APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 3 ppm
Critical Effect: Lacrimation
Reference: Hurtt et al. 1993
Point of Departure: $BMCL_{10}$ of 256.47 ppm
Uncertainty Factor: 100
LSE Graph Key: 1
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 3 ppm was derived for trans-1,2-dichloroethene based on lacrimation in pregnant rats exposed to trans-1,2-dichloroethene vapor in air on GDs 7–16. The MRL is based on a $BMCL_{10}$ of 256.47 ppm (unadjusted for exposure duration because exposure was concentration-dependent, not duration-dependent) and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Few animal studies have investigated effects of acute-duration inhalation exposure to trans-1,2-dichloroethene (Freundt et al. 1977; Gradiski et al. 1978; Hurtt et al. 1993). Gradiski et al. (1978) is an acute lethality study designed to estimate the LC_{50} value for a single 6-hour inhalation exposure to trans-1,2-dichloroethene. No information other than the estimated LC_{50} value (21,723 ppm) was reported. Therefore, this study does not provide suitable data for derivation of the acute-duration inhalation MRL. The Freundt et al. (1977) study examined effects of a single 8-hour exposure to 0, 200, 1,000, or 3,000 ppm in female Wistar rats (n=6). Separate groups of female rats were exposed to 0 or 200 ppm (8 hours/day, 5 days/week) for 1, 2, or 8 weeks. Histological changes to the respiratory tract (capillary hyperemia and alveolar distention) and decreased leukocyte count (24%) were observed at 200 ppm following the single 8-hour exposure. Leukocyte counts were also decreased by 24% at 1,000 ppm (data not reported for 3,000 ppm); therefore, effects did not exhibit dose-dependence. Following exposure to 200 ppm for 1–2 weeks, histological changes were observed to the respiratory tract (capillary hyperemia and alveolar distention), liver (slight fatty accumulation of liver lobules), and immune system (slight fatty accumulation in Kupffer cells). Statistical evaluation of incidence data for hepatic, respiratory, and immune effects (conducted for this report) showed no difference between exposed and control rats after 2 weeks of exposure. In addition, no hepatic effects were observed in a 90-day study in rats exposed up to 4,000 ppm of trans-1,2-dichloroethene (DuPont 1998). Given the low number of animals in each group (n=6), omission of test substance purity, and lack of statistical significance, findings in the Freundt et al. (1977) study are not considered reliable to serve as the basis of the MRL.

The study by Hurtt et al. (1993) was designed to evaluate developmental effects following gestational exposure of pregnant rats to 0, 2,000, 6,000, or 12,000 ppm of trans-1,2-dichloroethene on GDs 7–16 (see details below). Dams were evaluated for signs of clinical toxicity and developmental outcomes. NOAEL and LOAEL values for effects observed in this study are summarized Table A-1. The most sensitive effect observed in the Hurtt et al. (1993) study is an ocular irritation effect (lacrimation), with a LOAEL of 2,000 ppm; a NOAEL was not identified. Therefore, lacrimation was selected as the critical effect for acute-duration exposure. Data for lacrimation are summarized in Table A-2. Note that for systemic

effects (e.g., effects resulting from absorbed trans-1,2-dichloroethene), the most sensitive effect is increased resorption, with NOAEL and LOAEL values of 2,000 and 6,000 ppm, respectively. Early resorptions per litter were increased ($p \leq 0.05$) in the 6,000 and 12,000 ppm groups relative to concurrent controls; resorption data also showed a statistically significant trend across exposure concentrations. The study authors did not consider the increase in resorptions to be biologically significant because the resorption rate in concurrent controls (0.3/litter) was below historical controls for the performing laboratory for the previous 2 years (0.6–1.5/litter) and the resorption rates in treatment groups (0.6–1.1/litter) were within the recent historical control range. Given the higher LOAEL value for resorptions (compared to lacrimation) and the uncertainty regarding the biological significance of the increased resorptions per litter relative to concurrent controls but not the recent historical controls, these data would not be considered adequate to serve as the basis for an MRL. However, due to the potential for developmental toxicity at concentrations >2,000 ppm, concentrations higher than 2,000 ppm are not considered for development of the acute-duration inhalation MRL.

Table A-1. Summary of Effects Observed in Pregnant Rats Exposed to Inhaled trans-1,2-Dichloroethene on GDs 7–16

		NOAEL/LOAEL (ppm)	
System	Effect	NOAEL	LOAEL
Ocular	Lacrimation	ND	2,000
Developmental	Increased resorptions	2,000	6,000
	Decreased fetal body weight (females)	6,000	12,000
Neurological	Lethargy	6,000	12,000
Body weight	Decreased maternal body weight GDs 7–16	6,000	12,000

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Source: Hurtt et al. 1993

Table A-2. Incidence Data for Lacrimation and Resorptions Observed in Female Rats Exposed to trans-1,2-Dichloroethene on GDs 7–16

	Concentration (ppm)			
Effect	0	2,000	6,000	12,000
Incidence of lacrimation[a,b]	0/24	13/24[c]	22/24[c]	24/24[c]
Resorptions per litter[d]	0.3	0.6	0.8[e]	1.1[e]

[a]Number with lacrimation/number of exposed.
[b]Significant trend, $p \leq 0.0001$ (Cochran-Armitage test conducted for this report).
[c]Significantly different from control values, $p \leq 0.0001$ (Fisher's exact test conducted for this report).
[d]Significant trend, $p \leq 0.05$ (Cochran-Armitage test, as reported by Hurtt et al. 1993).
[e]Significantly different from control values, $p \leq 0.05$ (Fisher's exact test, as reported by Hurtt et al. 1993).

GD = gestation day

Source: Hurtt et al. 1993

Selection of the Principal Study: As discussed under *Selection of the Critical Effect*, Hurtt et al. (1993), a study designed to evaluate developmental effects, provides data that are suitable for derivation of the MRL. Data provided by other studies are not adequate for derivation of the MRL.

Summary of the Principal Study:

Hurtt ME, Valentine R, Alvarez L. 1993. Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat. Fundam Appl Toxicol 20(2):225-230.

Groups of 24 pregnant Crl:CD BR rats were exposed to nominal concentrations of 0, 2,000, 6,000, or 12,000 ppm of trans-1,2-dichloroethene (99.64%) vapor in air for 6 hours/day (whole-body inhalation) on GDs 7–16. The post-exposure period consisted of GDs 17–22. The dams (n=24) and fetuses were sacrificed on GD 22. Mean daily chamber concentrations (data not shown) were within ±5% of nominal concentrations. The following endpoints were assessed in dams: number of pregnant rats; lethality; maternal body weight on GDs 1, 7–17, and 22 and feed consumption on GDs 1–19 and 22; clinical signs of toxicity twice daily prior to and following exposures; liver and uterus weights (GD 22); and numbers of resorptions and corpora lutea (GD 22). The following assessments were conducted in fetuses: number of live and dead fetuses; number of males and females per litter; fetal weight; and external, internal, and skeletal malformations and variations.

No maternal deaths occurred. At the end of the exposure period (GD 16), maternal weight was decreased by 33% in rats exposed to 12,000 ppm, compared to controls. However, on GD 22, body weight in the 12,000 ppm group was similar to controls. Over the exposure period (GDs 7–17), maternal feed consumption was decreased by 12 and 16% in the 6,000 and 12,000 ppm groups, respectively. For clinical signs of toxicity, lacrimation was increased at all exposure levels relative to control during the exposure period (GDs 7–16) (see Table A-3); a significant trend across exposure levels was also observed. No lacrimation was observed during the post-exposure period (GDs 17–22). Brown, periocular staining, due to excessive lacrimation, was observed in the control (1/24), 2,000 (3/24), 6,000 (18/24), and 12,000 ppm (22/24) exposure groups, and it too resolved promptly following exposure. Lethargy was observed in 10/24 dams exposed to 12,000 ppm. The study authors noted that clinical signs of central nervous system depression (incoordination immediately following exposure) were observed in the 6,000 and 12,000 ppm groups, although incidence data were not reported; therefore, NOAEL and LOAEL values could not be determined for central nervous system depression. During the post-exposure period (GDs 17–22), combined incidences of alopecia and periocular staining were increased in the 6,000 (8/24) and 12,000 ppm (11/24) groups. Resorptions per litter were increased ($p \leq 0.05$) in the 6,000 and 12,000 ppm groups relative to concurrent controls (see Table A-3); as discussed above (Selection of the Critical Effect), there is uncertainty regarding the biological significance of the resorptions per litter relative to historical controls. Mean female fetal weight was decreased by 5.9%, compared to controls, at 12,000 ppm; no effect on mean male fetal weight was observed. No fetal external, internal, or skeletal malformations or variations were observed at any exposure level.

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 256.47 ppm for lacrimation was selected as the basis of the acute-duration inhalation MRL.

Benchmark dose (BMD) modeling was conducted to identify a point of departure (POD) using the incidence data for lacrimation in pregnant rats exposed to trans-1,2-dichloroethene for 6 hours/day on GDs 7–16 (Hurtt et al. 1993). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS; version 3.2) using a benchmark response (BMR) with 10% extra risk. Adequate model fit is judged by four criteria: chi-squared goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, BMCL (95% lower confidence limit on the benchmark response concentration [BMC]) that is not 10 times lower than the lowest non-zero concentration, and scaled residual at the data point

(except the control) closest to the predefined BMR. Adequate fit to the data was observed for the Dichotomous Hill, Log-Logistic, and Log-Probit models. Inadequate fit to the data was observed for the Gamma, Multistage, and Weibull models based on BMCLs ≥10 times lower than the lowest non-zero concentration and for the Logistic and Probit models based on chi-squared goodness-of-fit p-values <0.1. Among models providing adequate fit, the lowest $BMCL_{10}$ was selected as the POD when the difference between the $BMCL_{10}$ values estimated from these models was ≥3 fold; otherwise, the $BMCL_{10}$ from the model with the lowest Akaike Information Criterion (AIC) was chosen. In accordance with these selection criteria, the Log-Logistic model, a frequentist, unrestricted model, provided the best fit, with the lowest $BMCL_{10}$ of 256.47 ppm (Table A-3). The Log-Logistic model fit is shown in Figure A-1.

