); transient impairment in motor coordination
400 (367)	Incapacitated after 2 days, severe cerebellar lesions (100% incidence)	1,600 (367)	Slight degenerative changes in the cerebellum granule cells (65% incidence); sedation, hind-limb rigidity, transient impairment in motor coordination
		2,400 (505)	Slight degenerative changes in the cerebellum granule cells (100% incidence); sedation, hindlimb rigidity, impaired motor coordination

[a]Exposure concentration adjusted for continuous exposure.

Source: Landry et al. 1985

Adjustment of Intermittent Exposure: The NOAEL of 50 ppm concentration was adjusted from a 22-hour exposure to a continuous 24-hour exposure scenario:

$$NOAEL_{ADJ} = NOAEL \times \frac{22\ hours}{24\ hours} = 50\ ppm \times \frac{22\ hours}{24\ hours} = 46\ ppm$$

The human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted NOAEL by the default ratio of 1 for air:blood partition coefficient for humans and rats (partition coefficient values are not available for chloromethane):

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 46\ ppm \times 1 = 46\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient ratio for animals (a) to humans (h)

Uncertainty Factors and Modifying Factor: The following uncertainty factors were applied to the $NOAEL_{HEC}$ to derive the MRL:

- uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustments
- uncertainty factor of 10 for human variability
- modifying factor of 3 to account for the steep dose-response seen between the NOAEL and the LOAEL (e.g., 100% response rate in the animals evaluated at the LOAEL)

Subsequently, the MRL for acute-duration exposure to chloromethane via inhalation is:

$$MRL = \frac{NOAEL_{HEC}}{(UF\ x\ MF)} = \frac{46\ ppm}{90} = 0.5\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that neurological effects are a presumed health effect following inhalation exposure to chloromethane based on a low level of evidence from human studies and a high level of evidence from animal studies (see Appendix C).

In humans, there are multiple case reports that noted adverse neurological effects as the main observed outcome after exposure to chloromethane (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Minami 1998; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). Additionally, one occupational cohort study reported neurological effects, some lasting years after exposure, following accidental exposure to high levels of chloromethane from a refrigeration leak (Gudmundsson 1977). At lower concentration levels, neurological effects were not noted in an occupational cohort study (NIOSH 1976) or three human controlled trials (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980). In animals, a range of neurological effects have been observed in rats, mice, and dogs, including clinical signs of neurotoxicity, motor impairments, and lesions in the cerebellum and spinal cord. Neurological effects were observed following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b; Wolkowski-Tyl et al. 1983a, 1983b), intermediate durations (McKenna et al. 1981b; Smith and von Oettingen 1947b), or chronic durations (CIIT 1981).

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.3 ppm (0.6 mg/m^3)
Critical Effect: Impaired sensorimotor function
Reference: McKenna et al. 1981b
Point of Departure: NOAEL of 51 ppm
($NOAEL_{HEC}$ of 9 ppm)
Uncertainty Factor: 30
LSE Graph Key: 44
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.3 ppm was derived for chloromethane based on neurological effects including impaired sensorimotor performance (wire maneuver) in female Sprague-Dawley rats following exposure to chloromethane for 93 days (5 days/week, 6 hours/day) (McKenna et al. 1981b). The MRL is based on a NOAEL of 51 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 9 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: Based on systematic review (see Appendix C), it was determined that hepatic, neurological, and male reproductive effects were presumed health effects associated with inhalation exposure. These presumed health effects were subsequently the focus of the intermediate-duration MRL evaluation.

For presumed health effects, the lowest reported LOAELs from intermediate-duration inhalation studies were 149 ppm for neurological effects, 399 ppm for hepatic effects, and 472 ppm for male reproductive effects (Table A-3). Based on available data, the nervous system appears to be the most sensitive target of chloromethane toxicity and is selected as the critical effect for the intermediate-duration inhalation MRL.

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Neurological effects					
Sprague-Dawley rat	93 days 5 days/week 6 hours/day	51 (9)	149 (27)	Impaired sensorimotor function (wire maneuver)	McKenna et al. 1981b

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
CD-1 mouse	93 days 5 days/week 6 hours/day	399 (71)	ND	No adverse effects	McKenna et al. 1981b
Monkey (NS)	120 days 6 days/week 6 hours/day	300 (64)	500 (107)[a] (SLOAEL)	Progressive debility, prostration, loss of consciousness	Smith and von Oettingen 1947b
Mouse (NS)	266 days 6 days/week 6 hours/day	300 (64)	500 (107)[a] (SLOAEL)	Persistent neuromuscular abnormalities, impaired gait, hindlimb paralysis	Smith and von Oettingen 1947b
Guinea pig (NS)	266 days 6 days/week 6 hours/day	300 (64)	500 (107)[a] (SLOAEL)	Persistent neuromuscular abnormalities, impaired gait, hindlimb drag	Smith and von Oettingen 1947b
Dog (NS)	211 days 6 days/week 6 hours/day	300 (64)	500 (107) (SLOAEL)	Severe clinical signs of neurotoxicity (e.g., tremors, spasticity, impaired gait)	Smith and von Oettingen 1947b
Hepatic effects					
Sprague-Dawley rat	93 days 5 days/week 6 hours/day	149 (27)	399 (71)	Increased relative liver weight	McKenna et al. 1981b
CD-1 mouse	93 days 5 days/week 6 hours/day	149 (27)	399 (71)	Increased relative liver weight	McKenna et al. 1981b
B6C3F1 mouse	90 days 5 days/week 6 hours/day	368 (66)	741 (132)	Increased relative liver weight	Mitchell et al. 1979
B6C3F1 mouse	6 months 5 days/week 6 hours/day	224 (40)	997 (178)	Hepatocellular degeneration	CIIT 1981
Male reproductive effects					
Fischer 344 rat	12–19 weeks per generation 5–7 days/week 6 hours/day	151 (32)	472 (101)	Decreased number of fertile F0 males, decreased number of litters per copulation plug in F0 rats	Hamm et al. 1985

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Fischer 344 rat	6 months 5 days/week 6 hours/day	224 (40)	997 (178)	Degeneration and atrophy of seminiferous tubules; sperm granulomas	CIIT 1981
Sprague-Dawley rat	93 days 5 days/week 6 hours/day	399 (71)	ND	No adverse effects (fertility not assessed)	McKenna et al. 1981b
Fischer 344 rat	90 days 5 days/week 6 hours/day	1,473 (263)	ND	No adverse effects (fertility not assessed)	Mitchell et al. 1979

[a]Decreased survival observed at this concentration

ADJ = adjusted for intermittent exposure; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The 93-day rat study (McKenna et al. 1981b) was selected as the principal study because it provides the highest NOAEL below the lowest LOAEL for the critical effect (neurotoxicity).

Summary of the Principal Study:

McKenna MJ, Burek JD, Henck JW, et al. 1981b. Methyl chloride: A 90-day inhalation toxicity study in rats, mice and beagle dogs. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0511317. 408120723. 47002B3B17.

McKenna et al. (1981b) exposed Sprague-Dawley rats (10/sex/group) to chloromethane at nominal concentrations of 0, 50, 150, or 400 ppm for 93 days (5 days/week, 6 hours/day). Analytical concentrations were 0, 51, 149, and 399 ppm, respectively. Animals were observed daily for clinical signs of toxicity. Body weights were measured twice weekly for the first 4 weeks and weekly thereafter. Sensorimotor responses were tested in 5/sex/group weekly for the first 4 weeks of exposure, and every other week thereafter. Sensorimotor tests included evaluation of body position, respiration, piloerection, exophthalmos, tremor, corneal reflex, pinna reflex, tail pinch, toe pinch, righting reflex, grasp irritability, visual placing, wire maneuver, and hindlimb clasping. Blood and urine were collected for hematology and urinalysis prior to the initiation of exposure and at study termination. Serum clinical chemistry endpoints were evaluated at time of necropsy. All animals underwent gross necropsy, and the following organ weights were measured: brain, heart, liver, kidneys, and testes. Histopathological examination of a comprehensive set of tissues was conducted on all rats in the control and 399-ppm group.

