APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: Available data were not considered adequate for derivation of an acute-duration inhalation MRL for 1,1-dichloroethene.

Rationale for Not Deriving an MRL: No exposure-response human data are available. The lowest LOAEL for acute-duration inhalation exposure of laboratory animals is a serious LOAEL of 15 ppm for a study in which death and maternal body weight loss occurred in rats exposed to 1,1-dichloroethene vapor for 22–23 hours/day during GDs 6–16 (EPA 1977a).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: March 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL 0.001 ppm (1 ppb)
Critical Effect: Necrosis in nasal olfactory epithelium
Reference: NTP 2015a
Point of Departure: $BMCL_{10}$ of 1.59 ppm ($BMCL_{HEC}$ of 0.036 ppm)
Uncertainty Factor: 30
LSE Graph Key: 40
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.001 ppm (1 ppb) has been derived for 1,1-dichloroethene based on increased incidences of necrosis in nasal olfactory epithelium of male F344/N rats exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 14 weeks (NTP 2015a). The MRL is based on a $BMCL_{10}$ of 1.59 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.036 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No exposure-response human data are available. Table A-1 summarizes candidate critical effects from intermediate-duration inhalation studies in laboratory animals. The lowest LOAEL is 6.25 ppm for nasal lesions in male and female rats, depressed body weight gain in female mice, and increased relative kidney weight in female mice exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 14 weeks (NTP 2015a). The kidney weight increase at 6.25 ppm in female mice is of questionable toxicological significance because it occurred in the absence of exposure-related increases in histopathologic kidney lesions. Seriously depressed body weight gain was reported at all exposure levels (6.25–100 ppm) among the female mice (27–41% less than that of controls) and at exposure concentrations ≥12.5 ppm among the male mice (24–38% less than that of controls). Mean final body weights of the 6.25, 12.5, 25, 50, and 100 ppm groups of female mice were 12, 9, 12, 18, and 15%, respectively, less than that of controls. Mean final body weights of the 12.5, 25, and 50 ppm groups of male mice were 10, 15, and 16%, respectively, less than that of controls. However, in a similarly designed 105-week study, there were no effects on body weight in the male or female mice during the first 13 weeks of exposures at 6.25, 12.5, or 25 ppm (NTP 2015a). Body weight effects in the female mice of the 14-week study were not considered as a critical effect for MRL derivation because the female mouse body weight data from the 2-year study (for weeks 1–13, 14–52, and 53–103) did not corroborate the result from the 14-week study.

The nasal lesions in the male and female rats were selected to represent the critical effects of intermediate-duration inhalation exposure to 1,1-dichloroethene because they represent the lowest reliable LOAEL (6.25 ppm).

Table A-1. Summary of Candidate Critical Effects for Deriving an Intermediate-Duration Inhalation MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Body weight effects					
B6C3F1/N mouse	14 weeks (5 days/week 6 hours/day)	ND F	6.25 F	Depressed body weight gain	NTP 2015a
Respiratory effects					
F344/N rat	14 weeks (5 days/week 6 hours/day)	ND	6.25	Lesions in olfactory epithelium	NTP 2015a
B6C3F1/N mouse	14 weeks (5 days/week 6 hours/day)	6.25	12.5	Increased lung weight	NTP 2015a
Hepatic effects					
F344/N rat	14 weeks (5 days/week 6 hours/day)	6.25 M	12.5 M	Hepatic centrilobular cytoplasmic alterations	NTP 2015a
Renal effects					
B6C3F1/N mouse	14 weeks (5 days/week 6 hours/day)	6.25 M ND F	12.5 M 6.25 F	M: nephropathy F: increased kidney weight	NTP 2015a

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

Selection of the Principal Study: The 14-week inhalation study in rats (NTP 2015a) identified the lowest less serious LOAEL (6.25 ppm) for 1,1-dichloroethene exposure-related effects considered to be toxicologically significant. Therefore, the 14-week inhalation study of rats (NTP 2015a) was selected as the principal study for deriving an intermediate-duration inhalation MRL.

Summary of the Principal Study:

NTP. 2015a. NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (inhalation studies). NTP TR 582. National Toxicology Program. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Groups of F344/N rats (10/sex/group; 5–7 weeks of age) were exposed (whole body) to 1,1-dichloroethene vapor for 6 hours/day (+10 minutes), 5 days/week for 14 weeks at 0, 6.25, 12.5, 25, 50, or 100 ppm. Evaluations included survival, clinical signs, body weight, hematology, clinical chemistry, selected organ weights, and gross and histopathology. The following targets of toxicity were identified:

- ***Respiratory:*** There were no exposure-related effects on lung weight. Significantly increased incidences of selected nasal lesions were observed in both males and females. Incidence data are presented in Table A-2. Olfactory epithelium atrophy, mineralization, and necrosis occurred in males and females at all exposure levels; none of these lesions occurred in control males or females.

- ***Hepatic:*** Hepatic centrilobular cytoplasmic alterations were observed in males at 12.5 ppm (6/10 rats) and all males at higher exposure levels. Exposure-related liver lesions in female rats were limited to hepatocellular cytoplasmic vacuolization in all females exposed at 50 and 100 ppm.

- ***Renal:*** Slightly increased relative kidney weights were noted in males at 6.25, 12.5, and 100 ppm (3–7% greater than controls), but not at 25 or 50 ppm. Females exhibited exposure concentration-related significantly increased relative kidney weights at exposure levels ≥12.5-ppm (6–16% greater than controls). There was no evidence of exposure-related increased incidences of renal lesions in males or females (NOAEL of 100 ppm).

- ***Reproductive:*** At the highest exposure level (100 ppm), males exhibited 5% decreased sperm motility and 15–16% decreased spermatid count.

Table A-2. Selected Nasal Lesion Incidences in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 14 Weeks

	1,1-Dichloroethene exposure level (ppm)					
Lesion type	0	6.25	12.5	25	50	100
Males						
Olfactory epithelium						
Atrophy	0/10[a]	4/10[b] (1.0)	10/10[c] (1.0)	10/10[c] (1.7)	10/10[c] (2.2)	10/10[c] (2.7)
Mineralization[d]	0/10	10/10[c] (1.3)	10/10[c] (2.0)	10/10[c] (2.9)	10/10[c] (3.0)	10/10[c] (2.6)
Necrosis	0/10	2/10 (1.0)	6/10[c] (1.0)	9/10[c] (1.0)	7/10[c] (1.7)	10/10[c] (1.6)
Turbinate						
Atrophy	0/10	0/10	10/10[c] (1.0)	10/10[c] (2.0)	10/10[c] (2.3)	10/10[c] (3.0)
Females						
Olfactory epithelium						
Atrophy	0/10	2/10 (1.0)	10/10[c] (1.0)	10/10[c] (1.3)	10/10[c] (1.7)	10/10[c] (2.4)
Mineralization[d]	0/10	5/10[b] (1.0)	9/10[c] (1.3)	10/10[c] (1.9)	10/10[c] (2.1)	10/10[c] (2.3)
Necrosis	0/10	1/10 (1.0)	3/10 (1.3)	6/10[c] (1.5)	10/10[c] (2.2)	10/10[c] (3.0)
Turbinate						
Atrophy	0/10	0/10	10/10[c] (1.0)	10/10[c] (2.0)	10/10[c] (2.2)	10/10[c] (3.0)
Males and females (combined incidences)						
Olfactory epithelium						
Atrophy	0/20	6/20[e]	20/20[f]	20/20[f]	20/20[f]	20/20[f]
Mineralization[d]	0/20	15/20[f]	19/20[f]	20/20[f]	20/20[f]	20/20[f]
Necrosis	0/20	3/20	9/20[f]	15/20[f]	17/20[f]	20/20[f]
Turbinate						
Atrophy	0/20	0/20	20/20[f]	20/20[f]	20/20[f]	20/20[f]

[a]Incidence (severity;1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[b]Significantly different from chamber control incidence by the Poly-3 test ($p<0.05$).
[c]Significantly different from chamber control incidence by the Poly-3 test ($p<0.01$).
[d]Mineralization was described as "deposits of greyish-blue material in the basement membrane, often underlying an atrophic epithelium or disrupting the epithelium, and most often affecting the lateral walls and turbinates." The deposits were not actually within the olfactory epithelium and of unknown toxicological significance.
[e]Significantly different from chamber control incidence by Fisher's exact test ($p<0.05$) performed by SRC, Inc.
[f]Significantly different from chamber control incidence by Fisher's exact test ($p<0.01$) performed by SRC, Inc.

Source: NTP 2015a

Selection of the Point of Departure for the MRL: A $BMCL_{10}$ of 1.59 ppm for olfactory epithelium necrosis in male rats estimated from the frequentist-restricted 3-degree Multistage model was selected as the point of departure (POD) for the intermediate-duration inhalation MRL for 1,1-dichloroethene.

The lowest LOAEL identified in the NTP (2015a) 14-week rat study was 6.25 ppm for increased incidence of nasal lesions in males and females. Within olfactory epithelium, atrophy and necrosis were observed at the lowest exposure level tested (6.25 ppm). Deposits of greyish-blue material in the basement membrane, often underlying an atrophic epithelium or disrupting the epithelium, and most often affecting the lateral walls and turbinates, were reported as mineralization in olfactory epithelium. Although these deposits occurred at 100% incidence in all groups of 1,1-dichloroethene-exposed male rats and at 50% in the 6.25 ppm females and 100% in all other exposed groups of females, their occurrence within the region of the basement membrane (rather than the olfactory epithelium) is of questionable toxicological significance. Therefore, mineralization was not considered as a candidate critical effect for deriving an intermediate-duration inhalation MRL for 1,1-dichloroethene. However, atrophy and necrosis are considered reliable exposure-related adverse effects and were considered candidate critical effects. Atrophy in the turbinates was not considered as a candidate critical effect because this lesion was not observed at the lowest exposure level (6.25 ppm).

The incidence data for atrophy and for necrosis in the olfactory epithelium of the male and the female rats were fit to all standard dichotomous models in the EPA Benchmark Dose Software (BMDS, version 3.1.2) using a benchmark response (BMR) of 10% change in incidence from controls. Based on relatively similar male and female exposure concentration-response data for atrophy and for necrosis in olfactory epithelium, incidence data for both sexes were also combined to increase the statistical power of the benchmark result. Analysis of the data for necrosis in males and females using EPA's Categorical Regression Analysis (Cater 3.1) software confirmed the acceptability of combining male and female incidence data. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ±2 units) at the data points (except the control) closest to the predefined BMR, BMCL values that are not 10 times lower than the lowest non-zero dose, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike Information Criterion (AIC) was chosen.

Model predictions for nasal olfactory epithelium atrophy in the male rats are presented in Table A-3. Most models provided adequate fit to the data; the multistage 1-degree and Weibull models did not provide adequate fit because the BMDL was 10 times lower than the lowest non-zero concentration and because the lower limited includes zero, respectively. The $BMCL_{10}$ values varied by >3-fold; therefore, the lowest $BMCL_{10}$ (0.73 ppm) considered as a potential POD.