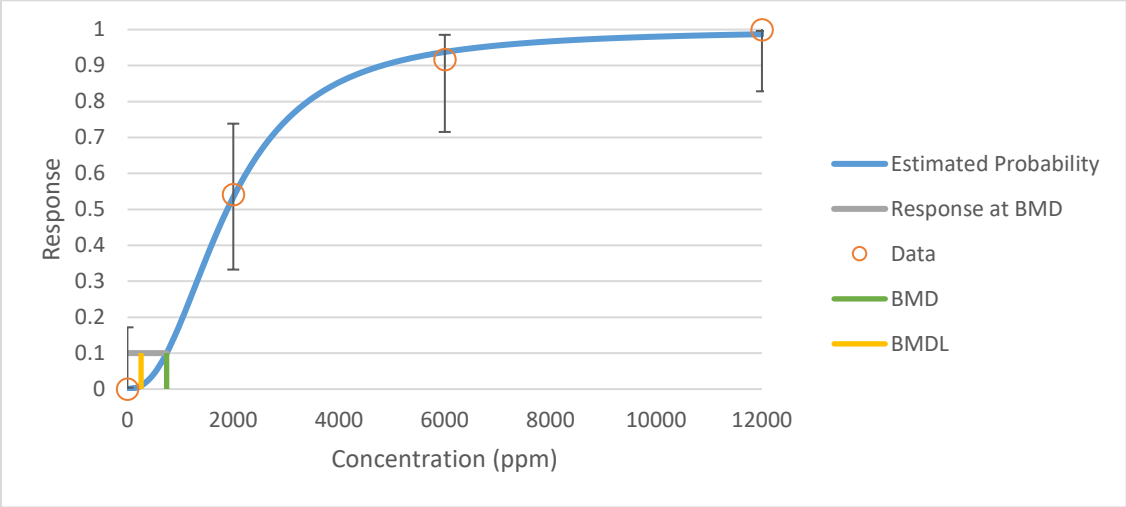
Table A-3. BMD Constant Variance Model Predictions for Lacrimation in Pregnant Crl:CD BR Rats Exposed to trans-1,2-Dichloroethene 6 Hours/Day on GDs 7–16 (Hurtt et al. 1993)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	740.277	256.469	0.479	53.667	-0.001	-0.001
Gamma[d]	371.821	189.742	0.709	53.103	-0.001	-0.001
Log-Logistic[e,f]	**740.279**	**256.470**	**0.778**	**51.667**	**-0.001**	**-0.001**
Multistage Degree 3[g]	281.357	191.599	0.835	52.936	-0.001	-0.001
Multistage Degree 2[g]	295.758	190.767	0.956	51.010	-0.001	-0.001
Multistage Degree 1[g]	253.774	188.209	0.898	51.252	-0.001	-0.001
Weibull[d]	344.544	190.057	0.722	53.076	-0.001	-0.001
Logistic	839.119	589.146	0.047	58.780	-1.583	-1.583
Log-Probit	698.499	230.591	0.571	53.379	-0.001	-0.001
Probit	839.333	607.962	0.045	58.926	-1.547	-1.547

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. BMCLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected (Log-Logistic).
[g]Betas restricted to ≥0.

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

Figure A-1. Fit of Log-Logistic Model to Incidence of Lacrimation in Pregnant Crl:CD BR Rats Exposed to trans-1,2-Dichloroethene 6 Hours/Day on Gestation Days 7–16 (Hurtt et al. 1993)



Calculations

Adjustment for Intermittent Exposure: Not applicable. The critical effect (lacrimation) is related to the concentration of trans-1,2-dichloroethene in air; therefore, no adjustment was made to a continuous 24-hour exposure.

Human Equivalent Concentration: Not applicable. The critical effect (lacrimation) is related to the concentration of trans-1,2-dichloroethene in air and does not depend upon absorption into the body.

Uncertainty Factor: The $BMCL_{10}$ is divided by a total uncertainty factor of 100:

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

$MRL = BMCL_{10} \div UFs$

$256.47 \text{ ppm} \div (10x10) = 2.6 \text{ ppm} \approx 3 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: An experimental study in two human subjects reported slight burning of the eyes during exposure to trans-1,2-dichloroethene concentrations of 950 ppm after 5 minutes, 1,200 ppm after 10 minutes, and 1,000 ppm for 30 minutes (Lehmann and Schmidt-Kehl 1936). No eye irritation was noted following exposure to 275 ppm for 5 minutes or 825 ppm for 10 minutes; 1,000 ppm was the only concentration tested for 30 minutes. The dose-response relationship for ocular irritation is uncertain as only two subjects were tested, purity of the test substance was not reported, and precision of methods used to measure trans-1,2-dichloroethene concentrations has not been established. However, these results indicate that humans exposed to trans-1,2-dichloroethene vapor in the air develop eye irritation at concentrations as low as 950 ppm. In laboratory animals, instillation of 0.01 mL trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in ocular irritation, transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c), demonstrating clear evidence that trans-

1,2-dichloroethene is an eye irritant and corroborating the selection of lacrimation as a suitable endpoint to derive the acute-duration inhalation MRL.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: Few studies have assessed the adverse effects of intermediate-duration inhalation exposure to trans-1,2-dichloroethene (DuPont 1998; Freundt et al. 1977). DuPont (1998) did not find any adverse effect in male and female rats (15/group/sex) exposed to concentrations up to 4,000 ppm (6 hours/day, 5 days/week) for 90 days. This study examined comprehensive toxicological endpoints, including histopathologic assessments. Since the DuPont (1998) study did not find adverse effects, it cannot serve as the basis for an intermediate-duration inhalation MRL for trans-1,2-dichloroethene.

The Freundt et al. (1977) study found histological changes to the respiratory tract (capillary hyperemia and alveolar distention), liver (slight fatty accumulation of liver lobules), and immune system (slight fatty accumulation in Kupffer cells) in female rats (n=6) exposed to 200 ppm (8 hours/day, 5 days/week) for 8 or 16 weeks. However, these findings were not corroborated by the DuPont (1998) study at a much higher exposure level (4,000 ppm). In addition, Freundt et al. (1977) has several weaknesses: purity of the test substance was not reported so that potential for contaminants in the test substance was not assessed; a small number of animals (n=6) were exposed; and statistical evaluation of the histological data was not presented. Given these weaknesses and lack of corroborating data, findings in this study are not considered reliable.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies in humans or animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: The database of studies evaluating acute-duration oral exposure to trans-1,2-dichloroethene in laboratory animals consists of single-dose, acute lethality studies (Barnes et al. 1985; Hayes et al. 1987; Munson et al. 1982) and repeated-dose studies that did not observe toxicologically significant adverse effects (Barnes et al. 1985; Munson et al. 1982; NTP 2002; Shopp et al. 1985). Acute-duration lethality studies, designed to estimate LD_{50} values, did not report adverse effects at sublethal levels. The only effects observed in repeated-dose studies were decreased fibrinogen levels (12%) and prothrombin time (7%) in male mice administered 210 mg/kg/day by gavage for 14 days (Barnes et al. 1985). However, these results are clinically inconsistent. Decreased fibrinogen would be expected to increase prothrombin time (e.g., longer time to formation of fibrinogen clot); however, prothrombin time was decreased. Therefore, the toxicological significance of these findings is uncertain. No adverse hematopoietic or hepatic effects were observed in male and female rats exposed to 5,591 and 4,500 mg/kg/day, respectively, for 5 days (NTP 2002). Munson et al. (1982) did not observe adverse hematological (including fibrinogen levels and prothrombin time), hepatic, or immunological (humoral and cellular immunity) effects in male mice exposed to 220 mg/kg/day for 20 days. No effects on humoral and cellular immune function were observed in male mice exposed to 210 mg/kg/day for 14 days (Shopp et al. 1985). Therefore, available data are not adequate to derive an acute-duration oral MRL for trans-1,2-dichloroethene.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.2 mg/kg/day
Critical Effect: Decreased humoral immunity
Reference: Shopp et al. 1985
Point of Departure: $BMDL_{1SD}$ of 16.75 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 13
Species: Mouse

MRL Summary: An intermediate-duration oral MRL of 0.2 mg/kg/day was derived for trans-1,2-dichloroethene based on decreased humoral immunity in male mice exposed to trans-1,2-dichloroethene in drinking water for 90 days. The MRL is based on a $BMDL_{1SD}$ of 16.75 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the toxicity of intermediate-duration oral exposure of laboratory animals to trans-1,2-dichloroethene. Reliable NOAEL and LOAEL values are summarized in Table A-4.

Table A-4. Summary of Effects Observed in Laboratory Animals Exposed to Oral trans-1,2-Dichloroethene for Intermediate Durations

Species	Duration (Route)	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	Effect	Reference
Mice (CD-1)	90 days (W)	ND (M) ND (F)	17 (M) 23 (F)	Increased serum glucose	Barnes et al. 1985
Mice (CD-1)	90 days (W)	17 (M) 452 (F)	175 (M) ND (F)	Decreased humoral immunity	Shopp et al. 1985
Rats (F-344)	14 weeks (diet)	190 (M) 780 (F)	380 (M) 1,580 (F)	Decreased erythrocyte counts	NTP 2002
Mice (B6C3F1)	14 weeks (diet)	8,065 (M) 3,760 (F)	ND (M) 7,925 (F)	Decreased terminal body weight	NTP 2002
Rats (Sprague-Dawley)	14 weeks (W)	3,114 (M) 2,809 (F)	ND (M) ND (F)	No effects observed[a]	Hayes et al. 1987

[a]Evaluations conducted in this study were lethality, body weight, hematological, hepatic, renal, and reproductive endpoints; serum glucose was also assessed.