Two rats died prior to study termination, 1 female at 51 ppm and 1 female at 399 ppm. These deaths were not attributed to exposure. No clinical signs of toxicity were noted. A dose-related trend toward reduced body weight gain was noted in female rats; however, no statistically or biologically significant findings were observed. No exposure-related changes in clinical chemistry, hematology, or urinalysis were

observed. The only exposure-related change in organ weights was a 10% increase in relative liver weights in male rats at 399 ppm. No exposure-related gross or microscopic lesions were observed.

Sensorimotor testing showed a significant decrease in the ability of female rats to perform the wire maneuver (inability of the animals to raise their hindquarters to the top of the wire while grasping with forelimbs) at 399 ppm beginning at day 16 and 149 ppm beginning at day 40, and persistent throughout the remainder of the study. Hindlimb clasping was significantly impaired in female rats at 399 ppm beginning on day 66 through the end of the study. In males, hindlimb clasping was transiently impaired at ≥149 ppm, observed only on days 16–39.

Selection of the Point of Departure for the MRL: The NOAEL of 51 ppm for neurological effects in the study by McKenna et al. (1981b) was selected as the point of departure (POD). While the study authors reported statistical results for sensorimotor testing, quantitative data were not provided; therefore, BMD modeling was not used to derive this MRL.

Adjustment of Intermittent Exposure: The NOAEL of 51 ppm concentration was adjusted for a continuous exposure scenario:

$$NOAEL_{ADj} = NOAEL \times \frac{6\ hours}{24\ hours} \times \frac{5\ \text{days}}{7\ \text{days}} = 51\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ \text{days}}{7\ \text{days}} = 9\ ppm$$

The human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted NOAEL by the default ratio of 1 for air:blood partition coefficient for humans and rats (partition coefficient values are not available for chloromethane):

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 9\ ppm \times 1 = 9\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient ratio for animals (a) to humans (h)

Uncertainty Factors used in MRL derivation: The following uncertainty factors were applied to the $NOAEL_{HEC}$ to derive the MRL:

- uncertainty factor of 3 for extrapolation from animals to humans with application of dosimetric adjustment
- uncertainty factor of 10 for human variability.

Subsequently, the inhalation MRL for intermediate-duration exposure to chloromethane is:

$$MRL = \frac{NOAEL_{HEC}}{(UF)} = \frac{9\ ppm}{30} = 0.3\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that neurological effects are a presumed health effect following inhalation exposure to chloromethane based on a low level of evidence from human studies and a high level of evidence from animal studies (see Appendix C).

In humans, there are multiple case reports that noted adverse neurological effects as the main observed outcome after exposure to chloromethane (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Minami 1998; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). Additionally, one occupational cohort study reported neurological effects, some lasting years after exposure, following accidental exposure to high levels of chloromethane from a refrigeration leak (Gudmundsson 1977). At lower concentration levels, neurological effects were not noted in an occupational cohort study (NIOSH 1976) or three human controlled trials (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980). In animals, a range of neurological effects have been observed in rats, mice, and dogs, including clinical signs of neurotoxicity, motor impairments, and lesions in the cerebellum and spinal cord. Neurological effects were observed following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b; Wolkowski-Tyl et al. 1983a, 1983b), intermediate durations (McKenna et al. 1981b; Smith and von Oettingen 1947b), or chronic durations (CIIT 1981).

The study author conclusions in the principal study were critically evaluated in deriving the intermediate-duration inhalation MRL. McKenna et al. (1981b) concluded that the wire maneuver findings in female rats may represent a mild muscle weakness but did not attribute findings to chemical exposure because: (1) all groups showed decreased ability as time progressed (attributed to increased body weight), and (2) findings were not associated with any discernable neuromuscular incoordination or apparent neurological deficit in the current study, and (3) no "observable effects of a CNS or neuromuscular character" in rats exposed to concentrations up to 1,500 ppm by Mitchell et al. (1979). However, there are issues with each point of the argument made by McKenna et al. (1981b). First, no statistically significant or biologically relevant body weight effects were noted in exposed female rats, compared to controls. Second, the lack of overt incoordination/deficit argument is considered invalid, as detailed sensorimotor testing is designed to identify subtle deficits not obvious in cage-side observations. Additionally, the study authors neglected to acknowledge or discuss the statistical changes in another sensorimotor test (hindlimb clasping), which found deficits in female rats at the highest exposure concentration. Lastly, Mitchell et al. (1979) only performed cage-side evaluations and did not conduct detailed sensorimotor testing; therefore, findings (or lack thereof) from that study are not directly comparable to the study by McKenna et al. (1981b). Taken together, impairments on the wire maneuver and hindlimb clasping tests provide evidence of sensorimotor dysfunction at ≥149 ppm that is considered toxicologically relevant, especially when considering consistent evidence of progressive dose- and duration-dependent motor impairments (particularly in the hind limbs) observed in other studies and species following inhalation exposure (e.g., Chellman et al. 1986b; Landry et al. 1985; Morgan et al. 1982; Smith and von Oettingen 1947b).

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chloromethane
CAS Numbers:	74-87-3
Date:	September 2023
Profile Status:	Final
Route:	Inhalation
Duration:	Chronic
MRL:	0.03 ppm (0.06 mg/m^3)
Critical Effect:	Swelling and slight degeneration of axons in the spinal cord
Reference:	CIIT (1981)
Point of Departure:	LOAEL of 51 ppm ($LOAEL_{HEC}$: 9 ppm)
Uncertainty Factor:	300
LSE Graph Key:	60, 61
Species:	Mouse

MRL Summary: A chronic-duration inhalation MRL of 0.03 ppm was derived for chloromethane based on neurotoxicity (swelling and degeneration of axons in the spinal cord) in mice exposed to concentrations ≥51 ppm for 18 or 24 months (6 hours/day, 5 days/week); no NOAEL was identified (CIIT 1981). The MRL is based on a LOAEL of 51 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($LOAEL_{HEC}$) of 9 ppm and divided by a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

Selection of the Critical Effect: Only one chronic-duration inhalation study evaluated potential adverse effects of chloromethane in rats and mice (CIIT 1981). Exposure-related nonneoplastic effects reported in this study included neurological effects in mice at ≥51 ppm; cardiovascular effects in mice at ≥224 ppm and rats at 997 ppm; body weight, hepatic, renal, and male reproductive effects in rats and mice at 997 ppm; and decreased survival and spleen effects in mice at 997 ppm. Of these effects, the most sensitive (neurotoxicity) was selected as the critical effect.

Selection of the Principal Study: The chronic mouse study (CIIT 1981) was selected as the principal study because it provides the lowest POD for the critical effect (neurotoxicity).

Summary of the Principal Study:

CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Battelle-Columbus Laboratories. Submitted to the U.S. Environmental Protection Agency under section 4. 40-8120717. OTS0511310.

CIIT (1981) exposed groups of B6C3F1 mice (117–123/sex/group) to chloromethane in whole-body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to 24 months. Analytically measured concentrations were 0, 51, 224, and 997 ppm, respectively. Animals were checked twice daily for mortality, morbidity, and clinical signs of toxicity. Body weights were measured prior to exposure, weekly for the first 6 months, and biweekly thereafter. Neurofunctional assessments were conducted after 18 and 24 months of exposure, including posture and gait analysis, facial tone, and reflexes. Ophthalmological examinations were performed prior to exposure and within a week of scheduled sacrifice. Groups of animals were sacrificed at 6 months (9–11/sex/group), 12 (10/sex/group), 18 (5–10/sex/group), or 24 months (all surviving animals) after the

initial exposure and underwent gross necropsy. At sacrifice, blood was collected for hematology and clinical chemistry analysis and urine was collected for urinalysis. Weights were recorded for the lungs, heart, brain, liver, kidneys, and gonads. A complete set of tissues was examined for histopathological changes from all animals at scheduled sacrifice or were sacrificed/died prematurely.

