APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 0.03 ppm
Critical Effect: Necrosis of the olfactory epithelium (minimal to mild; nasal level IV)
Reference: Kirkpatrick 2001
Point of Departure: LOAEL of 58 ppm ($LOAEL_{HEC}$ of 7.5 ppm)
Uncertainty Factor: 270
LSE Graph Key: 6
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 0.03 ppm was derived for 1,1,2-trichloroethane based on necrosis in the olfactory epithelium (nasal level IV) of male and female rats exposed to 58 ppm 1,1,2-trichloroethane for 4 hours (Kirkpatrick 2001). The MRL is based on a LOAEL of 58 ppm which was converted to a human equivalent concentration ($LOAEL_{HEC}$) of 7.5 ppm and divided by a total uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability) and a modifying factor of 3 for an incomplete database.

Selection of the Critical Effect: In the only acute-duration study that subjected tissues to histopathological examinations (Kirkpatrick 2001), rats exposed to 1,1,2-trichloroethane for 4 hours showed evidence of respiratory tract damage (necrosis of the olfactory epithelium at nasal levels III, IV, and V) at ≥58 ppm. This effect was seen at a lower concentration than hepatocellular necrosis in the same study (≥181 ppm). Several other acute-duration inhalation toxicity studies of 1,1,2-trichloroethane identified liver damage and/or neurological effects (Bonnet et al. 1980; Carlson 1973; de Ceaurriz et al. 1981; Gehring 1968; Lazarew 1929; Takahara 1986a). The majority of the studies identified changes in serum blood chemistry related to liver function (at ≥800 ppm) or clinical signs of neurotoxicity (at ≥418 ppm); gross or microscopic pathology examinations were not performed.

The LOAEL for respiratory effects is lower than the LOAELs for other target systems identified in acute-duration studies (hepatic and neurological effects). NOAEL and LOAEL values for acute-duration inhalation exposure are summarized in Table A-1.

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

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects					
F344 rat	4 hours	ND	58	Necrosis of the olfactory epithelium	Kirkpatrick 2001
F344 rat	4 hours	170 (females) 205 (males)	840 (females) 1,474 (males)	Increased protein content of BALF (females)	Kirkpatrick 2001
Liver effects					
F344 rat	4 hours	58	181	Hepatocellular necrosis	Kirkpatrick 2001
Mouse (NS)	3 hours	ND	800	Increased ALT and liver triglycerides; decreased plasma triglycerides and ATP	Takahara 1986a
Albino rat	2 hours	890	2,080	Increased ALT	Carlson 1973
Swiss-Webster mouse	15 hours	ND	3,750	Increased ALT	Gehring 1968
Neurological effects					
Swiss OF_1 mouse	4 hours	ND	418	CNS depression	de Ceaurriz et al. 1981
F344 rat	4 hours	ND	840 (females) 1,474 (males)	Sleepiness; decreased respiration	Kirkpatrick 2001
F344 rat	4 hours	ND	1,527	Sleepiness; decreased respiration	Kirkpatrick 2001
Sprague-Dawley rat	6 hours	ND	1,654	Somnolent	Bonnet et al. 1980
Mouse (NS)	2 hours	1,833	2,749	Lie down on side; loss of reflex control	Lazarew 1929
Swiss-Webster mouse	15 hours	ND	3,750	Anesthesia	Gehring 1968

ALT = alanine aminotransferase; BALF = bronchoalveolar lavage fluid; CNS = central nervous system; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified

Selection of the Principal Study: The study of Kirkpatrick (2001) was selected as the principal study for deriving an acute-duration inhalation MRL for 1,1,2-trichloroethane because it identified the lowest reliable LOAEL for respiratory effects in the only study that performed histopathological examinations.

Summary of the Principal Study:

Kirkpatrick DT. 2001. Acute inhalation toxicity (with histopathology) study of 1,1,2-trichloroethane (1,1,2-TCE) in rats. WIL Research Laboratories, Inc. HAP Task Force. EPA-HQ-OPPT-2002-0056-0039. WIL-417001. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0039. March 07, 2018.

F344 rats (5/sex/group) were exposed whole-body to 1,1,2-trichloroethane (purity 99.56%) as a vapor at nominal concentrations of 0, 50, 200, and 1,500 ppm for 4 hours and sacrificed 24 hours after cessation of exposure. Actual (measured) concentrations were 0, 58, 181, and 1,527 ppm. Animals were monitored for mortality and clinical signs of toxicity. The response to a noise stimulus was assessed at the midpoint of exposure. One day following exposure, detailed physical examinations were performed and body weights were measured. At necropsy, organ weights of the adrenals, brain, kidneys, liver, lungs, ovaries, and testes were recorded. Respiratory tract tissues were examined microscopically in all control and exposed animals; the liver, kidneys, and stomach were additionally examined in animals in the control and high-exposure groups.

Three females exposed at 1,527 ppm died on the day following exposure; although the cause of death was not specified, necrosis of the liver, kidneys, and/or respiratory tract tissues was observed. No mortality occurred in males or in other groups of exposed females. All animals exposed at 1,527 ppm showed sleepiness, decreased respiration, and clear discharge of the eyes immediately following exposure; these signs, in addition to lethargy, hypothermia, and reddish-brown urine, were noted on the day following exposure. The incidence of the absence of a response to a noise stimulus was increased in rats exposed at 1,527 ppm but was not strictly exposure-related. Rats exposed to 181 and 1,527 ppm lost weight from study days 0 to 1; within 1 day of exposure, the body weights of rats exposed to 1,527 ppm were significantly lower by 13% compared to controls. At scheduled necropsy, pale liver, dark areas in the stomach, liver, intestines, and urinary bladder were observed at 1,527 ppm. Relative kidney and adrenal gland weights were significantly increased by 19 and 40%, respectively, in 1,527 ppm males; no significant effects were observed in females, possibly due to the low number of surviving animals. Histopathological changes were noted primarily in the liver and respiratory tract tissues. Hepatocellular centrilobular necrosis was observed in 0/5 males and 4/5 females (minimal to mild) exposed at 181 ppm and 5/5 males and 2/2 females (moderate to severe) exposed at 1,527 ppm, compared to 0/10 controls. The incidence and severity of necrosis of the olfactory epithelium (nasal levels III, IV, and V) increased in an exposure-related manner. Based on statistical analyses (Fisher's exact test) performed for this analysis, the male and female combined incidence of necrosis was significantly increased at all exposure concentrations at nasal level IV (affecting a small number of cells), and at 181 and 1,527 ppm at nasal levels III and V. The severity of the lesions were graded as minimal (2/5 males and 3/5 females) or mild (2/5 females) at 58 ppm, mild (5/5 males and 5/5 females) at 181 ppm, and mild (3/5 males) or moderate (1/5 males and 2/2 females) at 1,527 ppm. There was no evidence of necrosis in these tissues in control animals.

Selection of the Point of Departure for the MRL: The LOAEL of 58 ppm was selected as the point of departure (POD) for deriving an acute-duration inhalation MRL for 1,1,2-trichloroethane. Incidence data for necrosis of the olfactory epithelium in rats (level IV; any severity) are shown in Table A-2.

Table A-2. Incidence of Necrosis of the Olfactory Epithelium in F344 Rats Exposed to 1,1,2-Trichloroethane for 4 Hours

	Exposure concentration (ppm)			
Target	0	50	200	1,500
Measured	0	58	181	1,527
Necrosis; level IV	0/10 (0%)	7/10 (70%)	10/10 (100%)	7/7 (100%)[a]

[a]Data for three females that died on the day following exposure were excluded from analyses.

Source: Kirkpatrick 2001

These data were not considered amenable to benchmark dose (BMD) modeling because the lowest tested concentration shows a response that is substantially higher than the benchmark response (BMR) of 10% (i.e., 70% of animals were affected at 58 ppm). Thus, the data provide limited information on the dose-response relationship at lower concentrations. In addition, since the response was 100% at the two highest tested exposure concentrations, higher exposure concentrations did not reduce the uncertainty associated with the shape of the dose-response curve.