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; W = drinking water

The lowest LOAEL observed in intermediate-duration oral studies is 17 mg/kg/day for increased serum glucose in male mice exposed for 90 days, although the increase did not exhibit dose-dependence (Barnes et al. 1985). Compared to controls, serum glucose was increased by 27, 20, and 24% at doses of 17, 175, and 387 mg/kg/day, respectively. Similar non-dose-dependent increases were observed in females; at doses of 23, 224, and 452 mg/kg/day, serum glucose was increased by 28, 20, and 28%, respectively. In contrast to these findings, no effects on glucose levels were observed in male or female rats at doses up to 3,114 and 2,809 mg/kg/day, respectively, in another study (Hayes et al. 1987). Given the lack of a dose-response and that no effects on glucose levels were observed at much higher oral doses in the study by Hayes et al. (1987), the possible relationship between exposure to trans-1,2-dichloroethene and serum glucose levels is uncertain. Therefore, decreased serum glucose was not selected as the critical effect for derivation of the intermediate-duration oral MRL.

The next lowest LOAEL is 175 mg/kg/day for decreased humoral immunity in male mice exposed to trans-1,2-dicloroethene in drinking water for 90 days (Shopp et al. 1985). Suppression in humoral immunity in male mice, as measured by reductions in spleen AFCs directed against sRBCs, was observed at all doses tested in a dose-dependent manner; decreases were 6.9, 26.1, and 26.4% at doses of 17, 175, and 387 mg/kg/day, respectively. Other tests of immune function (spleen cell response to B cell mitogen lipopolysaccharide and hemagglutination titers) did not show suppression of humoral immunity. However, the sRBC AFC response is considered the “gold standard” for evaluating T-cell-dependent antibody responses and is considered one of the best predictors of immunotoxicity in mice (Ladics 2007). Note that conclusions made by Shopp et al. (1985) regarding trans-1,2-dichloroethene-induced humoral immune suppression are conflicting. In the study abstract, the study authors concluded that, “a marked suppression in humoral immune status was observed in male mice exposed to all three levels of DCE, as indicated by a decreased ability of spleen cells to produce antibody against sheep erythrocytes (sRBC).” In contrast, the discussion section of the paper states that, “there were some immunological changes that occurred following 90 days of exposure to the compound in the drinking water. IgM AFC was significantly decreased at all dose levels. This decrease was not severe enough to depress the functional ability of the humoral immune system, as evidenced by normal hemagglutination titers and spleen cell response to LPS.” ATSDR considers the dose-related decrease in humoral immunity based on the sRBC assay to be an appropriate critical effect for derivation of the intermediate-duration oral MRL and is a biologically relevant effect to human health. ATSDR’s conclusions are supported by the EPA Integrated Risk Information System (IRIS) derivation of the reference dose (RfD) for trans-1,2-dichloroethane(IRIS 2010b). EPA “evaluated the findings from Shopp et al. (1985) and determined, in contrast to the study authors, that suppression in the number of AFCs in male CD-1 mice represents functional suppression of the humoral immune system and not general toxicity.” Furthermore, EPA states that, “serum anti-sRBC IgM values are a general measure of the antibody response because these values reflect antibodies produced from multiple sources, including spleen, lymph nodes, and bone marrow. Therefore, the AFC assay is not expected to provide evidence of chemical immunosuppression at the level of splenic antibody production that might not be identified by measurements of serum levels of anti-sRBC IgM.”

Other intermediate-duration oral studies identified higher LOAELs than the LOAEL for decreased humoral immunity (175 mg/kg/day). NTP (2002) identified a LOAEL of 380 mg/kg/day in male rats for mild decreases in erythrocyte counts (3.1–7.1%) and a LOAEL of 7,925 mg/kg/day in female rats for a 10.7% decrease in terminal body weight. Hayes et al. (1987) did not observe any adverse effects at doses up to 3,114 and 2,809 mg/kg/day in male and female rats, respectively, via drinking water for 90 days. Therefore, decreased humoral immunity, with a LOAEL of 175 mg/kg/day identified from the Shopp et al. (1985) study, was selected as the critical effect for derivation of the intermediate-duration oral MRL for trans-1,2-dichhloroethene. This selection was made based on the following: the critical effect for the Shopp et al. (1985) study produced the lowest LOAEL (i.e., is the most sensitive) for endpoints exhibiting dose-responses, is an endpoint suitable for evaluation of immunotoxicity, and is relevant for human health.

Selection of the Principal Study: As summarized in Table A-4, the lowest LOAELs observed in intermediate-duration oral studies were 17 mg/kg/day for increased serum glucose in male mice exposed for 90 days (Barnes et al. 1985) and 175 mg/kg/day for decreased humoral immunity in male mice (Shopp et al. 1985). As discussed above, the possible relationship between exposure to trans-1,2-dichloroethene and serum glucose levels is uncertain, and effects on serum glucose were not corroborated at much higher doses (Hayes et al. 1987). Other studies either observed effects at doses >175 mg/kg/day or did not identify effects at the highest doses tested (Hayes et al. 1987; NTP 2002). Therefore, the Shopp et al. (1985) study was selected as the principal study for the MRL.

Summary of the Principal Study:

Shopp GM Jr, Sanders VM, White KL, et al. 1985. Humoral and cell-mediated immune status of mice exposed to trans-1,2-dichloroethylene. Drug Chem Toxicol 8:393-407.

Male and female mice were exposed to trans-1,2-dichloroethene (98% purity) at 0, 0.1, 1.0, or 2.0 mg/mL in drinking water for 90 days; respective daily doses of 0, 17, 175, and 387 mg/kg/day in males and 0, 23, 224, and 452 mg/kg/day in females were calculated by the study authors based on body weight and water intake. As described in Barnes et al. (1985), the treatment water was prepared as a 1% solution of emulphor (a polyethoxylated vegetable oil used to stabilize volatile chemicals in aqueous solutions [Sanzgiri and Bruckner 1997]) in deionized water. The water bottles were changed every 3–4 days and <10% of the trans-1,2-dichloroethene was lost during these intervals. Immunological effects of trans-1,2-dichloroethene were evaluated in several assays. The number of animals per group varied for each assay as noted below.

Three assays were used to evaluate the humoral immune status: (1) quantitation of spleen IgM AFCs on days 4 and 5 after *in vivo* exposure to sRBCs (n=12 in control group and n=8 per treatment group); (2) *ex vivo* hemagglutination titers to sRBC (n=23 in control group and n=6–11 per treatment group); and (3) spleen cell response to the B cell mitogen lipopolysaccharide (LPS) (n=2–9 per group). Cell-mediated immunity was evaluated in three assays: (1) delayed-type hypersensitivity response to sRBC (n=16–19 per group); (2) popliteal lymph node proliferation in response to sRBC (n=11–20 per group); and (3) spleen cell response to the T cell mitogen concanavalin (ConA) (n=2–9 per group). In addition, the following were assessed: number of peritoneal exudate cells (PEC) recruited; number of PEC to adhere to plastic; chemotactic ability of the recruited cells; and phagocytic ability of the adherent cells. The functional ability of the fixed macrophages of the reticuloendothelial system was assessed by measuring the vascular clearance rate and tissue rate of ^{51}Cr-labeled sRBC (thymus, bone marrow).

Results of the humoral immune assay for spleen IgM AFC on days 4 and 5 after *in vivo* exposure to sRBC showed a decreased response in male mice; this was not observed in female mice. Expressed in terms of AFC/spleen weight, the day 4 response showed a statistically significant, dose-dependent decrease in the magnitude of response at all doses and the day 5 response showed a decreased magnitude at the highest dose. Expressed in terms of AFC/10^6 spleen cells, the day 4 response was decreased in the mid- and high-dose groups and the day 5 response was decreased at the highest dose. Although no statistically significant change in spleen weight was observed, spleen weights decreased in magnitude with increasing dose, suggesting a potential decrease in the number of spleen cells at higher doses. Due to potential variation in the total number of cells in the spleens, results expressed in terms of AFC/10^6 spleen cells are considered more reliable than AFC/spleen weight. In addition, the response to sRBC challenge on day 4 appears to be more sensitive than on day 5. Results of this day 4 assay are summarized in Table A-5.

Table A-5. Antibody-Forming Cell Response to sRBC in Male CD-1 Mice Exposed to trans-1,2-Dichloroethene in Drinking Water for 90 Days[a]

	Dose (mg/kg/day)			
	0	17	175	387
AFC/10^6 spleen cells	2,200±125[b]	2,048±152 (6.9)	1,625±136[c] (26.1)	1,618±226[c] (26.4)

[a]Responses were observed on day 4 after *in vivo* exposure to sRBC.
[b]Mean±SE; numbers in parentheses are the percent decreased relative to control; n=12 for control group and n=8 for all other groups.
[c]$p<0.05$ versus concurrent control group.

AFC = antibody-forming cell; SE = standard error; sRBC = sheep red blood cell

Source: Shopp et al. (1985)

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 16.75 mg/kg/day for decreased humoral response was selected as the basis of the intermediate-duration oral MRL.

BMD modeling was conducted to identify the POD from incidence data for humoral response to sRBC in male mice exposed orally to trans-1,2-dichloroethene for 90 days. The data were fit to all available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 standard deviation (1SD). Adequate model fit is judged by four criteria: chi squared goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, BMDL (95% lower confidence limit on the BMD) that is not 10 times lower than the lowest non-zero dose, and scaled residual at the data point (except the control) closest to the predefined BMR. Among the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was ≥3 fold; otherwise, the BMDL from the model with the lowest AIC was chosen. The Exponential 4 (CV-normal) model provided the best fit. The model predictions for the humoral response to sRBC are presented in Table A-6 and the fit of the selected model (Exponential 4) is presented Figure A-2. Note that the $BMDL_{1SD}$ of 16.75 mg/kg/day is essentially identical to the empirical NOAEL of 17 mg/kg/day.