The number of unscheduled deaths was increased in both males (78%) and females (61%) at 997 ppm, compared to control (63 and 28%, respectively). Body weights were decreased at 997 ppm by 15–18% by 12 months; however, body weight effects were not noted in surviving animals at 18 or 24 months. Clinical signs of neurotoxicity (tremor, paralysis) were seen in both sexes, along with abnormal functional test neurological results (restricted use of rear legs, abnormal gait, poor extensor thrust, leg rigidity) at 997 ppm. No exposure-related changes in ophthalmology or hematology were observed. Clinical chemistry findings were restricted to increased serum ALT in at 12 and 18 months at 997 ppm (not assessed at 24 months due to 100% mortality). Exposure-related changes in organ weight included increased absolute and/or relative heart weight in female mice at 997 ppm after 18 months and at 224 ppm at 24 months, and increased absolute and relative liver weight in females at 997 ppm after 18 months. Histopathological findings identified the CNS as a sensitive target of toxicity. Axonal swelling and degenerative changes of minimal severity were observed in the spinal cord nerves, cauda equina, and dorsal root in the spinal cord at ≥51 ppm after exposure for ≥18 months. In the brain, minimal-to-moderate degeneration of the cerebellar granule cell neurons was observed at 997 ppm after exposure for ≥18 months. Table A-4 provides a summary of neurological effects observed in the chronic exposure study by CIIT (1981). Other exposure-related nonneoplastic findings at 997 ppm following exposure for ≥18 months included hepatic lesions (centrilobular degeneration, karyomegaly, and cytomegaly), renal tubule hyperplasia, testicular seminiferous tubule degeneration and atrophy, splenic atrophy, and lymphoid depletion of the spleen and thymus. Carcinogenic findings included renal cortex adenocarcinomas and metastatic fibrosarcoma in the lungs of male mice at 997 ppm.

Table A-4. Summary of Neurological Effects Observed in Mice Following Chronic-Duration Inhalation Exposure to Chloromethane

Concentration (ppm)	Effect
51	Swelling and degeneration of axons in the spinal cord 18 months: 4/5 males, 10/10 females
224	Swelling and degeneration of axons in the spinal cord 18 months: 5/5 male, 10/10 females
997	Tremor and paralysis Swelling and degeneration of axons in the spinal cord 18 months: 3/7 males; no data on females 24 months: 13/18 females Minimal-to-mild degeneration of cerebellar granule cell neurons 18–24 months: 45/47 males, 35/37 females (minimal-to-moderate)

Source: CIIT 1981

Selection of the Point of Departure for the MRL: The LOAEL of 51 ppm for neurological effects in the study by CIIT (1981) was selected as the POD. Given that the data do not show a monotonic graded-dose response (Table A-4), BMD modeling was not used to derive this MRL.

Adjustment for Intermittent Exposure: The LOAEL was adjusted from intermittent exposure to account for a continuous exposure scenario:

$$LOAEL_{ADj} = LOAEL \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 51\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 9\ ppm$$

The HEC was calculated by multiplying the duration-adjusted LOAEL by the default ratio of 1 for air:blood partition coefficient for humans and rats (partition coefficient values are not available for chloromethane):

$$LOAEL_{HEC} = LOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 9\ ppm \times 1 = 9\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient ratio for animals (a) to humans (h)

Uncertainty factors used in MRL derivation: The following uncertainty factors were then applied to the $LOAEL_{HEC}$ to derive the MRL.

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

Subsequently, the MRL becomes:

$$MRL = \frac{LOAEL_{HEC}}{UFs} = \frac{9\ ppm}{300} = 0.03\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that neurological effects are a presumed health effect following inhalation exposure to chloromethane based on a low level of evidence from human studies and a high level of evidence from animal studies (see Appendix C).

There are shortcomings of the CIIT (1981) study that were considered in deriving the chronic-duration inhalation MRL. Specifically, some of the females were initially mis-sexed and placed in male cages. These animals were kept in their originally assigned cages for the study duration. Still, all animals received their assigned dose, regardless of sex. Therefore, this is unlikely to be of consequence to the study results. In addition, 4 months after the beginning of the study, mice from the 50-ppm group were accidentally exposed to 1,000 ppm, and 1,000 ppm group mice were accidentally exposed to 50 ppm for 3 days at 5.5 hours/day. CIIT (1981) acknowledged that this was a serious mistake but concluded that the mistake did not affect the validity of the results of the study, given the length of the dosing regimen. Additionally, no neurological effects were recorded at either 50 or 1,000 ppm at 6 months, so there appears to be little effect of this error on the results of the study. Therefore, ATSDR has concluded that CIIT (1981) is adequate to inform a chronic-duration inhalation MRL that provides appropriate public health protection. In contrast, EPA (2001) opted to base the chronic reference concentration (RfC) on Landry et al. (1985) due to concerns over procedural errors in CIIT (1981) and cerebellar lesions and mortality at lower administered concentrations in Landry et al. (1985) compared to CIIT (1981), suggesting increased sensitivity C57BL/6 mice, compared to B6C3F1 mice. However, it is not consistent with ATSDR guidance to use an acute-duration study (e.g., Landry et al. 1985) to inform a chronic-duration MRL. Of note, the chronic MRL of 0.03 ppm (0.06 mg/m^3) based on spinal cord lesions reported in the chronic study by CIIT (1981) is comparable to the chronic RfC of 0.09 mg/m^3 based on the acute study by Landry et al. (1985).

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: The database for deriving an acute-duration oral MRL is inadequate. The only identified study evaluating oral exposure to chloromethane was an acute-duration gavage study in which the hepatotoxic effects of chloroform, carbon tetrachloride, dichloroethane, and chloromethane were compared in rats (Reynolds and Yee 1967). In this study, no exposure-related histopathological changes were observed in rats exposed to a single dose of 420 mg/kg; no additional endpoints were evaluated. Due to the limited scope of this study and the lack of exposure-related effects, this study is not considered appropriate for derivation of an acute-duration oral MRL.

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No intermediate-duration oral studies were located for chloromethane. Subsequently, no MRL is proposed.

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration oral studies were located for chloromethane. Subsequently, no MRL is proposed.

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROMETHANE

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 chloromethane.

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 chloromethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of chloromethane 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 chloromethane are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for chloromethane released for public comment in 2022; thus, the literature search was restricted to studies published between January 2018 and June 2022. The following main databases were searched in June 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 chloromethane. 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 chloromethane 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	
06/2022	(74-87-3[rn] AND (2018:3000[mhda] OR 2018:3000[crdat] OR 2018:3000[edat] OR 2018:3000[dp])) OR ((("Chlormethan"[tw] OR "Chloromethane"[tw] OR "Methane, chloro-"[tw] OR "Methyl chloride"[tw] OR "Methylchloride"[tw] OR "Monochloromethane"[tw]) AND (2018:3000[crdat] OR 2018:3000[edat] OR 2018:3000[dp])) NOT medline[sb])
NTRL	
06/2022	"Chlormethan" OR "Chloromethane" OR "Methane, chloro-" OR "Methyl chloride" OR "Methylchloride" OR "Monochloromethane"
Toxcenter	
06/2022	FILE 'TOXCENTER' ENTERED AT 13:37:02 ON 15 JUN 2022 CHARGED TO COST=EH038.13.03.LB.04 L1 4179 SEA FILE=TOXCENTER 74-87-3 L2 4020 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 3345 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 348 SEA FILE=TOXCENTER L3 AND PY>=2018 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?) 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