Table A-3. Model Predictions for Incidence of Nasal Olfactory Epithelium Atrophy in Male F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	4.74	2.85	0.997	17.76	-6.96×10^{-2}	-3.90×10^{-4}
Gamma[d]	3.85	1.69	0.981	18.21	-2.69×10^{-1}	-3.90×10^{-4}
Log-Logistic[e]	4.74	2.85	1.000	15.76	-6.96×10^{-2}	-3.90×10^{-4}
Multistage Degree 5[f,g]	**3.81**	**0.73**	**1.000**	**15.53**	$\mathbf{-7.19 \times 10^{-2}}$	$\mathbf{-3.90 \times 10^{-4}}$
Multistage Degree 4[f]	3.79	0.74	1.000	15.55	-8.79×10^{-2}	-3.90×10^{-4}
Multistage Degree 3[f]	3.55	0.83	1.000	15.72	-2.30×10^{-1}	-3.90×10^{-4}
Multistage Degree 2[f]	2.37	0.74	0.952	17.13	-3.90×10^{-4}	-3.90×10^{-4}
Multistage Degree 1[f]			0.529	20.95	-3.90×10^{-4}	-3.90×10^{-4}
Weibull[c]			0.833	19.74	-4.16×10^{-4}	-4.16×10^{-4}
Logistic	4.46	2.26	1.000	15.54	-1.02×10^{-2}	-1.14×10^{-1}
Log-Probit	5.35	2.85	1.000	15.46	-1.13×10^{-4}	-3.90×10^{-4}
Probit	2.16	1.37	0.673	21.26	-1.09	-1.09

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Multistage 5 degree model).

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

Model predictions for nasal olfactory epithelium atrophy in the female rats are presented in Table A-4. The 1-degree Multistage model (the BMCL is 10 times lower than the lowest non-zero dose) and the Weibull model (lower limit includes zero) provided inadequate fit to the data. Visual inspection of the 2-degree Multistage model revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points closest to the control value; therefore, the model fit was considered inadequate. All other models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. The $BMCL_{10}$ of 3.48 ppm from the model with the lowest AIC (Logistic model) was selected as a potential POD based on nasal olfactory epithelium atrophy in the female rats because the $BMCL_{10}$ values estimated from models with adequate varied by <3-fold.

Table A-4. Model Predictions for Incidence of Nasal Olfactory Epithelium Atrophy in Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	5.46	4.15	0.997	12.60	-1.60×10^{-1}	-3.90×10^{-4}
Gamma[d]	4.72	3.19	0.892	15.88	-5.66×10^{-1}	-3.92×10^{-4}
Log-Logistic[e]	5.46	4.15	0.989	14.60	-1.60×10^{-1}	-3.90×10^{-4}
Multistage Degree 5[f]	4.72	1.49	0.996	12.62	-3.56×10^{-1}	-3.90×10^{-4}
Multistage Degree 4[f]	4.63	1.49	0.994	12.74	-4.17×10^{-1}	-3.90×10^{-4}
Multistage Degree 3[f]	4.05	1.68	0.950	13.66	-8.21×10^{-1}	-3.90×10^{-4}
Multistage Degree 2[f,g]	2.76	1.26	0.661	16.59	-3.90×10^{-4}	-3.90×10^{-4}
Multistage Degree 1[f]			0.152	22.55	-3.90×10^{-4}	-3.90×10^{-4}
Weibull[c]			0.493	19.06	-4.96×10^{-4}	-4.96×10^{-4}
Logistic[h]	**5.40**	**3.48**	**1.000**	**12.17**	$\mathbf{-5.34 \times 10^{-2}}$	$\mathbf{-7.10 \times 10^{-2}}$
Log-Probit	5.86	4.35	1.000	14.01	-7.59×10^{-4}	-3.90×10^{-4}
Probit	2.80	1.74	0.454	19.69	-8.49×10^{-1}	-8.49×10^{-1}

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Visual inspection of the 2-degree Multistage model fit revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points close to the control value and the model fit was considered inadequate.
[h]Recommended model. Most models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Among the models providing adequate fit, the model with the lowest AIC was selected (Logistic).

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

Model predictions for combined incidences of nasal olfactory epithelium atrophy in the male and female rats are presented in Table A-5. The 1-degree Multistage model provided inadequate fit to the dataset (goodness-of-fit p-value <0.1). All other models provided adequate fit to the data. The Log-Probit model $BMCL_{10}$ of 4.29 ppm (model with the lowest AIC) was selected as a potential POD based on combined incidences of nasal olfactory epithelium atrophy in the male and female rats.

Table A-5. Model Predictions for Incidence of Nasal Olfactory Epithelium Atrophy in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	5.07	4.15	0.981	29.25	-1.42×10^{-1}	-5.52×10^{-4}
Gamma[d]	4.27	3.24	0.852	30.80	-5.53×10^{-1}	-5.54×10^{-4}
Log-Logistic[e]	5.07	4.15	0.981	29.25	-1.42×10^{-1}	-5.52×10^{-4}
Multistage Degree 5[f]	4.23	1.45	0.998	26.90	-2.51×10^{-1}	-5.52×10^{-4}
Multistage Degree 4[f]	4.18	1.50	0.997	27.00	-3.00×10^{-1}	-5.52×10^{-4}
Multistage Degree 3[f]	3.81	1.89	0.967	27.87	-6.75×10^{-1}	-5.52×10^{-4}
Multistage Degree 2	2.56	1.49	0.408	34.12	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 1[f]			0.019	43.82	-5.71×10^{-4}	-5.71×10^{-4}
Weibull[c]	2.40	2.40	0.339	35.29	-5.53×10^{-4}	-5.53×10^{-4}
Logistic	4.89	3.46	1.000	26.65	-3.47×10^{-2}	-1.30×10^{-1}
Log-Probit[g]	**5.58**	**4.29**	**1.000**	**26.44**	$\mathbf{-3.03 \times 10^{-4}}$	$\mathbf{-5.52 \times 10^{-4}}$
Probit	2.46	1.76	0.190	39.36	-1.37	-1.37

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold) and the model with the lowest AIC was selected. Therefore, the Log-Probit is the recommended model.

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

Model predictions for nasal olfactory epithelium necrosis in the male rats are presented in Table A-6. The Gamma, 5-degree Multistage, 1-degree Multistage, Weibull, Logistic, and Probit models provided inadequate fit to the dataset (goodness-of-fit p-value <0.1); the Log-Probit model also did not provide adequate fit (BMCL was 10 times lower than the lowest non-zero dose). Among the models providing adequate fit to the data, the $BMCL_{10}$ of 1.59 ppm from the model with the lowest AIC (2-degree Multistage) was selected as a potential POD because the $BMCL_{10}$ values varied by <3-fold.

Table A-6. Model Predictions for Incidence of Nasal Olfactory Epithelium Necrosis in Male F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	4.82	0.79	0.112	55.22	$3.96x10^{-2}$	$-3.92x10^{-4}$
Gamma[d]			0.085	53.29	$-3.98x10^{-4}$	$-3.98x10^{-4}$
Log-Logistic[e]	2.53	0.72	0.207	51.85	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Multistage Degree 5[f]			0.086	53.29	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Multistage Degree 4[f]	2.23	1.59	0.147	51.29	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Multistage Degree 3[f]	**2.23**	**1.59**	**0.147**	**51.29**	**$-3.90x10^{-4}$**	**$-3.90x10^{-4}$**
Multistage Degree 2[f,g]	**2.23**	**1.59**	**0.147**	**51.29**	**$-3.90x10^{-4}$**	**$-3.90x10^{-4}$**
Multistage Degree 1[f]			0.085	53.29	$-3.91x10^{-4}$	$-3.91x10^{-4}$
Weibull[c]			0.085	53.29	$-4.24x10^{-3}$	$-4.24x10^{-3}$
Logistic			0.013	60.60	$-6.67x10^{-1}$	-1.66
Log-Probit			0.119	53.91	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Probit			0.015	60.84	$-6.67x10^{-1}$	-1.67

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Five models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold) and the model with the lowest AIC was selected. Therefore, the 2-degree Multistage is the recommended model.

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

Model predictions for nasal olfactory epithelium necrosis in the female rats are presented in Table A-7. All models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. However, visual inspection of the 1-degree Multistage fit revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points closest to the control value; therefore, the model fit was considered inadequate. All other models provided adequate fit. The Probit model $BMCL_{10}$ of 5.41 ppm (corresponding to the lowest AIC among models providing adequate fit) was selected as a potential POD based on nasal olfactory epithelium necrosis in the female rats because the $BMCL_{10}$ values varied by <3-fold.

Table A-7. Model Predictions for Incidence of Nasal Olfactory Epithelium Necrosis in Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	7.57	4.05	0.800	38.47	$4.79x10^{-1}$	$-3.90x10^{-4}$
Gamma[d]	7.03	2.97	0.852	39.29	$2.54x10^{-1}$	$-3.92x10^{-4}$
Log-Logistic[e]	7.57	4.05	0.800	38.47	$4.79x10^{-1}$	$-3.90x10^{-4}$
Multistage Degree 5[f]	5.27	2.31	0.731	42.30	$-2.01x10^{-1}$	$-1.13x10^{-3}$
Multistage Degree 4[f]	5.20	2.37	0.925	40.35	$-2.08x10^{-1}$	$-4.34x10^{-4}$
Multistage Degree 3[f]	5.44	2.49	0.974	38.45	$-1.58x10^{-1}$	$-4.08x10^{-4}$
Multistage Degree 2	6.45	2.66	0.936	38.76	$4.91x10^{-2}$	$-4.03x10^{-4}$
Multistage Degree 1[f,g] 3	2.52	1.75	0.542	40.86	$-3.91x10^{-4}$	$-3.91x10^{-4}$
Weibull[c]	6.94	3.07	0.913	38.87	$1.92x10^{-1}$	$-4.63x10^{-4}$
Logistic	8.80	5.74	0.897	37.70	$7.16x10^{-2}$	$-6.21x10^{-1}$
Log-Probit	7.40	4.16	0.831	38.16	$4.98x10^{-1}$	$-3.90x10^{-4}$
Probit[h]	8.23	5.41	0.940	37.26	$9.27x10^{-2}$	$-5.39x10^{-1}$

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]The 1-degree Multistage model was judged to provide inadequate fit to the data based on visual inspection of the predicted dose-response curve.
[h]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Probit).

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

Model predictions for combined incidences of nasal olfactory epithelium necrosis in the male and female rats are presented in Table A-8. The Logistic and Probit models provided inadequate fit to the dataset (goodness-of-fit p-value <0.1). All other models provided adequate fit to the data. The Log-Probit model $BMCL_{10}$ of 2.57 ppm (corresponding to the lowest AIC) was selected as a potential POD based on combined incidences of nasal olfactory epithelium necrosis in the male and female rats because the $BMCL_{10}$ values varied by <3-fold.

Table A-8. Model Predictions for Incidence of Nasal Olfactory Epithelium Necrosis in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	4.58	2.46	0.680	91.76	-1.93×10^{-1}	-5.52×10^{-4}
Gamma[d]	3.20	1.87	0.552	91.98	-6.21×10^{-1}	-7.70×10^{-3}
Log-Logistic[e]	4.58	2.46	0.680	91.76	-1.93×10^{-1}	-5.84×10^{-4}
Multistage Degree 5[f]	2.45	1.87	0.731	89.98	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 4[f]	2.46	1.86	0.717	90.07	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 3[f]	2.47	1.85	0.539	92.15	-7.06×10^{-4}	-7.06×10^{-4}
Multistage Degree 2	2.55	1.85	0.700	90.19	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 1[f]	2.36	1.84	0.709	90.31	-6.13×10^{-4}	-6.13×10^{-4}
Weibull[c]	2.94	1.86	0.543	92.06	-5.52×10^{-4}	-5.52×10^{-4}
Logistic			0.039	99.21	-5.87×10^{-1}	-1.67
Log-Probit[g]	**4.66**	**2.57**	**0.841**	**89.51**	$\mathbf{-2.26 \times 10^{-1}}$	$\mathbf{-5.52 \times 10^{-4}}$
Probit			0.038	99.73	-5.95×10^{-1}	-1.66

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Log-Probit).