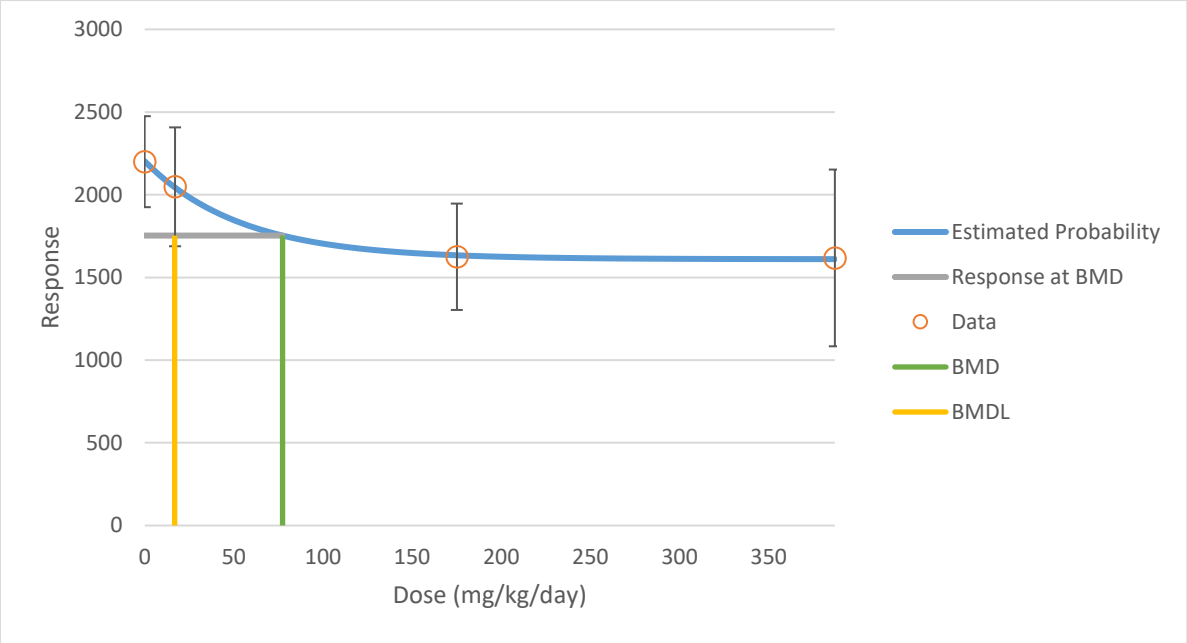
Table A-6. Results from BMD Analysis (Constant Variance) of Humoral Immune Response to Sheep Red Blood Cells in Male CD-1 Mice Exposed to trans-1,2-Dichloroethene in Drinking Water for 90 days (Shopp et al. 1985)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]	284.039	164.570	0.314	550.161	0.652	0.625
Exponential 3[d]	284.051	164.568	0.314	550.161	0.652	0.625
Exponential 4[d,e]	**77.273**	**16.752**	**0.936**	**549.849**	**0.030**	**-0.016**
Exponential 5[d]	72.786	16.764	NA	551.843	-0.007	0.005
Hill[d]	45.978	13.323	NA	551.843	0.000	0.000
Polynomial Degree 3[d]	309.206	195.007	0.260	550.540	0.596	0.721
Polynomial Degree 2[d]	309.207	195.005	0.260	550.540	0.596	0.721
Power[d]	309.205	195.014	0.260	550.540	0.596	0.721
Linear	309.206	195.005	0.260	550.540	0.596	0.721

[a]BMD and BMDLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. The difference between the BMDLs estimated from these models was ≥3 fold, therefore the lowest $BMDL_{1SD}$ of models with adequate fit was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-2. Fit of Exponential 4 (Constant Variance) Model to Humoral Immune Response to Sheep Red Blood Cells in Male Mice Exposed to trans-1,2-Dichloroethene in Drinking Water for 90 Days (Shopp et al. 1985)



Calculations

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{1SD} \div UFs$

$16.75 \text{ mg/kg/day} \div (10x10) = 0.2 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The Shopp et al. (1985) study was the only intermediate-duration oral study that evaluated humoral immunity. No supporting studies were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: Two epidemiological studies have investigated effects of chronic-duration oral exposure to trans-1,2-dichloroethene (Ji et al. 2016; Ruckart et al. 2013). An increased risk of gallstone disease was positively associated with trans-1,2-dichloroethene levels in adipose tissue in a case-control study of the general population (Ji et al. 2016). Results were stratified by quartiles based on the concentration of trans-1,2-dichloroethene in adipose tissue (ng/g lipid weight): Q1 12.82–721.7; Q2 721.7–1,351; Q3 1,351–2,558; and Q4 2,558–18,135. ORs were increased ($p \leq 0.05$) in Q2 (3.49; 95% CI 1.93, 6.33), Q3 (2.38; 95% CI 1.32, 4.27), and Q4 (2.48; 95% CI 1.38, 4.46), respectively, relative to Q1. In addition, the concentration of trans-1,2-dichloroethene in adipose tissue of patients with gallstone disease (mean: 1,542 ng/g lipid weight) was significantly higher ($p=0.008$) compared to patients without gallstone disease (mean: 1,213 ng/g lipid weight). However, concentrations of trans-1,2-dichloroethene in adipose tissue have not been correlated with blood levels or external exposure concentrations. Ruckart et al. (2013) did not find an association between exposure to trans-1,2-dichloroethene and birth defects (neural tube defects or oral cleft defects) in children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water. Based on the available epidemiological studies, data are inadequate for derivation of a chronic-duration oral MRL.

No chronic-duration oral studies in animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: No adequate acute-duration inhalation studies were identified for cis-1,2-dichloroethene. Thus, an acute-duration inhalation MRL cannot be derived.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies in humans or animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for cis-1,2-dichloroethene

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

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: One study evaluating acute-duration oral exposure of cis-1,2-dichloroethene was identified (EPA/AMRL 1990; McCauley et al. 1995). In this study, male and female rats (10/sex/group) were exposed to 0, 97, 290, 970, or 1,900 mg/kg/day cis-1,2-dichloroethene in corn oil by gavage for 14 days. Effects were observed in the hematological, hepatic, and neurological systems.

Hematological effects. Assessment of hematological parameters found that hematocrit was decreased by 8-11% at doses of 290, 970, and 1,900 mg/kg/day, relative to controls, in female rats; however, no decreases were observed for erythrocyte count or hemoglobin concentration. The toxicological significance of decreased hematocrit in the absence of decreased erythrocyte counts and hemoglobin is uncertain. No hematological effects were observed in males administered up to 1,900 mg/kg/day for 14 days.

Hepatic effects. No histopathological findings were observed in the liver in male or female rats. Increases in relative liver weights were observed in both males and females and ranged from 15% at 97 mg/kg/day to 38% at 1,900 mg/kg/day. In addition, cholesterol was increased by 40% in female, but not in male, rats at the highest dose tested of 1,900 mg/kg/day. However, given the absence of histopathological changes or changes in serum liver enzymes (e.g., AP, ALT, AST), the toxicological significance of increased relative liver weights and cholesterol cannot be determined.

Neurological effects. Clinical signs of neurotoxicity (lethargy and ataxia) were observed in the "high dose groups;" however, NOAEL and LOAEL values could not be determined because incidence data were not reported. No histopathological findings were observed in brain tissue.

Results of the 14-day oral study by EPA/AMRL (1990), and McCauley et al. (1995) do not provide suitable data to derive an acute-duration oral MRL for cis-1,2-dichloroethene.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: One study evaluating intermediate-duration oral exposure of cis-1,2-dichloroethene was identified (EPA/AMRL 1990; McCauley et al. 1995). In this study, male and female rats (10/sex/group) were exposed to 0, 32, 97, 290, or 870 mg/kg/day cis-1,2-dichloroethene in corn oil by gavage for 90 days. Body weight and hematological effects were observed with treatment.

Body weight effects. At the highest dose tested, body weight gain over the 90-day exposure period in male rats was decreased by 37%, compared to controls. However, terminal body weight in this group was similar to terminal body weight of the control group. Therefore, the decrease in body weight gain does not appear to be toxicologically significant. No treatment-related effects on body weight gain or terminal body weight were observed in female rats.

Hematological effects. Hematocrit and hemoglobin concentration were decreased in male and female rats. In male rats, hematocrit was decreased by 5.8, 8.9, and 8.9% at doses of 290, 970, and 1,900 mg/kg/day, respectively, and hemoglobin concentration was decreased by 6.0% at doses of 970 and 1,900 mg/kg/day. No effects on erythrocyte count were observed. In female rats, hematocrit was decreased by 9.9 and 6.5% at doses of 290 and 870 mg/kg/day, respectively; erythrocyte counts and hemoglobin concentration were decreased by 5.9 and 3.9%, respectively, in the 290 mg/kg/day group, but not in the 870 mg/kg/day group, indicating that these changes were not related to treatment with cis-1,2-dichloroethene. The toxicological significance of decreased hematocrit and hemoglobin concentration in the absence of decreased erythrocyte count is uncertain.