Table B-2. Database Query Strings

Database search date	Query string
	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
	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 126 SEA FILE=TOXCENTER L4 AND L37
	L39 5 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
	L40 8 SEA FILE=TOXCENTER L38 AND BIOSIS/FS
	L41 113 SEA FILE=TOXCENTER L38 AND CAPLUS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L42 0 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 121 DUP REM L39 L40 L41 (5 DUPLICATES REMOVED) L*** DEL 5 S L38 AND MEDLINE/FS L*** DEL 5 S L38 AND MEDLINE/FS L44 5 SEA FILE=TOXCENTER L43 L*** DEL 8 S L38 AND BIOSIS/FS L*** DEL 8 S L38 AND BIOSIS/FS L45 6 SEA FILE=TOXCENTER L43 L*** DEL 113 S L38 AND CAPLUS/FS L*** DEL 113 S L38 AND CAPLUS/FS L46 110 SEA FILE=TOXCENTER L43 L47 116 SEA FILE=TOXCENTER (L44 OR L45 OR L46) NOT MEDLINE/FS D SCAN L47

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2022	74-87-3
NTP	
06/2022	“74-87-3” “Methyl chloride” “Chloromethane” “Chlormethan” “Methane, chloro-” “Methylchloride” “Monochloromethane”
Regulations.gov	
06/2022	Limited to dockets, or documents with DocType: Notice, Posted 01/01/2018 to 06/16/2022, Agency: EPA "Methyl chloride" "74-87-3"; "Chlormethan"; "Methane, chloro-"; "Methylchloride"; "Monochloromethane"; "Chloromethane"
NIH RePORTER	
09/2022	Fiscal Year: Active Projects; Text Search: "Chlormethan" OR "Chloromethane" OR "Methane, chloro-" OR "Methyl chloride" OR "Methylchloride" OR "Monochloromethane" (advanced) Limit to: Project 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): 183
- Number of records identified from other strategies: 26
- Total number of records to undergo literature screening: 209

B.1.2 Literature Screening

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

- 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.

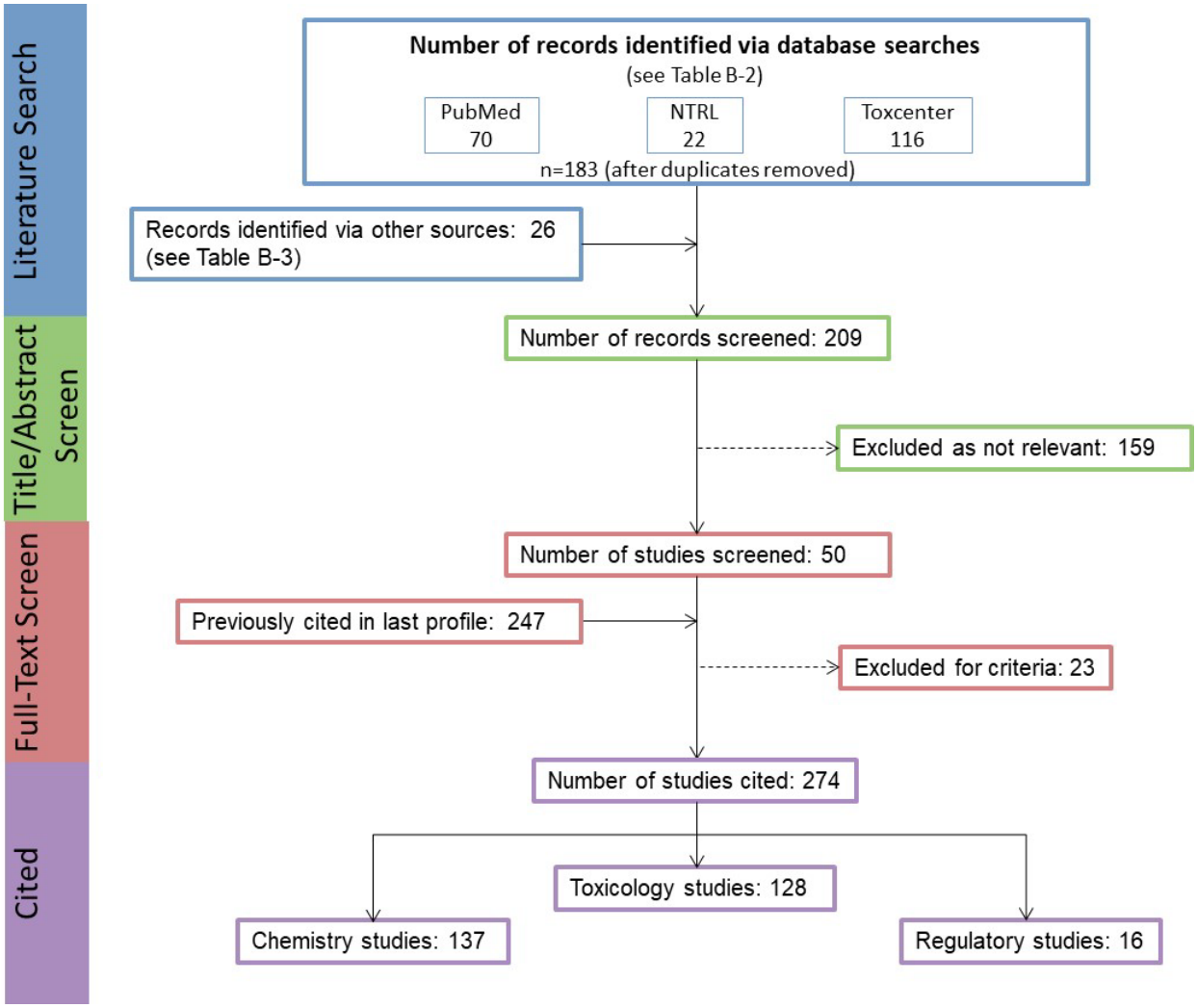
- Number of titles and abstracts screened: 209
- Number of studies considered relevant and moved to the next step: 50

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: 50
- Number of studies cited in the pre-public draft of the toxicological profile: 247
- Total number of studies cited in the profile: 274

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

Figure B-1. June 2022 Literature Search Results and Screen for Chloromethane



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

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 chloromethane, 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 chloromethane:

- 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 chloromethane. The inclusion criteria used to identify relevant studies examining the health effects of chloromethane 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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of chloromethane. 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 draft toxicological profile for chloromethane released for public comment in 2022. See Appendix B for the databases searched and the search strategy.

A total of 209 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

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 chloromethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 209 records were reviewed; 1 document was considered to meet the health effects inclusion criteria in Table C-1 and was 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 56 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 56 documents (96 studies), 35 documents (65 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 Chloromethane and overviews of the results of the inhalation and oral exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-2 and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for chloromethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include a limited number of controlled exposure and epidemiological studies and numerous case reports. When evaluated together, these studies suggest that the cardiovascular and neurological systems may be susceptible to chloromethane toxicity. Animal studies examined a comprehensive set of endpoints following inhalation exposure; oral studies were limited to a single acute-duration study evaluating hepatic endpoints, and no dermal studies were identified. Cardiovascular, hepatic, neurological, male reproductive, and developmental effects were considered sensitive outcomes following inhalation exposure in animals (i.e., effects were observed at low concentrations). Epidemiological and

experimental studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review; case studies were not included in the systematic review. There were 65 studies (published in 35 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Chloromethane 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			3										2				3
			2										1				1
Case control																	3
																	1
Population		1															
Case series		1	7	11	2		6	5		3			15	1		1	
			7	11	1		6	5		3			15	1		1	
Experimental		1	1		1								3				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

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 Chloromethane 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	13	9	3	6	4		18	19	2	2	4	5	27	16	3	3	
	9	6	1	1	2		15	13			2	3	26	11	3	3	
Intermediate-duration	7	10	7	6	7	7	8	8	7	5	4	7	13	8	2		
	4	3	1				4	1				1	6	2			
Chronic-duration	6	6	6	6	6	6	6	6	6	6	6	6	6	6			2
	4		4				4	3				2	2	5			1
Oral Studies																	
Acute-duration							1										
Intermediate-duration																	
Chronic-duration																	
Dermal studies																	
Acute-duration																	
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?