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

Best-fitting model predictions for atrophy and for necrosis in nasal olfactory epithelium of the male and female rats are presented in Table A-9. Among the best-fitting models, the lowest predicted BMC_{10} was 2.23 ppm for incidences of olfactory epithelium necrosis in the male rats estimated from the 2-degree Multistage model; the corresponding $BMCL_{10}$ of 1.59 ppm was selected as the POD. The 2-degree model is presented in Figure A-1.

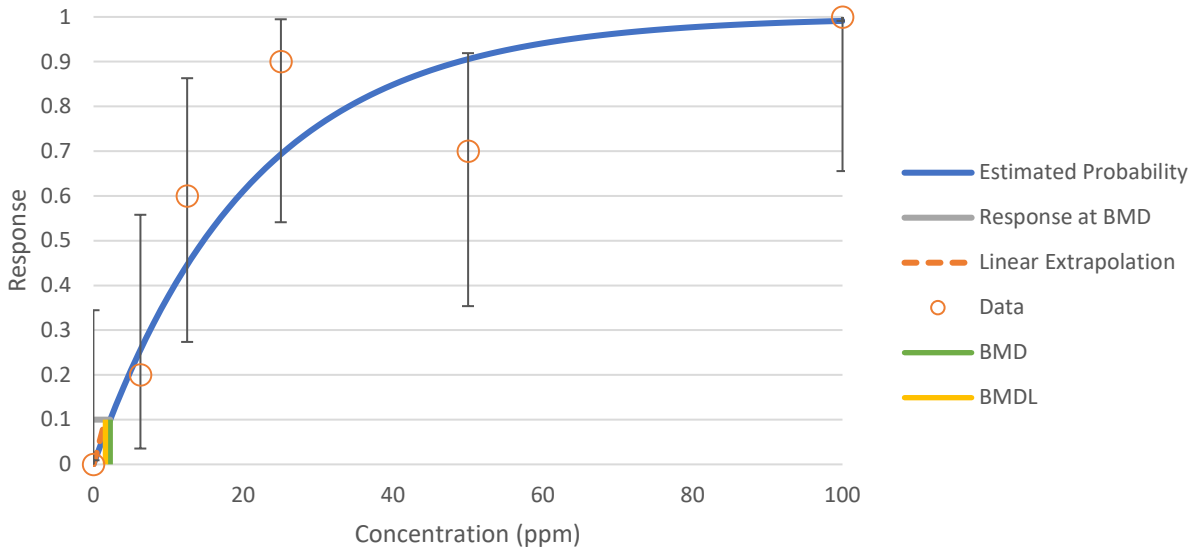
Table A-9. BMC_{10} and $BMCL_{10}$ Values from the Best-Fitting Models for Selected Nonneoplastic Lesions in Nasal Olfactory Epithelium of Male and Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks

Lesion type	Sex	Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Atrophy	Male	Multistage 5-degree	3.81	0.73
	Female	Logistic	5.40	3.48
	Combined	Log-Probit	5.58	4.29
Necrosis	**Male**	**Multistage 2-degree**	**2.23**	**1.59[a]**
	Female	Probit	8.23	5.41
	Combined	Log-Probit	4.66	2.57

[a]The $BMCL_{10}$ of 1.59 ppm for necrosis in the male rats was selected as the preferred POD for deriving an intermediate-duration inhalation MRL for 1,1-dichloroethene because it corresponds to the lowest BMC_{10} (2.23 ppm) among the group of best-fitting models for nasal olfactory epithelium lesions.

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

Figure A-1. Fit of 2-Degree Multistage Model for Nasal Olfactory Epithelium Necrosis in Male F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks



Intermittent Exposure: The $BMCL_{10}$ of 1.59 ppm was adjusted from intermittent exposure to a continuous exposure scenario according to the following equation:

$$BMCL_{ADJ} = BMCL_{10} \text{ of } 1.59 \text{ ppm} \times (6 \text{ hours}/24 \text{ hours}) \times (5 \text{ days}/7 \text{ days}) = 0.28 \text{ ppm}$$

Human Equivalent Concentration: To calculate a HEC, the $BMCL_{ADJ}$ was multiplied by the regional gas dose ratio (rat:human) for the extrathoracic region of the respiratory tract ($RGDR_{ET}$). The $RGDR_{ET}$ was calculated using the following equation:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H}$$

where:
ET = extrathoracic region
V_E = minute volume (mL/minute)
SA = surface area (cm^2)
A = animal (rat)
H = human

EPA (1994) rat and human respiratory surface area (SA) reference values for the extrathoracic region:
Human: 200 cm^2
Rat: 15.0 cm^2

EPA (1994) reference values for minute volumes (V_e):
Human: 13.8 L/minute
Rat: 0.1319 L/minute

Therefore:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H} = \frac{\frac{131.9\ mL/min}{15\ cm^2}}{\frac{13{,}800\ mL/min}{200\ cm^2}} = 0.13$$

$BMCL_{HEC} = BMCL_{ADJ}$ x $RGDR_{ET}$ = 0.28 ppm x 0.13 = 0.036 ppm

Uncertainty Factor: The $BMCL_{HEC}$ of 0.036 ppm was divided by a total uncertainty factor of 30:

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

MRL = $BMCL_{HEC}$ ÷ UFs
0.036 ppm ÷ (3 x 10) = 0.0012 ppm ≈ 0.001 ppm (1 ppb)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The nasal cavity was among the most sensitive targets of toxicity in male and female F344/N rats and B6C3F1/N mice intermittently exposed to 1,1-dichloroethene vapor for 14 or 105 weeks (NTP 2015a).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: March 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.001 ppm (1 ppb)
Critical Effect: Necrosis of nasal olfactory epithelium
Reference: NTP 2015a
Point of Departure: $BMCL_{10}$ of 1.59 ppm ($BMCL_{HEC}$ of 0.036 ppm)
Uncertainty Factor: 30
LSE Graph Key: 40
Species: Rat

MRL Summary: The intermediate-duration inhalation MRL of 0.001 ppm (1 ppb) was adopted as the chronic-duration inhalation MRL for 1,1-dichloroethene. The intermediate MRL is based on a $BMCL_{10}$ of 1.59 ppm for increased necrosis of the nasal olfactory epithelium in rats exposed to 1,1-dichloroethene for 14 weeks. The $BMCL_{10}$ was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.036 ppm and divided by a total uncertainty factor of 30 (for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No exposure-response human data are available. Table A-10 summarizes candidate critical effects from chronic-duration inhalation studies in laboratory animals. Nasal lesions (nasal turbinate atrophy, hyperostosis, metaplasia of respiratory olfactory epithelium) in mice were selected as the critical effects of chronic-duration inhalation exposure to 1,1-dichloroethene because they occurred at the lowest LOAEL (6.25 ppm).

Table A-10. Summary of Candidate Critical Effects for Deriving a Chronic-Duration Inhalation MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Body weight effects					
B6C3F1/N mouse	105 weeks (5 days/week 6 hours/day)	6.25 M 12.5 F	12.5 M 25 F	Depressed body weight	NTP 2015a
Respiratory effects					
F344/N rat	105 weeks (5 days/week 6 hours/day)	ND	25[a]	Multiple types of nasal lesions	NTP 2015a
B6C3F1/N mouse	105 weeks (5 days/week 6 hours/day)	ND	6.25	Multiple types of nasal lesions	NTP 2015a
Hepatic effects					
F344/N rat	105 weeks (5 days/week 6 hours/day)	ND	25[a]	Chronic inflammation, diffuse fatty change	NTP 2015a

Table A-10. Summary of Candidate Critical Effects for Deriving a Chronic-Duration Inhalation MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Sprague-Dawley rat	18 months (5 days/week 6 hours/day)	ND	25	Midzonal fatty change at 12 months	Quast et al. 1986
Renal effects					
B6C3F1/N mouse	105 weeks (5 days/week 6 hours/day)	ND 25 F	6.25 M	Renal tubule hyperplasia at 6.25 ppm; renal cysts at 25 ppm	NTP 2015a
Swiss mouse	52 weeks (5 days/week 4 hours/day)	ND	25	Unspecified regressive lesions	Maltoni et al. 1985
Swiss mouse	52 weeks (4–5 days/week 4 hours/day)	ND	25	Abscesses and nephritis	Maltoni et al. 1985

[a]Lowest exposure concentration tested in the rats of the NTP (2015a) 2-year study.

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

Selection of the Principal Study: The 105-week inhalation study of B6C3F1/N mice (NTP 2015a) was selected as the principal study because it identified the lowest LOAEL for 1,1-dichloroethene toxicity.

Summary of the Principal Study:

NTP. 2015a. NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (inhalation studies). NTP TR 582. National Toxicology Program. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Groups of B6C3F1/N mice (50/sex/group; 5-6 weeks of age) were exposed (whole body) to 1,1-dichloroethene vapor for 6 hours/day (+10 minutes), 5 days/week for 14 weeks at 0, 6.25, 12.5, or 25-ppm. Evaluations included survival, clinical signs, body weight, and gross and histopathology. The following targets of toxicity were identified:

- ***Death:*** Survival among the 6.25 and 25 ppm males was significantly greater than that controls; survival among the 6.25 and 25 ppm females was significantly less than that of controls.

- ***Body weight:*** Mean body weights of 6.25 ppm males and females were comparable to those of respective controls. Mean body weights for 12.5 and 25 ppm males were comparable to those of controls during the first 13 weeks of exposures; thereafter, mean body weights of 12.5 and 25 ppm males averaged 10–11 and 17–19%, respectively, less than controls. Mean body weight for 12.5 ppm females was within 95% that of controls throughout the study. Mean body weight of 25 ppm females was comparable to controls during the first 13 weeks of exposures and averaged 14–20% less than controls thereafter.

- ***Respiratory:*** There were no indications of exposure-related increased incidences of nonneoplastic lesions in the lungs. Significantly increased incidences of selected nasal lesions were observed in both males and females at all exposure levels tested (6.25, 12.5, and 25 ppm). Incidence data are presented in Table A-11.

- ***Renal:*** Significantly increased incidences of renal tubule hyperplasia were observed in 6.25, 12.5, and 25 ppm groups of male mice (8/50, 22/50, and 16/50, respectively; no incidences in controls). This lesion was not considered for MRL derivation because it was considered a preneoplastic lesion. At 25 ppm, increased incidence of renal casts was observed in males.

- ***Cancer:*** At all 1,1-dichloroethene exposure levels (6.25, 12.5, and 25 ppm), male mice exhibited significantly increased incidences of renal tubule adenoma, carcinoma, and adenoma or carcinoma combined. Female mice exhibited significantly increased incidences of alveolar/bronchiolar carcinoma at 12.5 ppm (but not at 25 ppm), hepatocellular carcinoma at 25 ppm, hepatocellular adenoma or carcinoma combined at 12.5 and 25 ppm, hemangiosarcoma in the liver at 25 ppm, and hemangioma or hemangiosarcoma (combined) in all organs (combined) at 25 ppm.