Based on the results of the EPA/AMRL (1990), and McCauley et al. (1995) study, data are not adequate for derivation of an intermediate-duration oral MRL for cis-1,2-dichloroethene.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for cis-1,2-dichloroethene

Rationale for Not Deriving an MRL: No chronic-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

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

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 1,2-dichloroethene.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,2-dichloroethene. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,2-dichloroethene 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 1,2-dichloroethene are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The literature search was conducted to update the Toxicological Profile for 1,2-Dichloroethene released in 1996. All literature cited in the previous (1996) toxicological profile were considered for inclusion in the updated profile. The initial literature search, which was performed in May 2017 and October 2021, was restricted to studies added to databases since January 1994. An updated literature search was performed after the Toxicological Profile for 1,2-Dichloroethene Draft for Public Comment was released in August 2023 to identify any additional studies added to databases between September 2021 and December 2023.

APPENDIX B

The following main databases were searched in May 2017, October 2021, and/or December 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER
- National Library of Medicine's TOXLINE (May 2017 only)

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,2-dichloroethene. 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 1,2-dichloroethene 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	
12/2023	((540-59-0[rn] OR 156-59-2[rn] OR 156-60-5[rn] OR 25323-30-2[rn] OR "1,2-dichloroethylene"[nm]) AND 2021/09/01:3000[mhda]) OR (("1,2-DCE"[tw] OR "1,2-Dichloraethen"[tw] OR "1,2-Dichloroethene"[tw] OR "1,2-Dichloroethylene"[tw] OR "Acetylene dichloride"[tw] OR "Dichloro-1,2-ethylene"[tw] OR "Dioform"[tw] OR "sym-Dichloroethylene"[tw] OR "(Z)-1,2-Dichloroethene"[tw] OR "(Z)-1,2-Dichloroethylene"[tw] OR "Acetalyne dichloride"[tw] OR "cis-Acetylene dichloride "[tw] OR "cis-1,2-Dichloroethene"[tw] OR "cis-1,2-Dichloroethylene"[tw] OR "cis-Dichloroethylene"[tw] OR "HCC 1130c"[tw] OR "R 1130c"[tw] OR "(1Z)-1,2-dichloro-Ethene "[tw] OR "1,2-Dichloroethylene"[tw] OR "(E)-1,2-Dichloroethene"[tw] OR "(E)-1,2-Dichloroethylene"[tw] OR "HCC 1130t"[tw] OR "R 1130t"[tw] OR "trans-1,2-Dichloroethene"[tw] OR "trans-1,2-Dichloroethylene"[tw] OR "trans-Acetylene dichloride"[tw] OR "trans-Dichloroethylene"[tw] OR "(1E)-1,2-dichloro-Ethene"[tw] OR "1,2-Dichloroethylene"[tw] OR "1,2-trans-Dichloroethylene"[tw] OR "Dichloroethene"[tw] OR "Dichloroethenes"[tw] OR "Dichloroethylene"[tw] OR "Dichloroethylenes"[tw]) AND (2021/09/01:3000[edat] OR 2021/09/01:3000[crdat]))
10/2021	((540-59-0[rn] OR 156-59-2[rn] OR 156-60-5[rn] OR "1,2-DCE"[tw] OR "1,2-Dichloraethen"[tw] OR "1,2-Dichloroethene"[tw] OR "1,2-Dichloroethylene"[tw] OR "Acetylene dichloride"[tw] OR "Dichloro-1,2-ethylene"[tw] OR "Dioform"[tw] OR "sym-Dichloroethylene"[tw] OR "(Z)-1,2-Dichloroethene"[tw] OR "(Z)-1,2-Dichloroethylene"[tw] OR "Acetalyne dichloride"[tw] OR "cis-Acetylene dichloride "[tw] OR "cis-1,2-Dichloroethene"[tw] OR "cis-1,2-Dichloroethylene"[tw] OR "cis-Dichloroethylene"[tw] OR "HCC 1130c"[tw] OR "R 1130c"[tw] OR "(1Z)-1,2-dichloro-Ethene "[tw] OR "1,2-Dichloroethylene"[tw] OR "(E)-1,2-Dichloroethene"[tw] OR "(E)-1,2-Dichloroethylene"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "HCC 1130t"[tw] OR "R 1130t"[tw] OR "trans-1,2-Dichloroethene"[tw] OR "trans-1,2-Dichloroethylene"[tw] OR "trans-Acetylene dichloride"[tw] OR "trans-Dichloroethylene"[tw] OR "(1E)-1,2-dichloro-Ethene"[tw] OR "1,2-Dichloroethylene"[tw] OR "1,2-trans-Dichloroethylene"[tw]) AND (1994/01/01 : 3000[dp] OR 1994/01/01 : 3000[mhda] OR 1994/01/01 : 3000[edat])) OR ((("Dichloroethenes"[tw] OR "Dichloroethene"[tw] OR "Dichloroethylene"[tw] OR "1,2-Dichloroethylene"[tw]) AND (1994/01/01 : 3000[dp] OR 1994/01/01 : 3000[mhda] OR 1994/01/01 : 3000[edat])) NOT medline[sb])
Toxline	
05/2017	("1 2-dce" OR "1 2-dichlor-aethen" OR "1 2-dichloroethene" OR "1 2-dichloroethylene" OR "acetylene dichloride" OR "dichloro-1 2-ethylene" OR "dioform" OR "sym-dichloroethylene" OR " (z) -1 2-dichloroethene" OR " (z) -1 2-dichloroethylene" OR "acetalyne dichloride" OR "cis-acetylene dichloride " OR "cis-1 2-dichloroethene" OR "cis-1 2-dichloroethylene" OR "cis-dichloroethylene" OR "hcc 1130c" OR "r 1130c" OR " (1z) -1 2-dichloro-ethene " OR "1 2-dichloroethylene" OR " (e) -1 2-dichloroethene" OR " (e) -1 2-dichloroethylene" OR "hcc 1130t" OR "r 1130t" OR "trans-1 2-dichloroethene" OR "trans-1 2-dichloroethylene" OR "trans-acetylene dichloride" OR "trans-dichloroethylene" OR " (1e) -1 2-dichloro-ethene" OR "1 2-dichloroethylene" OR "1 2-trans-dichloroethylene" OR "dichloroethenes" OR "dichloroethene" OR "dichloroethylene" OR "1 2-dichloroethylene" OR 540-59-0 [rn] OR 156-59-2 [rn] OR 156-60-5 [rn] OR 25323-30-2 [rn]) AND 1999:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("1 2-dce" OR "1 2-dichlor-aethen" OR "1 2-dichloroethene" OR "1 2-dichloroethylene" OR "acetylene dichloride" OR "dichloro-1 2-ethylene" OR "dioform" OR "sym-dichloroethylene" OR " (z) -1 2-dichloroethene" OR " (z) -1 2-dichloroethylene" OR "acetalyne dichloride" OR "cis-acetylene dichloride " OR "cis-1 2-dichloroethene" OR "cis-1 2-dichloroethylene" OR "cis-dichloroethylene" OR "hcc 1130c" OR "r 1130c" OR " (1z) -1 2-dichloro-ethene " OR "1 2-dichloroethylene" OR " (e) -1 2-dichloroethene" OR " (e) -1 2-dichloroethylene" OR "hcc 1130t" OR "r 1130t" OR "trans-1 2-dichloroethene" OR "trans-1 2-dichloroethylene" OR "trans-acetylene dichloride" OR "trans-dichloroethylene" OR " (1e) 1 2-dichloro-ethene" OR "1 2-dichloroethylene" OR "1 2-trans-dichloroethylene" OR "dichloroethenes" OR "dichloroethene" OR "dichloroethylene" OR "1 2-dichloroethylene" OR 540-59-0 [rn] OR 156-59-2 [rn] OR 156-60-5 [rn] OR 25323-30-2 [rn]) AND 1994:1998 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
NTRL	
12/2023	Date Published 2020 to 2023 "1,2-DCE" OR "1,2-Dichlor-aethen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "Acetylene dichloride" OR "Dichloro-1,2-ethylene" OR "Dioform" OR "sym-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "Acetalyne dichloride" OR "cis-Acetylene dichloride " OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichloroethylene" OR "HCC 1130c" OR "R 1130c" OR "(1Z)-1,2-dichloro-Ethene " OR "1,2-Dichloroethylene" OR "(E)-1,2-Dichloroethene" OR "(E)-1,2-Dichloroethylene" OR "HCC 1130t" OR "R 1130t" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethylene" OR "(1E)-1,2-dichloro-Ethene" OR "1,2-Dichloroethylene" OR "1,2-trans-

Table B-2. Database Query Strings

Database search date	Query string
	Dichloroethylene" OR "Dichloroethene" OR "Dichloroethenes" OR "Dichloroethylene" OR "Dichloroethylenes"
10/2021	"1,2-DCE" OR "1,2-Dichlor-aethen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "Acetylene dichloride" OR "Dichloro-1,2-ethylene" OR "Dioform" OR "sym-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "Acetalyne dichloride" OR "cis-Acetylene dichloride" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichloroethylene" OR "HCC 1130c" OR "R 1130c" OR "(1Z)-1,2-dichloro-Ethene " OR "1,2-Dichloroethylene" OR "(E)-1,2-Dichloroethene" OR "(E)-1,2-Dichloroethylene" OR "HCC 1130t" OR "R 1130t" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethylene" OR "(1E)-1,2-dichloro-Ethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethylene" OR "Dichloroethenes" OR "Dichloroethene" OR "Dichloroethylene"
Toxcenter	
12/2023	FILE 'TOXCENTER' ENTERED AT 15:00:27 ON 14 DEC 2023 L1 6007 SEA 540-59-0 OR 156-59-2 OR 156-60-5 OR 25323-30-2 L2 5247 SEA L1 NOT PATENT/DT L3 230 SEA L2 AND ED>=20210901 L40 226 DUP REM L3 (4 DUPLICATES REMOVED) D SCAN L40
10/2021	FILE 'TOXCENTER' ENTERED AT 14:43:29 ON 05 OCT 2021 CHARGED TO COST=EH038.10.01.04 L1 5720 SEA FILE=TOXCENTER 540-59-0 OR 156-59-2 OR 156-60-5 OR 25323-30-2 L2 5589 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 4869 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 340 SEA FILE=TOXCENTER L3 AND ED>20170501 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)