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

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 chloromethane health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Chloromethane – Epidemiology Studies

Reference	Risk of bias criteria and ratings: 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?***	Detection bias – **Is there confidence in the outcome assessment?***	Selective reporting bias – Were all measured outcomes reported?	Risk of bias tier
Outcome: Cardiovascular effects							
Cohort studies							
Holmes et al. 1986	++	–	+	–	–	++	Second
Rafnsson and Gudmundsson 1997	++	–	+	–	++	++	Second
Rafnsson and Kristbjornsdottir 2014	++	–	+	–	++	++	Second
Outcome: Neurological effects							
Cohort studies							
Gudmundsson 1977	–	– –	–	–	–	+	Third
Population studies							
NIOSH 1976	++	–	++	+	++	++	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Chloromethane – 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 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: Cardiovascular effects								
Inhalation acute exposure								
Stewart et al. 1980	–	–	–	–	+	–	++	Third
Outcome: Neurological effects								
Inhalation acute exposure								
Putz-Anderson et al. 1981a	–	–	–	– –	+	+	+	Second
Putz-Anderson et al. 1981b	–	–	–	–	+	+	+	Second
Stewart et al. 1980	–	–	–	–	+	–	++	Third

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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: Cardiovascular effects									
Inhalation acute exposure									
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First
von Oettingen et al. 1949, 1950 (dog)	–	–	–	–	+	++	–	+	Third
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (6 month, mouse)	++	++	+	–	++	+	++	++	First
McKenna et al. 1981b (rat)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (dog)	++	–	++	–	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	–	+	–	++	++	–	+	Second
Mitchell et al. 1979 (mouse)	++	–	+	–	– –	++	–	+	Second
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (12 months, mouse)	++	++	+	–	++	+	++	++	First
CIIT 1981 (18 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	–	++	+	++	++	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (24 months, mouse)	++	++	+	–	++	+	++	++	First
Outcome: Hepatic effects									
Inhalation acute exposure									
Burek et al. 1981 (48 hours, rat)	++	–	++	–	++	++	+	++	First
Burek et al. 1981 (72 hours, rat)	++	–	++	–	++	++	+	++	First
Chellman et al. 1986a (rat)	–	+	++	–	+	++	++	++	First
Chellman et al. 1986b (mouse)	–	+	++	–	–	+	+	+	First
Dunn and Smith 1947 (rat)	–	–	–	–	–	–	–	–	Third
Dunn and Smith 1947 (mouse)	–	–	–	–	–	–	–	–	Third
Dunn and Smith 1947 (guinea pig)	–	–	–	–	–	–	–	–	Third
Landry et al. 1985 (continuous, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (continuous, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (intermittent, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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
Landry et al. 1985 (intermittent, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First
Morgan et al. 1982 (B6C3F1 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C3H mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C57Bl/6 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (rat)	–	+	++	–	+	++	–	++	Second
Wolkowski-Tyl et al. 1981b, 1983b (mouse)	+	–	+	–	++	++	–	++	Second
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (6 months, mouse)	++	++	+	–	++	+	++	++	First
Dunn and Smith 1947 (rat)	–	–	–	–	–	–	–	–	Third
McKenna et al. 1981b (rat)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	–	++	–	+	++	+	+	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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
McKenna et al. 1981b (dog)	++	–	++	–	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	–	+	–	++	++	–	+	Second
Mitchell et al. 1979 (mouse)	++	–	+	–	– –	++	–	+	Second
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (12 months, mouse)	++	++	+	–	++	+	++	++	First
CIIT 1981 (18 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	–	++	+	++	++	First
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (24 months, mouse)	++	++	+	–	++	+	++	++	First
Outcome: Neurological effects									
Inhalation acute exposure									
Burek et al. 1981 (48 hours, rat)	++	–	++	–	++	++	+	++	First
Burek et al. 1981 (72 hours, rat)	++	–	++	–	++	++	+	++	First
Chellman et al. 1986a (rat)	–	+	++	–	+	++	++	++	First
Chellman et al. 1986b (mouse, 6 hours)	–	+	++	–	–	+	+	+	First
Chellman et al. 1986b (mouse, 2 weeks)	–	+	++	–	–	+	+	+	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Risk of bias tier
Jiang et al. 1985 (mouse)	–	–	++	–	++	+	+	+	First
Landry et al. 1985 (continuous, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (continuous, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (intermittent, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (intermittent, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First
Morgan et al. 1982 (B6C3F1 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C3H mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C57Bl/6 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (rat)	–	+	++	–	+	++	–	++	Second
Smith and von Oettingen 1947a, 1947b (monkey)	–	–	–	–	–	++	–	–	Third

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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
Smith and von Oettingen 1947a, 1947b (rat)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (mouse)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (guinea pig)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (dog)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (cat)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (rabbit)	–	–	–	–	–	++	–	–	Third
von Oettingen 1949, 1950 (mouse)	–	–	–	–	–	++	–	–	Third
von Oettingen 1949, 1950 (dog)	–	–	–	–	+	++	–	–	Third
Wolkowski-Tyl et al. 1983a (mouse)	–	–	++	–	+	++	–	++	Second
Wolkowski-Tyl et al. 1983b (mouse)	+	–	+	–	++	++	–	++	Second

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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									
CIIT 1981 (6 months, rat)	++	++	+	–	++	++	+	++	First
CIIT 1981 (6 months, mouse)	++	++	+	–	++	+	+	++	First
McKenna et al. 1981b (rat)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (dog)	++	–	++	–	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	–	+	–	++	++	–	+	Second
Mitchell et al. 1979 (mouse)	++	–	+	–	– –	++	–	+	Second
Smith and von Oettingen 1947a, 1947b (monkey)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (rat)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (mouse)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (guinea pig)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (dog)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (cat)	–	–	–	–	–	++	–	–	Third

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Risk of bias tier
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	–	+	++	+	++	First
CIIT 1981 (12 months, mouse)	++	++	+	–	+	+	+	++	First
CIIT 1981 (18 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	–	++	+	++	++	First
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (24 months, mouse)	++	++	+	–	++	+	++	++	First
Outcome: Male reproductive effects									
Inhalation acute exposure									
Burek et al. 1981 (48 hours, rat)	++	–	++	–	++	++	+	++	First
Burek et al. 1981 (72 hours, rat)	++	–	++	–	++	++	+	++	First
Chapin et al. 1984 (rat)	–	–	++	–	++	++	+	++	First
Chellman et al. 1986a (rat)	–	+	++	–	+	+	++	++	First
Chellman et al. 1986c (rat)	–	+	++	–	–	+	+	+	First
Chellman et al. 1987 (rat)	+	+	++	–	+	++	+	+	First
Morgan et al. 1982 (rat)	–	+	++	–	+	++	–	++	Second
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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
Working et al. 1985a (rat)	+	–	++	–	–	++	+	++	First
Working et al. 1985b (rat)	++	–	++	–	+	++	–	++	Second
Working and Bus 1986 (rat)	+	–	+	–	+	+	+	++	First
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (6 months, mouse)	++	++	+	–	+	+	++	++	First
Hamm et al. 1985 (rat)	+	–	–	–	–	+	+	++	Second
McKenna et al. 1981b (rat)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (beagle)	++	–	++	–	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	–	+	–	++	++	–	+	Second
Mitchell et al. 1979 (mouse)	++	–	+	–	++	++	–	+	Second
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (12 months, mouse)	++	++	+	–	+	+	++	++	First
CIIT 1981 (18 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	–	+	+	++	++	First
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – 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 there 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
CIIT 1981 (24 months, mouse)	++	++	+	–	+	+	++	++	First
Outcome: Developmental effects									
Inhalation acute exposure									
Wolkowski-Tyl et al. 1983a (mouse)	–	–	++	–	+	++	+	++	First
Wolkowski-Tyl et al. 1983a (rat)	–	–	++	+	++	++	+	++	First
Wolkowski-Tyl et al. 1983b (mouse)	+	–	+	–	++	++	+	++	First
Inhalation intermediate exposure									
Hamm et al. 1985 (rat)	+	–	–	–	–	+	+	++	Second
Theuns-van Vliet 2016 (rabbit)	–	–	++	–	++	++	–	+	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

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 chloromethane 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 chloromethane 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-11, C-12, and C-13, 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-11. 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-12. 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-13. 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 cardiovascular, hepatic, renal, neurologic, reproductive and developmental effects.