Table A-11. Selected Nasal Lesion Incidences in Male and Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 105 Weeks

	1,1-Dichloroethene exposure level (ppm)			
Lesion type	0	6.25	12.5	25
Males				
Hyperostosis	1/50[a] (2.0)	27/50[b] (1.3)	45/49 (2.1)	48/49 (2.2)
Olfactory epithelium metaplasia	17/50 (1.2)	39/50[b] (1.2)	47/49[b] (1.6)	48/49[b] (1.8)
Turbinate atrophy	0/50	46/50[b] (1.1)	46/49[b] (2.1)	47/49[b] (2.8)
Females				
Hyperostosis	0/50	13/50[b] (1.2)	45/50[b] (2.0)	48/50[b] (2.2)
Olfactory epithelium metaplasia	3/50 (1.0)	29/50[b] (1.1)	49/50[b] (1.6)	50/50[b] (1.9)
Turbinate atrophy	0/50	46/50[b] (1.0)	50/50[b] (2.3)	49/50[b] (2.8)
Males and females (combined incidences)				
Hyperostosis	1/100	40/100[c]	90/99[c]	96/99[c]
Olfactory epithelium metaplasia	20/100	68/100[c]	96/99[c]	98/99[c]
Turbinate atrophy	0/100	92/100[c]	96/99[c]	96/99[c]

[a]Incidence (severity;1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[b]Significantly different from chamber control incidence by the Poly-3 test ($p<0.01$).
[c]Significantly different from chamber control incidence by Fisher's exact test ($p<0.01$) performed by SRC, Inc.

Source: NTP 2015a

Selection of the Point of Departure for the MRL: A $BMCL_{10}$ of 1.46 ppm for olfactory epithelial metaplasia in female mice estimated using the frequentist unrestricted Probit model was selected as the POD for the chronic-duration inhalation MRL for 1,1-dichloroethene.

The lowest LOAEL identified in the NTP (2015a) 105-week mouse study was 6.25 ppm for increased incidence of nasal lesions in males and females. Both male and female mice exhibited significantly increased incidence of hyperostosis, metaplasia of respiratory olfactory epithelium, and turbinate atrophy

at the lowest exposure level tested (6.25 ppm). The incidence data for nasal turbinate hyperostosis and olfactory epithelium metaplasia in the male and female mice were fit to all standard dichotomous models in EPA's BMDS (version 3.1.2) using a BMR of 10% change in incidence from controls. Based on relatively similar male and female exposure concentration-response data, incidences were combined to increase the statistical power of the benchmark result; this procedure was employed for incidences of hyperostosis as well as olfactory epithelium metaplasia. Turbinate atrophy in the male and female mice was not fit to the models because 92% incidence occurred at the lowest exposure level tested. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ±2 units) at the data points (except the control) closest to the predefined BMR, BMCL values that are not 10 times lower than the lowest non-zero concentration, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen.

Model predictions for hyperostosis in the nasal cavity of the male mice are presented in Table A-12. The 3-degree Multistage and 1-degree Multistate models provided inadequate fit to the data (goodness-of-fit p-value <0.1 and BMDL 10 times lower than the lowest non-zero dose, respectively). BMCLs for models providing adequate fit differed by <3-fold. Therefore, the lowest AIC was selected as a potential POD.

Table A-12. Model Predictions for Hyperostosis in the Nasal Cavity of Male B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Dose near BMC	Control group
Dichotomous Hill			NA	124.27	$9.46x10^{-7}$	$6.48x10^{-7}$
Gamma[d]			0.154	124.08	$1.31x10^{-2}$	$1.31x10^{-2}$
Log-Logistic[e,f]	**2.84**	**1.66**	**0.573**	**122.57**	**$4.63x10^{-3}$**	**$4.63x10^{-3}$**
Multistage Degree 3[g]			0.106	124.91	$3.29x10^{-2}$	$3.29x10^{-2}$
Multistage Degree 2[g]			0.106	124.91	$3.29x10^{-2}$	$3.29x10^{-2}$
Multistage Degree 1[g]			0.215	123.53	$6.77x10^{-2}$	$6.77x10^{-2}$
Weibull[d]			0.134	124.41	$2.25x10^{-2}$	$2.25x10^{-2}$
Logistic			<0.0001	128.75	-1.43	-1.43
Log-Probit	2.57	1.42	0.328	123.15	$9.15x10^{-3}$	$9.15x10^{-3}$
Probit			<0.0001	134.73	-1.75	-1.75

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (2-degree Multistage).
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable

None of the models provided adequate fit to the incidence data. With the exception of the Dichotomous Hill model, the models failed to meet adequate fit (p-value for goodness of fit <0.01). For the Dichotomous Hill model, the p-value for goodness of fit was near unity (0.999), suggesting a forced fit because it hits a model boundary. Thus, the BMC and BMCL estimated from the Dichotomous Hill model was questionable for use a POD for MRL derivation.

None of the models provided adequate fit to the male and female mice combined incidence data for hyperostosis (i.e., goodness-of-fit p-values <0.1 for all models).

None of the models provided adequate fit to the olfactory epithelium metaplasia data for male mice. For the Logistic and Probit models, the goodness-of-fit p-values were <0.1; for the remaining models, the BMCL was 10 times lower than the lowest non-zero dose.

Model predictions for olfactory epithelium metaplasia in the nasal cavity of the female mice are presented in Table A-13. The 1-degree and 3-degree Multistage model provided inadequate fit to the data (goodness-of-fit p-value <0.1). BMCLs for models providing adequate fit differed by <3-fold. Therefore, the $BMCL_{10}$ of 1.46 ppm was selected as a potential POD because the Probit model provided the lowest AIC among models with adequate fit to the data.

Table A-13. Model Predictions for Olfactory Epithelium Metaplasia in Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	3.97	2.81	0.868	106.6	$7.42x10^{-3}$	$-6.75x10^{-4}$
Gamma[d]	3.27	1.81	0.989	106.5	$1.95x10^{-4}$	$-2.00x10^{-5}$
Log-Logistic[e]	3.96	2.81	0.869	106.6	$7.06x10^{-3}$	$-9.07x10^{-4}$
Multistage Degree 3[f]			NA	108.5	$3.72x10^{-5}$	$3.72x10^{-5}$
Multistage Degree 2[f]	2.18	0.94	0.870	104.8	$5.18x10^{-2}$	$5.18x10^{-2}$
Multistage Degree 1[f]			0.023	113.4	$1.70x10^{-1}$	$1.70x10^{-1}$
Weibull[d]	2.53	1.39	0.996	106.5	$1.07x10^{-4}$	$1.07x10^{-4}$
Logistic	2.16	1.61	0.929	104.7	$1.97x10^{-1}$	$1.97x10^{-1}$
Log-Probit	3.73	2.56	0.964	106.5	$1.63x10^{-3}$	$-2.51x10^{-4}$
Probit[g]	**1.91**	**1.46**	**0.988**	**104.6**	**$7.35x10^{-2}$**	**$7.35x10^{-2}$**

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Probit).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable

Model predictions for combined incidences of olfactory epithelium metaplasia in the male and female mice are presented in Table A-14. The LogLogistic model was the only model to provide adequate fit to the data (goodness-of-fit p-value >0.1). The $BMCL_{10}$ of 1.96 ppm was selected as a potential POD.

Table A-14. Model Predictions for Olfactory Epithelium Metaplasia in Male and Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill			NA	271.52	-1.16×10^{-7}	-1.87×10^{-7}
Gamma[d]			0.0139	273.66	4.38×10^{-2}	4.38×10^{-2}
Log-Logistic[e,f]	**2.95**	**1.96**	**0.2450**	**270.62**	**1.62×10^{-2}**	**1.62×10^{-2}**
Multistage Degree 3[g]			0.0133	275.24	1.13×10^{-1}	1.13×10^{-1}
Multistage Degree 2[g]			0.0134	275.24	1.13×10^{-1}	1.13×10^{-1}
Multistage Degree 1[g]			0.0553	274.05	2.12×10^{-1}	2.12×10^{-1}
Weibull[d]			0.0149	274.34	7.88×10^{-2}	7.88×10^{-2}
Logistic			0.0024	271.95	-1.58×10^{-1}	-1.58×10^{-1}
Log-Probit			0.0742	271.99	3.37×10^{-2}	3.37×10^{-2}
Probit			<0.0001	278.41	-7.91×10^{-1}	-7.91×10^{-1}

[a]BMC and BMCL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model. Log-Logistic is the only model which provided adequate fit.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable

Table A-15 summarizes the BMC_{10} and $BMCL_{10}$ values for the nasal lesion incidences in the male and female mice exposed to 1,1-dichloroethene for 6 hours/day, 5 days/week for 105 weeks (NTP 2015a). The BMC_{10} of 1.91 ppm for olfactory epithelium metaplasia in the female mice was selected because it represents the lowest BMC_{10} among the best-fitting models for nasal lesions. The corresponding $BMCL_{10}$ of 1.46 ppm serves as the POD for deriving a chronic-duration inhalation MRL for 1,1-dichloroethene. The Probit model for olfactory epithelial metaplasia in female mice is presented in Figure A-2.

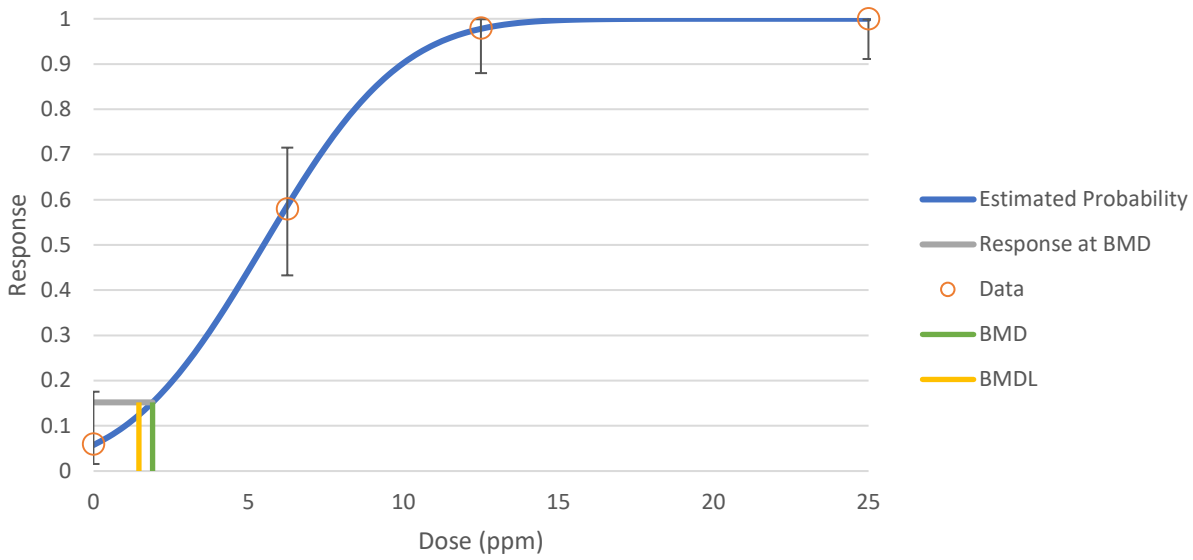
Table A-15. BMC_{10} and $BMCL_{10}$ Values from the Best-Fitting Models for Selected Nonneoplastic Nasal Lesions in B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks

Lesion type	Sex	Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Turbinate Hyperostosis	Male	Log-Logistic	2.84	1.66
	Female	NA		
	Combined	NA		
Olfactory epithelium Metaplasia	Male	NA		
	Female	**Probit**	**1.91**	**1.46[a]**
	Combined	Log-Logistic	2.95	1.96