Table B-2. Database Query Strings

Database search date	Query string
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 133 SEA FILE=TOXCENTER L4 AND L37
	L39 4 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
	L40 7 SEA FILE=TOXCENTER L38 AND BIOSIS/FS
	L41 122 SEA FILE=TOXCENTER L38 AND CAPLUS/FS
	L42 0 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)

Table B-2. Database Query Strings

Database search date	Query string
	L43 131 DUP REM L39 L40 L41 (2 DUPLICATES REMOVED) D SCAN L43 L44 935 SEA FILE=TOXCENTER 25323-30-2 L45 924 SEA FILE=TOXCENTER L44 NOT TSCATS/FS L46 688 SEA FILE=TOXCENTER L45 NOT PATENT/DT L47 40 SEA FILE=TOXCENTER L46 AND ED>20170501 L48 13 SEA FILE=TOXCENTER L47 AND L37 L*** DEL 4 S L38 AND MEDLINE/FS L*** DEL 4 S L38 AND MEDLINE/FS L49 4 SEA FILE=TOXCENTER L43 L*** DEL 7 S L38 AND BIOSIS/FS L*** DEL 7 S L38 AND BIOSIS/FS L50 7 SEA FILE=TOXCENTER L43 L*** DEL 122 S L38 AND CAPLUS/FS L*** DEL 122 S L38 AND CAPLUS/FS L51 120 SEA FILE=TOXCENTER L43 L52 0 SEA FILE=TOXCENTER L48 NOT (L49 OR L50 OR L51)
05/2017	(FILE 'HOME' ENTERED AT 09:05:27 ON 05 APR 2017) FILE 'TOXCENTER' ENTERED AT 09:05:48 ON 05 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 4437 SEA 540-59-0 OR 156-59-2 OR 156-60-5 L2 859 SEA 25323-30-2 L3 5208 SEA L1 OR L2 L4 5077 SEA L3 NOT TSCATS/FS L5 4442 SEA L4 NOT PATENT/DT L6 2662 SEA L5 AND PY>=1999 ACTIVATE TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR

Table B-2. Database Query Strings

Database search date	Query string
	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 (NONHUMAN MAMMALS)/ORGN
	L37 QUE L35 OR L36
	L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L39 QUE L37 OR L38

	L40 647 SEA L6 AND L39
	L41 36 SEA L40 AND MEDLINE/FS
	L42 31 SEA L40 AND BIOSIS/FS
	L43 574 SEA L40 AND CAPLUS/FS
	L44 6 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L45 621 DUP REM L41 L42 L44 L43 (26 DUPLICATES REMOVED)
	L*** DEL 36 S L40 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 36 S L40 AND MEDLINE/FS L46 36 SEA L45 L*** DEL 31 S L40 AND BIOSIS/FS L*** DEL 31 S L40 AND BIOSIS/FS L47 30 SEA L45 L*** DEL 574 S L40 AND CAPLUS/FS L*** DEL 574 S L40 AND CAPLUS/FS L48 549 SEA L45 L*** DEL 6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 6 SEA L45 L50 585 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS L51 510 SEA L50 NOT 25323-30-2 D SCAN L51 L52 75 SEA L50 NOT L51 D SCAN L52 (FILE 'HOME' ENTERED AT 11:02:51 ON 31 MAY 2017) FILE 'TOXCENTER' ENTERED AT 11:03:35 ON 31 MAY 2017 CHARGED TO COST=EH011.13.01.01 L1 5239 SEA 540-59-0 OR 156-59-2 OR 156-60-5 OR 25323-30-2 L2 5108 SEA L1 NOT TSCATS/FS L3 4469 SEA L2 NOT PATENT/DT L4 765 SEA L3 AND PY>=1994 AND PY<=1998 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

Table B-2. Database Query Strings

Database search date	Query string
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 190 SEA L4 AND L37
	L39 8 SEA L38 AND MEDLINE/FS
	L40 15 SEA L38 AND BIOSIS/FS
	L41 159 SEA L38 AND CAPLUS/FS
	L42 8 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 170 DUP REM L39 L40 L42 L41 (20 DUPLICATES REMOVED)
	L*** DEL 8 S L38 AND MEDLINE/FS
	L*** DEL 8 S L38 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L44 8 SEA L43 L*** DEL 15 S L38 AND BIOSIS/FS L*** DEL 15 S L38 AND BIOSIS/FS L45 12 SEA L43 L*** DEL 159 S L38 AND CAPLUS/FS L*** DEL 159 S L38 AND CAPLUS/FS L46 143 SEA L43 L*** DEL 8 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 8 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 7 SEA L43 L48 162 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
12/2023; 10/2021	Compounds searched: 540-59-0; 156-59-2; 156-60-5; 25323-30-2
NTP	
12/2023	Date limited 2020-present "540-59-0" "156-60-5" "Dichloroethene" "Dichloroethylene" "156-59-2" "25323-30-2" "1,2-Dichloroethene" "1,2-Dichloroethylene" "Acetylene dichloride" "Dichloroethylenes" "Dichloroethenes"
10/2021	"540-59-0" "156-59-2" "156-60-5" "25323-30-2" "Dichloroethene" "Dichloroethylene" "Acetylene dichloride" "Dichloroethylenes"
Regulations.gov	
12/2023	Restricted to docket or EPA notices: "156-60-5" "540-59-0" "156-59-2" "25323-30-2" dichloroethylene dichloroethene
NIH RePORTER	
9/2024	Search Criteria: Fiscal Year: Active Projects Text Search: "1,2-DCE" OR "1,2-Dichlor-aethen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "Acetylene dichloride" OR "Dichloro-1,2-ethylene" OR "Dioform" OR "sym-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "Acetalyne dichloride" OR "cis-Acetylene dichloride " OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichloroethylene" OR "HCC 1130c" OR "R 1130c" OR "(1Z)-1,2-dichloro-Ethene " OR "1,2-Dichloroethylene" OR "(E)-1,2-Dichloroethene" OR "(E)-1,2-Dichloroethylene" OR "HCC 1130t" OR "R 1130t" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethylene" OR "(1E)-1,2-dichloro-Ethene" OR "1,2-Dichloroethylene" OR "1,2-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	trans-Dichloroethylene" OR "Dichloroethene" OR "Dichloroethenes" OR "Dichloroethylene" OR "Dichloroethylenes" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
05/2022	" Text Search: "1,2-DCE" OR "1,2-Dichlor-aethen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "Acetylene dichloride" OR "Dichloro-1,2-ethylene" OR "Dioform" OR "sym-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "Acetalyne dichloride" OR "cis-Acetylene dichloride " OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichloroethylene" OR "HCC 1130c" OR "R 1130c" OR "(1Z)-1,2-dichloro-Ethene " OR "1,2-Dichloroethylene" OR "(E)-1,2-Dichloroethene" OR "(E)-1,2-Dichloroethylene" OR "HCC 1130t" OR "R 1130t" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethylene" OR "(1E)-1,2-dichloro-Ethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethylene" (advanced) " Limit to: Project Title, Project Terms, Project Abstracts
Other	Includes additional reference identified throughout the assessment process, which may include studies found by tree searching; recommended by intraagency, interagency, peer, or public reviewers; or published more recently than the date of literature search(es). Additional references include those for specific regulations or guidelines and publications found by targeted searches for specific information (e.g., searches for reviews of general [not chemical-specific] mechanisms of toxicity).

The 2021 pre-public comment search results were:

- Number of records identified from PubMed, Toxline, NTRL, and TOXCENTER (after duplicate removal): 1,873
- Number of records identified from other strategies: 99
- Total number of records to undergo literature screening: 1,972

The 2023 post-public comment search results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 381
- Number of records identified from other strategies: 54
- Total number of records to undergo literature screening: 435

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,2-dichloroethene during the pre- and post-public comment drafts:

- Title and abstract screen
- Full text screen

One reviewer conducted screening of the titles, abstracts, and full text articles.

Pre-Public Comment 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.

