APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances 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*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 1 ppm (6 mg/m^3)
Critical Effect: Neurological endpoint of decreased performance in psychomotor tests
Reference: Mackay et al. 1987
Point of Departure: LOAEL of 175 ppm (950 mg/m^3); $LOAEL_{ADJ}$ of 119 ppm (650 mg/m^3)
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Human

MRL Summary: An acute-duration inhalation MRL of 1 ppm (6 mg/m^3) was derived for 1,1,1-trichloroethane based on a neurological endpoint of decreased performance in psychomotor tests in humans administered 1,1,1-trichloroethane via inhalation (Mackay et al. 1987). The MRL is based on a LOAEL of 175 ppm, which was applied to a PBPK model to estimate the 24-hour continuous exposure concentration for exposed humans that would result in the same estimated internal dose. This resulted in an adjusted LOAEL of 119 ppm, which was then divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of 1,1,1-trichloroethane following acute-duration inhalation exposure, although the majority of the studies with more sensitive endpoints focused on neurological endpoints (Evans and Balster 1993; Gamberale and Hultengren 1973; Mackay et al. 1987; Nilsson 1986b; NIOSH 1975; Stewart et al. 1969). Evans and Balster (1993) observed convulsions in mice after 4 days of 24 hour/day exposure to 500 ppm 1,1,1-trichloroethane, which is regarded as a serious effect. Thus, only effects observed at concentrations <500 ppm were considered for the critical effect. Nilsson (1986b) observed a reduction in brain cyclic guanosine monophosphate (cGMP) at 100 ppm, although these results were only presented graphically and were observed in a mouse model rather than in a human. Human studies are generally preferred to animal studies when available, and both Gamberale and Hultengren (1973) and Mackay et al. (1987) were studies conducted in humans. The data from these human studies suggest that decreased performance in psychomotor tests is the most sensitive endpoint following acute-duration inhalation exposure. A summary of select LOAELs is presented in Table A-1.

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

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Human	4 exposures 30 minutes/exposure	239.2	338.3	12.8% decrease in reaction time, 22.6% decrease in perceptual speed, 9.8% decrease in manual dexterity	Gamberale and Hultengren 1973
Human	3.5 hours		175	10–15% decrease in simple reaction time	Mackay et al. 1987

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

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse NS	4 hours	50	100	~33% decrease in brain cGMP	Nilsson 1986b

cGMP = cyclic guanosine monophosphate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

Selection of the Principal Study: Mackay et al. (1987) evaluated the neurological and toxicological effects of 1,1,1-trichloroethane inhalation in humans. The LOAEL reported by Mackay et al. (1987) for a 10–15% decrease in simple reaction time was the lowest among the studies evaluating acute-duration inhalation exposure in humans. The Mackay et al. (1987) study was also selected by the EPA for the derivation of an acute-duration inhalation reference concentration (RfC) for 1,1,1-trichloroethane. The same methodology used to derive the acute-duration inhalation RfC was used to derive the acute-duration inhalation MRL.

Summary of the Principal Study:

Mackay CJ, Campbell L, Samuel AM, et al. 1987. Behavioral changes during exposure to 1,1,1-trichloroethane: Time-course and relationship to blood solvent levels. Am J Ind Med 11:223-240.

Twelve male volunteers participated in the experiment. Exposures were to 0, 175, or 350 ppm of 1,1,1-trichloroethane for 3.5 hours. Each volunteer was exposed to all three exposure concentrations in a balanced design, with a minimum of 2 weeks between exposures for any one individual. Test performance was assessed immediately before entering the exposure chamber and 20, 60, 120, and 180 minutes after entry. Tests were conducted for three psychomotor tasks (simple reaction time, choice reaction time, and tracking ability) and two cognitive tasks (syntactic reasoning and concentration). Volunteers also completed a stress-arousal checklist as part of the test battery. Blood levels of 1,1,1-trichloroethane were measured after 0, 20, 60, 120, and 180 minutes of exposure. Statistical analysis of variance to determine the main effects of exposure and duration was performed for the various tests, but pairwise statistical comparisons were not made.

The tests for simple reaction time, choice reaction time and tracking ability all showed impaired psychomotor performance in volunteers exposed to 1,1,1-trichloroethane concentrations of 175 and 350 ppm. Effects were detected as soon as 20 minutes after the start of exposure at both concentrations. The test for simple reaction time appeared to be the most sensitive, exhibiting a 10–15% increase over baseline values. Observed performance changes correlated with 1,1,1-trichloroethane absolute blood levels. Performance in the cognitive tasks was not adversely affected by exposure, and neither was the self-reported mood of the volunteers. None of the subjects complained of headache, discomfort, or nausea.

Selection of the Point of Departure for the MRL: The lowest concentration administered, 175 ppm (950 mg/m^3), is a LOAEL for neurobehavioral effects. Benchmark dose (BMD) modeling was unable to be performed adequately because the study authors did not provide standard deviations of the means with their results. EPA (2006) used a PBPK model by Reitz et al. (1988) to estimate the internal dose in humans exposed to 950 mg/m^3 1,1,1-trichloroethane for 1 hour. The estimated internal dose is 1.33 mg/L.

Adjustment for Intermittent Exposure: The Reitz et al. (1988) model was used to estimate the 24-hour continuous exposure concentration that achieves the estimated internal dose of 1.33 mg/L. The resulting $LOAEL_{ADJ}$ is 119 ppm (650 mg/m^3).

Uncertainty Factor: The $LOAEL_{ADJ}$ is divided by a total uncertainty factor of 100:

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

MRL = LOAEL ÷ uncertainty factors
119 ppm ÷ (10 x 10) = 1.19 ppm (6.497 mg/m^3) ≈ 1 ppm (6 mg/m^3)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: EPA derived an acute-duration inhalation RfC for 1,1,1-trichloroethane of 1.1 ppm for a 24-hour exposure based on the Mackay et al. (1987) study. Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. All tasks tested were affected, including simple reaction time, choice reaction time, and tests for manual dexterity and perceptual speed. Statistically significant deficits were found as early as exposure period #2, during which the exposure concentration was 350 ppm. Muttray et al. (1999, 2000) found electroencephalogram changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. In contrast, no psychomotor effects were seen in volunteers exposed to 1,1,1-trichloroethane vapors at concentrations of 400–450 ppm for 4 hours once or twice in a 24-hour period (Salvini et al. 1971; Savolainen et al. 1981). Laine et al. (1996) found no consistent, statistically significant effects on electroencephalogram, visual-evoked potential, or equilibrium in a group of nine healthy male volunteers exposed to a constant 200 ppm of 1,1,1-trichloroethane vapors for 3 hours, followed by a 40-minute lunch break and a 40-minute afternoon exposure. A conservative approach was followed in the selection of Mackay et al. (1987) as the critical study for derivation of an acute-duration inhalation MRL because it identified the lowest LOAEL for psychomotor effects in humans following acute-duration inhalation exposure to 1,1,1-trichloroethane and was supported by results of Gamberale and Hultengren (1973) and Muttray et al. (1999, 2000). The choice of critical effect (neurological changes) is supported by animal studies, although exposure levels eliciting neurobehavioral and neurophysiological effects were much higher than those eliciting psychomotor effects in humans. For example, increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (De Ceaurriz et al. 1983). Dow Chemical (1990) reported 1,1,1-trichloroethane-induced alterations in flash-evoked potential, somatosensory-evoked potential, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours/day on 4 consecutive days.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.7 ppm (4 mg/m^3)
Critical Effect: Neurological endpoint of increased GFAP in brain indicative of neuronal damage
Reference: Rosengren et al. 1985
Point of Departure: NOAEL of 70 ppm
Uncertainty Factor: 100
LSE Graph Key: 74
Species: Gerbil

MRL Summary: An intermediate-duration inhalation MRL of 0.7 ppm (4 mg/m^3) was derived for 1,1,1-trichloroethane based on neurological endpoint of increased GFAP in gerbils administered 1,1,1-trichloroethane via continuous inhalation exposure (Rosengren et al. 1985). The MRL is based on a NOAEL of 70 ppm divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect*:** A number of studies have evaluated the toxicity of 1,1,1-trichloroethane following intermediate-duration inhalation exposure. Prendergast et al. (1967) observed substantial reductions in body weight gain at 380 ppm for both dogs and rabbits when exposed 24 hours/day for 90 days. This exposure resulted in a 51% reduction in body weight gain for dogs and a 66% reduction in body weight gain for rabbits; both of these endpoints are classified as serious LOAELs. Thus, only two studies, Rosengren et al. (1985) and MacEwen and Vernot (1974), observed effects at concentrations <380 ppm; a summary of these LOAELs is presented in Table A-2.

Table A-2. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to 1,1,1-Trichloroethane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Gerbil Mongolian	3 months 24 hours/day	70	210 (serious LOAEL)	20% increase in GFAP	Rosengren et al. 1985
Hepatic effects					
Mouse NS	14 weeks 24 hours/day		250	Fatty changes in the liver	MacEwen and Vernot 1974

GFAP = glial fibrillary acid protein; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

The available data suggest that increased GFAP in the brain is the most sensitive endpoint following intermediate-duration inhalation exposure. In gerbils, a 20% increase in GFAP in the brain was seen at concentrations of 210–1,000 ppm, and a NOAEL of 70 ppm was observed (Rosengren et al. 1985).