A summary of the initial confidence ratings for each outcome is presented in Tables C-14, C-15, C-16, and C-17. 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 Tables C-14, C-15, C-16, and C-17.

Table C-14. Presence of Key Features of Study Design for Chloromethane—Observational Epidemiology Studies

Reference	Key features				
	Controlled Exposure	Exposure prior to outcome	Outcome assess on individual level	Comparison group	Initial study confidence
Outcome: Cardiovascular effects					
Cohort studies					
Holmes et al. 1986	No	Yes	Yes	Yes	Moderate
Rafnsson and Gudmundsson 1997	No	Yes	Yes	Yes	Moderate
Rafnsson and Kristbjornsdottir 2014	No	Yes	Yes	Yes	Moderate
Outcome: Neurological effects					
Cohort studies					
Gudmundsson 1977	No	Yes	Yes	No	Low
Population studies					
NIOSH 1976	No	Yes	Yes	Yes	Moderate

Table C-15. Presence of Key Features of Study Design for Chloromethane—Experimental Controlled Human 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: Cardiovascular effects					
Inhalation acute exposure					
Stewart et al. 1980	Yes	No	No	Yes	Low
Outcome: Neurological effects					
Inhalation acute exposure					
Putz-Anderson et al. 1981a	Yes	Yes	Yes	Yes	High
Putz-Anderson et al. 1981b	Yes	Yes	Yes	Yes	High
Stewart et al. 1980	Yes	No	Yes	Yes	Moderate

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Cardiovascular effects					
Inhalation acute exposure					
McKenna et al. et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate
McKenna et al. et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
von Oettingen et al. 1949, 1950	No	Yes	Yes	No	Low
Inhalation intermediate exposure					
CIIT 1981 (6 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (6 months, mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	No	Yes	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (12 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Burek et al. 1981 (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986a (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986b (mouse)	Yes	Yes	Yes	Yes	High
Landry et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
Dunn and Smith 1947 (rat)	No	Yes	Yes	No	Low
Dunn and Smith 1947 (mouse)	No	Yes	Yes	No	Low
Dunn and Smith 1947 (guinea pig)	No	Yes	Yes	No	Low
McKenna et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
McKenna et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
Morgan et al. 1982 (mouse)	Yes	Yes	Yes	Yes	High
Morgan et al. 1982 (rat)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
CIIT 1981 (6 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (6 months, mouse)	Yes	Yes	Yes	Yes	High
Dunn and Smith 1947 (rat)	No	Yes	Yes	No	Low
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	No	Yes	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (12 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute exposure					
Burek et al. 1981 (rat)	Yes	Yes	No	Yes	Moderate
Chellman et al. 1986a (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986b (mouse, 6 hours)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986b (mouse, 2 weeks)	Yes	Yes	Yes	Yes	High
Jiang et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
Landry et al. 1985 (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate
McKenna et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
Morgan et al. 1982 (mouse)	Yes	Yes	Yes	Yes	High
Morgan et al. 1982 (rat)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Smith and von Oettingen 1947a, 1947b (monkey)	No	No	Yes	No	Low
Smith and von Oettingen 1947a, 1947b (rat)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (mouse)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (guinea pig)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (dog)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (cat)	No	No	Yes	No	Very low
Smith and von Oettingen 1947a, 1947b (rabbit)	Yes	No	Yes	No	Low
von Oettingen 1949, 1950 (mouse)	No	Yes	Yes	No	Low
von Oettingen 1949, 1950 (dog)	No	Yes	No	No	Very low
Wolkowski-Tyl et al. 1983a (mouse)	Yes	Yes	Yes	Yes	High
Wolkowski-Tyl et al. 1983b (mouse)	Yes	Yes	No	Yes	Moderate
Inhalation intermediate exposure					
CIIT 1981 (6 months, Rat)	Yes	Yes	No	Yes	Moderate
CIIT 1981 (6 months, mouse)	Yes	Yes	No	Yes	Moderate
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	Yes	No	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High
Smith and von Oettingen 1947a, 1947b (monkey)	No	No	Yes	No	Low
Smith and von Oettingen 1947a, 1947b (rat)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (mouse)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (guinea pig)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (dog)	Yes	Yes	Yes	No	Moderate

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Smith and von Oettingen 1947a, 1947b (cat)	No	No	Yes	No	Very low
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	No	Yes	Moderate
CIIT 1981 (12 months mouse)	Yes	Yes	No	Yes	Moderate
CIIT 1981 (18 months, rats	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Male reproductive effects					
Inhalation acute exposure					
Burek et al. 1981 (rat)	Yes	Yes	Yes	Yes	High
Chapin et al. 1984 (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986a (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986c (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1987 (rat)	Yes	Yes	Yes	Yes	High
Morgan et al. 1982 (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate
McKenna et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
Working et al. 1985a (rat)	Yes	Yes	Yes	Yes	High
Working et al. 1985b (rat)	Yes	Yes	Yes	Yes	High
Working and Bus 1986 (rat)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
CIIT 1981 (6 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (6 months, mouse)	Yes	Yes	Yes	Yes	High
Hamm et al. 1985 (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	No	Yes	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (12 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation acute exposure					
Wolkowski-Tyl et al. 1983a (mouse)	Yes	Yes	Yes	Yes	High
Wolkowski-Tyl et al. 1983a (rat)	Yes	Yes	Yes	Yes	High
Wolkowski-Tyl et al. 1983b (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Hamm et al. 1985 (rat)	Yes	Yes	Yes	Yes	High
Theuns-van Vliet 2016 (rabbit)	Yes	Yes	Yes	Yes	High