Human Equivalent Concentration: The LOAEL of 58 ppm was converted to a human equivalent concentration (HEC) of 7.5 ppm using the following equation:

$$LOAEL_{HEC} = LOAEL \times RGDR_{ET}$$

where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) for the extrathoracic region. Extrathoracic regional gas doses were calculated for each species as follows: V_E (minute volume) ÷ SA_{ET} (surface area of the extrathoracic region); where V_E = 137 mL/minute (based on reference body weight for male and female rats, 0.180 kg) and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$$LOAEL_{[HEC]} = LOAEL \times RGDR_{ET}$$
$$LOAEL_{[HEC]} = 58 \text{ ppm} \times (137 \text{ mL/minute} \div 15 \text{ cm}^2)/(13{,}800 \text{ mL/minute} \div 200 \text{ cm}^2)$$
$$LOAEL_{[HEC]} = 58 \text{ ppm} \times 0.13$$
$$LOAEL_{[HEC]} = 7.5 \text{ ppm}$$

Uncertainty Factor and Modifying Factor: The $LOAEL_{HEC}$ was divided by a total uncertainty factor of 90 and a modifying factor of 3:

- 3 for extrapolation from a minimal LOAEL; the study authors classified the severity of necrosis as minimal to mild because necrosis affected a small number of cells.
- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability
- 3 as a modifying factor for database deficiency because the only acute exposure data are from a single 4-hour exposure study.

$$MRL = LOAEL_{HEC} \div (UFs \times MF)$$
$$7.5 \text{ ppm} \div (3 \times 3 \times 10 \times 3) = 0.03 \text{ ppm}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Histopathological changes to the olfactory epithelium (vacuolization/microcyst formation) were observed following intermediate-duration oral exposure to 1,1,2-trichloroethane (Kirkpatrick 2002).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: March 2021
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.002 ppm
Critical Effect: Lesions of the olfactory epithelium (vacuolization/microcyst formation)
Reference: Kirkpatrick 2002
Point of Departure: $BMCL_{10}$ of 3.15 ppm ($BMCL_{HEC}$ of 0.07 ppm)
Uncertainty Factor: 30
LSE Graph Key: 13
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.002 ppm was derived for 1,1,2-trichloroethane based on an increase in the incidence of vacuolization/microcyst formation in the olfactory epithelium of male and female rats exposed to 40 ppm 1,1,2-trichloroethane 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002). The MRL is based on a $BMCL_{10}$ of 3.15 ppm, which was adjusted to continuous duration exposure, converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.07 ppm, and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: Only one study evaluated intermediate-duration inhalation toxicity of 1,1,2-trichloroethane (Kirkpatrick 2002). This study identified two targets of toxicity: the respiratory tract and the liver.

Based on a comparison of the lowest LOAEL for these endpoints, the respiratory tract appears to be the most sensitive target of toxicity. At concentrations of 40 and 100 ppm, significantly increased incidences of atrophy and vacuolization/microcyst formation of the olfactory epithelium were observed in male and female rats; the incidence of respiratory epithelial metaplasia of the olfactory epithelium was also significantly increased at 100 ppm (Kirkpatrick 2002). The incidence of these respiratory effects was not significantly increased at 15 ppm relative to controls. A significantly increased incidence of liver effects (namely hepatocellular vacuolization) was seen in the same study at 100 ppm only. Although increased cholesterol was noted in female rats exposed at concentrations as low as 40 ppm, the toxicological significance of this effect is unclear in the absence of effects on other serum chemistry parameters (AST, ALT) and liver weight, and the small magnitude of change in this parameter (within 20% of control values at all concentrations).

Selection of the Principal Study: Kirkpatrick (2002) was selected as the principal study because it was the only study that evaluated the toxicity of 1,1,2-trichloroethane following intermediate-duration exposure.

Summary of the Principal Study:

Kirkpatrick DT. 2002. A 90-day inhalation toxicity study of 1,1,2-trichloroethane (1,1,2-TCE) in rats (with satellite groups for pharmacokinetic evaluations in rats and mice) WIL Research Laboratories, Inc. HAP Task Force. EPA-HQ-OPPT-2002-0046-0003. WIL-417002. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0003.

Fischer 344 CDF Crl:BR rats (10/sex/group) were exposed whole-body to 1,1,2-trichloroethane (purity 99.5%) as a vapor at 0, 15, 40, and 100 ppm 6 hours/day, 5 days/week for 13 weeks. Rats were monitored for mortality and clinical signs of toxicity. Food consumption and body weights were measured weekly. Hematology and clinical chemistry parameters were evaluated at study termination. Ophthalmological examinations were performed. All animals were subjected to necropsy; organ weights of kidneys, liver, lungs, heart, brain, spleen, adrenals, thymus, thyroid, parathyroid, ovaries, testes, and epididymides were recorded. Comprehensive histopathological examinations were performed on all animals in the high-exposure and control groups; select tissues (liver, kidneys, and respiratory tissues) were examined in all dose groups. Cross-sections of nasal tissues from six nasal levels were prepared using methods described by Morgan (1991).

No significant, exposure-related effects on mortality, clinical signs of toxicity, food consumption, or body weights were reported. There were no significant effects on hematology parameters or on serum chemistry measurements indicative of liver function. Male rats exposed to 100 ppm and female rats exposed to 40 and 100 ppm showed significantly increased levels of serum cholesterol; however, this effect was not strictly dose related. Serum glucose was significantly decreased in 100 ppm females (but not males). Ophthalmological examinations did not reveal differences between exposed rats and controls. No significant, exposure-related macroscopic changes were reported. Rats of both sexes exposed to 40 and 100 ppm showed lesions of the olfactory epithelium of the nasal turbinates, including atrophy and vacuolization/microcyst formation; respiratory epithelial metaplasia was observed at 100 ppm. Hepatocellular vacuolization of minimal in severity occurred in rats of both sexes. Incidences of vacuolization/microcyst formation and atrophy are presented in Table A-3.

Table A-3. Incidence of Nasal Olfactory Epithelial Lesions in F344 Rats Exposed to 1,1,2-Trichloroethane 6 Hours/Day, 5 Days/Week for 13 Weeks

	Exposure concentration (ppm)			
	0	15	40	100
Vacuolization/microcyst formation	2/20 (10%)	6/20 (30%)	10/20 (50%)	18/20 (90%)
Atrophy	0/20 (0%)	0/20 (0%)	13/20 (65%)	17/20 (85%)

Source: Kirkpatrick 2002

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 3.15 ppm for increased incidence vacuolization/microcyst formation of the olfactory epithelium was selected as the POD for the MRL.

BMD modeling was conducted to identify a POD using exposure concentrations of 0, 15, 40, and 100 ppm. The data were fit to all available dichotomous models in EPA's Benchmark Software (BMDS version 3.1.2). A BMR of 10% was selected in the absence of data that would support a lower BMR. Adequate model fit was judged by four criteria: (1) goodness-of-fit statistics (p-value >0.1); (2) scaled residual at the data point (except the control) closest to the predefined BMR; (3) BMCL that is not 10 times lower than the lowest non-zero dose; and (4) visual inspection of the dose-response curve. None of the BMD models provided adequate fit to the atrophy data. For vacuolization/microcyst formation of the olfactory epithelium, all models provided adequate fit to the data. The Dichotomous Hill model was not run because the model requires a minimum of five dose levels. The range of $BMCL_{10}$ values was >3-fold; therefore, the model with the lowest $BMCL_{10}$ (Log-Logistic) was selected. Details of the modeling results for vacuolization/microcyst formation are in Table A-4. The fit of the Log-Logistic model is presented in Figure A-1.