Selection of the Principal Study: Rosengren et al. (1985) evaluated neurological and toxicological effects of 1,1,1-trichloroethane inhalation in humans. The NOAEL reported by Rosengren et al. (1985) for an increase in GFAP was the lowest among the studies evaluating intermediate-duration inhalation exposure.

Summary of the Principal Study:

Rosengren LE, Aurell A, Kjellstrand P, et al. 1985. Astrogliosis in the cerebral cortex of gerbils after long-term exposure to 1,1,1-trichloroethane. Scand J Work Environ Health 11:447-455.

Groups of Mongolian gerbils (four/sex) were exposed to 70, 210, or 1,000 ppm of 1,1,1-trichloroethane vapor (cleaning grade, containing 5% dioxane-free stabilizers) continuously for 3 months. Each exposure group was paired with a control group consisting of eight sex-matched littermates of the test group. At the end of the exposure period, all animals were held for 4 months prior to sacrifice. Upon sacrifice, brains were weighed and prepared for analyses for the astroglial proteins, S-100 and GFAP, both of which are biomarkers for astrogliosis. Astrogliosis is the activation of cellular processes in the central nervous system aimed at protecting and repairing damage to the brain in response to neural toxicity. Astrogliosis is generally accompanied by a rapid synthesis of GFAP (Eng et al. 2000); thus, an increase in GFAP is considered one of the first indicators of a deviation from normal physiology (Brahmachari et al. 2006).

Levels of GFAP in the sensorimotor cerebral cortex were significantly increased in gerbils exposed to 210 or 1,000 ppm of 1,1,1-trichloroethane, but not those exposed to 70 ppm. Levels of S-100 were not affected by treatment. Total protein levels were also unaffected by treatment. Brain weight was significantly reduced in gerbils exposed to 1,000 ppm.

Selection of the Point of Departure for the MRL: The lowest concentration administered, 70 ppm, is a NOAEL for neurotoxic effects. BMD modeling was not attempted as the data representing measurements of GFAP were not presented in a way that allowed for precise measurement of response.

Adjustment for Intermittent Exposure: As the gerbils in Rosengren et al. (1985) were continuously exposed for 3 months, there was no need to adjust for intermittent exposure. Therefore, the NOAEL of 70 ppm was not adjusted for exposure duration.

Uncertainty Factor: The NOAEL is divided by a total uncertainty factor of 100

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

MRL = NOAEL ÷ uncertainty factors
70 ÷ (10 x 10) = 0.7 ppm (4 mg/m^3)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The choice of neurological effects as the critical end point of 1,1,1-trichloroethane toxicity is supported by both human and animal studies, which identified the nervous system as a particularly sensitive target of 1,1,1-trichloroethane toxicity following short-term exposures. For example, Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. Mackay et al. (1987) reported psychomotor deficits in human subjects exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours. Increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (De Ceaurriz et al. 1983). Dow Chemical (1990) reported 1,1,1-trichloroethane-induced alterations in flash-evoked potential, SEP, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours/day on 4 consecutive days. Mattsson et al. (1993) noted decreased forelimb grip

strength in rats exposed to 2,000 ppm of 1,1,1-trichloroethane, 6 hours/day, 5 days/week for 13 weeks. Bowen and Balster (2006) observed a 166% increase in locomotor activity in mice exposed to 6,000 ppm of 1,1,1-trichloroethane, 30 minutes/day for 15 days.

Qualitative and quantitative analysis of GFAP has shown it to be a sensitive and specific indicator of gliosis, a hallmark feature of injury to the central nervous system (O'Callaghan and Sriram 2005). O'Callaghan and Sriram (2005) examined the effects of numerous known toxicants on GFAP and reported an increase in GFAP that is rapid, linked to the location of damage, and can occur at doses well below those associated with behavioral change. Although Rosengren et al. (1985) observed an increase in GFAP that was not accompanied by an increase in another marker of gliosis, S-100; there are no known or established relationships between changes in GFAP and changes in S-100 (O'Callaghan and Sriram 2005). This suggests that the increase in GFAP observed in Rosengren et al. (1985) is a valid indicator of neurotoxicity, even without additional neurotoxic or behavioral observations accompanying the change.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: An MRL has not been derived for chronic-duration inhalation exposure to 1,1,1-trichloroethane because the database is insufficient. No adverse effects were observed in humans occupationally exposed to 1,1,1-trichloroethane at exposures up to 200 ppm (Kramer et al. 1978; Maroni et al. 1977). NOAELs and LOAELs for animals exposed chronically to inhaled 1,1,1-trichloroethane are summarized in Table A-3. The only noncancer endpoint observed in the chronic-duration inhalation database in animals was mild histopathological changes in the liver of rats exposed to 1,500 ppm 1,1,1-trichloroethane for 104 weeks (5 days/week, 6 hours/day), with a NOAEL of 500 ppm (Quast et al. 1988). However, no quantitative data or statistical analyses were reported regarding the incidence of hepatic lesions. Therefore, the Quast et al. (1988) study does not provide adequate information to serve as the principal study for derivation of the chronic-duration inhalation MRL. Other studies in rats and mice did not observe adverse effects at exposure levels up to 1,500 and 3,181 ppm, respectively (Ohnishi et al. 2013; Quast et al. 1988). The only other finding observed was hepatocellular adenoma in female mice at 201 ppm (Ohnishi et al. 2013); however, this effect cannot be used for derivation of the chronic-duration inhalation MRL because MRLs are based on noncancer endpoints. Therefore, a chronic-duration inhalation MRL for 1,1,1-trichloroethane was not derived.

Table A-3. Summary of NOAELs and LOAELs in Chronic-Duration Inhalation Studies on 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic effects					
Rat F344	104 weeks 5 days/week 6 hours/day	500	1,500	Mild liver histopathology (accentuation of the normal hepatic lobular pattern, alteration in the size of the hepatocytes)	Quast et al. 1988
Rat F344	104 weeks 5 days/week 6 hours/day	3,181			Ohnishi et al. 2013
Mouse B6C3F1	104 weeks 5 days/week 6 hours/day	1,500			Quast et al. 1988

Table A-3. Summary of NOAELs and LOAELs in Chronic-Duration Inhalation Studies on 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse BDF1	104 weeks 5 days/week 6 hours/day		201 F (SLOAEL)	CEL: Hepatocellular adenoma	Ohnishi et al. 2013

Adjusted daily dose = $intermittent\ dose \times \frac{exposure\ hours}{24\ hours} \times \frac{exposure\ days}{7\ days}$

ADJ = adjusted; CEL = cancer effect level; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL: serious lowest-observed-adverse-effect level

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL due to insufficient information that could be used to identify sensitive endpoints.

Rationale for not deriving an MRL: An MRL has not been derived for acute-duration oral exposure (≤14 days) to 1,1,1-trichloroethane. The effects of acute-duration oral exposure of 1,1,1-trichloroethane have not been well studied. Six acute oral exposure studies were reported in four publications: two studies reporting LC_{50} data in mice and guinea pigs (Torkelson et al. 1958) and four studies that only evaluated a few toxicity endpoints (Bruckner et al. 2001; Platt and Cockrill 1969; Spencer et al. 1990). None of the available studies examined comprehensive toxicological endpoints. The lowest LOAEL was reported by Spencer et al. (1990) for neurological effects in female rats orally exposed to 705 mg/kg via gavage for 4 days; a NOAEL was not identified. Neurological effects were increased latency in flash-evoked potentials and a decrease in electroencephalogram at low power frequency. However, due to the lack of studies evaluating comprehensive effects, the acute oral database is considered inadequate for derivation of an acute-duration oral MRL.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 2 mg/kg/day
Critical Effect: Reduction in body weight gain
Reference: NTP 2000
Point of Departure: $BMDL_{10}$ of 208 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 14
Species: Mouse

***MRL Summary*:** An intermediate-duration oral MRL of 2 mg/kg/day was derived for 1,1,1-trichloroethane based on a decrease in body weight gain in mice given diets containing encapsulated 1,1,1-trichloroethane (NTP 2000). The MRL is based on a $BMDL_{10}$ of 208 mg/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect*:** A number of studies have evaluated the toxicity of 1,1,1-trichloroethane following intermediate-duration oral exposure; the potential endpoints examined include kidney and liver effects (Bruckner et al. 2001; NTP 2000), developmental and reproductive effects (Dow Chemical 1993; George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b, 2000), and body weight effects (Bruckner et al. 2001; George et al. 1989; NTP 2000). The LOAELs for these studies range from 500 to 4,800 mg/kg/day. Table A-4 has a summary of relevant effect levels.