[a]The $BMCL_{10}$ of 1.46 ppm for olfactory epithelial metaplasia in female mice was selected as the preferred POD for deriving a chronic-duration inhalation MRL for 1,1-dichloroethene because it corresponds to the lowest BMC_{10} (1.91 ppm) among the group of best-fitting models for nasal lesions.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); MRL = minimum risk level; NA = not applicable (no model provided adequate fit to the data); POD = point of departure

Figure A-2. Fit of Probit Model for Olfactory Epithelial Metaplasia Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 105 Weeks



Intermittent Exposure: The $BMCL_{10}$ of 1.46 ppm was adjusted from intermittent exposure to a continuous exposure scenario according to the following equation:

$BMCL_{ADJ}$ = $BMCL_{10}$ (1.46 ppm) x 6 hours/24 hours x 5 days/7 days = 0.261 ppm

Human Equivalent Concentration: To calculate a HEC, the $BMCL_{ADJ}$ was multiplied by the regional gas dose ratio (mouse:human) for $RGDR_{ET}$. The $RGDR_{ET}$ was calculated according to the EPA (1994) equation 4-18:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H}$$

where:
ET = extrathoracic region
V_E = minute volume (mL/minute)
SA = surface area (cm^2)
A = animal (mouse)
H = human

SA_{ET} values for the mouse (3 cm^2) and humans (200 cm^2) were taken from Table 4-4 of EPA (1994). The chronic minute volume (V_E) for the male B6C3F1 mouse was taken from Table 1-4 of EPA (1988b) in which it was presented as 0.060 m^3/day (41.67 mL/minute). According to EPA (1994), the default minute volume for humans is 13,800 mL/minute. Therefore:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H} = \frac{\frac{41.67\ mL/min}{3\ cm^2}}{\frac{13{,}800\ mL/min}{200\ cm^2}} = 0.20$$

The $BMCL_{HEC}$ = $BMCL_{ADJ}$ x $RGDR_{ET}$ = 0.261 ppm x 0.20 = 0.052 ppm

Uncertainty Factor: The $BMCL_{HEC}$ of 0.052 ppm was divided by a total uncertainty factor of 30:

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

MRL = $BMCL_{HEC}$ ÷ UFs
0.028 ppm ÷ (3 x 10) = 0.0017 ppm ≈0.002 ppm

This MRL is slightly higher than the intermediate-duration inhalation MRL of 0.001 ppm. Thus, the intermediate-duration inhalation MRL based on increased incidences of necrosis of the nasal olfactory epithelium in male rats was adopted as the chronic MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The nasal cavity was among the most sensitive targets of toxicity in male and female F344/N rats and B6C3F1/N mice intermittently exposed to 1,1-dichloroethene vapor for 14 or 105 weeks (NTP 2015a).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: Available data were not considered adequate for derivation of an acute-duration oral MRL for 1,1-dichloroethene.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Many acute-duration studies employed fasted animals which are known to be more sensitive than nonfasted rats to 1,1-dichloroethene-induced adverse effects following oral exposure. The increased sensitivity to 1,1-dichloroethene in fasted animals appears to be related to toxicokinetic parameters. Levels of radioactivity in liver, kidneys, and lungs of fasted rats treated with ^{14}C-1,1-dichloroethene were significantly greater than levels in nonfasted rats (McKenna et al. 1978a). 1,1-Dichloroethene-induced hepatic lesions appeared earlier and were more extensive in fasted rats compared to nonfasted rats (Jaeger et al. 1974; McKenna et al. 1978b; Reynolds and Moslen 1977). Liver mixed function oxidase activity in fasted animals following 1,1-dichloroethene exposure was greater than that in similarly treated nonfasted animals (McKenna et al. 1978b; Nakajima et al. 1982). Due to increased sensitivity to 1,1-dichloroethene toxicity among fasted animals, only oral data from nonfasted animals (i.e., normal diet) were considered for MRL derivation. Some studies did not provide dose-response data because only a single dose level was used. Table A-16 summarizes available results from acute-duration oral studies in laboratory animals. Among studies that employed multiple dose levels and nonfasted animals, the lowest LOAEL is 100 mg/kg/day for 11% depressed body weight in female rats administered 1,1-dichloroethene by gavage for 14 days (NTP 1982). Given the limited database of information for the gavage exposure route and no information regarding the effects of acute-duration dietary or drinking water exposure, it is not considered appropriate to derive an acute-duration oral MRL for 1,1-dichloroethene at this time.

Table A-16. Summary of Potential Candidate Critical Effects for Deriving an Acute-Duration Oral MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Body weight effects					
F344/N rat	14 days 1 time/day (GO)	100 M 50 F	500 M 100 F	Depressed body weight	NTP 1982
Respiratory effects					
C57BL/6 male mouse	Once (GO)	ND	100	Reversible cellular changes in Clara cells (club cells) of bronchiolar epithelium	Forkert and Reynolds 1982
Hepatic effects					
F344/N rat	14 days 1 time/day (GO)	500 M 250 F	1,000 M 500 F	Liver necrosis at lethal dose levels	NTP 1982

Table A-16. Summary of Potential Candidate Critical Effects for Deriving an Acute-Duration Oral MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
B6C3F1 mouse	14 days 1 time/day (GO)	100	500	Liver necrosis at lethal dose level	NTP 1982

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

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: Available data were not considered adequate for derivation of an intermediate-duration oral MRL for 1,1-dichloroethene.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-17 summarizes potential candidate critical effect PODs from intermediate-duration oral studies in laboratory animals. The 90-day gavage studies of rats and mice (NTP 1982) were the only available intermediate-duration oral studies in which treatment-related adverse effects were observed. Given the limited database of information for the gavage exposure route and no information regarding the effects of intermediate-duration dietary or drinking water exposure, it is not considered appropriate to derive an intermediate-duration oral MRL for 1,1-dichloroethene at this time.

Table A-17. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
F344/N rat	90 days 5 days/week 1 time/day (GO)	40	100	Hepatocytomegaly in males; fibrosis, pigmentation, bile duct hyperplasia in females	NTP 1982
B6C3F1 mouse	90 days 5 days/week 1 time/day (GO)	40	100	Liver necrosis and other cellular changes at lethal dose level	NTP 1982

GO = gavage in oil; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.05 mg/kg/day
Critical Effect: Hepatic midzonal fatty change
References: Humiston et al. 1978; Quast et al. 1983
Point of Departure: $BMDL_{10}$ of 4.51 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 28
Species: Rat

MRL Summary: An MRL of 0.05 mg/kg/day has been derived for chronic-duration oral exposure to 1,1-dichloroethene based on hepatic effects (hepatic midzonal fatty change) in female Sprague-Dawley rats receiving 1,1-dichloroethene from the drinking water for up to 2 years (Humiston et al. 1978; Quast et al. 1983). The MRL is based on a $BMDL_{10}$ of 4.51 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: No dose-response human data are available. Relatively limited data are available regarding the effects of chronic-duration oral exposure of animals to 1,1-dichloroethene. Two groups of investigators found no evidence of 1,1-dichloroethene toxicity at the highest dose levels tested, although these doses were ≤20 mg/kg/day (Maltoni et al. 1985; NTP 1982). A single 2-year drinking water study reported increased incidences of hepatocellular hypertrophy and midzonal fatty changes (the only reported adverse effect) in male and female rats at estimated 1,1-dichloroethene doses of 20 and 9 mg/kg/day, respectively (Humiston et al. 1978; Quast et al. 1983). A NOAEL of 10 mg/kg/day was identified for the male rats; the LOAEL of 9 mg/kg/day for the female rats was the lowest dose tested.

Selection of the Principal Studies: The 2-year rat study (Humiston et al. 1978; Quast et al. 1983) was selected as the principal study for deriving a chronic-duration oral MRL for 1,1-dichloroethene because it identified the lowest LOAEL (9 mg/kg/day) for nonneoplastic effects.

Summary of the Principal Studies:

Humiston CG, Quast JF, Wade CE, et al. 1978. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical USA. Chem Mfgs Assn. Submitted to the U.S. EPA under TSCA section FYI.

Quast JF, Humiston CG, Wade CE, et al. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fundam Appl Toxicol 3(1):55-62.

In the principal study, groups of Sprague-Dawley rats (48/sex/group; 80/sex for controls; 6–7 weeks of age) were administered 1,1-dichloroethene in the drinking water for 2 years at 50, 100, or 200 ppm (author-estimated doses of 7, 10, and 20 mg/kg/day, respectively, for males, and 9, 14, and 30 mg/kg/day, respectively, for females). Controls consisted of 80 rats/sex that received drinking water without 1,1-dichloroethene. Rats were monitored for survival, clinical signs, body weight, and food intake. Blood and urine were collected from at least five rats/sex/group at 6, 12, 18, and 23 months for

hematology and urinalysis. Clinical chemistry evaluations were performed on 5 rats/sex/group at 6, 12, and 18 months, and from all surviving rats from each group in which <10 rats remained at terminal sacrifice. At sacrifice, weights of brain, heart, liver, kidneys, and testes were recorded. Comprehensive gross pathological examinations were performed on all rats. Comprehensive histopathologic examinations were performed on control and high-dose rats; histopathology was also performed on selected target organs and grossly recognized neoplastic changes in low- and mid-dose rats.

There were no significant treatment-related differences from controls in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry, or organ weight. The sole treatment-related observation was microscopic changes in the liver (minimal amount of hepatocellular swelling with midzonal fatty change). The incidences of midzonal fatty change in the controls, low-, mid-, and high-dose rats are presented in Table A-18. Incidences of midzonal fatty change were significantly increased in the high-dose males (20 mg/kg/day) and mid- (14 mg/kg/day) and high-dose (30 mg/kg/day) females. Incidences of minimal hepatocellular swelling, summarized in Table A-18, were significantly increased in females at all 1,1-dichloroethene dose levels. The mid-dose (10 mg/kg/day) and high-dose (20 mg/kg/day) are considered male rat NOAEL and LOAEL levels, respectively, for histopathologic liver effects. The low-dose (9 mg/kg/day) is considered a minimum LOAEL for the female rat, based on the minimal nature of hepatocellular swelling at that dose level.

Table A-18. Incidence Data for Selected Nonneoplastic Liver Lesions in Male and Female Sprague-Dawley Rats Administered 1,1-Dichloroethene in the Drinking Water for up to 2 Years[a]

Lesion type				
Males				
Time-weighted average dose (mg/kg/day)	0	7	10	20
Minimal hepatocellular hypertrophy	0/76	0/46	1/45	3/42[b]
Minimal midzonal fatty change	12/76	4/46	13/45	18/42[c]
Females				
Time-weighted average dose (mg/kg/day)	0	9	14	30
Minimal hepatocellular hypertrophy	3/79	7/48[b]	11/45[c]	20/48[c]
Minimal midzonal fatty change	10/79	12/48	14/45[b]	22/48[c]

[a]Incidence in animals dying or killed between 13 and 24 months.
[b]Significantly different from control incidence according to Fisher's exact test ($p<0.05$).
[c]Significantly different from control incidence according to Fisher's exact test ($p<0.01$).

Sources: Humiston et al. 1978; Quast et al. 1983

Selection of the Point of Departure for the MRL: A $BMDL_{10}$ of 4.51 mg/kg/day for hepatic midzonal fatty changes in female rats estimated using the frequentist-restricted Gamma model was selected as the POD for the chronic-duration oral MRL for 1,1-dichloroethene.