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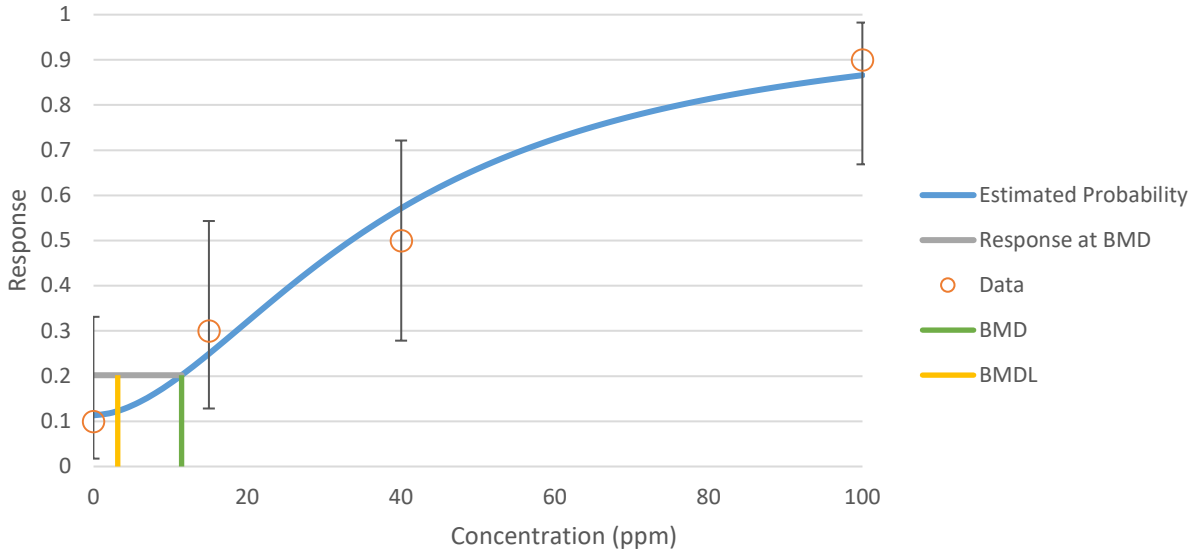
Table A-4. Results from BMD Analysis of Vacuolization/Microcyst Formation of the Olfactory Epithelium in Male and Female Fischer 344 Rats Administered 1,1,2-Trichloroethane for 13 Weeks (Kirkpatrick 2002)

Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	p-value[a]	AIC	Scaled residuals[b]	
					Dose near BMC	Control group
Dichotomous Hill	11.45	3.15	0.336	85.10	0.52	-0.19
Gamma[c]	9.18	4.15	0.546	84.53	0.33	-0.08
Log-Logistic[d,e]	**11.45**	**3.15**	**0.336**	**85.10**	**0.52**	**-0.19**
Multistage Degree 3[f]	7.38	4.23	0.785	84.24	-0.07	-0.07
Multistage Degree 2[f]	8.02	4.20	0.694	84.32	0.28	-0.08
Multistage Degree 1[f]	5.72	4.06	0.709	82.88	0.14	0.14
Weibull[c]	9.05	4.17	0.591	84.45	0.34	-0.09
Logistic	13.34	9.85	0.675	82.99	0.51	-0.66
Log-Probit	11.42	3.49	0.339	85.08	0.48	-0.14
Probit	12.97	9.90	0.677	82.98	0.49	-0.65

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals for dose group near the BMC and for the control group
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Recommended model. All models provided adequate fit to the data. The BMCLs for models providing adequate fit were not sufficiently close (differed by >3 fold). Therefore, the model with the lowest BMCL was selected (log-logistic model)
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk)

Figure A-1. Fit of Log-Logistic Model to Data on 1,1,2-Trichloroethane, Incidence of Vacuolization/Microcyst Formation in Male and Female Rats



Two PODs were considered for the MRL:

- BMC_{10} of 11.45 ppm based on increased incidence vacuolization/microcyst formation of the olfactory epithelium
- LOAEL of 40 ppm based on increased incidence atrophy of the olfactory epithelium.

The $BMC_{10}$of 11.45 ppm for increased incidence vacuolization/microcyst formation of the olfactory epithelium was selected as the basis of the MRL since it provided the lowest POD. The corresponding $BMCL_{10}$ was 3.15 ppm.

Intermittent Exposure: The $BMCL_{10}$ of 3.15 was adjusted for intermittent exposure to a continuous exposure scenario according to the following equitation:

$$BMCL_{ADJ} = BMCL_{10} \text{ of } 3.15 \text{ ppm} \times (6 \text{ hours}/24 \text{ hours}) \times (5 \text{ days}/7 \text{ days}) = 0.056 \text{ ppm}$$

Human Equivalent Concentration: The $BMCL_{ADJ}$ of 0.56 ppm was converted to a human equivalent concentration (HEC) of 0.07 ppm using the following equation:

$$BMCL_{HEC} = BMCL_{ADJ} \times RGDR_{ET}$$

where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) for the extrathoracic region. Extrathoracic regional gas doses were calculated for each species as follows: V_E (minute volume) ÷ SA_{ET} (surface area of the extrathoracic region); where V_E = 137 mL/minute (based on reference body weight for males and females, 0.180 kg) and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$$BMCL_{HEC} = BMCL_{ADJ} \times RGDR_{ET}$$
$$BMCL_{HEC} = 0.56 \text{ ppm} \times (137 \text{ mL/minute} \div 15 \text{ cm}^2)/(13{,}800 \text{ mL/minute} \div 200 \text{ cm}^2)$$
$$BMCL_{HEC} = 0.56 \text{ ppm} \times 0.13$$
$$BMCL_{HEC} = 0.073 \text{ ppm}$$

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

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

$MRL = BMCL_{HEC} \div UFs$
$0.073 \text{ ppm} \div (3 \times 10) = 0.0024 \approx 0.002 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Histopathological changes to the olfactory epithelium (necrosis) were observed following acute-duration oral exposure to 1,1,2-trichloroethane (Kirkpatrick 2001).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: March 2021
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: No chronic-duration inhalation studies were identified for 1,1,2-trichloroethane.

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.5 mg/kg/day
Critical Effect: Increased liver enzymes (AST and ALT)
Reference: Tyson et al. 1983
Point of Departure: NOAEL of 46 mg/kg
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.5 mg/kg/day was derived for 1,1,2-trichloroethane based on increased liver enzymes (AST and ALT) in male rats administered 1,1,2-trichloroethane via gavage (Tyson et al. 1983). The MRL is based on a NOAEL of 46 mg/kg and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: In an acute toxicity study of male Sprague-Dawley rats administered a single gavage dose of 1,1,2-trichloroethane, a substantial elevation in liver enzymes (AST and ALT) was observed 48 hours after administration of approximately 92 mg/kg; no increases in these liver enzymes were observed at 46 mg/kg compared to controls (Tyson et al. 1983). The increase in liver enzymes was observed at a lower dose than effects on liver histopathology (congestion, fatty degeneration, and edema) in dogs administered 433 mg/kg/day (Wright and Schaffer 1932), or increased enzymatic activity of ALT, sorbital dehydrogenase [SDH], or glutamate dehydrogenase in Wistar rats administered 667 mg/kg/day (Xia and Yu 1992).

NOAEL and LOAEL values for acute-duration oral exposure are summarized in Table A-5. The LOAEL for increased liver enzymes is lower than LOAELs identified for other acute effects. Gait impairment and decreased body weight gain (males) were observed at 200 mg/kg in a well-conducted acute neurotoxicity study (Beck 2004). Although motor activity was reported to be significantly decreased in males at 55 mg/kg in this study (Beck 2004), this effect was transient (observed during only a small window of time, without significant effects on mean total or ambulatory counts), showed high variability, and was not consistent across sexes (nonsignificant increases in motor activity counts were observed in females during the same time period). Several other acute toxicity studies of mice and dogs with 1,1,2-trichloroethane also reported neurological effects at doses higher than that eliciting liver effects in the Tyson et al. (1983) study. Results included sedation in male mice at ≥450 mg/kg/day (White et al. 1985), taste aversion in male mice at ≥100 mg/kg/day (toxicological significance uncertain; Kallman et al. 1983), motor impairment in mice at 128 mg/kg/day (Borzelleca 1983), and drowsiness in dogs at ≥289 mg/kg/day (Wright and Schaffer 1932). LOAELs for effects on other target systems identified in acute-duration toxicity studies (effects on body weight and the gastrointestinal and renal systems) were higher than the LOAEL for increased liver enzymes in male rats.

Selection of the Principal Study: The Tyson et al. (1983) study was selected as the principal study for deriving an acute-duration oral MRL for 1,1,2-trichloroethane because it identified the lowest reliable LOAEL for acute effects.