Table A-4. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Intermediate-Duration Oral MRL for 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	Effect	Reference
Hepatic effects						
Rat Sprague-Dawley	13 weeks 5 days/week (GO)		500		144% increase in SDH activity	Bruckner et al. 2001
Rat F344/N	13 weeks (F)	2,500 F	5,000 F		11% decrease in relative liver weight	NTP 2000
		2,400 M	4,800 M	4,621	12% decrease in relative liver weight	
Renal effects						
Rat F344/N	13 weeks (F)	600 M	1,200 M		7/10 showed chronic inflammation	NTP 2000

Table A-4. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Intermediate-Duration Oral MRL for 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	Effect	Reference
Body weight						
Mouse B6C3F1	13 weeks (F)	1,340 F	2,820 F	380/2,192 (body weight gain/terminal body weight)	22% decrease in body weight gain	NTP 2000
Mouse B6C3F1	13 weeks (F)	1,340 F	850 M	208/678 (body weight gain/terminal body weight)	18% decrease in body weight gain	NTP 2000
Rat F344/N	13 weeks (F)	2,400 M	4,800 M	3,844 (terminal body weight)	10% decrease in final body weight	NTP 2000

[a]BMR is 10% relative deviation.

(F) = food; F = female(s); (GO) = gavage in oil vehicle; LOAEL = lowest-observed-adverse-effect level; M= male(s); NOAEL = no-observed-adverse-effect level; SDH = sorbitol dehydrogenase

The available data suggest that decreases in body weight gain are the most appropriate endpoint following intermediate-duration oral exposure. In female mice, decreased body weight gain was observed at 2,820 mg/kg/day, and in male mice, decreased body weight and body weight gain were observed at 850 mg/kg/day(NTP 2000). Although renal effects were seen at 1,200 mg/kg/day, chronic renal inflammation is a nonspecific effect, and hyaline degeneration in renal tubules occurred at 100% incidence at the LOAEL, which prevents any reasonable modeling of a dose-response relationship. There were also lower doses administered in the Bruckner et al. (2001) study that yielded changes in liver enzymes. Specifically, in Sprague-Dawley rats, increased SDH enzyme activity was observed following intermediate-duration exposure to 500 mg/kg/day via gavage. However, it may not be appropriate, in this case, to base an MRL on an effect level from a gavage study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism). No other intermediate-duration oral study exhibited the hepatic effects observed in Bruckner et al. (2001).

Selection of the Principal Study: NTP (2000) conducted a study on effects of 1,1,1-trichloroethane oral exposure in rats and mice. There was a dose-related decrease in final mean body weight gain in male B6C3F1 mice at 5,000 ppm; mean body weight gain progressively decreased from 11.2 g at 5,000 ppm to 8.7 g at 80,000 ppm.

Summary of the Principal Study:

NTP. 2000. Technical report on the toxicity studies of 1,1,1-trichloroethane (CAS No. 71-55-6) administered in microcapsules in feed to F344/N rats and B6C3F1 mice. National Toxicology Program. (41) NIH 004402.

Groups of male and female B6C3F1 mice (10 per group) were fed diets containing 0 (untreated feed); 0 (microcapsule vehicle in feed); 5,000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 850, 1,750, 3,500, 7,370, and 15,000 mg/kg in male mice and 1,340, 2,820, 5,600,

11,125, and 23,000 mg/kg in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3–4 days. Water consumption was not reported. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and the three highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

There were no exposure-related deaths and no indications of treatment-related or histopathological effects. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, final mean body weight and mean body weight gain of all treatment groups of male and female mice were lower than those of respective vehicle controls (see Table A-5). The final mean body weights in the 5,000, 10,000, 20,000, 40,000, and 80,000 ppm groups were 91, 91, 88, 90, and 85% (males) and 97, 93, 89, 88, and 84% (females) of the respective vehicle control means. As demonstrated in Table A-5, the treatment-related effects on final mean body weight and body weight gain reached the level of statistical significance in all treated groups of male mice and ≥20,000-ppm female mice, relative to vehicle controls. The 10,000-ppm group of female mice exhibited a significantly lower mean body weight gain, but not final mean body weight, relative to vehicle controls. NTP (2000) estimated the dose of 10,000 ppm (1,750 and 2,820 mg/kg/day in male and female mice, respectively) to represent a NOAEL. According to ATSDR policy, a treatment-related change in body weight ≥10% (relative to controls) may be considered to represent an adverse effect. Therefore, the 20,000 ppm (3,500 and 5,600 mg/kg/day in males and females, respectively) level is considered to represent a LOAEL for decreased mean terminal body weight (≥10% lower than control values).

Table A-5. Body Weight Data for Mice Administered 1,1,1-Trichloroethane in the Diet for 13 Weeks

Dose (mg/kg/day)	Final mean body weight (g) (±SE)	Percent of control[a] (final body weight)	Mean weight gain (g) (±SE)	Percent of control[a] (body weight gain)
Males				
Vehicle control	36.9±0.7		13.7±0.5	
850	33.6±0.7[b]	91	11.2±0.5[b]	82
1,750	33.7±0.6[b]	91	10.8±0.5[b]	79
3,500	32.7±0.5[b]	88	9.9±0.4[b]	72
7,370	33.1±0.5[b]	90	10.0±0.3[b]	73
15,000	31.3±0.4[b]	85	8.7±0.3[b]	64
Females				
Vehicle control	29.3±0.8		11.2±0.8	
1,340	28.4±0.6	97	9.6±0.7	86
2,820	27.2±0.8	93	8.7±0.6[b]	78
5,600	26.0±0.8[b]	89	7.5±0.7[b]	67
11,125	25.8±0.7[b]	88	7.2±0.6[b]	64
23,000	24.5±0.5[b]	84	6.2±0.5[b]	55

[a]Percent decrease relative to vehicle control.
[b]Significantly different (p≤0.01) from the vehicle control group.

SE = standard error

Source: NTP 2000

***Selection of the Point of Departure for the MRL*:** BMD modeling was conducted to identify a point of departure (POD) using the body weight gain data in male mice given diets containing encapsulated 1,1,1-trichloroethane. Male mean body weight gain data from B6C3F1 mice, using the vehicle control as the control group, were selected for BMD analysis (Table A-5). This analysis used only terminal bodyweight of the male mice whereas the MRL previously derived for this duration of exposure was based on the terminal body weight of male and female mice in the study. The data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.2) using a benchmark response (BMR) of 10% relative deviation from the vehicle control, as this change in body weight is the minimal level of change generally considered to be biologically significant, according to the EPA BMD guidance (EPA 2012). Default setting for the application of restrictions were used. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen, since all BMDLs from the viable estimated models were within a 3-fold range. BMDS recommended the frequentist restricted Hill model with constant variance for body weight gain, and after verifying the model fit by the four criteria listed above, this model was selected as the basis for estimating this MRL. The only viable model output was this frequentist restricted Hill model, and as such, the BMD/BMDL values for MRL derivation are presented in Table A-6 and the fit of the selected model is presented in Figure A-1.

Table A-6. Selected Results from BMD Analysis of Body Weight Gain in Male Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls), 850, 1,750, 3,500, 7,300, or 15,000 mg/kg/day (NTP 2000)

					Scaled residual[b]	
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	p-Value[a]	AIC	Dose above BMD	Dose below BMD
Exponential 2 (CV, normal)	4,258.10	3,267.94	<0.0001	230.72	-2.13	3.51
Exponential 3 (CV, normal)	4,258.06	3,267.95	<0.0001	230.72	-2.13	3.51
Exponential 4 (CV, normal)	529.27	304.03	0.09	214.29	-0.97	0.31
Exponential 5 (CV, normal)	527.41	304.03	0.09	214.29	-0.96	0.31
Hill (CV, normal)	**401.75**	**207.93**	**0.29**	**211.54**	**0.12**	**0.12**
Polynomial Degree 5 (CV, normal)	5,014.06	4,447.11	<0.0001	232.31	-2.20	3.69
Polynomial Degree 4 (CV, normal)	5,014.06	4,010.10	<0.0001	232.31	-2.20	3.69
Polynomial Degree 3 (CV,- normal)	5,014.06	4,010.14	<0.0001	232.31	-2.20	3.69
Polynomial Degree 2 (CV, normal)	5,014.06	4,010.18	<0.0001	232.31	-2.20	3.69

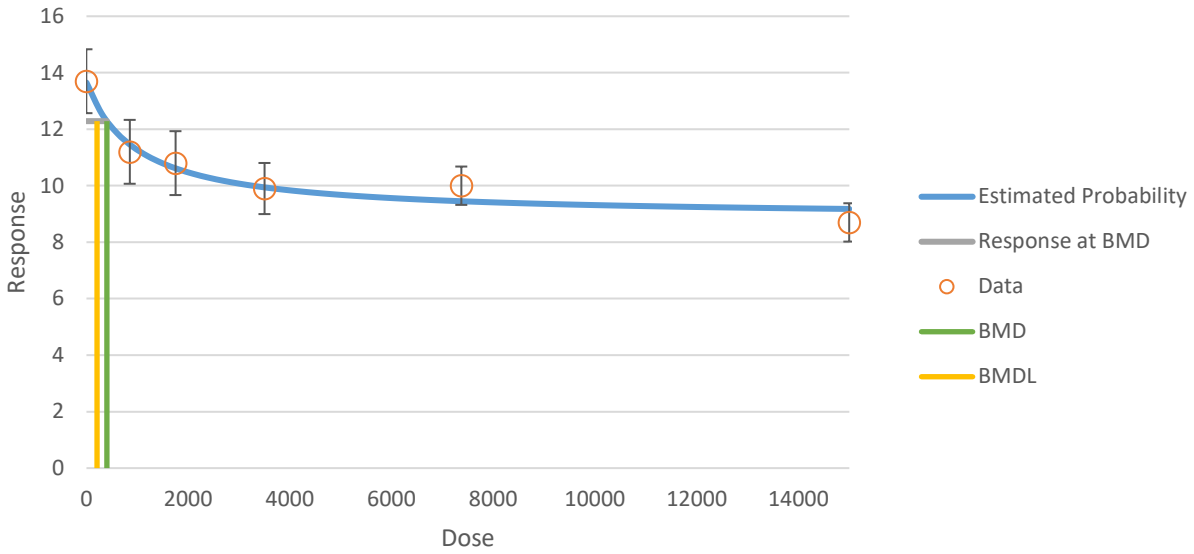
Table A-6. Selected Results from BMD Analysis of Body Weight Gain in Male Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls), 850, 1,750, 3,500, 7,300, or 15,000 mg/kg/day (NTP 2000)