The lowest LOAEL identified in the 2-year rat study (Humiston et al. 1978; Quast et al. 1983) was 9 mg/kg/day for increased hepatocellular hypertrophy in female rats. Incidence data for these effects are presented in Table A-18.

The incidence data for hepatocellular hypertrophy and for midzonal fatty change in the female rats were fit to all standard dichotomous models in EPA's BMDS (version 3.1.2) using a BMR of 10% change in incidence from controls. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ±2 units) at the data points (except the control) closest to the predefined BMR, BMDL that was not 10 times lower than the lowest non-zero dose, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all 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 model predictions for hepatocellular hypertrophy are presented in Table A-19. Most models provided adequate fit to the data; the dichotomous Hill model because the goodness of fit test could not be calculated. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (1-degree Multistage) was selected as a potential POD.

Table A-19. Model Predictions for Hepatocellular Hypertrophy in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Humiston et al. 1978; Quast et al. 1983)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill			NA	188.65	-2.41×10^{-5}	3.01×10^{-6}
Gamma[d]	7.33	4.82	0.711	186.78	-2.21×10^{-1}	1.30×10^{-2}
Log-Logistic[e]	7.52	4.13	0.747	186.75	-1.94×10^{-1}	1.40×10^{-2}
Multistage Degree 3[f]	7.02	4.81	0.685	186.81	-2.72×10^{-1}	2.38×10^{-2}
Multistage Degree 2[f]	7.02	4.81	0.685	186.81	-2.73×10^{-1}	2.47×10^{-2}
Multistage Degree 1[f,g]	6.46	4.79	0.897	184.87	-4.10×10^{-1}	7.14×10^{-2}
Weibull[d]	7.27	4.81	0.706	186.79	-2.32×10^{-1}	1.51×10^{-2}
Logistic	12.12	10.06	0.276	187.28	1.12	-9.81×10^{-1}
Log-Probit[g]	**7.79**	**2.66**	**0.793**	**186.71**	$\mathbf{-1.51 \times 10^{-1}}$	$\mathbf{1.17 \times 10^{-2}}$
Probit	11.25	9.33	0.372	186.64	3.48×10^{-1}	-7.95×10^{-1}

[a]BMD and BMDL 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 for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMDLs differed by >3-fold; therefore, the models with the lowest BMDL (Log-Probit) was selected as best-fitting model.

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., $_{10}$ = exposure dose associated with 10% extra risk); NA = not applicable

The model predictions for midzonal fatty change are presented in Table A-20. The Dichotomous Hill model and Log-Probit models did not provide adequate to the data (saturated model and BMDL 10 times lower than lowest non-zero dose, respectively). The BMDLs for the models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected (Gamma) and the $BMDL_{10}$ was considered a potential POD.

Table A-20. Model Predictions for Hepatic Midzonal Fatty Change in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Humiston et al. 1978; Quast et al. 1983)

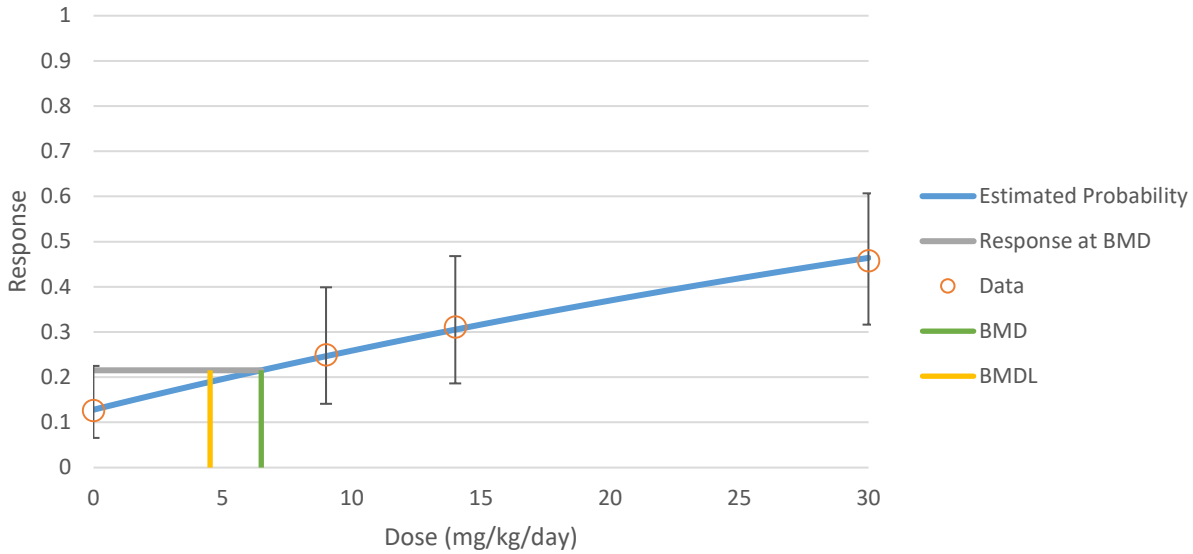
Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill			NA	244.01	-3.64×10^{-3}	3.77×10^{-4}
Gamma[d,e]	**6.49**	**4.51**	**0.991**	**240.02**	**5.52×10^{-2}**	**-3.99×10^{-2}**
Log-Logistic[f]	6.26	3.64	0.994	242.01	-4.81×10^{-3}	3.82×10^{-4}
Multistage Degree 3[g]	6.49	4.51	0.991	240.02	5.52×10^{-3}	-3.99×10^{-2}
Multistage Degree 2[g]	6.49	4.51	0.991	240.02	5.52×10^{-2}	-3.99×10^{-2}
Multistage Degree 1[g]	6.49	4.51	0.991	240.02	5.52×10^{-2}	-3.99×10^{-2}
Weibull[d]	6.49	4.51	0.991	240.02	5.52×10^{-2}	-3.99×10^{-2}
Logistic	10.02	7.97	0.645	240.89	4.38×10^{-1}	-5.48×10^{-1}
Log-Probit			0.978	242.01	1.59×10^{-2}	-1.50×10^{-3}
Probit	9.53	7.55	0.698	240.72	4.08×10^{-1}	-4.71×10^{-1}

[a]BMD and BMDL 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 for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Recommended model. Most models provided adequate fit to the data. BMDLs differed by <3-fold; therefore, the models with the lowest AIC (Gamma) was selected as best-fitting model.
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

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., $_{10}$ = exposure dose associated with 10% extra risk); NA = not applicable

From the best-fitting models, a BMD_{10} of 7.79 mg/kg/day for hepatocellular hypertrophy (Log-Probit model Table A-19) and a BMD_{10} of 6.49 mg/kg/day for midzonal fatty change (Gamma model, Table A-20) were estimated. The $BMDL_{10}$ of 4.51 mg/kg/day for midzonal fatty change in the female rats was selected as the POD for the MRL because it had the lowest BMD_{10}. The fit of the Gamma model to the midzonal fatty changes incidence data is presented in Figure A-3.

Figure A-3. Fit Gamma Model for Hepatic Midzonal Fatty Change in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years



Uncertainty Factor: The $BMDL_{10}$ of 4.51 mg/kg/day was divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{10} \div UFs$
$MRL = 4.51 \text{ mg/kg/day} \div (10 \times 10) = 0.045 \text{ mg/kg/day} \approx 0.05 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Support is limited to similar findings in the male rats of the principal study, albeit at a higher dose level (20 mg/kg/day) than the LOAEL of 9 mg/kg/day observed in the female rats.

Agency Contacts (Chemical Managers): Malcolm Williams

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 1,1-dichloroethene released for public comment in 2019; thus, the literature search was restricted to studies published between December 2015 and March 2020. The following main databases were searched in March 2020:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,1-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 1,1-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	
03/2020	((75-35-4[rn] OR "vinylidene chloride"[nm] OR "1,1-Dce"[tw] OR "1,1-Dichloroethene"[tw] OR "1,1-Dichloroethylene"[tw] OR "as-Dichloroethylene"[tw] OR "asym-Dichloroethylene"[tw] OR "Vinylidene chloride"[tw] OR "Vinylidene dichloride"[tw] OR "Vinylidine chloride"[tw]) AND (2016/12/01 : 3000[mhda] OR 2016/12/01 : 3000[crdt] OR 2016/12/01 : 3000[edat] OR 2015/12/01 : 3000[dp])) OR ((("1,1"[tw] AND (dichloroethene[tw] OR dce[tw] OR Dichloroethylene[tw])) AND (2016/12/01 : 3000[mhda] OR 2016/12/01 : 3000[crdt] OR 2016/12/01 : 3000[edat] OR 2015/12/01 : 3000[dp])) NOT medline[sb]) OR ("1,1-Dichlorethylene"[tw] OR "Dichloroethylene, 1,1-"[tw] OR "Diofan A 565S"[tw] OR "Ethene, 1,1-dichloro-"[tw] OR "Ethylene, 1,1-dichloro-"[tw] OR "F 1130a"[tw] OR "HCC 1130a"[tw] OR "Iso-dichloroethylene"[tw] OR "R 1130a"[tw])
NTRL	
03/2020	"1,1-Dce" OR "1,1-Dichloroethene" OR "1,1-Dichloroethylene" OR "as-Dichloroethylene" OR "asym-Dichloroethylene" OR "Vinylidene chloride" OR "Vinylidene dichloride" OR "Vinylidine chloride" OR "1,1-Dichlorethylene" OR "Dichloroethylene, 1,1-" OR "Diofan A 565S" OR "Ethene, 1,1-dichloro-" OR "Ethylene, 1,1-dichloro-" OR "F 1130a" OR "HCC 1130a" OR "Iso-dichloroethylene" OR "R 1130a" ("1,1" AND (dichloroethene OR dce OR Dichloroethylene)) "1,1-Dichlorethylene" OR "Dichloroethylene, 1,1-" OR "Diofan A 565S" OR "Ethene, 1,1-dichloro-" OR "Ethylene, 1,1-dichloro-" OR "F 1130a" OR "HCC 1130a" OR "Iso-dichloroethylene" OR "R 1130a"
Toxcenter	
03/2020	FILE 'TOXCENTER' ENTERED AT 16:46:45 ON 27 MAR 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 3835 SEA FILE=TOXCENTER 75-35-4 L2 156 SEA FILE=TOXCENTER L1 AND ED>=20161201 L4 186 SEA FILE=TOXCENTER L1 AND PY>2015 L5 205 SEA FILE=TOXCENTER L2 OR L4 L6 205 SEA FILE=TOXCENTER L5 NOT TSCATS/FS L7 143 SEA FILE=TOXCENTER L6 NOT PATENT/DT ACT TOXQUERY/Q --------- L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,

Table B-2. Database Query Strings

Database search date	Query string
	IT)
	L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L23 QUE (ENDOCRIN? AND DISRUPT?)
	L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L30 QUE (NEPHROTOX? OR HEPATOTOX?)
	L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L33 QUE 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 OR L32
	L34 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?)