Table A-5. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to 1,1,2-Trichloroethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Crl:CD(SD) IGS rat	Once	95	200	Gait impairment on study day 0 (4/14 males; 5/12 females; 0/12 controls)	Beck 2004
CD-1 mouse	Once	30	100	Taste aversion	Kallman et al. 1983
CD-1 mouse	Once	ND	128	Motor impairment	Borzelleca 1983
Dog (NS)	Once	144	289	Drowsiness	Wright and Schaffer 1932
CD-1 mouse	Once	ND	450	Sedation	White et al. 1985
Liver effects					
Sprague-Dawley rat	Once	46	92	Increased AST and ALT	Tyson et al. 1983
Dog (NS)	Once	144	433	Mild congestion, fatty degeneration and edema	Wright and Schaffer 1932
Wistar rat	Once	ND	667	Increased ALT, SDH, glutamate dehydrogenase	Xia and Yu 1992
Other effects					
Dog (NS)	Once	ND	144	Mild congestion and cloudy swelling of the kidneys	Wright and Schaffer 1932
Wistar-derived Alderley Park rat	7 days	ND	180	Decreased body weight gain	Platt and Cockrill 1969
Crl:CD(SD) IGS rat	Once	95	200	Decreased body weight gain in males	Beck 2004
Dog (NS)	Once	144	433	Mild congestion and inflammation of the gastrointestinal tract	Wright and Schaffer 1932

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; SDH = sorbitol dehydrogenase

Summary of the Principal Study:

Tyson CA, Hawk-Prather K, Story DL, et al. 1983. Correlations of *in vitro* and *in vivo* hepatotoxicity for five haloalkanes. Toxicol Appl Pharmacol 70:289-302.

In an acute toxicity study, male Sprague-Dawley rats (number per group not specified) were administered 1,1,2-trichloroethane as a single dose via gavage. Data were presented graphically in Figure 9 of the study report. Doses were estimated using GrabIt! Software; doses were approximately 0, 0.34, 0.69, and 1.71 mmol/kg, or 0, 46, 92, and 228 mg/kg (based on molecular weight of 133.4 g/mol for 1,1,2-trichloroethane). The enzymatic activities of ALT and AST were evaluated 6, 24, and/or 48 hours after dosing. No other evaluations of hepatic toxicity were reported.

Enzyme levels (mean±standard deviation) for the control group were reported in the text of the study. ALT and AST in untreated controls were 45±10 and 83±21 U/L, respectively at 6, 24, and 48 hours post-exposure; the number of animals evaluated at each of these time points was 3, 5 and 5, respectively. Based on data from Figure 9 of the study report (obtained via GrabIt! Software or embedded in the figure), 48 hours after treatment at 92 and 228 mg/kg, ALT and AST activities were increased by approximately 7.2- and 15-fold, respectively, compared to controls (statistical analyses were not performed); values are summarized in Table A-6. In the 46 mg/kg group, there was no significant change in liver enzymes.

Table A-6. Effects on Liver Enzymes in Male Sprague-Dawley Rats Exposed to 1,1,2-Trichloroethane as a Single Gavage Dose[a]

	Dose (mg/kg)			
Effect	0	46	92	228
ALT (U/L); 24 hours	45±10[b]	29	60	1,811[c]
ALT (U/L); 48 hours		38	323	3,975[c]
AST (U/L); 24 hours	83±21[b]	72	163	4,428[c]
AST (U/L); 48 hours		77	1,248[c]	8,781[c]

[a]Data for administered doses and enzyme levels were obtained from Figure 9 of the study using GrabIt! Software.
[b]Mean±standard deviation at 6, 24, and 48 hours (as reported in the text of the study).
[c]Measured values as reported in Figure 9 of the study.

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Tyson et al. 1983

Selection of the Point of Departure for the MRL: The NOAEL of 46 mg/kg was selected as the POD for deriving an acute-duration oral MRL for 1,1,2-trichloroethane. BMD modeling could not be conducted because information required to perform modeling (e.g., animal numbers, measures of variance) was not reported.

Uncertainty Factor: The NOAEL of 46 mg/kg was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

MRL = NOAEL ÷ UFs
46 mg/kg ÷ (10 x 10) = 0.46 mg/kg/day ≈ 0.5 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: In male mice administered 1,1,2-trichloroethane via a single intraperitoneal injection, the reported ED_{50} values for increased serum ALT were approximately 144 mg/kg (based on the ED_{50} reported in mL/kg) and 240 mg/kg (based on the ED_{50} reported in mmol/kg) (Klaassen and Plaa 1966). No non-neoplastic liver lesions (based on histopathological examinations) were observed in rats treated at up to 92 mg/kg/day or mice treated at up to 390 mg/kg/day via gavage for 78 weeks (NCI 1978).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.04 mg/kg/day
Critical Effect: Immunotoxicity (decreased hemagglutination titers) and mild hepatotoxicity
Reference: Sanders et al. 1985
Point of Departure: NOAEL of 3.9 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 18
Species: Mouse

MRL Summary: An intermediate-duration oral MRL of 0.04 mg/kg/day was derived for 1,1,2-trichloroethane based on immunological effects observed in male and female mice exposed to 44 mg/kg/day 1,1,2-trichloroethane in drinking water for 90 days (Sanders et al. 1985). The MRL is based on a NOAEL of 3.9 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effects: In an intermediate-duration oral toxicity study, male and female mice administered 1,1,2-trichloroethane in the drinking water for 90 days showed dose-related effects on the humoral immune system (a reduction in hemagglutination titers) at ≥44 mg/kg/day (Sanders et al. 1985). NOAEL and LOAEL values for reduced hemagglutination titers were identified as 3.9 and 44 mg/kg/day, respectively, in females and 4.4 and 46 mg/kg/day, respectively, in males. In addition, the ability of thioglycolate-recruited peritoneal exudate cells (PECs) to phagocytize sRBCs was significantly reduced in males at 305 mg/kg/day. Cell-mediated immunity was unaffected in both sexes. Immune effects were observed at lower doses than effects on body weight (≥69 mg/kg/day; Mylchreest 2006; Story et al. 1986; White et al. 1985; Wilson 2005), developmental effects (82.2 mg/kg/day; Mylchreest 2006), and increased liver weight (384 mg/kg/day; White et al.1985). No other intermediate-duration oral toxicity studies evaluated immune function. NOAEL and LOAEL values for intermediate-duration oral exposure are summarized in Table A-7.

Table A-7. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,1,2-Trichloroethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
CD-1 mouse	90 days	3.9 F 4.4 M	44 F 46 M	Decreased hemagglutination titers	Sanders et al. 1985
Osborne-Mendel rat	5 days/week, 7 weeks	ND	69	Decreased body weight	Story et al. 1986
Crl:CD(SD) IGS rat	Two generations	40.6	82.2	Decreased body weight gain during gestation (P1 and F1 females)	Mylchreest 2006
				Decreased F1 and F2 pup weights (PNDs 4–21)	
Crl:CD(SD) IGS rat	GDs 6–20	48	111	Decreased body weight gain	Wilson 2005
CD-1 mouse	90 days	46 M	305 M	Decreased body weight in males	White et al. 1985
		44 F	384 F	Increased relative and absolute liver weight	

F = female; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Selection of the Principal Study: The intermediate-duration database identifies the immune system as the most sensitive target of 1,1,2-trichloroethane. The Sanders et al. (1985) study was selected as the principal study for deriving an intermediate-duration oral MRL for 1,1,2-trichloroethane because it identified the lowest LOAEL of 44 mg/kg/day (NOAEL of 3.9 mg/kg/day).

Summary of the Principal Study:

Sanders VM, White KL, Shopp Jr GM, et al. 1985. Humoral and cell-mediated immune status of mice exposed to 1,1,2-trichloroethane. Drug Chem Toxicol 8(5):357-372.

Sanders et al. (1985) administered 1,1,2-trichloroethane (purity 95%) at 0, 20, 200, and 2,000 ppm in the drinking water to male and female CD-1 mice (time-weighted average doses of 0, 4.4, 46, and 305 mg/kg/day for males and 0, 3.9, 44, and 384 mg/kg/day for females based on measured water intake and body weight data were calculated by study authors) for 90 days. Immunological endpoints were examined in 8–25 mice/sex/group. Humoral immune status was assessed by measuring the numbers of splenic AFCs to sRBCs (on peak day 4 and on day 5), hemagglutination titers, and the response of splenic lymphocytes to lipopolysaccharide (LPS; a B-cell mitogen) and concanavalin A (con A; a T-cell mitogen). Cell-mediated immune function parameters included delayed-type hypersensitivity (DTH) and popliteal lymph node responses to sRBCs. Additional immunological endpoints evaluated were the ability of macrophages of the reticuloendothelial system (RES) to clear sRBC from the vascular system and distribute them to the liver, spleen, thymus, lungs, and kidneys; numbers of PECs (recruitable, adherent, chemotaxis) and their ability to phagocytize sRBCs, and DNA synthesis in the bone marrow.