					Scaled residual[b]	
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	p-Value[a]	AIC	Dose above BMD	Dose below BMD
Power (CV, normal)	5,014.05	4,010.59	<0.0001	232.31	-2.20	3.69
Linear (CV, normal)	5,014.06	4,010.56	<0.0001	232.31	-2.20	3.69

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% relative deviation from control); CV = constant variance

Figure A-1. Fit of Hill Model to Data on Mean Body Weight Gain (in g) in Male Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls), 850, 1,750, 3,500, 7,300, or 15,000 mg/kg/day



Uncertainty Factor: The $BMDL_{10}$ of 208 mg/kg/day was divided by a total uncertainty factor of 100 (10 for human variability and 10 for extrapolation from animals to humans), resulting in an MRL of 2 mg/kg/day.

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

$MRL = BMDL_{10} \div$ uncertainty factors
$208 \text{ mg/kg/day} \div (10 \times 10) = 2.08 \text{ mg/kg/day} \approx 2 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information: Decreased body weight appears to be a sensitive effect in other intermediate- and chronic-duration studies by oral or inhalation routes of exposure, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1988).

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL due to lack of comprehensive toxicity evaluations.

Rationale for not deriving an MRL: An MRL has not been derived for chronic-duration oral exposure to 1,1,1-trichloroethane. The only noncancer effect following chronic-duration oral exposure to 1,1,1-trichloroethane was decreased body weight observed in two gavage studies (Maltoni et al. 1986; NCI 1977). Maltoni et al. (1986) identified a LOAEL of 500 mg/kg/day (only dose tested) for a 12% decrease in terminal body weight in female rats relative to control. At this same dose, leukemia was also observed. It is likely that decreased terminal body weight was secondary to leukemia rather than a primary effect of 1,1,1-trichloroethane on body weight. This uncertainty precludes body weight effect to derive the MRL. NCI (1977) reported an 18% decrease terminal body weight at 2,807 mg/kg/day (lowest dose tested) in male and female mice. In this study, 22/50 females died and 28/50 males died at the 2,807 mg/kg/day dose. Therefore, a LOAEL of 2,807 mg/kg/day cannot be used to derive a chronic-duration oral MRL.

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

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,1,1-TRICHLOROETHANE

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 1,1,1-trichloroethane.

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 1,1,1-trichloroethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,1,1-trichloroethane 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 1,1,1-trichloroethane 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

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

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

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for 1,1,1-Trichloroethane released for public comment in 2023; thus, the literature search was restricted to studies published between January 2020 and May 2023. The following main databases were searched in May 2023:

- 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 1,1,1-trichloroethane. 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 1,1,1-trichloroethane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
05/2023	(71-55-6[rn] OR "1,1,1-trichloroethane"[nm] OR "1,1,1-TCA"[tw] OR "1,1,1-TCE"[tw] OR "1,1,1-Trichloreothane"[tw] OR "1,1,1-Trichlorethan"[tw] OR "1,1,1-Trichlorethane"[tw] OR "1,1,1-Trichloro-Ethane"[tw] OR "1,1,1-Trichloroethane"[tw] OR "Aerothene TT"[tw] OR "alpha-trichloroethane"[tw] OR "Baltana"[tw] OR "Chlorotene"[tw] OR "Chlorothene"[tw] OR "Chlorten"[tw] OR "Cleanite"[tw] OR "Dowclene LS"[tw] OR "Ethana NU"[tw] OR "Ethane, 1,1,1-trichloro-"[tw] OR "F 140a"[tw] OR "Genklene LB"[tw] OR "HCC 140a"[tw] OR "ICI-CF 2"[tw] OR "Inhibisol"[tw] OR "Methyl chloroform"[tw] OR "methyl trichloromethane"[tw] OR "Methylchloroform"[tw] OR "Methyltrichloromethane"[tw] OR "Tafclean"[tw] OR "Three One A"[tw] OR "Three One S"[tw] OR "Tri-ethane"[tw] OR "Trichlorethane"[tw] OR "Trichloro-1,1,1-ethane"[tw] OR "Trichloroethane"[tw] OR "Trichloroethane, 1,1,1-"[tw] OR "Trichloromethylmethane"[tw] OR "Tricloroethane"[tw] OR "Triethane"[tw] OR "α-Trichloroethane"[tw]) AND (2020/10/01:3000[mhda] OR 2020/10/01:3000[crdt] OR 2020/10/01:3000[edat] OR 2020:3000[dp])
NTRL	
05/2023	Date limit 2020-2023 Search Titles OR Keywords; "1,1,1-TCA" OR "1,1,1-TCE" OR "1,1,1-Trichloreothane" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloro-Ethane" OR "1,1,1-Trichloroethane" OR "Aerothene TT" OR "alpha-trichloroethane" OR "Baltana" OR "Chlorotene" OR "Chlorothene" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Ethane, 1,1,1-trichloro-" OR "F 140a" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "methyl trichloromethane" OR "Methylchloroform" OR "Methyltrichloromethane" OR "Tafclean" OR "Three One A" OR "Three One S" OR "Tri-ethane" OR "Trichlorethane" OR "Trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloroethane, 1,1,1-" OR "Trichloromethylmethane" OR "Tricloroethane" OR "Triethane" OR "α-Trichloroethane"
Toxcenter	
05/2023	FILE 'TOXCENTER' ENTERED AT 19:48:14 ON 25 MAY 2023 L1 8750 SEA FILE=TOXCENTER 71-55-6 L2 8278 SEA FILE=TOXCENTER L1 NOT TSCATS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L3 7680 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 220 SEA FILE=TOXCENTER L3 AND ED>=20201001 L5 261 SEA FILE=TOXCENTER L3 AND PY>2019 L6 270 SEA FILE=TOXCENTER L4 OR L5 ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L22 QUE (ENDOCRIN? AND DISRUPT?) L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L29 QUE (NEPHROTOX? OR HEPATOTOX?)

Table B-2. Database Query Strings

Database search date	Query string
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 L33 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?) L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L35 QUE L32 OR L33 OR L34 L36 QUE (NONHUMAN MAMMALS)/ORGN L37 QUE L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 --------- L40 128 SEA FILE=TOXCENTER L6 AND L39 L41 7 SEA FILE=TOXCENTER L40 AND MEDLINE/FS L42 121 SEA FILE=TOXCENTER L40 NOT MEDLINE/FS L43 126 DUP REM L41 L42 (2 DUPLICATES REMOVED) L*** DEL 7 S L40 AND MEDLINE/FS L*** DEL 7 S L40 AND MEDLINE/FS L44 7 SEA FILE=TOXCENTER L43 L*** DEL 121 S L40 NOT MEDLINE/FS L*** DEL 121 S L40 NOT MEDLINE/FS L45 119 SEA FILE=TOXCENTER L43 L46 119 SEA FILE=TOXCENTER (L44 OR L45) NOT MEDLINE/FS D SCAN L46

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
05/2023	Compounds searched: 71-55-6
NTP	
05/2023	"71-55-6" "1,1,1-Trichloroethane" "Trichloroethane" "Trichloromethylmethane" "1,1,1-TCA" "1,1,1-TCE" "1,1,1-Trichloro-Ethane" "Chlorothene" "Methylchloroform" "Tricloroethane" "Methyl chloroform" "Ethane, 1,1,1-trichloro-"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Regulations.gov	
05/2023	Docket search (not date limited) Notice search (limited to posted date 2020 to 2023-05-25) "71-55-6" Trichloroethane Chlorothene "Methyl chloroform" Methylchloroform Trichloromethylmethane Trichlorethane
NIH RePORTER	
09/2023	Fiscal Year: Active Projects Text Search (advanced): "1,1,1-TCA" OR "1,1,1-TCE" OR "1,1,1-Trichloreothane" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloro-Ethane" OR "1,1,1-Trichloroethane" OR "Aerothene TT" OR "alpha-trichloroethane" OR "Baltana" OR "Chlorotene" OR "Chlorothene" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Ethane, 1,1,1-trichloro-" OR "F 140a" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "methyl trichloromethane" OR "Methylchloroform" OR "Methyltrichloromethane" OR "Tafclean" OR "Three One A" OR "Three One S" OR "Tri-ethane" OR "Trichlorethane" OR "Trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloroethane, 1,1,1-" OR "Trichloromethylmethane" OR "Tricloroethane" OR "Triethane" OR "α-Trichloroethane" Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 211
- Number of records identified from other strategies: 82
- Total number of records to undergo literature screening: 293

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,1,1-trichloro-ethane:

- 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.