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Cardiovascular effects		
Inhalation acute exposure		
Human studies		
Stewart et al. 1980	Low	Moderate
Rafnsson and Gudmundsson 1997	Moderate	
Rafnsson and Kristbjornsdottir 2014	Moderate	
Animal studies		
McKenna et al. et al. 1981a (Beagle)	Moderate	Moderate
McKenna et al. et al. 1981a (cat)	Moderate	
von Oettingen et al. 1949, 1950	Low	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Animal studies		
CIIT 1981 (6 months, rat)	High	High
CIIT 1981 (6 months, mouse)	High	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	
Mitchell et al. 1979 (mouse)	High	
Inhalation chronic exposure		
Human studies		
Holmes et al. 1986	Moderate	Moderate
Animal studies		
CIIT 1981 (12 months, rat)	High	High
CIIT 1981 (12 months, mouse)	High	
CIIT 1981 (18 months, rat)	High	
CIIT 1981 (18 months, mouse)	High	
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Hepatic effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	High	High
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse)	High	
Dunn and Smith 1947 (rat)	Low	
Dunn and Smith 1947 (mouse)	Low	
Dunn and Smith 1947 (guinea pig)	Low	
Morgan et al. 1982 (mouse)	High	
Morgan et al. 1982 (rat)	High	
Landry et al. 1985 (mouse)	Moderate	
McKenna et al. 1981a (dog)	Moderate	
McKenna et al. 1981a (cat)	Moderate	
Inhalation intermediate exposure		
CIIT 1981 (6 months, rat)	High	High
CIIT 1981 (6 months, mouse)	High	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Mitchell et al. 1979 (mouse)	High	
Inhalation chronic exposure		
Animal studies		
CIIT 1981 (12 months, rat)	High	High
CIIT 1981 (12 months, mouse)	High	
CIIT 1981 (18 months, rat)	High	
CIIT 1981 (18 months, mouse)	High	
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	Moderate	High
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse, 6 hours)	High	
Chellman et al. 1986b (mouse, 2 weeks)	High	
Jiang et al. 1985 (mouse)	Moderate	
Morgan et al. 1982 (mouse)	High	
Morgan et al. 1982 (rat)	High	
Landry et al. 1985 (mouse)	High	
McKenna et al. 1981a (dog)	Moderate	
McKenna et al. 1981a (cat)	Moderate	
Smith and von Oettingen 1947a, 1947b (monkey)	Low	
Smith and von Oettingen 1947a, 1947b (rat)	Moderate	
Smith and von Oettingen 1947a, 1947b (mouse)	Moderate	
Smith and von Oettingen 1947a, 1947b (guinea pig)	Moderate	
Smith and von Oettingen 1947a, 1947b (dog)	Moderate	
Smith and von Oettingen 1947a, 1947b (cat)	Very low	
Smith and von Oettingen 1947a, 1947b (rabbit)	Low	
von Oettingen 1949, 1950 (mouse)	Low	
von Oettingen 1949, 1950 (dog)	Very low	
Wolkowski-Tyl et al. 1983a (mouse)	High	
Wolkowski-Tyl et al. 1983b (mouse)	Moderate	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Human studies		
Gudmundsson 1977	Low	High
NIOSH 1976	Moderate	
Putz-Anderson et al. 1981a	High	
Putz-Anderson et al. 1981b	High	
Stewart et al. 1980	Moderate	
Inhalation intermediate exposure		
Animal studies		
CIIT 1981 (6 months, rat)	Moderate	High
CIIT 1981 (6 months, mouse)	Moderate	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	
Mitchell et al. 1979 (mouse)	Moderate	
Smith and von Oettingen 1947a, 1947b (monkey)	Low	
Smith and von Oettingen 1947a, 1947b (rat)	Moderate	
Smith and von Oettingen 1947a, 1947b (mouse)	Moderate	
Smith and von Oettingen 1947a, 1947b (guinea pig)	Moderate	
Smith and von Oettingen 1947a, 1947b (dog)	Moderate	
Smith and von Oettingen 1947a, 1947b (cat)	Very low	
Inhalation chronic exposure		
Animal studies		
CIIT 1981 (12 months, rat)	Moderate	High
CIIT 1981 (12 months, mouse)	Moderate	
CIIT 1981 (18 months, rat)	High	
CIIT 1981 (18 months, mouse)	High	
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Male reproductive effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	High	High
Chapin et al. 1984 (rat)	High	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986c (rat)	High	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Chellman et al. 1987 (rat)	High	
Morgan et al. 1982 (rat)	High	
McKenna et al. 1981a (dog)	Moderate	
McKenna et al. 1981a (cat)	Moderate	
Working et al. 1985a	High	
Working et al. 1985b	High	
Working and Bus 1986	High	
Inhalation intermediate exposure		
Animal studies		
CIIT 1981 (6 months, rat)	High	
CIIT 1981 (6 months, mouse)	High	
Hamm et al. 1985 (rat)	High	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	High
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	
Mitchell et al. 1979 (mouse)	High	
Inhalation chronic exposure		
Animal studies		
CIIT 1981 (12 months, rat)	High	
CIIT 1981 (12 months, mouse)	High	
CIIT 1981 (18 months, rat)	High	
CIIT 1981 (18 months, mouse)	High	High
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Wolkowski-Tyl et al. 1983a (mouse)	High	
Wolkowski-Tyl et al. 1983a (rat)	High	High
Wolkowski-Tyl et al. 1983b (mouse)	High	
Inhalation intermediate exposure		
Animal studies		
Hamm et al. 1985 (rat)	High	High
Theuns-van Vliet 2016 (rabbit)	High	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 cardiovascular, renal, hepatic, neurologic, reproductive, and developmental effects are presented in Table C-18. 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 chloromethane exposure is presented in Table C-19.

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

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Cardiovascular effects			
Human studies	Moderate	-1 risk of bias -1 imprecision	Very low
Animal studies	Moderate	-1 unexplained inconsistency -1 imprecision	Very low
Outcome: Hepatic Effects			
Animal studies	High	None	High
Outcome: Neurological Effects			
Human studies	High	-1 risk of bias -1 imprecision	Low
Animal studies	High	+Consistency +Large magnitude of effect	High
Outcome: Male reproductive Effects			
Animal studies	High	None	High
Outcome: Developmental Effects			
Animal studies	High	-1 indirectness -1 unexplained inconsistency	Low

Table C-19. Confidence in the Body of Evidence for Chloromethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Cardiovascular	Very low	Very low
Hepatic	No data	High
Neurological	Low	High
Reproductive	No data	High
Developmental	No data	Low

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 chloromethane, 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 chloromethane is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Chloromethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Cardiovascular	Very low	Health effect	Inadequate
Hepatic	No data	No data	Inadequate
Neurological	Low	Health effect	Low
Male Reproductive	No data	No data	Inadequate
Developmental	No data	No data	Inadequate
Animal studies			
Cardiovascular	Very low	Health effect	Inadequate
Hepatic	High	Health effect	High
Neurological	High	Health effect	High
Male Reproductive	High	Health effect	High
Developmental	Low	Health effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

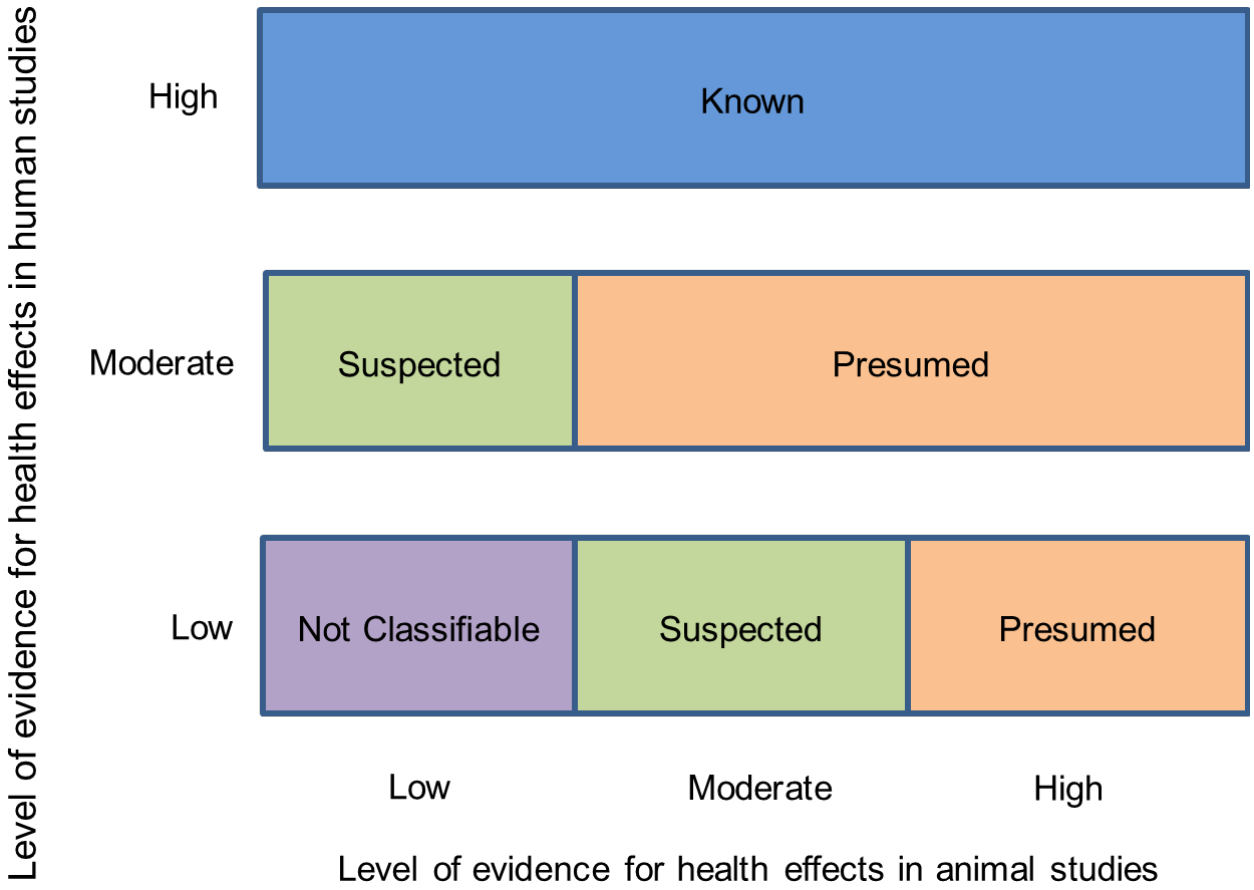
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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 chloromethane are listed below and summarized in Table C-21.