Sanders et al. (1985) found that hemagglutination titers (expressed as $\log_2$ titers) were significantly decreased in male and female mice at ≥44 mg/kg/day relative to controls. Based on the transformation of $\log_2$ titers to antibody dilutions, hemagglutination levels were decreased 47 and 59% in males treated at 46 and 305 mg/kg/day, respectively, and 40 and 45% in females treated at 44 and 384 mg/kg/day, respectively. Changes in the activity of fixed macrophages of the RES to clear and distribute sRBCs (observed in females only) were not considered treatment-related due to variations in the direction and magnitude of effects. In male mice treated at 305 mg/kg/day, PECs showed a reduced ability to phagocytize sRBCs (55–56% lower than controls over a 20–45-minute period). No effects on the humoral immune response based on AFC counts or the response of splenic lymphocytes to B-cell and T-cell mitogens were observed, and cell-mediated immune responses were unaffected by treatment. No significant time- or dose-related effects on bone marrow DNA synthesis were observed.

Selection of the Point of Departure for the MRL: The NOAEL of 3.9 mg/kg/day was selected as the POD for deriving an intermediate-duration oral MRL for 1,1,2-trichloroethane. These data were not amenable to BMD modeling because information required to perform modeling (e.g., animal numbers) was not reported.

Uncertainty Factor: The NOAEL of 3.9 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

MRL = NOAEL ÷ UFs
3.9 mg/kg/day ÷ 100 = 0.039 mg/kg/day ≈ 0.04 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: An acute-duration study in mice exposed to 1,1,2-trichloroethane in drinking water at up to 38 mg/kg/day for 14 days did not identify any significant treatment-related effects on humoral or cell-mediated immunity; this study

used lower doses than those used in the intermediate-duration study and did not evaluate a comprehensive set of immunological parameters (Sanders et al. 1985). A 90-day drinking water study in mice reported an 18% increase in relative spleen weight in females (but not males); no increase in thymus weight was observed in males or females (White et al. 1985). However, immune function was not examined in this study. The available chronic-duration studies did not identify histopathological changes to the spleen, lymph nodes, bone marrow, or thymus of rats (treated at up to 92 mg/kg/day for 78 weeks) or mice (treated at up to 390 mg/kg/day for 78 weeks); however, immune system function was not evaluated (NCI 1978).

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: March 2021
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration oral MRL was derived for 1,1,2-trichloroethane because the available data are insufficient for identifying a critical effect. No adverse effects were identified in rats administered 1,1,2-trichloroethane via gavage at doses up to 92 mg/kg/day 5 days/week for 78 weeks (NCI 1978). The only adverse effects found in mice administered 1,1,2-trichloroethane via gavage at up to 390 mg/kg/day 5 days/week for 78 weeks were increased mortality at 195 mg/kg/day, an increased incidence of hepatocellular carcinomas at ≥195 mg/kg/day, and adrenal pheochromocytomas at 390 mg/kg/day (NCI 1978).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,1,2-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 1,1,2-trichloroethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,1,2-trichloroethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,1,2-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 1,1,2-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
    - Neurological effects
    - Reproductive effects
    - Developmental effects

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 1,1,2-trichloroethane released for public comment in 2019; thus, the literature search was restricted to studies published between March 2016 and June 2020. The following main databases were searched in June 2020:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,1,2-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 1,1,2-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	
06/2020	(79-00-5[rn] OR "1,1,2-trichloroethane"[nm] OR "1,1,2-Trichlorethane"[tw] OR "1,1,2-Trichloroethane"[tw] OR "1,2,2-Trichloroethane"[tw] OR "beta-Trichloroethane"[tw] OR "Vinyl trichloride"[tw] OR "Vinyltrichloride"[tw]) AND (2017/03/01:3000[mhda] OR 2017/03/01:3000[crdt] OR 2017/03/01:3000[edat] OR 2016/03/01:3000[dp]) OR ("1,1,2-TCA"[tw] OR "Ethane, 1,1,2-trichloro-"[tw] OR "Trichloroethane, 1,1,2-"[tw] OR "β-Trichloroethane"[tw])
NTRL	
06/2020	"1,1,2-Trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "beta-Trichloroethane" OR "Vinyl trichloride" OR "Vinyltrichloride" OR "1,1,2-TCA" OR "Ethane, 1,1,2-trichloro-" OR "Trichloroethane, 1,1,2-" OR "β-Trichloroethane" Date Published: 2016 to 2020
Toxcenter	
06/2020	FILE 'TOXCENTER' ENTERED AT 16:20:05 ON 03 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 2548 SEA FILE=TOXCENTER 79-00-5 L2 2362 SEA FILE=TOXCENTER L1 NOT PATENT/DT L6 142 SEA FILE=TOXCENTER L2 AND ED>=2016 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))

Table B-2. Database Query Strings

Database search date	Query string
	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?) 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 (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 57 SEA FILE=TOXCENTER L6 AND L37 L41 56 DUP REM L38 (1 DUPLICATE REMOVED) ANSWERS '1-56' FROM FILE TOXCENTER

Table B-2. Database Query Strings

Database search date	Query string
	D SCAN L41

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2020	Compounds searched: 79-00-5
NTP	
06/2020	79-00-5 "1,1,2-Trichlorethane" "1,1,2-Trichloroethane" "1,2,2-Trichloroethane" "beta-Trichloroethane" "Vinyl trichloride" "Vinyltrichloride" "1,1,2-TCA" "Ethane, 1,1,2-trichloro-" "Trichloroethane, 1,1,2-" "β-Trichloroethane"
Regulations.gov	
06/2020	Compounds searched: 79-00-5
NIH RePORTER	
08/2020	Text Search: "1,1,2-Trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "beta-Trichloroethane" OR "Vinyl trichloride" OR "Vinyltrichloride" OR "1,1,2-TCA" OR "Ethane, 1,1,2-trichloro-" OR "Trichloroethane, 1,1,2-" OR "β-Trichloroethane" OR Trichlorethane (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 86
- Number of records identified from other strategies: 26
- Total number of records to undergo literature screening: 110

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,1,2-trichloroethane:

- 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: 110

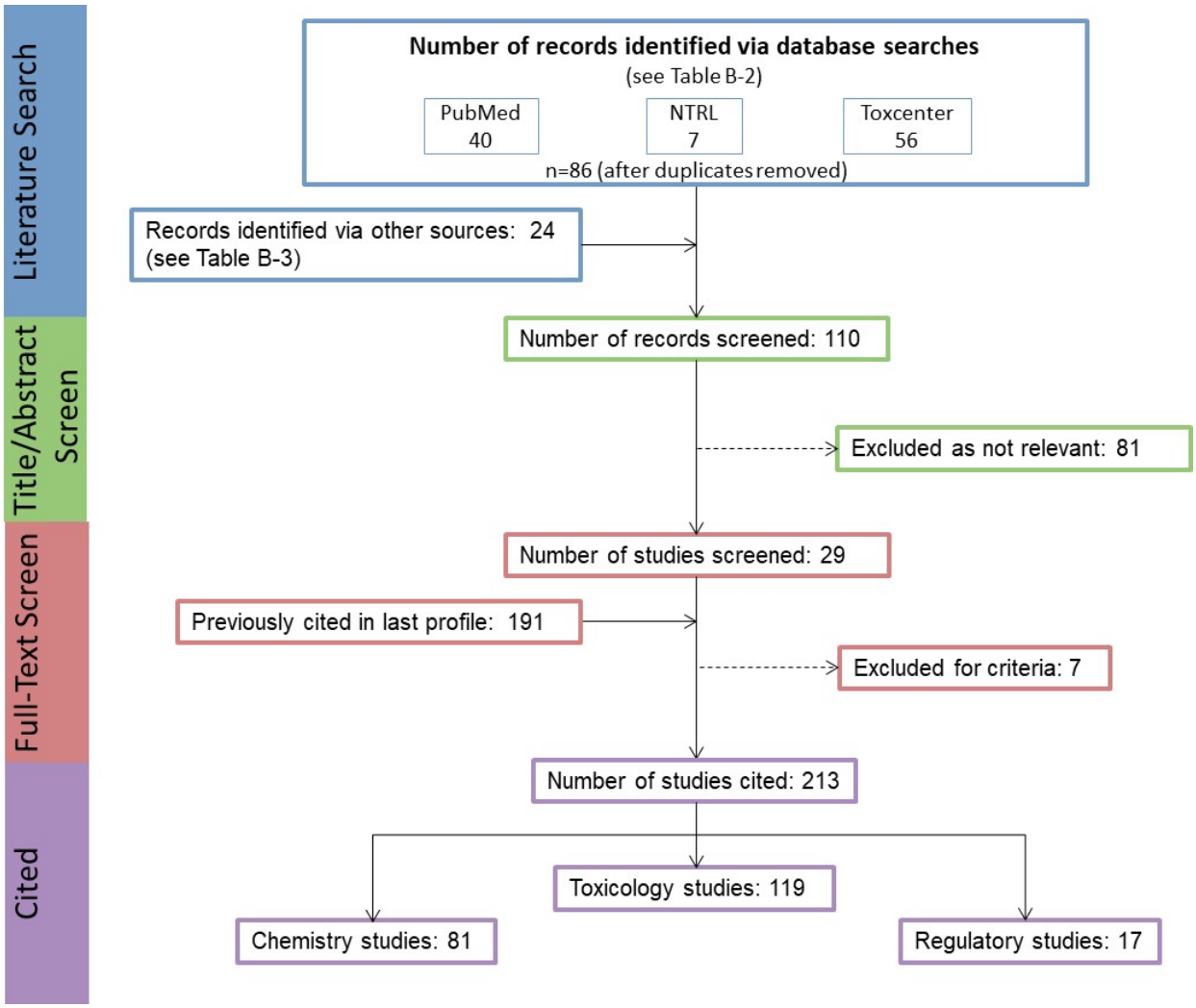
- Number of studies considered relevant and moved to the next step: 29

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: 29
- Number of studies cited in the pre-public draft of the toxicological profile: 191
- Total number of studies cited in the profile: 213

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

Figure B-1. June 2020 Literature Search Results and Screen for 1,1,2-Trichloroethane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1,2-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 1,1,2-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 1,1,2-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 1,1,2-trichloroethane. The inclusion criteria used to identify relevant studies examining the health effects of 1,1,2-trichloroethane are presented in Table C-1.

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

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

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

Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

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.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of 1,1,2-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 1,1,2-trichloroethane released for public comment in 2019. See Appendix B for the databases searched and the search strategy.

A total of 110 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 1,1,2-trichloroethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 110 records were reviewed; 0 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 31 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 31 documents, 38 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

A summary of the extracted data for each study is presented in the Supplemental Document for 1,1,2-trichloroethane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables (Tables 2-1, 2-2, and 2-3, respectively).

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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1,2-trichloroethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The only available human studies evaluating noncancer effects are dermal studies (limited in scope) and one case-control study examining the association between the proximity to industrial air releases of chlorinated solvents (including 1,1,2-tricholoroethane) and birth defects (Brender et al. 2014). Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin irritation, and skin sensitization. Respiratory, hepatic, neurological, and

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Table C-3. Overview of the Health Outcomes for 1,1,2-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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

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

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Table C-4. Overview of the Health Outcomes for 1,1,2-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	0	2	0	0	0	0	4	0	0	0	0	0	6	0	0	0	0
	0	2	0	0	0	0	4	0	0	0	0	0	6	0	0	0	0
Intermediate-duration	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral studies																	
Acute-duration	3	1	0	2	1	0	5	2	0	0	0	1	6	1	1	0	0
	2	0	0	2	0	0	3	1	0	0	0	0	5	0	0	0	0
Intermediate-duration	5	1	0	0	1	0	1	1	0	0	0	1	1	1	2	0	0
	4	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0	0
Chronic-duration	2	2	2	2	2	2	2	2	2	0	0	2	2	2	0	0	2
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Dermal studies																	
Acute-duration	0	0	0	0	0	0	0	1	4	0	0	0	1	0	0	0	0
	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
Intermediate-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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.

immunological effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Thirty-eight studies (published in 31 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

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?

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

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 1,1,2-trichloroethane health effects studies observed in animal experimental studies (human studies did not evaluate respiratory, hepatic, neurological or immunological outcomes) are presented in Table C-8.

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects									
Inhalation acute exposure									
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	++	+	++	++	++	++	++	++	First
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	++	+	++	++	++	++	++	++	First
Oral acute exposure									
White et al. 1985 (mouse; CD-1; 14 days)	+	+	++	+	++	+	++	++	First
Inhalation intermediate exposure									
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	++	++	++	++	++	++	++	++	First
Oral intermediate exposure									
White et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	–	++	Second
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First
Outcome: Hepatic effects									
Inhalation acute exposure									
Carlson 1973 (rat; albino)	–	+	+	+	+	–	–	+	Second
Gehring 1968 (mouse; Swiss Webster)	–	+	+	+	+	–	–	+	Second
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	++	+	++	++	++	++	++	++	First
Takahara 1986a (mouse)	–	+	–	+	+	–	–	+	Second

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Oral acute exposure									
Platt and Cockrill 1969 (rat; Wistar-derived)	+	+	+	+	+	–	–	+	Second
Tyson et al. 1983 (rat; Sprague-Dawley)	–	+	+	+	+	–	+	+	First
White et al. 1985 (mouse; CD-1; 14 days)	+	+	++	+	++	+	++	++	First
Wright and Schaffer 1932 (dog)	– –	+	–	+	+	+	–	+	Second
Xia and Yu 1992 (rat; Wistar)	+	+	–	+	–	+	–	+	Second
Inhalation intermediate exposure									
Kirkpatrick 2002 (rat; F344)	++	++	++	++	++	++	++	++	First
Oral intermediate exposure									
White et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	+	++	First
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First
Outcome: Neurological effects									
Inhalation acute exposure									
Bonnet et al. 1980 (rat; Sprague-Dawley)	–	+	+	+	–	–	–	+	Second
de Ceaurriz et al. 1981 (mouse; Swiss OF_1)	–	+	+	+	–	+	–	+	Second
Gehring 1968 (mouse; Swiss-Webster)	–	+	+	+	+	–	–	+	Second

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Lazarew 1929 (mouse)	–	+	+	+	–	–	–	+	Second
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	++	+	++	++	++	++	++	++	First
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	++	+	++	++	++	++	++	++	First
Oral acute exposure									
Beck 2004 (rat; Crl:CD(SD)IGS)	++	++	++	++	++	++	++	++	First
Borzelleca 1983 (mouse; CD-1)	–	+	+	+	–	–	–	+	Second
Kallman et al. 1983 (mouse; CD-1)	+	+	++	+	++	++	+	++	First
Kallman and Kaempf 1984 (mouse; CD-1)	+	+	++	+	++	++	+	++	First
White et al. 1985 (mouse; CD-1; once)	+	+	++	+	+	+	+	++	First
Wright and Schaffer 1932 (dog)	– –	+	–	+	+	+	–	+	Second
Oral intermediate exposure									
Maurissen et al. 2005 (rat; F344/DUCRL)	++	++	++	++	++	++	++	++	First
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Immunological effects									
Oral acute exposure									
Sanders et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	++	++	First
Oral intermediate exposure									
Sanders et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	++	++	First
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First

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 1,1,2-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 1,1,2-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 in Distiller, 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-9, C-10, and C-11, 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-9. 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-10. 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-11. 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 respiratory, hepatic, neurological, and immunological effects observed in animal experimental studies are presented in Table C-12.

A summary of the initial confidence ratings for each outcome is presented in Table C-13. 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-13.