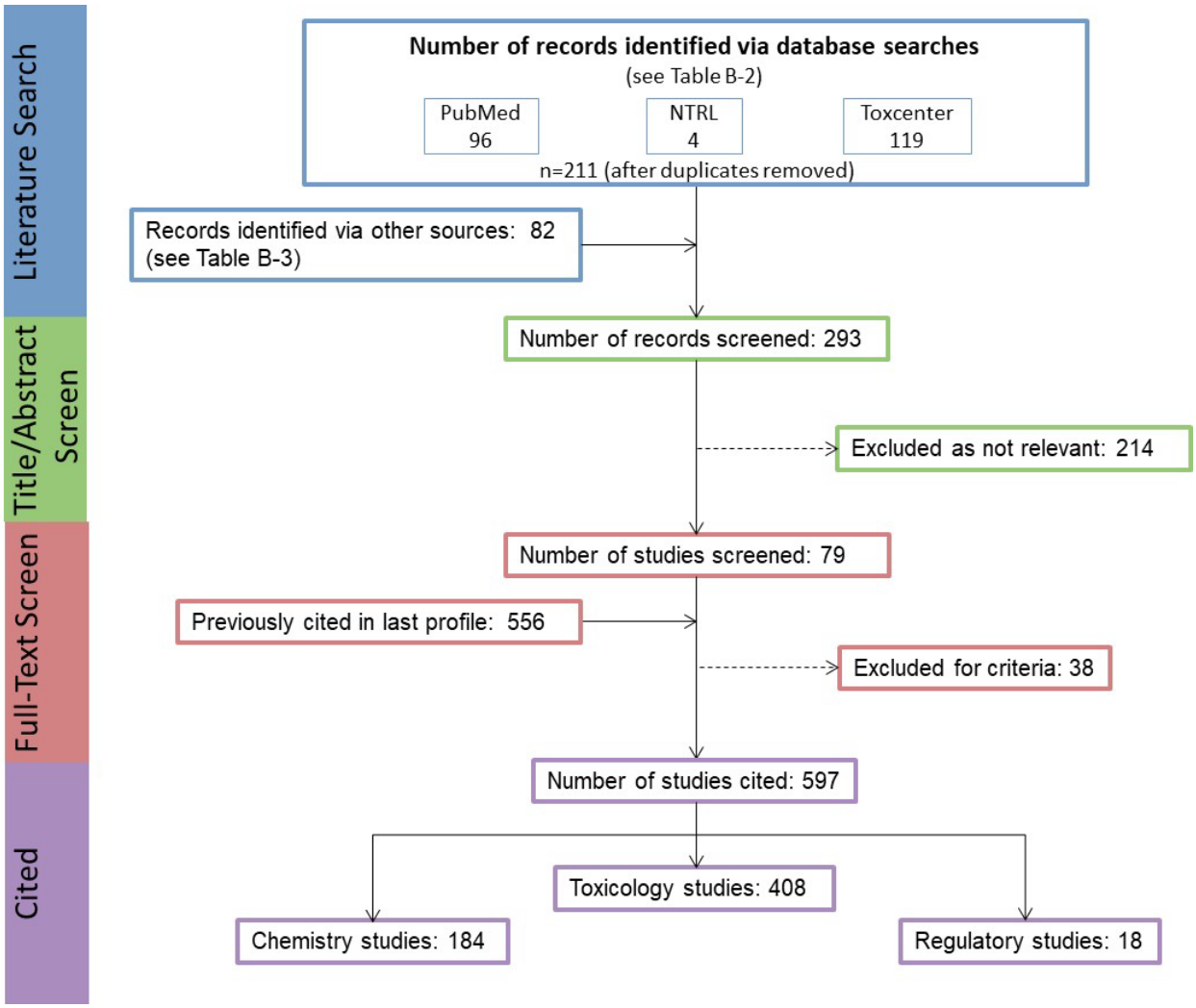
- Number of titles and abstracts screened: 293
- Number of studies considered relevant and moved to the next step: 79

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: 79
- Number of studies cited in the pre-public draft of the toxicological profile: 556
- Total number of studies cited in the profile: 597

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

Figure B-1. May 2023 Literature Search Results and Screen for 1,1,1-Trichloroethane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1,1-TRICHLOROETHANE

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 1,1,1-trichloroethane, 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 1,1,1-trichloroethane:

- 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 1,1,1-trichloroethane. The inclusion criteria used to identify relevant studies examining the health effects of 1,1,1-trichloroethane 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 were conducted to identify studies examining the health effects of 1,1,1-trichloroethane. 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 1,1,1-Trichloroethane released for public comment in 2023. See Appendix B for the databases searched and the search strategy.

A total of 293 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 1,1,1-trichloroethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 293 records were reviewed; no new documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 144 health effect documents (documents cited in older versions of the profile) was performed.

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 1,1,1-Trichloroethane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile.

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1,1-trichloroethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The human studies assessed for the systematic review examined a limited number of endpoints and reported neurological, respiratory, cardiovascular, dermal, reproductive, and developmental effects. Case studies were not included in the systematic review. Animal studies examined a comprehensive set of endpoints following inhalation, oral, or dermal exposure. Evaluation of the literature indicated the most sensitive endpoints associated with 1,1,1-trichloroethane exposure include neurological and hepatic endpoints as effects were observed at low doses, and are supported by common reports of these effects in case studies. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for 1,1,1-Trichloroethane 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 1	3 1		2 0		6 0	2 0					13 8	1 0			2 1
Case control									2 1					3 0			12 1
Population					1 0								2 0		1 1	1 1	
Case series																	
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 1,1,1-Trichloroethane 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	8	2	2		1		9	2	1	3	1	1	31	3	4		
	2	0	1		0		1	1	1	2	0	0	21	1	2		
Intermediate-duration	30	26	19	3	16	1	32	29	1	1		21	9	14	1		
	12	2	0	0	0	0	4	0	0	0		0	2	2	1		
Chronic-duration	4	3	2	2	4	2	3	4	1	1		3	4	2	1		2
	0	0	0	0	0	0	2	1	0	1		0	1	0	0		0
Acute-duration	4						5	1					2				
	0						1	0					2				
Intermediate-duration	4	1	1				2	2					1	6	6		
	3	1	0				2	0					1	0	1		
Chronic-duration	2	22	2	2	2	2	2	2	2			2	2	2	1		1
	1	0	0	0	0	0	0	0	0			0	0	0	0		1
Dermal studies																	
Acute-duration																	
Intermediate-duration	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	
	0	0	1	1	0	0	0	0	1	0	0	1	0	0		0	
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of 1,1,1-trichloroethane health effects studies (observational epidemiology, human exposure, 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 1,1,1-Trichloroethane—Observational 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: Hepatic effects							
Cohort studies, inhalation							
Kramer et al. 1978	+	+	–	+	+	+	First
Kelafant et al. 1994	+	+	+	–	+	+	First
Outcome: Neurological effects							
Cohort studies, inhalation							
Kelafant et al. 1994	+	+	+	–	+	+	First
Maroni et al. 1977	+	–	+	–	+	+	First
Population studies, inhalation							