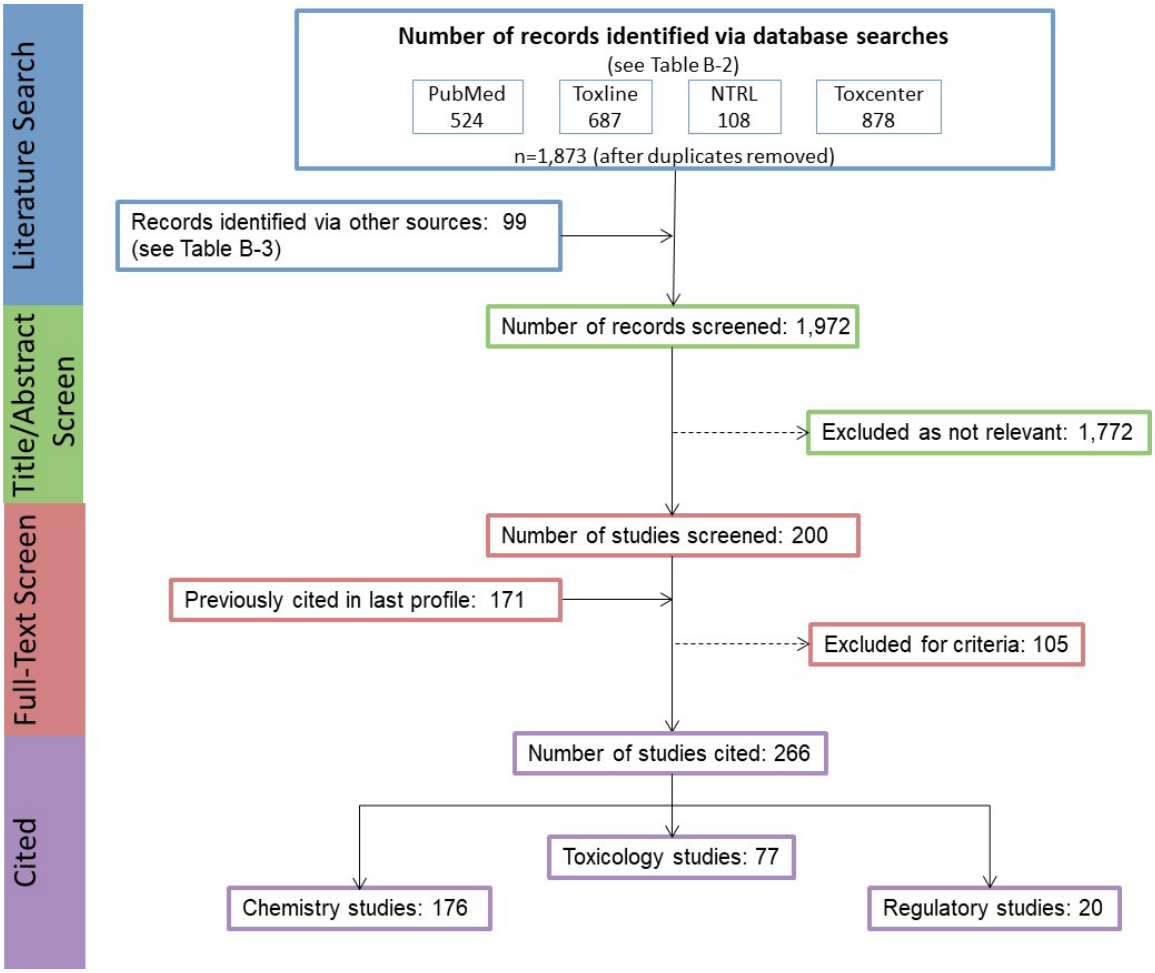
- Number of titles and abstracts screened: 1,972
- Number of studies considered relevant and moved to the next step: 200

Pre-Public Comment 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: 200
- Number of studies cited in the previous toxicological profile: 171
- Total number of studies cited in the profile: 266

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

Figure B-1. October 2021 Pre-Public Comment Literature Search Results and Screen for 1,2-Dichloroethene*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

Post-Public Comment 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.

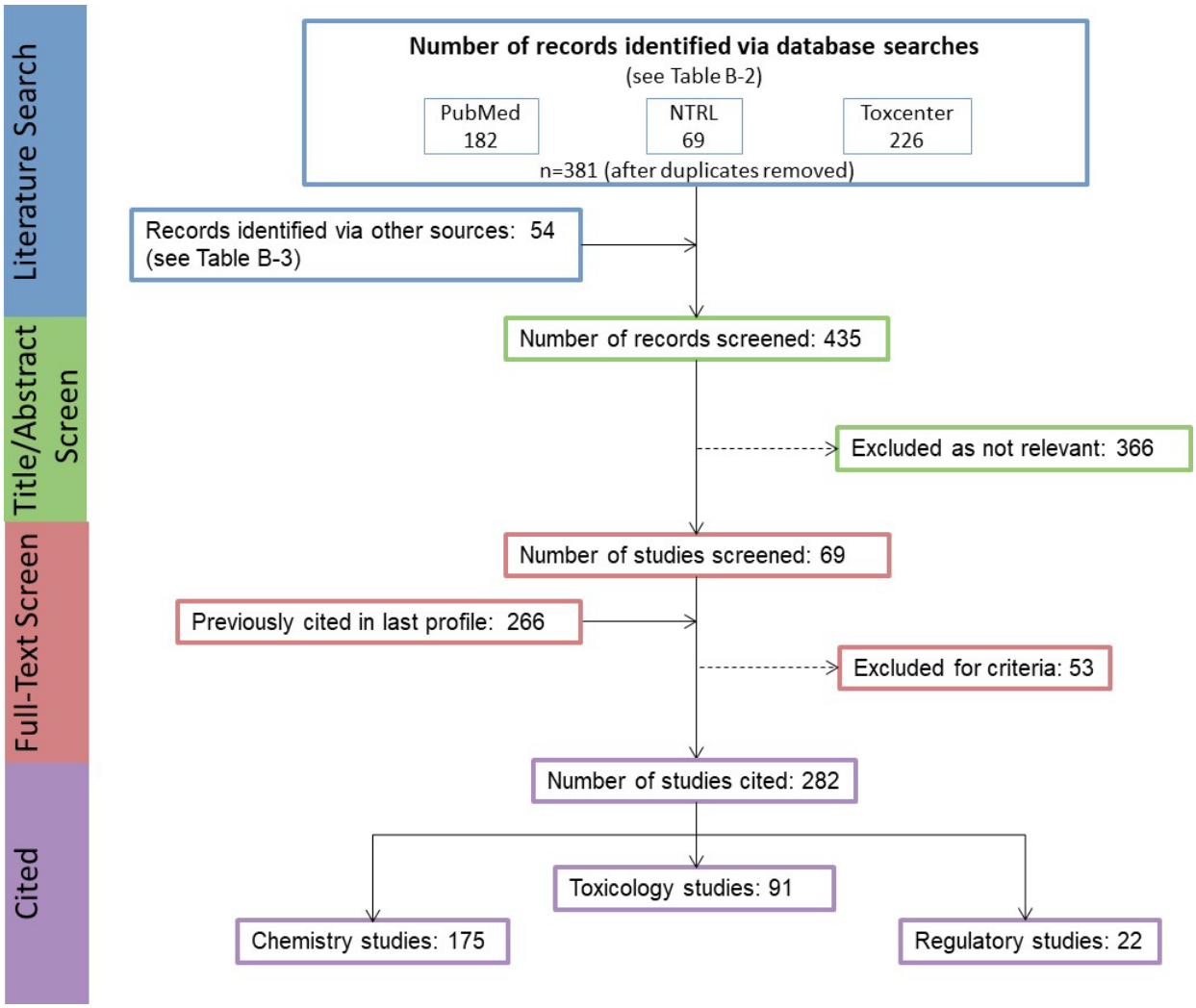
- Number of titles and abstracts screened: 435
- Number of studies considered relevant and moved to the next step: 69

Post-Public Comment 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: 69
- Number of studies cited in the pre-public draft of the toxicological profile: 266
- Total number of studies cited in the profile: 282

A summary of the results of the post-public comment literature search and screening is presented in Figure B-2.

Figure B-2. December 2023 Post-Public Comment Literature Search Results and Screen for 1,2-Dichloroethene*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,2-DICHLOROETHENE

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 1,2-dichloroethene, 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 1,2-dichloroethene:

- 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 1,2-dichloroethene. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dichloroethene are presented in Table C-1.

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

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

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

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

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

C.2. LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of 1,2-dichloroethene. 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 literature searches were intended to update the Toxicological Profile for 1,2-Dichloroethene. See Appendix B for the databases searched and the search strategy.

A total of 1,972 and 435 records relevant to all sections of the toxicological profile were identified in the initial and update literature search, respectively.

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 1,2-dichloroethene.

Title and Abstract Screen. In the Title and Abstract Screen step, 43 documents (inclusive of both literature searches) 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 23 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 23 documents (43 studies), 5 documents (6 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for 1,2-dichloroethene and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 through 2-5, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,2-dichloroethene identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a limited range of effects; one study reported hepatic effects resulting from exposure to trans-1,2-dichloroethene. Animal studies examined several endpoints following inhalation, oral, or dermal exposure. The oral exposure studies examined most endpoints and reported body weight, hematological, ocular, dermal, immunological, neurological, and developmental. Of these effects, ocular and immunological were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 6 studies (published in 5 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for trans-1,2-Dichloroethene Evaluated In Human Studies

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

APPENDIX C

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

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for animal experimental studies are presented in Table C-5. 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 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 animal experimental studies are presented in Table C-6.

APPENDIX C

Table C-6. Summary of Risk of Bias Assessment for trans-1,2-Dichloroethene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Ocular Effects										
Inhalation acute exposure										
Hurtt et al. 1993 (10-day)	++	+	+	+	++	+	+	++	na	First
Inhalation intermediate exposure										
DuPont 1998 (90-day)	++	+	++	+	++	++	+	++	na	First
Dermal (instillation into eye)										
DuPont 1988c	–	+	+	+	+	+	+	+	na	First
Outcome: Immune Effects (oral only)										
Oral acute exposure										
Munson et al. 1982 (14-day gavage)	–	+	–	+	+	–	++	+	na	First
Shopp et al. 1985 (14-day gavage)	–	+	+	+	+	+	++	+	na	First
Oral intermediate exposure										
Shopp et al. 1985 (90-day drinking water)	–	+	+	+	+	+	++	+	na	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

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

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to trans-1,2-dichloroethene 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 vinyl acetate and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for experimental animal studies are presented in Table C-7. 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-7. 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 ocular and immune observed in animal experimental studies are presented in Table C-8.

A summary of the initial confidence ratings for each outcome is presented in Table C-9. 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.

Table C-8. Presence of Key Features of Study Design for trans-1,2-Dichloroethene —Experimental Animal Studies

	Key feature				
Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Ocular Effects					
Inhalation acute exposure					
Hurtt et al. 1993 (10-day)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
DuPont 1998 (90-day)	Yes	Yes	Yes	Yes	High
Dermal (instillation into eye)					
DuPont 1988c	No	No	Yes	No	Very low
Outcome: Immune Effects (oral only)					
Oral acute exposure					
Munson et al. 1982 (14-day gavage)	No	Yes	Yes	Yes	Moderate
Shopp et al. 1985 (14-day gavage)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Shopp et al. 1985 (90-day drinking water)	Yes	No	Yes	Yes	Moderate

Table C-9. Initial Confidence Rating for trans-1,2-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Ocular Effects		
Inhalation acute exposure		
Animal studies		
Hurtt et al. 1993 (10-day)	High	High
Inhalation intermediate exposure		
Animal studies		
DuPont 1998 (90-day)	High	High
Dermal acute exposure		
Animal studies		
DuPont 1988c	Very low	Very low
Outcome: Immune Effects (oral only)		
Oral acute exposure		
Animal studies		
Munson et al. 1982 (14-day gavage)	Moderate	High
Shopp et al. 1985 (14-day gavage)	High	
Oral intermediate exposure		
Animal studies		
Shopp et al. 1985 (90-day drinking water)	Moderate	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 ocular and immune effects are presented in Table C-10. If the confidence ratings for a particular outcome were based on more than one type of 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 1,2-dichloroethene exposure is presented in Table C-11.