Table C-12. Presence of Key Features of Study Design for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	Yes	No	Yes	Yes	High
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	Yes	No	Yes	Yes	High
Oral acute exposure					
White et al. 1985 (mouse; CD-1; 14 days)	Yes	Yes	No	Yes	Moderate
Inhalation intermediate exposure					
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
White et al. 1985 (mouse; CD-1)	Yes	Yes	No	Yes	Moderate
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	Yes	Yes	High
NCI 1978 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Carlson 1973 (rat; albino)	Yes	Yes	No	Yes	Moderate
Gehring 1968 (mouse; Swiss Webster)	No	Yes	No	No	Very Low
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	Yes	No	Yes	Yes	High
Takahara 1986a (mouse)	No	Yes	No	No	Very Low
Oral acute exposure					
Platt and Cockrill 1969 (rat; Wistar-derived)	Yes	Yes	No	Yes	Moderate
Tyson et al. 1983 (rat; Sprague-Dawley)	No	No	No	No	Very Low
White et al. 1985 (mouse; CD-1; 14 days)	Yes	Yes	Yes	Yes	High
Wright and Schaffer 1932 (dog)	No	No	Yes	No	Very Low
Xia and Yu 1992 (rat; Wistar)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Kirkpatrick 2002 (rat; F344)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
White et al. 1985 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	Yes	Yes	High
NCI 1978 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High

Table C-12. Presence of Key Features of Study Design for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Neurological effects					
Inhalation acute exposure					
Bonnet et al. 1980 (rat; Sprague-Dawley)	No	Yes	Yes	No	Low
de Ceaurriz et al. 1981 (mouse; Swiss OF_1)	No	Yes	No	No	Very Low
Gehring 1968 (mouse; Swiss-Webster)	No	Yes	No	No	Very Low
Lazarew 1929 (mouse)	No	No	No	No	Very Low
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	Yes	No	Yes	Yes	High
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	Yes	No	Yes	Yes	High
Oral acute exposure					
Beck et al. 2004	Yes	Yes	Yes	Yes	High
Borzelleca 1983 (mouse; CD-1)	No	No	Yes	No	Very Low
Kallman et al. 1983 (mouse; CD-1)	Yes	Yes	No	Yes	Moderate
Kallman and Kaempf 1984 (mouse; CD-1)	Yes	No	No	No	Low
White et al. 1985 (mouse; CD-1; once)	No	Yes	Yes	No	Low
Wright and Schaffer 1932 (dog)	No	No	Yes	No	Very Low
Oral intermediate exposure					
Maurissen et al. 2005 (rat; F344/DUCRL)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse; B6C3F1)	Yes	Yes	No	Yes	Moderate
Outcome: Immunological effects					
Oral acute exposure					
Sanders et al. 1985 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Sanders et al. 1985 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse; B6C3F1)	Yes	Yes	No	Yes	Moderate

Table C-13. Initial Confidence Rating for 1,1,2-Trichloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	High	High
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	High	
Inhalation intermediate exposure		
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	High	High
Oral acute exposure		
White et al. 1985 (mouse; CD-1)	Moderate	Moderate
Oral intermediate exposure		
White et al. 1985 (mouse; CD-1)	Moderate	Moderate
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	High	High
NCI 1978 (mouse; B6C3F1)	High	
Outcome: Hepatic effects		
Inhalation acute exposure		
Carlson 1973 (rat; albino)	Moderate	High
Gehring 1968 (mouse; Swiss Webster)	Very Low	
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	High	
Takahara 1986a (mouse)	Very Low	
Inhalation intermediate exposure		
Kirkpatrick 2002 (rat; F344)	High	High
Oral acute exposure		
Platt and Cockrill 1969 (rat; Wistar-derived)	Moderate	High
Tyson et al. 1983 (rat; Sprague-Dawley)	Very Low	
White et al. 1985 (mouse; CD-1)	High	
Wright and Schaffer 1932 (dog)	Very Low	
Xia and Yu 1992 (rat; Wistar)	Moderate	
Intermediate inhalation exposure		
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	High	High
Oral intermediate exposure		
White et al. 1985 (mouse; CD-1)	High	High
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	High	High
NCI 1978 (mouse; B6C3F1)	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Bonnet et al. 1980 (rat; Sprague-Dawley)	Low	High
de Ceaurriz et al. 1981 (mouse; Swiss OF_1)	Very Low	
Gehring 1968 (mouse; Swiss-Webster)	Very Low	
Lazarew 1929 (mouse)	Very Low	
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	High	
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	High	

Table C-13. Initial Confidence Rating for 1,1,2-Trichloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral acute exposure		
Beck 2004 (rat; Crl:CD(SD)IGS)	High	High
Borzelleca 1983 (mouse; CD-1)	Very Low	
Kallman et al. 1983 (mouse; CD-1)	Moderate	
Kallman and Kaempf 1984 (mouse; CD-1)	Low	
White et al. 1985 (mouse; CD-1)	Low	
Wright and Schaffer 1932 (dog)	Very Low	
Oral intermediate exposure		
Maurissen et al. 2005 (rat; F344/DUCRL)	High	High
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	Moderate	Moderate
NCI 1978 (mouse; B6C3F1)	Moderate	
Outcome: Immunological effects		
Oral acute exposure		
Sanders et al. 1985 (mouse; CD-1)	High	High
Oral intermediate exposure		
Sanders et al. 1985 (mouse; CD-1)	High	High
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	Moderate	Moderate
NCI 1978 (mouse; B6C3F1)	Moderate	

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 respiratory, hepatic, neurological, and immunological effects are presented in Table C-14. 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 1,1,2-trichloroethane exposure is presented in Table C-15.

Table C-14. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Animal studies	High	None	High
Outcome: Hepatic effects			
Animal studies	High	None	High
Outcome: Neurological effects			
Animal studies	High	None	High
Outcome: Immunological effects			
Animal studies	High	-1 unexplained inconsistency	Moderate

Table C-15. Confidence in the Body of Evidence for 1,1,2-Trichloroethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	No data	High
Hepatic effects	No data	High
Neurological effects	No data	High
Immunological effects	No data	Moderate

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 (Table C-8). 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

  - 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 1,1,2-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 1,1,2-trichloroethane is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for 1,1,2-Trichloroethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Animal studies			
Respiratory effects following inhalation exposure	High	Health effect	High
Hepatic effects	High	Health effect	High
Neurological effects	High	Health effect	High
Immunological effects	Moderate	Health effect	Moderate

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

- **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

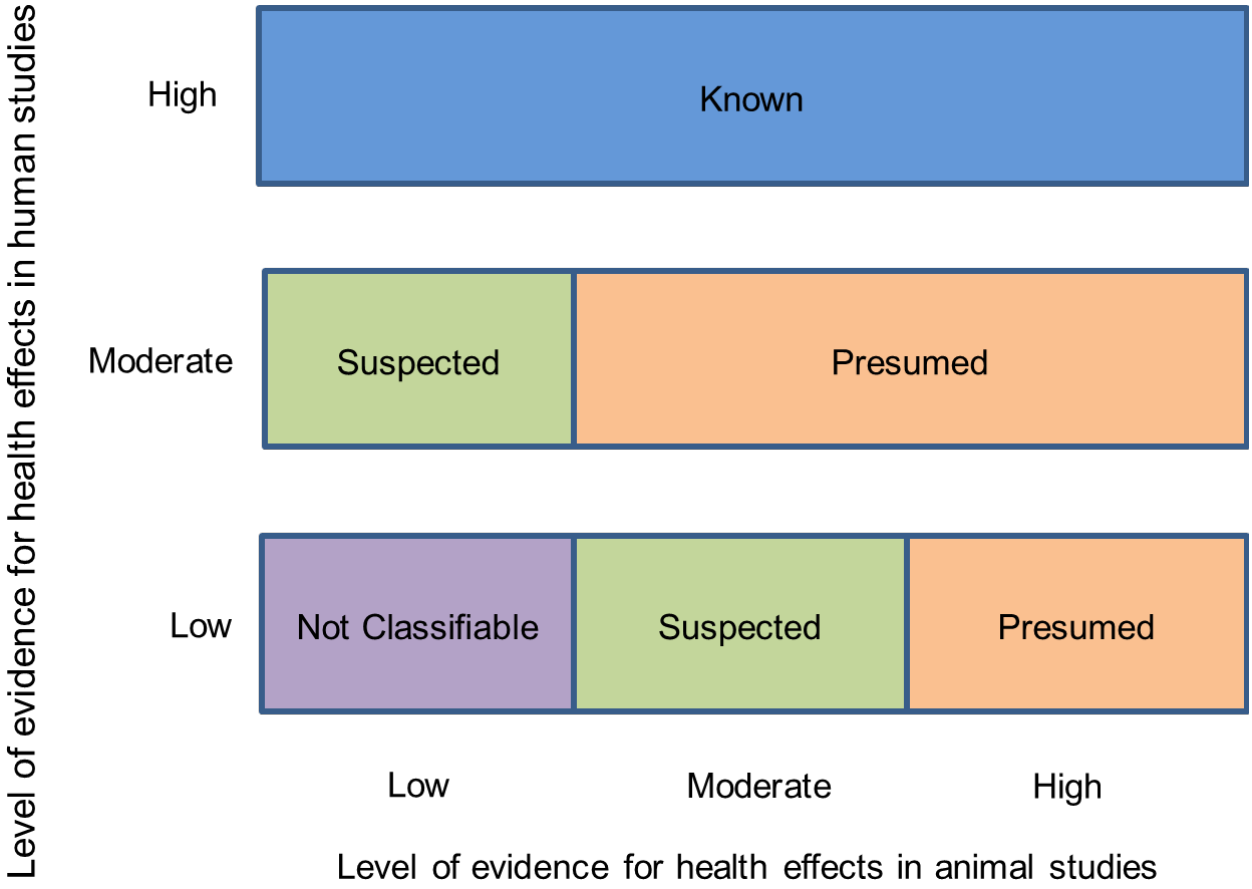
- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