++ = 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 1,1,1-Trichloroethane—Controlled Exposure 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 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
Outcome: Hepatic effects								
Inhalation acute-duration exposure								
Stewart et al. 1961	–	–	–	+	++	+	+	First
Stewart et al. 1969	–	–	–	+	–	+	+	Second
Outcome: Neurological effects								
Inhalation acute-duration exposure								
Gamberale and Hultengren 1973	++	–	–	++	–	++	++	First
Laine et al. 1996	–	–	–	+	+	+	+	First
Stewart et al. 1969	–	–	–	+	–	+	+	Second
Muttray et al. 2000	+	+	-	–	+	+	–	First
Savolainen et al. 1981	–	–	–	++	–	+	+	Second
Stewart et al. 1961	–	–	–	+	++	+	+	First
Salvini et al. 1971	–	–	–	++	–	+	+	Second
Torkelson et al. 1958	–	–	–	+	+	–	–	Second
Mackay et al. 1987	–	–	–	+	–	+	+	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-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—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
Outcome: Hepatic									
Inhalation acute-duration exposure									
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Cornish and Adefuin 1966 (rat)	–	–	+	–	+	++	+	+	First
Cornish and Adefuin 1966 (rat)	–	–	+	–	+	++	+	+	First
Herd et al. 1974 (dog)	–	–	+	–	+	++	+	+	First
Koizumi et al. 1983 (rat)	–	–	+	–	+	++	+	+	First
Lal and Shah 1970 (mouse)	–	–	+	–	–	+	+	+	Second
McNutt et al. 1975 (mouse)	+	–	+	–	+	++	+	+	First
Inhalation intermediate-duration exposure									
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (monkey)	–	–	+	–	+	++	+	+	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—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
Calhoun et al. 1981 (rat)	++	–	+	–	+	++	+	+	First
Calhoun et al. 1981 (mouse)	++	–	+	–	+	++	+	+	First
NTP 2000 (rat)	–	–	++	–	++	++	++	++	First
NTP 2000 (mouse)	–	–	++	–	++	++	++	++	First
Toftgard et al. 1981 (rat)	–	–	+	–	+	+	+	+	First
Torkelson et al. 1958 (monkey)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Truffert et al. 1977 (rat)	–	–	+	–	+	–	+	+	Second
Inhalation chronic-duration exposure									
NCI 1977 (rat)	–	+	+	–	–	++	+	+	First
NCI 1977 (mouse)	–	+	+	–	–	++	+	+	First
Ohnishi et al. 2013 (rat)	++	–	++	–	+	++	++	++	First
Ohnishi et al. 2013 (mouse)	++	–	++	–	+	++	++	++	First
Oral acute-duration exposure									
Bruckner et al. 2001 (rat)	–	–	++	–	++	++	+	+	First
Bruckner et al. 2001 (rat)	–	–	++	–	++	++	+	+	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—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
Platt and Cockrill 1969 (rat)	–	–	+	–	++	–	+	+	Second
Torkelson et al. 1958 (mouse)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Tyson et al. 1983 (rat)	–	–	+	–	+	+	+	+	First
Oral intermediate-duration exposure									
Bruckner et al. 2001 (rat)	–	–	++	–	+	++	+	+	First
Outcome: Neurological									
Inhalation acute-duration exposure									
Bowen et al. 1996a (mouse)	–	–	++	–	++	+	++	++	First
Balster et al. 1982 (mouse)	–	–	++	–	++	+	++	++	First
Bonnet et al. 1980 (rat)	–	–	++	–	++	++	++	++	First
Bowen et al. 1996a (mouse)	–	–	++	–	++	+	++	++	First
Bowen et al. 1996b (mouse)	–	–	++	–	++	+	++	++	First
Bowen and Balster 1998 (mouse)	–	–	++	–	++	+	++	++	First
De Ceaurriz et al. 1981 (mouse)	–	–	++	–	++	+	++	++	First
Folbergrova et al. 1984 (rat)	–	–	++	–	++	+	++	++	First
Geller et al. 1982 (monkey)	–	–	++	–	++	+	++	++	First
Herd et al. 1974 (dog)	–	–	+	–	+	++	+	+	First
Horiguchi and Horiuchi 1971 (mouse)	–	–	–	–	+	–	–	+	Third

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—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
Hougaard et al. 1984 (rat)	–	–	+	–	++	+	+	+	First
Kjellstrand et al. 1985b (mouse)	–	–	+	–	++	–	++	++	First
Moser and Balster 1986 (mouse)	–	–	++	–	++	+	++	++	First
Moser and Balster 1985 (mouse)	–	–	++	–	+	+	++	++	First
Mullin and Krivanek 1982 (rat)	–	–	++	–	+	++	++	++	First
Nilsson 1986a (mouse)	–	–	++	–	++	+	++	++	First
Nilsson 1986b (mouse)	–	–	++	–	++	+	++	++	First
Paez-Martinez et al. 2003 (mouse)	–	–	++	–	++	++	++	++	First
Woolverton and Balster 1981 (mice)	–	–	++	–	++	+	++	++	First
You and Dallas 2000 (rat)	–	–	++	–	++	++	++	++	First
You and Dallas 2000 (mouse)	–	–	++	–	++	++	++	++	First
Inhalation intermediate-duration exposure									
Mattsson et al. 1993 (Mouse)	–	–	++	–	+	+	++	++	First
Moser and Balster 1985 (mouse)	–	–	++	–	+	+	++	++	First
NTP 2000 (rat)	–	–	++	–	++	++	++	++	First
NTP 2000 (mouse)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (monkey)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (monkey)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (rat)	–	–	++	–	++	++	++	++	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—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
Prendergast et al. 1967 (rat)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (guinea pig)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (guinea pig)	–	–	++	–	++	++	++	++	First
Rosengren et al. 1985 (gerbil)	–	–	++	–	++	+	++	++	First
Torkelson et al. 1958 (monkey)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rabbit)	–	–	+	–	+	++	++	++	First
Inhalation chronic-duration exposure									
NCI 1977 (rat)	–	+	+	–	–	++	+	+	First
NCI 1977 (mouse)	–	+	+	–	–	++	+	+	First
Ohnishi et al. 2013 (rat)	++	–	++	–	+	++	++	++	First
Ohnishi et al. 2013 (mouse)	++	–	++	–	+	++	++	++	First
Quast et al. 1988 (rat)	–	–	++	–	+	++	++	++	First
Oral acute-duration exposure									
Torkelson et al. 1958 (mouse)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—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
Oral intermediate-duration exposure									
Bruckner et al. 2001 (rat)	–	–	++	–	+	++	+	+	First
Oral chronic-duration exposure									
NCI 1977 (rat)	–	+	+	–	–	++	+	+	First
NCI 1977 (mouse)	–	+	+	–	–	++	+	+	First

++ = 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

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 1,1,1-trichloroethane 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 1,1,1-trichloroethane 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 neurological and hepatic effects observed in the observational epidemiology, human-controlled exposure, and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for 1,1,1-Trichloroethane—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Hepatic					
Cohort studies Inhalation					
Kramer et al. 1978	No	Yes	Yes	Yes	Moderate
Kelafant et al. 1994	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for 1,1,1-Trichloroethane—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Neurological					
Cohort studies Inhalation					
Kelafant et al. 1994	No	Yes	Yes	Yes	Moderate
Maroni et al. 1977	No	No	Yes	Yes	Low

Table C-15. Presence of Key Features of Study Design for 1,1,1-Trichloroethane—Human-Controlled Exposure Studies

Reference	Key features: Comparison group or aerved as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Appropriate statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Inhalation acute-duration exposure					
Stewart et al. 1961	Yes	Yes	Yes	No	Moderate
Stewart et al. 1969	No	Yes	Yes	No	Low
Outcome: Neurological effects					
Inhalation acute-duration exposure					
Gamberale and Hultengren 1973	Yes	Yes	Yes	Yes	High
Laine et al. 1996	Yes	Yes	Yes	Yes	High
Stewart et al. 1969	No	Yes	Yes	No	Low
Muttray et al. 2000	Yes	Yes	Yes	Yes	High
Savolainen et al. 1981	Yes	Yes	Yes	Yes	High
Stewart et al. 1961	Yes	Yes	Yes	No	Moderate
Salvini et al. 1971	Yes	Yes	Yes	Yes	High
Torkelson et al. 1958	No	No	Yes	No	Low
Mackay et al. 1987	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for 1,1,1-Trichloroethane— Experimental Animal Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	
Outcome: Hepatic effects					
Inhalation acute-duration exposure					
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Cornish and Adefuin 1966 (rat)	Yes	Yes	Yes	Yes	High
Cornish and Adefuin 1966 (rat)	Yes	Yes	Yes	Yes	High
Herd et al. 1974 (dog)	Yes	Yes	Yes	No	Moderate
Koizumi et al. 1983 (rat)	Yes	Yes	Yes	Yes	High
Lal and Shah 1970 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate-duration exposure					
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (monkey)	No	No	Yes	Yes	Low
Calhoun et al. 1981 (rat)	Yes	Yes	Yes	Yes	High
Calhoun et al. 1981 (mouse)	Yes	Yes	Yes	Yes	High
McNutt et al. 1975 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2000 (rat)	Yes	Yes	Yes	Yes	High
NTP 2000 (mouse)	Yes	Yes	Yes	Yes	High
Toftgard et al. 1981 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (monkey)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Truffert et al. 1977 (rat)	Yes	Yes	Yes	No	Moderate
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (rat)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for 1,1,1-Trichloroethane— Experimental Animal Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	
Oral acute-duration exposure	Yes	Yes	Yes	Yes	High
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Platt and Cockrill 1969 (rat)	Yes	No	Yes	No	Low
Torkelson et al. 1958 (mouse)	No	Yes	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	No	Yes	Yes	Yes	Moderate
Tyson et al. 1983 (rat)	Yes	No	Yes	No	Low
Oral intermediate-duration exposure					
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute-duration exposure					
Balster et al. 1982 (mouse)	Yes	Yes	Yes	Yes	High
Bonnet et al. 1980 (rat)	Yes	Yes	Yes	Yes	High
Bowen et al. 1996a (mouse)	Yes	Yes	Yes	Yes	High
Bowen et al. 1996b (mouse)	Yes	Yes	Yes	Yes	High
Bowen and Balster 1998 (mouse)	Yes	Yes	Yes	Yes	High
De Ceaurriz et al. 1981 (mouse)	Yes	Yes	Yes	No	Moderate
Folbergrova et al. 1984 (rat)	Yes	Yes	Yes	No	Moderate
Geller et al. 1982 (monkey)	Yes	No	Yes	No	Low
Herd et al. 1974 (dog)	Yes	Yes	Yes	No	Moderate
Horiguchi and Horiuchi 1971 (mouse)	No	Yes	Yes	No	Low
Hougaard et al. 1984 (rat)	Yes	Yes	Yes	Yes	High
Kjellstrand et al. 1985b (mouse)	Yes	Yes	Yes	No	Moderate
Moser and Balster 1986 (mouse)	Yes	Yes	Yes	Yes	High
Moser and Balster 1985 (mouse)	Yes	Yes	Yes	Yes	High
Mullin and Krivanek 1982 (rat)	Yes	Yes	Yes	Yes	High
Nilsson 1986a (mouse)	Yes	Yes	Yes	Yes	High
Nilsson 1986b (mouse)	Yes	Yes	Yes	Yes	High
Paez-Martinez et al. 2003 (mouse)	Yes	Yes	Yes	Yes	High
Woolverton and Balster 1981 (mouse)	Yes	Yes	Yes	Yes	High
You and Dallas 2000 (rat)	Yes	Yes	Yes	Yes	High
You and Dallas 2000 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for 1,1,1-Trichloroethane— Experimental Animal Studies