Table C-10. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Ocular effects			
Animal studies	High	-1 inconsistency in findings	Moderate
Outcome: Immune effects			
Animal studies	High	None	High

Table C-11. Confidence in the Body of Evidence for 1,2-Dichloroethene

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Ocular effects	None	Moderate
Immune effects	None	High

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-5 and C-6). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

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

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

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

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

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

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

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

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

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

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

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

In the seventh step of the systematic review of the health effects data for trans-1,2-dichloroethene, 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 trans-1,2-dichloroethene is presented in Table C-12.

Table C-12. Level of Evidence of Health Effects for trans-1,2-Dichloroethene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Animal studies			
Ocular effects	Moderate	Health effect	Moderate
Immune effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

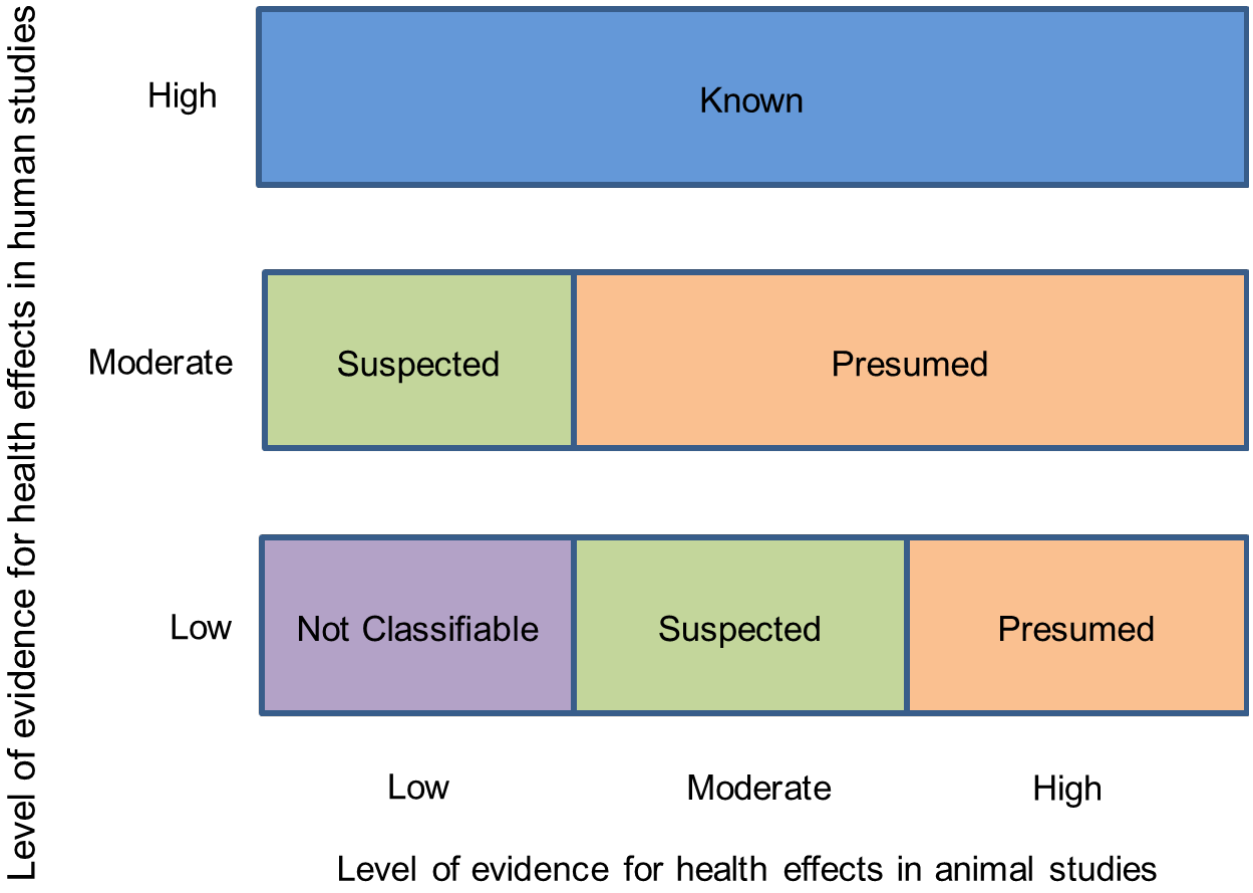
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing

evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below.

Figure C-1. Hazard Identification Scheme



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

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

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 trans-1,2-dichloroethene are listed below and summarized in Table C-13.

Table C-13. Hazard Identification Conclusions for trans-1,2-Dichloroethene

Outcome	Hazard identification
Ocular effects	Suspected
Immune effects	Presumed

Presumed Effects

- Immune effects
  - No human data.
  - High evidence of effects on humoral-mediated immunity following intermediate oral exposure (Shopp et al. 1985).

Suspected Effects

- Ocular effects
  - No human data.
  - Moderate evidence of ocular effects following acute inhalation exposure and eye instillation (DuPont 1988c; Hurtt et al. 1993).

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

APPENDIX D

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

Figure key[a] (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									

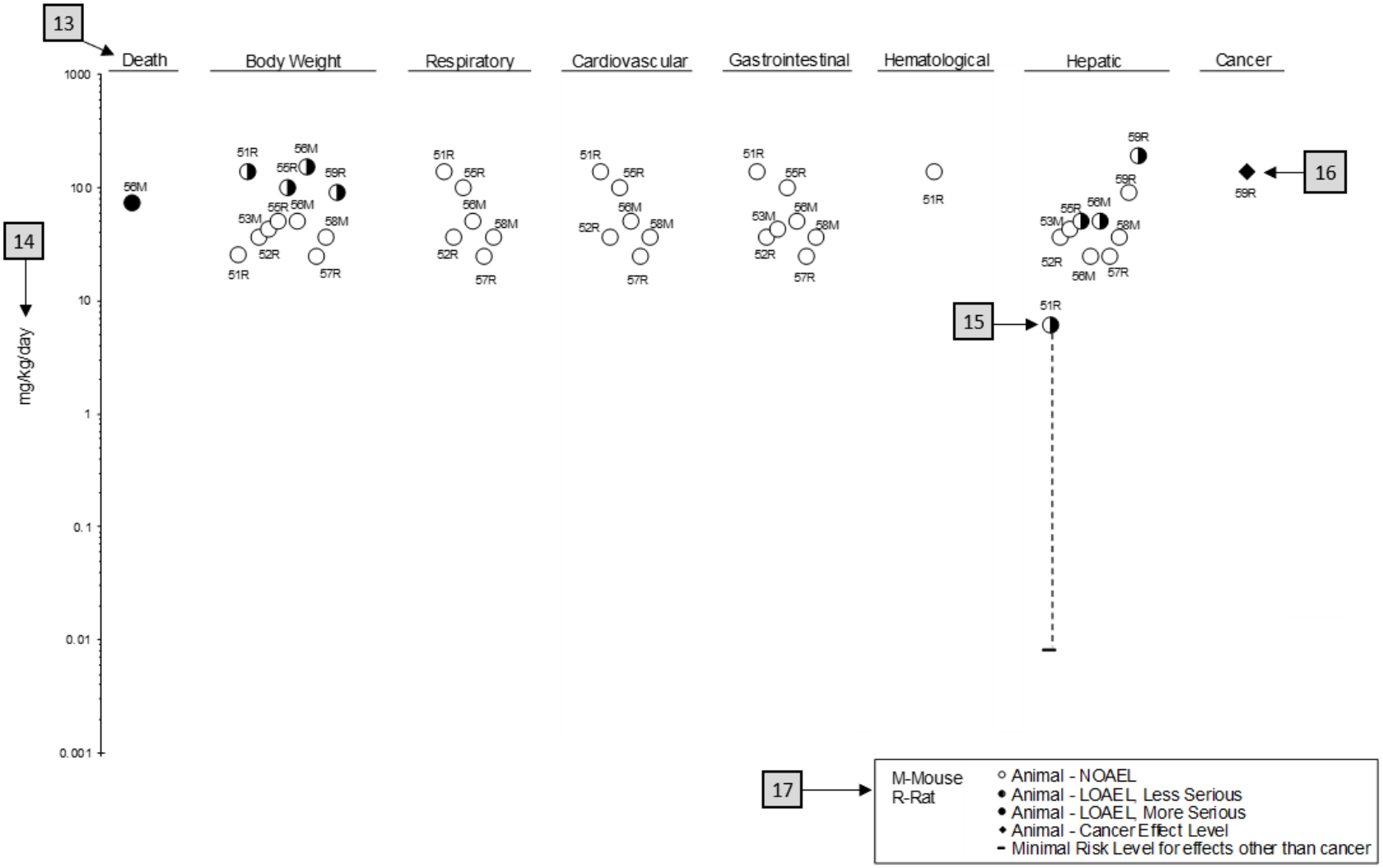
[a]The number corresponds to entries in Figure 2-x.

(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).

APPENDIX D

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinical Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.html).

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

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

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, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • 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 https://www.pehsu.net/.

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical or agent capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure 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
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result