The hazard identification conclusions for 1,1,2-trichloroethane are listed below and summarized in Table C-17.

Presumed Health Effects

- Respiratory effects following inhalation exposure
  - No human data
  - Acute- and intermediate-duration inhalation studies identified changes in the bronchoalveolar lavage fluid (increased protein content) and nasal lesions (vacuolization and microcyst formation, respiratory epithelial metaplasia, atrophy, and/or necrosis of the olfactory epithelium) in male and female rats (Kirkpatrick 2001, 2002).
- Hepatic effects
  - No human data
  - Liver effects (namely increased ALT and/or AST, increased liver weight, and/or histopathological changes including hepatocellular vacuolization and necrosis, fatty changes, and/or swelling) were identified in numerous acute- and intermediate-duration toxicity studies (via the inhalation and oral routes of exposure; Carlson 1973; Gehring 1968; Kirkpatrick 2001, 2002; Moody et al. 1981; Takahara 1986b; Tyson et al. 1983; unpublished data from Dow Chemical Co. as provided in Torkelson and Rowe 1981; White et al. 1985). However, liver lesions were not reported in rats and mice orally exposed to 1,1,2-trichloroethane for 78 weeks (NCI 1978).
- Neurological effects
  - No human data
  - Acute-duration inhalation toxicity studies in rats and mice predominantly identified clinical signs of neurotoxicity at sublethal exposure concentrations (Bonnet et al. 1980; de Ceaurriz et al. 1981; Gehring 1968; Kirkpatrick 2001; Lazarew 1929). In addition to clinical signs, reduced motor activity, gait impairment, and taste aversion (to saccharin) were observed in acute-duration oral toxicity studies in rats and mice (Beck 2004; Borzelleca 1983; Kallman et al. 1983). However, rats treated for up to 13 weeks with 1,1,2-trichloroethane in drinking water showed no effects on FOB tests or histopathology of nervous system organs and tissues (Maurissen et al. 2005). Likewise, there was no evidence of neurological effects (based on histopathology) in rats and mice treated orally with 1,1,2-trichloroethane for 78 weeks. Few repeated-dose studies have evaluated neurobehavioral effects (NCI 1978).

Suspected Health Effect

- Immunological effects
  - No human data
  - An intermediate-duration oral toxicity study identified a dose-related reduction in hemagglutination titers in male and female mice (Sanders et al. 1985). However, other immunological parameters (numbers of splenic antibody-forming cells, the response of splenic lymphocytes to mitogens, and macrophage activity) evaluated in the same study were not consistently affected. In addition, mice exposed to 1,1,2-trichloroethane for 14 days showed no significant, treatment-related immunological effects (based on similar humoral or cell-mediated immune response evaluations; Sanders et al. 1985). Chronic-duration studies in rats and mice identified NOAELs for immunological effects based on the absence of histopathological changes in the spleen, thymus, bone marrow, or lymph nodes; immunological function was not evaluated in these studies (NCI 1978).

Table C-17. Hazard Identification Conclusions for 1,1,2-Trichloroethane

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Hepatic effects	Presumed health effect
Neurological effects	Presumed health effect
Immunological effects	Suspected health effect

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), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page 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.

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

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

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

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

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

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

APPENDIX D

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

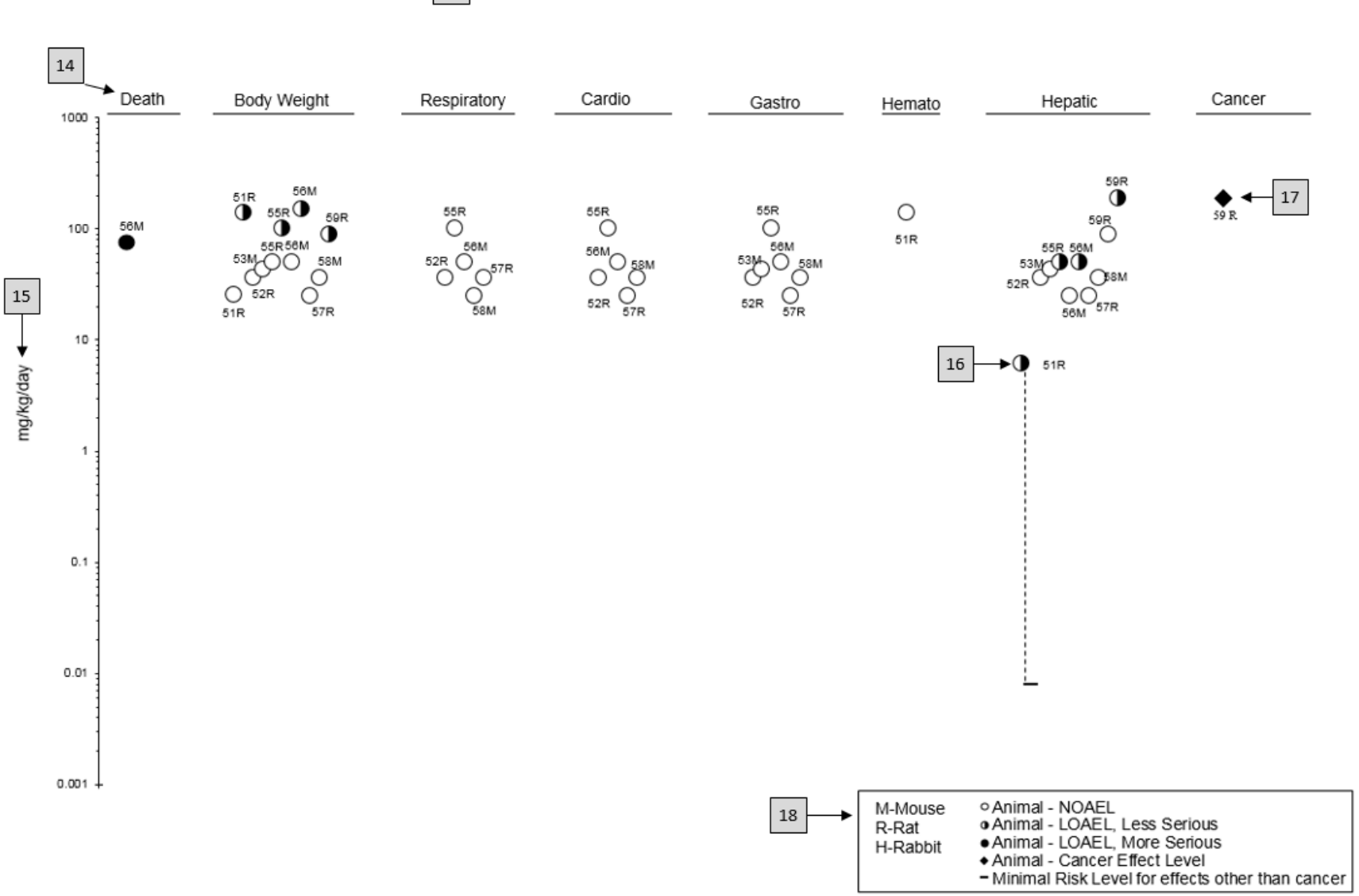
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

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

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

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result