Reference	Key features: Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Inhalation intermediate-duration exposure					
Mattsson et al. 1993 (rat)	Yes	Yes	Yes	Yes	High
Moser and Balster 1985 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2000 (rat)	Yes	Yes	Yes	Yes	High
NTP 2000 (mouse)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (monkey)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (monkey)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (guinea pig)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (guinea pig)	Yes	Yes	Yes	Yes	High
Rosengren et al. 1985 (gerbil)	Yes	Yes	Yes	Yes	High
Torkelson et al. 1958 (monkey)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rabbit)	Yes	No	Yes	Yes	Moderate
Truffert et al. 1977 (rat)	Yes	Yes	Yes	No	Moderate
Inhalation chronic-duration exposure					
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (rat)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Oral acute-duration exposure					
Torkelson et al. 1958 (mouse)	No	Yes	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	No	Yes	Yes	Yes	Moderate
Oral intermediate-duration exposure					
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic-duration exposure					
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table 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 Table C-17.

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Outcome: Hepatic effects		
Inhalation acute-duration exposure		
Animal studies		
Adams et al. 1950 (rat)	Moderate	High
Cornish and Adefuin 1966 (rat)	High	
Cornish and Adefuin 1966 (rat)	High	
Herd et al. 1974 (dog)	Moderate	
Koizumi et al. 1983 (rat)	High	
Lal and Shah 1970 (mouse)	High	
Inhalation intermediate-duration exposure		
Adams et al. 1950 (guinea pig)	Moderate	High
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (rat)	Moderate	
Adams et al. 1950 (rat)	Moderate	
Adams et al. 1950 (rat)	Moderate	
Adams et al. 1950 (monkey)	Low	
Calhoun et al. 1981 (rat)	High	
Calhoun et al. 1981 (mouse)	High	
McNutt et al. 1975 (mouse)	High	
NTP 2000 (rat)	High	
NTP 2000mouse)	High	
Toftgard et al. 1981 (rat)	Moderate	
Torkelson et al. 1958 (monkey)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Truffert et al. 1977 (rat)	Moderate	
Inhalation chronic-duration exposure		
NCI 1977 (rat)	High	High
NCI 1977 (mouse)	High	
Ohnishi et al. 2013 (rat)	High	
Ohnishi et al. 2013 (mouse)	High	

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Oral acute-duration exposure		
Bruckner et al. 2001 (rat)	High	High
Bruckner et al. 2001 (rat)	High	
Platt and Cockrill 1969 (rat)	High	
Torkelson et al. 1958 (mouse)	Low	
Torkelson et al. 1958 (guinea pig)	Moderate	
Tyson et al. 1983 (rat)	Low	
Oral intermediate-duration exposure		
Bruckner et al. 2001 (rat)	High	High
Oral chronic-duration exposure		
NCI 1977 (rat)	High	High
NCI 1977 (mouse)	High	
Human studies		
Kramer et al. 1978	Moderate	Moderate
Kelafant et al. 1994	Moderate	
Stewart et al. 1961	Moderate	
Stewart et al. 1969	Low	
Outcome: Neurological effects		
Animal studies		
Inhalation acute-duration exposure		
Balster et al. 1982 (mouse)	High	
Bonnet et al. 1980 (Rat)	High	
Bowen et al. 1996a (mouse)	High	
Bowen et al. 1996b (mouse)	High	
Bowen and Balster 1998 (mouse)	High	
De Ceaurriz et al. 1981 (mouse)	Moderate	
Folbergrova et al. 1984 (rat)	Moderate	
Geller et al. 1982 (monkey)	Low	
Herd et al. 1974 (dog)	Moderate	
Horiguchi and Horiuchi 1971 (mouse)	Low	
Hougaard et al. 1984 (rat)	High	
Kjellstrand et al. 1985b (mouse)	Moderate	
Moser and Balster 1986 (mouse)	High	
Moser and Balster 1985 (mouse)	High	
Mullin and Krivanek 1982 (rat)	High	
Nilsson 1986a (mouse)	High	
Nilsson 1986b (mouse)	High	
Paez-Martinez et al. 2003 (mouse)	High	

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Woolverton and Balster 1981 (mouse)	High	
You and Dallas 2000 (rat)	High	
You and Dallas 2000 (mouse)	High	
Inhalation intermediate-duration exposure		
Mattsson et al. 1993 (rat)	High	
Moser and Balster 1985 (mouse)	High	
NTP 2000 (rat)	High	
NTP 2000 (mouse)	High	
Prendergast et al. 1967 (monkey)	High	
Prendergast et al. 1967 (monkey)	High	
Prendergast et al. 1967 (rat)	High	
Prendergast et al. 1967 (rat)	High	
Prendergast et al. 1967 (guinea pig)	High	High
Prendergast et al. 1967 (guinea pig)	High	
Rosengren et al. 1985 (gerbil)	High	
Torkelson et al. 1958 (monkey)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Truffert et al. 1977 (rat)	Moderate	
Inhalation chronic-duration exposure		
NCI 1977 (rat)	High	
NCI 1977 (mouse)	High	
Ohnishi et al. 2013 (rat)	High	High
Ohnishi et al. 2013 (mouse)	High	
Quast et al. 1988 (rat)	High	
Oral acute-duration exposure		
Torkelson et al. 1958 (mouse)	Moderate	Moderate
Torkelson et al. 1958 (guinea pig)	Moderate	
Oral intermediate-duration exposure		
Bruckner et al. 2001 (rat)	High	High
Oral chronic-duration exposure		
NCI 1977 (rat)	High	High
NCI 1977 (mouse)	High	
Human studies		
Kelafant et al. 1994	Moderate	
Gamberale and Hultengren 1973	High	
Muttray et al. 2000	High	
Torkelson et al. 1958	Low	

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Mackay et al. 1987	High	
Stewart et al. 1961	Moderate	
Stewart et al. 1969	Low	
Savolainen et al. 1981	High	
Salvini et al. 1971	High	
Maroni et al. 1977	Low	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for neurological and hepatic 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 1,1,1-trichloroethane exposure is presented in Table C-19.

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Hepatic effects			
Animal studies	High	+1 Consistency in body of evidence +1 Dose response	High
Human studies	Moderate	+1 Consistency in body of evidence	High
Outcome: Neurological effects			
Animal studies	High	+1 Consistency in body of evidence	High
Human studies	High	+1 Consistency in body of evidence +1 Dose response	High

Table C-19. Confidence in the Body of Evidence for 1,1,1-Trichloroethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic effects	High	High
Neurological effects	High	High

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

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

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

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

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

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

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

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

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

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

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

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

In the seventh step of the systematic review of the health effects data for 1,1,1-trichloroethane, 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 1,1,1-trichloroethane is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for 1,1,1-Trichloroethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	High	No Health Effect	Low
Neurological effects	High	Health Effect	High
Animal studies			
Hepatic effects	High	Health Effect	High
Neurological effects	High	Health Effect	High

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:

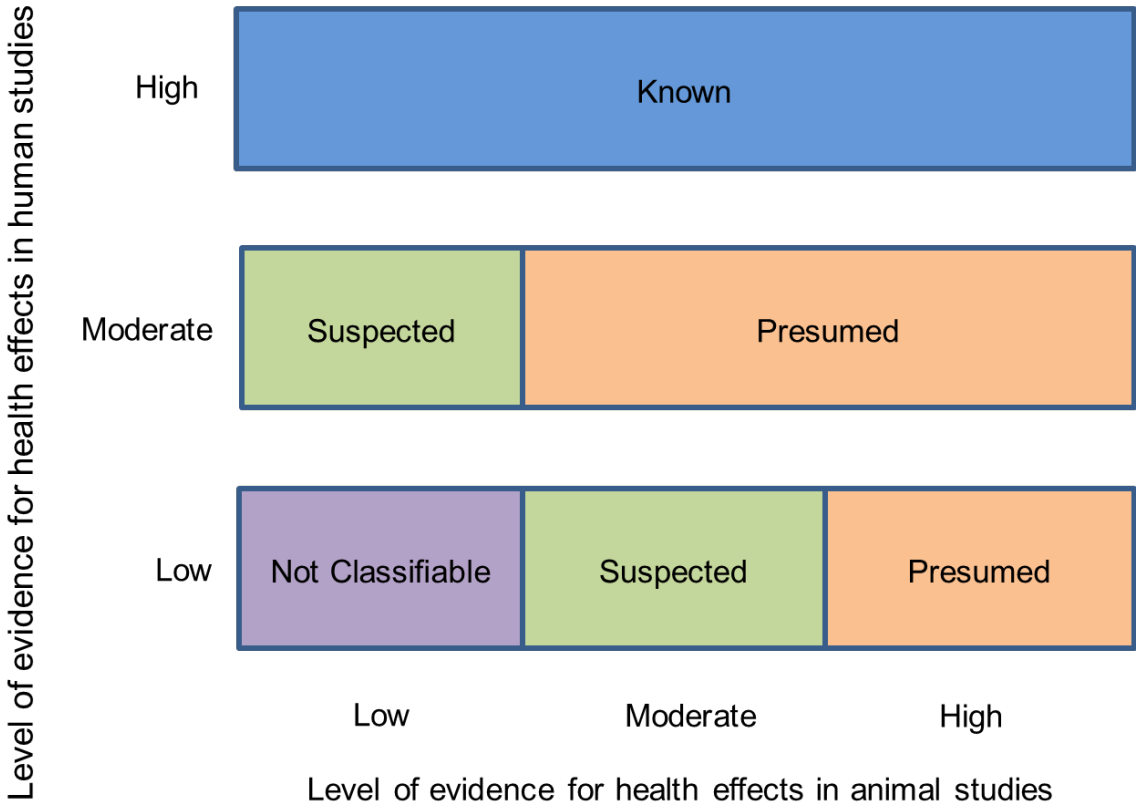
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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

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.

Figure C-1. Hazard Identification Scheme



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 1,1,1-trichloroethane are listed below and summarized in Table C-21.

Presumed Health Effects

- Neurological
  - Inhalation of 1,1,1-trichloroethane in humans caused impaired performance on cognitive tests, and loss of consciousness (Gamberale and Hultengren 1973; Kelafant et al. 1994; Mackay et al. 1987; Savolainen et al. 1981). Oral exposure to 1,1,1-trichloroetane did not cause neurological effects (Stewart and Andrews 1966). Dermal occupational exposure resulted in alterations in peripheral nerve activity (Howse et al. 1989; Liss 1988).
  - In animal studies, inhalation of 1,1,1-trichloroethane resulted in effects like those seen in humans: impaired performance in behavioral tests, ataxia, and unconsciousness in monkeys, rats, and mice (Geller et al. 1982; Horiguchi and Horiuchi 1971; Kjellstrand et al. 1985a; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Páez-Martínez et al. 2003; Torkelson et al. 1958; Woolverton and Balster 1981). Neurophysiological changes including changes in flash-evoked potential and electroencephalogram and more subtle changes in somatosensory-evoked potential were also seen (Evans and Balster 1993).
  - Acute-duration oral exposure to 1,1,1-trichloroethane caused marked changes in flash-evoked potential and electroencephalogram, and smaller changes in somatosensory-evoked potential (Spencer et al. 1990). Intermediate-duration exposure to 1,1,1-trichloroethane resulted in hyperexcitability followed by narcosis (Bruckner et al. 2001). No significant effects were found as result of dermal exposure in animals (Torkelson et al. 1958).
  - Based on high evidence from animal studies and high evidence from human studies, the changes in brain physiology and deficits in cognitive and motor tests after inhalation exposure are classified as known health effects.
- Hepatic
  - A low level of evidence for hepatic effects from human studies exists after inhalation exposure to 1,1,1-trichloroethane as all studies showed little to no effect (Kelafant et al. 1994; Kramer et al. 1978). No studies that examined hepatic effects after oral or dermal exposure to 1,1,1-trichloroethane in humans were identified.
  - High level of evidence in animal studies from different species including rats, mice, rabbits, and guinea pigs. Histopathological changes and necrosis were observed in livers of mice, rats, and guinea pigs (McNutt et al. 1975; Torkelson et al. 1958) after acute-duration inhalation exposure. Intermediate-duration inhalation exposure to 1,1,1-trichloroethane also showed fatty degeneration in liver in rats and guinea pigs (Adams et al. 1950). Chronic-duration inhalation exposure in mice caused a dose-dependent increase incidence of hepatocellular adenoma (Ohnishi et al. 2013).

- Acute-duration exposure to 1,1,1-trichloroethane induced liver enzyme activity in rats and mice (Fuller et al. 1970; Koizumi et al. 1983; Lal and Shah 1970).
- Oral exposure to 1,1,1-trichloroethane induced mild hepatotoxicity, including changes in liver enzyme activity (Bruckner et al. 2001) and reduction in levels of cytochrome P-450 (Vainio et al. 1976). Dermal exposure to 1,1,1-trichloroethane increased liver enzymes in rats (Viola et al. 1981) but not in rabbits (Torkelson et al. 1958).
- Based on high evidence from animal studies and low evidence from human studies, hepatocellular changes resulting from inhalation exposure are classified as a presumed health effect.

Table C-21. Hazard Identification Conclusions for 1,1,1-Trichloroethane

Outcome	Hazard identification
Hepatic effects	Presumed
Neurological effects	Known

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.

APPENDIX D

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

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

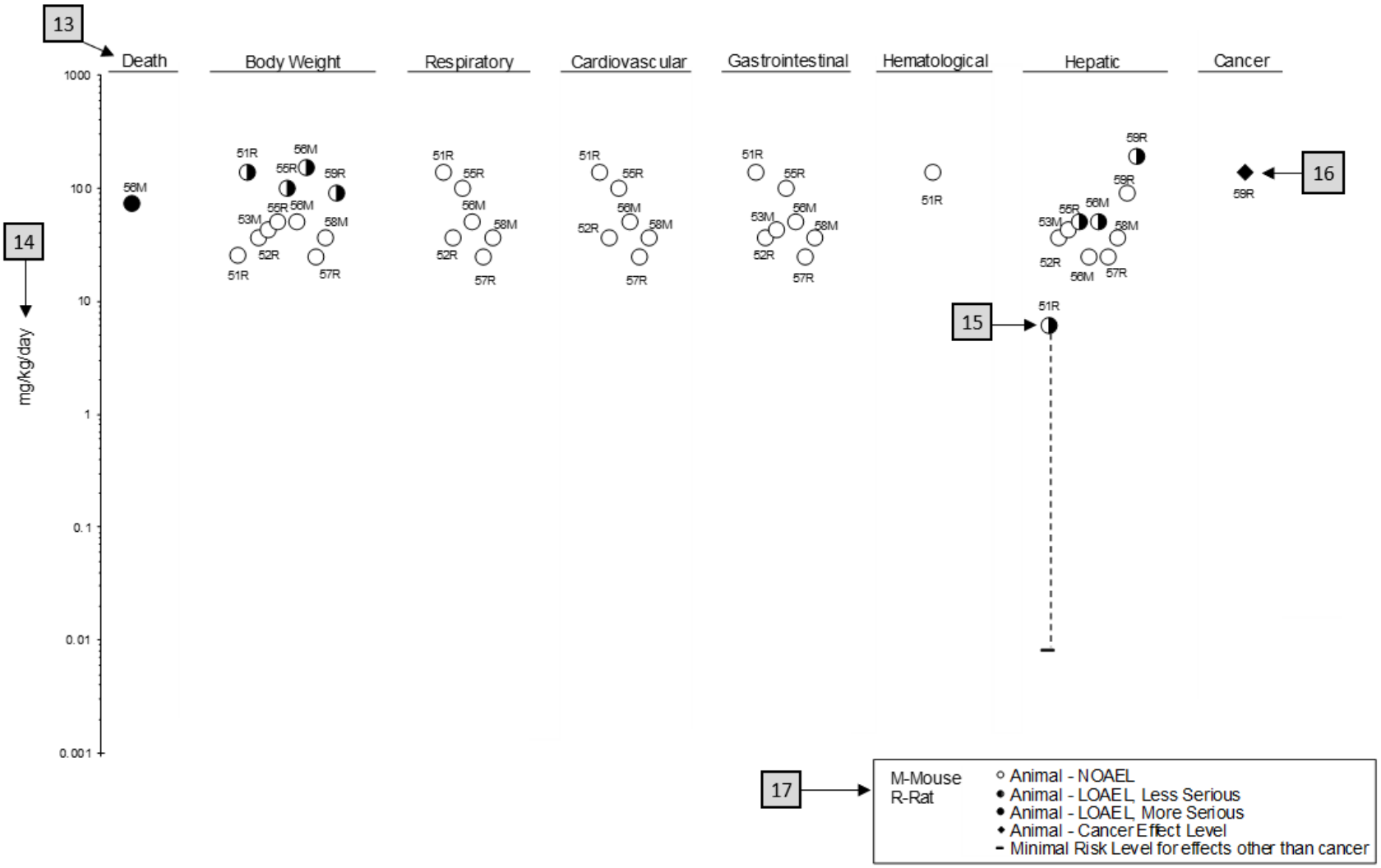
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX D

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:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-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