Table B-2. Database Query Strings

Database search date	Query string
	L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L36 QUE L33 OR L34 OR L35 L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L38 QUE L36 OR L37 --------- L39 54 SEA FILE=TOXCENTER L7 AND L38 L40 89 SEA FILE=TOXCENTER L7 NOT L39 L41 4 SEA FILE=TOXCENTER L39 AND MEDLINE/FS L43 50 SEA FILE=TOXCENTER L39 NOT MEDLINE/FS L44 52 DUP REM L41 L43 (2 DUPLICATES REMOVED) ANSWERS '1-52' FROM FILE TOXCENTER L*** DEL 4 S L39 AND MEDLINE/FS L*** DEL 4 S L39 AND MEDLINE/FS L45 4 SEA FILE=TOXCENTER L44 L*** DEL 50 S L39 NOT MEDLINE/FS L*** DEL 50 S L39 NOT MEDLINE/FS L46 48 SEA FILE=TOXCENTER L44 L47 48 SEA FILE=TOXCENTER (L45 OR L46) NOT MEDLINE/FS D SCAN L47

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
03/2020	Compounds searched: 75-35-4
NTP	
03/2020	75-35-4 "1,1-Dichloroethene" "1,1-Dichloroethylene" "Vinylidene chloride" "Vinylidine chloride" "1,1-Dce" "1,1-Dichloro-ethene" "1,1-Dichloro-ethylene" "1,1-Dichlorethylene" "Iso-dichloroethylene"
NIH RePORTER	
04/2020	Search Criteria: Text Search: "1,1-Dce" OR "1,1-Dichloroethene" OR "1,1-Dichloroethylene" OR "as-Dichloroethylene" OR "asym-Dichloroethylene" OR "Vinylidene chloride" OR "Vinylidene dichloride" OR "Vinylidine chloride" OR "1,1-Dichlorethylene" OR "Dichloroethylene, 1,1-" OR "Diofan A 565S" OR "Ethene, 1,1-dichloro-" OR "Ethylene, 1,1-dichloro-" OR "F 1130a" OR "HCC 1130a" OR "Iso-dichloroethylene" OR "R 1130a" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 102
- Number of records identified from other strategies: 48
- Total number of records to undergo literature screening: 150

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

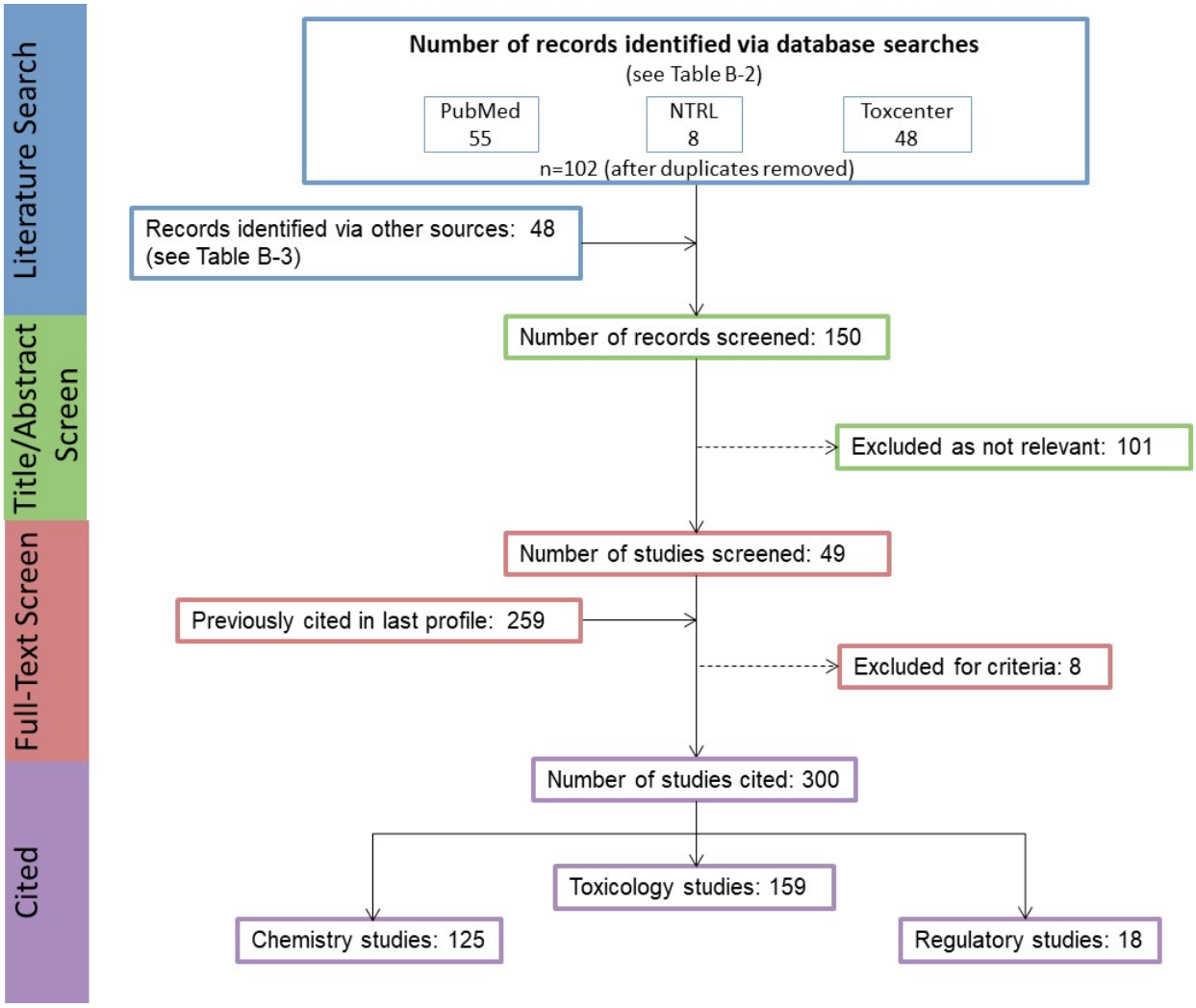
- Number of titles and abstracts screened: 150
- Number of studies considered relevant and moved to the next step: 49

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: 49
- Number of studies cited in the pre-public draft of the toxicological profile: 259
- Total number of studies cited in the profile: 300

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

Figure B-1. March 2020 Literature Search Results and Screen for 1,1-Dichloroethene



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1-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 1,1-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 1,1-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 1,1-dichloroethene. The inclusion criteria used to identify relevant studies examining the health effects of 1,1-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 was conducted to identify studies examining the health effects of 1,1-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 current literature search was intended to update the draft toxicological profile for 1,1-dichloroethene released for public comment in 2019. See Appendix B for the databases searched and the search strategy.

A total of 149 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of 1,1-dichloroethene.

Title and Abstract Screen. In the Title and Abstract Screen step, 150 records were reviewed; 0 documents were considered to meet the health effects inclusion criteria in Table C-1.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 50 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 50 documents, 90 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 1,1-Dichlorethene and overviews of the results of the inhalation and oral exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1-dichloroethene identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Human studies have evaluated a limited number of endpoints (hematological, hepatic, renal, and developmental. Animal studies have examined a number of endpoints including body weight, respiratory, cardiovascular, hematological, hepatic, renal, neurological, reproductive, developmental, and cancer. These data suggest that respiratory, hepatic, and renal effects are the most sensitive outcomes. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 90 studies (published in 50 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 1,1-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					1 0		1 0	1 0									
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort																	
Case control																	
Population															1 0		
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

Table C-4. Overview of the Health Outcomes for 1,1-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	12	4	1	0	0	0	17	9	0	0	0	0	1	1	6	0	0
	6	1	1	0	0	0	13	8	0	0	0	0	1	0	4	0	0
Intermediate-duration	6	9	0	0	1	0	15	7	0	0	0	0	0	3	0	0	0
	3	4	0	0	0	0	14	4	0	0	0	0	0	2	0	0	0
Chronic-duration	8	8	0	0	3	0	10	8	0	0	1	0	0	0	0	0	4
	1	3	0	0	0	0	4	3	0	0	1	0	0	0	0	0	4
Oral studies																	
Acute-duration	3	3	1	1	1	0	11	4	0	0	0	0	0	0	1	0	0
	2	2	0	1	1	0	10	4	0	0	0	0	0	0	0	0	0
Intermediate-duration	3	0	0	0	1	0	3	1	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Chronic-duration	4	4	2	1	1	0	5	5	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dermal studies																	
Acute-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Intermediate-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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

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

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 2015b). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of 1,1-dichloroethene health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for 1,1-Dichloroethene—Observational Epidemiology Studies

	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
Reference	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Hepatic effects							
Inhalation–cohort							
Ott et al. 1976	++	+	+	+	+	+	First
Outcome: Renal effects							
Oral–cross-sectional							
Ott et al. 1976	++	+	+	+	+	+	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

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects										
Inhalation acute exposure										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Zeller et al. 1979a (rat)	+	+	+	+	+	+	+	+	na	First
Oral acute exposure										
Chieco et al. 1981 (rat)	+	+	+	+	+	++	++	+	na	First
Forkert and Reynolds 1982 (mouse)	+	+	+	+	+	++	++	+	na	First
Forkert et al. 1985 (mouse)	+	na	na	na	na	++	++	+	na	First
Inhalation intermediate exposure										
Gage 1970 (rat)	+	+	+	+	+	++	++	+	na	First
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse 14 weeks)	+	+	++	+	+	++	++	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (guinea pig)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Inhalation chronic exposure										
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Oral chronic exposure										
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Outcome: Hepatic effects										
Inhalation acute exposure										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Jaeger 1977 (rat)	+	na	na	na	+	+	+	+	na	First
Jaeger et al. 1973a (rat)	+	na	na	na	+	+	+	+	na	First
Jaeger et al. 1974 (rat; fasted)	+	+	+	+	+	++	+	+	na	First
Jaeger et al. 1974 (rat; nonfasted)	+	+	+	+	+	++	+	+	na	First
Maltoni et al. 1985 (mouse)	+	+	+	+	+	+	+	+	na	First
McKenna et al. 1978a (rat)	+	+	+	+	+	++	+	+	na	First
Murray et al. 1979 (rat; 80 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rat; 160 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rabbit; 80 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rabbit; 160 ppm)	+	+	+	+	+	+	+	+	na	First
Reitz et al. 1980 (mouse)	+	+	+	+	+	+	+	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Short et al. 1977a, 1977b (rat)	+	+	+	+	+	+	+	+	na	First
Short et al. 1977a, 1977b (mouse)	+	+	+	+	+	+	+	+	na	First
Oral acute exposure										
Chieco et al. 1981 (rat; 200 mg/kg/day)	+	+	+	+	+	++	+	+	na	First
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	+	+	+	+	+	++	+	+	na	First
Jaeger et al. 1973b (rat)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat)	+	+	+	+	+	++	+	+	na	First
Kanz and Reynolds 1986 (rat)	+	+	+	+	+	++	+	+	na	First
Kanz et al. 1991 (rat)	+	+	+	+	+	++	+	+	na	First
Moslen et al. 1985 (rat)	+	+	+	+	+	++	+	+	na	First
Murray et al. 1979 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	+	+	+	++	+	+	na	First
NTP 1982 (mouse)	+	+	+	+	+	++	+	+	na	First
Reynolds et al. 1984 (rat)	+	+	+	+	+	++	+	+	na	First
Inhalation intermediate exposure										
Balmer et al. 1976 (rat)	+	+	+	+	+	+	+	+	na	First
Gage 1970 (rat)	+	+	+	+	+	++	++	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 16 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 14 weeks)	+	+	++	+	+	++	++	+	na	First
Plummer et al. 1990 (rat; continuous)	+	+	+	+	+	+	+	+	na	First
Plummer et al. 1990 (rat; intermittent)	+	+	+	+	+	+	+	+	na	First
Prendergast et al. 1967 (monkey)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (guinea pig)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Quast 1976 (rat)	+	+	+	+	+	+	+	+	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Oral intermediate exposure										
NTP 1982 (rat)	+	+	+	+	+	++	++	+	na	First
NTP 1982 (mouse)	+	+	+	+	+	++	++	+	na	First
Quast et al. 1983 (dog)	+	+	+	+	+	++	++	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation chronic exposure										
Lee et al. 1977, 1978 (rat)	+	+	+	+	+	++	+	+	na	First
Lee et al. 1977, 1978 (mouse)	+	+	+	+	+	++	+	+	na	First
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 105 weeks)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse; 105 weeks)	+	+	++	+	+	++	++	++	na	First
Oral chronic exposure										
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; multidose)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1983 (rat)	+	+	++	+	+	++	++	++	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Renal effects										
Inhalation acute exposure										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Jackson and Conolly 1985 (rat)	+	+	++	+	+	++	++	+	na	First
Maltoni et al. 1985 (mouse)	+	+	+	+	+	+	+	+	na	First
McKenna et al. 1978a (rat)	+	+	+	+	+	++	+	+	na	First
Short et al. 1977a, 1977b (rat)	+	+	+	+	+	+	+	+	na	First
Short et al. 1977a, 1977b (mouse)	+	+	+	+	+	+	+	+	na	First
Oral acute exposure										
Chieco et al. 1981 (rat)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat; single dose)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat; multidose)	+	+	+	+	+	++	+	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Jenkins and Andersen 1978 (rat; single dose)	+	+	+	+	+	++	+	+	na	First
Inhalation intermediate exposure										
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 16 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 14 weeks)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Oral intermediate exposure										
Quast et al. 1983 (dog)	+	+	+	+	+	++	++	+	na	First
Inhalation chronic exposure										
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 2015a (rat; 105 weeks)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse; 105 weeks)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Oral chronic exposure										
Maltoni et al. 1985 (rat; single dose)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; multidose)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1983 (mouse)	+	+	++	+	+	++	++	++	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 1,1-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 1,1-dichloroethene and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