Presumed Health Effects

- Hepatic effects following inhalation exposure
  - No evidence from human studies was evaluated in the systematic review.
  - High level of evidence of hepatic lesions in rats and mice following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Landry et al. 1985; Morgan et al. 1982), intermediate durations (CIIT 1981), or chronic durations (CIIT 1981).
- Neurologic effects following inhalation exposure
  - Low level of evidence from human studies, with one occupational cohort study reporting neurological effects, some lasting years after exposure, following exposure to high levels of chloromethane (Gudmundsson 1977), but one occupational cohort study (NIOSH 1976) and three human controlled trials that did not show significant nervous system effects with low levels of exposure to chloromethane (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980).
  - High level of evidence for a range of neurological effects in rats, mice, and dogs, including clinical signs of neurotoxicity, motor impairments, and lesions in the cerebellum and spinal cord. Neurological effects were observed following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b; von Oettingen et al. 1949, 1950; Wolkowski-Tyl et al. 1983a, 1983b), intermediate durations (McKenna et al. 1981b; Smith and von Oettingen et al. 1947b), or chronic durations (CIIT 1981).
- Male reproductive effects following inhalation exposure
  - No evidence from human studies was evaluated in the systematic review.
  - High level of evidence of adverse effects on the male reproductive system of rats, including sperm effects, testicular lesions, and infertility, following inhalation exposure for acute durations (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1986c, 1987; Morgan et al. 1982; Working and Bus 1986; Working et al. 1985a, 1985b), intermediate durations (CIIT 1981; Hamm et al. 1985), or chronic durations (CIIT 1981). In mice, testicular lesions were observed after chronic-duration inhalation exposure (CIIT 1981); reproductive function has not been assessed in mice.

Not Classifiable Health Effects

- Cardiovascular effects following inhalation exposure
  - Although occupational cohort studies suggest adverse cardiovascular outcomes (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014), the human data were considered inadequate for evaluating the potential hazard due to the moderate initial confidence in these studies, their imprecision, and the high risk of bias.
  - Animal data are inadequate to evaluate the potential hazard. One study in dogs reported increased blood pressure and heart rate followed by a precipitous drop in blood pressure prior to death at very high concentrations; these effects are likely secondary to CNS depression (von Oettingen 1949, 1950). No other studies evaluating cardiovascular function were identified. Some studies reported elevated heart weight in rats and mice following intermediate- or chronic-duration exposure (CIIT 1981; McKenna et al. 1981b); however, no histopathologic lesions were noted in any inhalation study (CIIT 1981; McKenna et al. 1981a, 1981b; Mitchell et al. 1979).
- Developmental effects following inhalation exposure
  - No evidence from human studies was evaluated in this systematic review for developmental endpoints.
  - Low evidence of an association between chloromethane exposure and adverse developmental outcomes. In rats, developmental effects were limited to decreased fetal growth and delayed skeletal development at concentrations associated with severe maternal toxicity (Wolkowski-Tyl et al. 1983a). In mice, heart malformations were observed following gestational exposure

(Wolkowski-Tyl et al. 1983a, 1983b). In rabbits, no developmental effects were noted following gestational exposure (Theuns-van Vliet 2016). The lack of cardiac findings in rats and rabbits brings into question whether the effects seen in the mice were specific to that species; and whether there is human health relevance for the cardiac malformation findings.

Table C-21. Hazard Identification Conclusions for Chloromethane

Outcome	Hazard identification
Cardiovascular	Not classifiable
Hepatic	Presumed
Neurologic	Presumed
Male reproductive	Presumed
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)

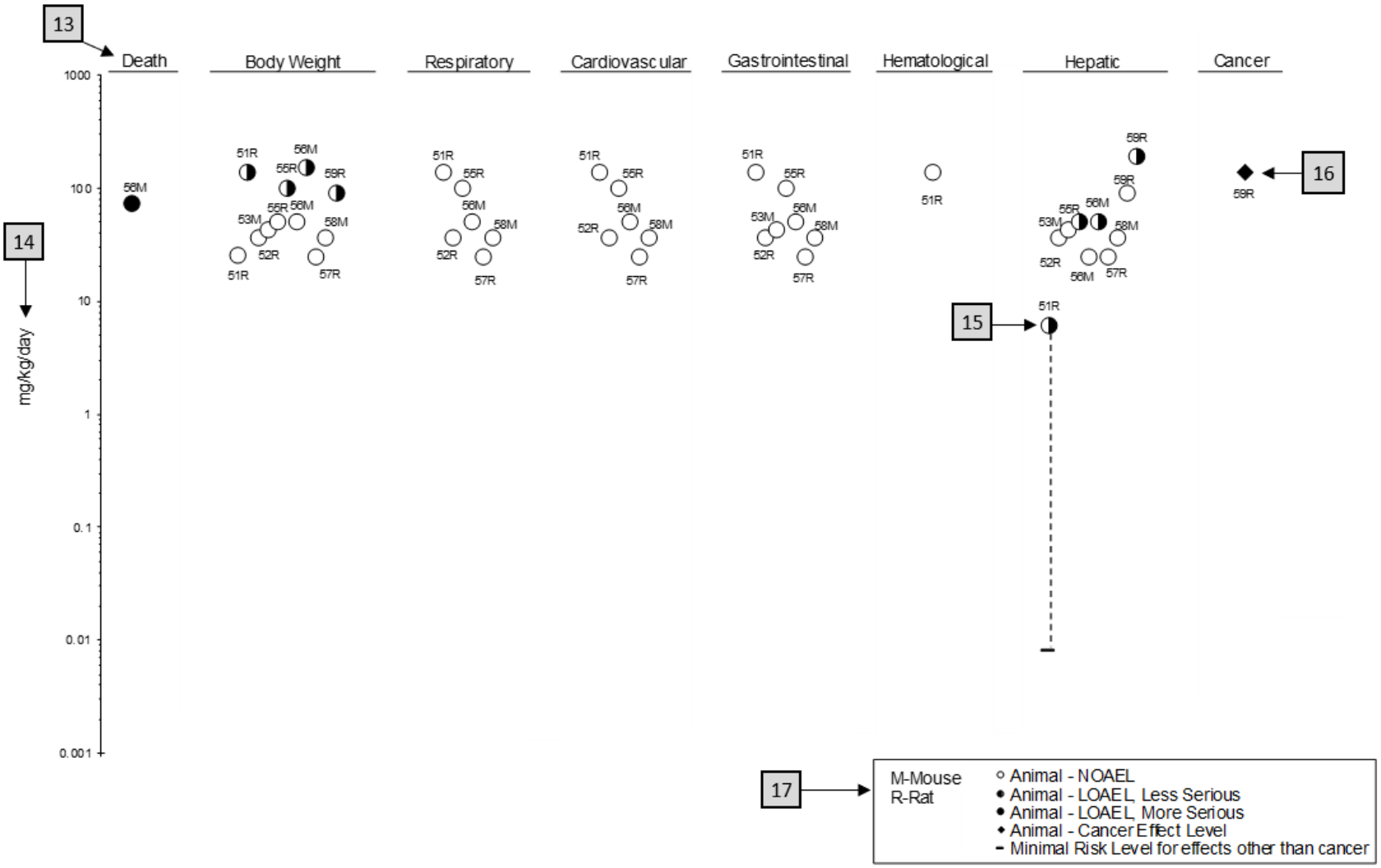
Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 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:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.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 tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX 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 Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	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