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

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

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

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

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

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

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

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

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

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

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, hepatic, and renal effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

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

Table C-13. Presence of Key Features of Study Design for 1,1-Dichloroethene—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Hepatic effects					
Inhalation–cohort					
Ott et al. 1976	No	Yes	Yes	Yes	Moderate
Outcome: Renal effects					
Oral–cross-sectional					
Ott et al. 1976	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Zeller et al. 1979a (rat)	No	Yes	No	No	Very Low
Oral acute exposure					
Chieco et al. 1981 (rat)	Yes	No	No	No	Very Low
Forkert and Reynolds 1982 (mouse)	Yes	No	Yes	No	Low
Forkert et al. 1985 (mouse)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Gage 1970 (rat)	Yes	No	No	No	Very Low
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse 14 weeks)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (guinea pig)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Quast et al. 1986 (rat)	Yes	No	No	No	Very Low
Inhalation chronic exposure					
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	No	No	Low
Oral chronic exposure					
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Jaeger 1977 (rat)	Yes	Yes	No	No	Low
Jaeger et al. 1973a (rat)	Yes	No	No	No	Very Low
Jaeger et al. 1974 (rat; fasted)	No	No	No	No	Very Low
Jaeger et al. 1974 (rat; nonfasted)	No	No	No	No	Very Low

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Maltoni et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
McKenna et al. 1978a (rat)	No	No	Yes	No	Very Low
Murray et al. 1979 (rat; 80 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rat; 160 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rabbit; 80 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rabbit; 160 ppm)	Yes	Yes	No	Yes	Moderate
Reitz et al. 1980 (mouse)	No	No	Yes	No	Very Low
Short et al. 1977a, 1977b (rat)	Yes	No	Yes	Yes	Moderate
Short et al. 1977a, 1977b (mouse)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Chieco et al. 1981 (rat; 200 mg/kg/day)	Yes	No	Yes	No	Low
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	Yes	No	Yes	No	Low
Jaeger et al. 1973b (rat)	Yes	Yes	No	Yes	Moderate
Jenkins and Andersen 1978 (rat)	Yes	No	No	Yes	Low
Kanz and Reynolds 1986 (rat)	Yes	No	Yes	Yes	Moderate
Kanz et al. 1991 (rat)	Yes	Yes	No	Yes	Moderate
Moslen et al. 1985 (rat)	Yes	No	No	Yes	Low
Murray et al. 1979 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	No	Moderate
NTP 1982 (mouse)	Yes	Yes	Yes	No	Moderate
Reynolds et al. 1984 (rat)	Yes	No	No	No	Very Low
Inhalation intermediate exposure					
Balmer et al. 1976 (rat)	Yes	Yes	Yes	Yes	High
Gage 1970 (rat)	Yes	No	Yes	No	Low
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low
NTP 2015a (rat; 16 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 14 weeks)	Yes	Yes	Yes	Yes	High
Plummer et al. 1990 (rat; continuous)	Yes	No	Yes	No	Low
Plummer et al. 1990 (rat; intermittent)	Yes	No	Yes	No	Low
Prendergast et al. 1967 (monkey)	Yes	Yes	No	No	Low

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (guinea pig)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Quast 1976 (rat)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (dog)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Lee et al. 1977, 1978 (rat)	Yes	Yes	Yes	No	Moderate
Lee et al. 1977, 1978 (mouse)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat; 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 105 weeks)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; multidose)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Renal effects					
Inhalation acute exposure					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Jackson and Conolly 1985 (rat)	Yes	Yes	Yes	Yes	High
Maltoni et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
McKenna et al. 1978a (rat)	No	No	Yes	No	Very Low
Short et al. 1977a, 1977b (rat)	Yes	No	Yes	Yes	Moderate
Short et al. 1977a, 1977b (mouse)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Chieco et al. 1981 (rat)	Yes	No	Yes	No	Low
Jenkins and Andersen 1978 (rat; single dose)	Yes	No	Yes	Yes	Moderate
Jenkins and Andersen 1978 (rat; multidose)	Yes	No	Yes	Yes	Moderate
Jenkins and Andersen 1978 (rat; single dose)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low
NTP 2015a (rat; 16 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 14 weeks)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Oral intermediate exposure					
Quast et al. 1983 (dog)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat; 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 105 weeks)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral chronic exposure					
Maltoni et al. 1985 (rat; single dose)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; multidose)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (mouse)	Yes	Yes	Yes	Yes	High

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	High
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Zeller et al. 1979a (rat)	Very Low	
Inhalation intermediate exposure		
Animal studies		
Gage 1970 (rat)	Very Low	High
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 14 weeks)	High	
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse 14 weeks)	High	
Prendergast et al. 1967 (rat)	Low	
Prendergast et al. 1967 (guinea pig)	Low	
Prendergast et al. 1967 (dog)	Very Low	
Quast et al. 1986 (rat)	Very Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; 104 weeks)	Low	High
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat)	High	
NTP 2015a (mouse)	High	
Quast et al. 1986 (rat)	Low	
Oral acute exposure		
Animal studies		
Chieco et al. 1981 (rat)	Very Low	Low
Forkert and Reynolds 1982 (mouse)	Low	
Forkert et al. 1985 (mouse)	Low	
Oral chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Moderate	High
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	Moderate	
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	
Outcome: Hepatic effects		
Inhalation acute exposure		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	High
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Jaeger 1977 (rat)	Low	
Jaeger et al. 1973a (rat)	Very Low	
Jaeger et al. 1974 (rat; fasted)	Very Low	
Jaeger et al. 1974 (rat; nonfasted)	Very Low	
Maltoni et al. 1985 (mouse)	Moderate	
McKenna et al. 1978a (rat)	Very Low	
Murray et al. 1979 (rat; 80 ppm)	Moderate	
Murray et al. 1979 (rat; 160 ppm)	Moderate	
Murray et al. 1979 (rabbit; 80 ppm)	Moderate	
Murray et al. 1979 (rabbit; 160 ppm)	Moderate	
Reitz et al. 1980 (mouse)	Very Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Short et al. 1977a, 1977b (rat)	Moderate	
Short et al. 1977a, 1977b (mouse)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Balmer et al. 1976 (rat)	High	High
Gage 1970 (rat)	Low	
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 16 days)	High	
NTP 2015a (rat; 14 weeks)	High	
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse; 14 weeks)	High	
Plummer et al. 1990 (rat; continuous)	Low	
Plummer et al. 1990 (rat; intermittent)	Low	
Prendergast et al. 1967 (monkey)	Low	
Prendergast et al. 1967 (rat)	Low	
Prendergast et al. 1967 (guinea pig)	Low	
Prendergast et al. 1967 (dog)	Very Low	
Quast 1976 (rat)	High	
Quast 1986 (rat)	Moderate	
Inhalation chronic exposure		
Human studies		
Ott et al. 1976	Moderate	Moderate
Animal studies		
Lee et al. 1977, 1978 (rat)	Moderate	High
Lee et al. 1977, 1978 (mouse)	Moderate	
Maltoni et al. 1985 (rat; 104 weeks)	Low	
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat; 105 weeks)	High	
NTP 2015a (mouse; 105 weeks)	High	
Quast et al. 1986 (rat)	High	
Oral acute exposure		
Animal studies		
Chieco et al. 1981 (rat; 200 mg/kg/day)	Low	Moderate
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	Low	
Jaeger et al. 1973b (rat)	Moderate	
Jenkins and Andersen 1978 (rat)	Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Kanz and Reynolds 1986 (rat)	Moderate	
Kanz et al. 1991 (rat)	Moderate	
Moslen et al. 1985 (rat)	Low	
Murray et al. 1979 (rat)	Moderate	
NTP 1982 (rat)	Moderate	
NTP 1982 (mouse)	Moderate	
Reynolds et al. 1984 (rat)	Very Low	
Oral intermediate exposure		
Animal studies		
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	High
Quast et al. 1983 (dog)	High	
Oral chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Moderate	
Maltoni et al. 1985 (rat; multidose)	Moderate	
NTP 1982 (rat)	High	High
NTP 1982 (mouse)	High	
Quast et al. 1983 (rat)	High	
Outcome: Renal effects		
Inhalation acute exposure		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Jackson and Conolly 1985 (rat)	High	High
Maltoni et al. 1985 (mouse)	Moderate	
McKenna et al. 1978a (rat)	Very Low	
Short et al. 1977a, 1977b (rat)	Moderate	
Short et al. 1977a, 1977b (mouse)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 16 days)	High	
NTP 2015a (rat; 14 weeks)	High	High
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse; 14 weeks)	High	
Prendergast et al. 1967 (rat)	Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Prendergast et al. 1967 (dog)	Very Low	
Inhalation chronic exposure		
Human studies		
Ott et al. 1976	Moderate	Moderate
Animal studies		
Maltoni et al. 1985 (rat; 104 weeks)	Low	High
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat; 105 weeks)	High	
NTP 2015a (mouse; 105 weeks)	High	
Quast et al. 1986 (rat)	High	
Oral acute exposure		
Animal studies		
Chieco et al. 1981 (rat)	Low	Moderate
Jenkins and Andersen 1978 (rat; single dose)	Moderate	
Jenkins and Andersen 1978 (rat; multidose)	Moderate	
Jenkins and Andersen 1978 (rat; single dose)	Moderate	
Oral intermediate exposure		
Animal studies		
Quast et al. 1983 (dog)	High	High
Oral chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; single dose)	Moderate	High
Maltoni et al. 1985 (rat; multidose)	Moderate	
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	
Quast et al. 1983 (mouse)	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, hepatic, renal, and cancer effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with 1,1-dichloroethene exposure is presented in Table C-17.

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Animal studies	High	None	High
Outcome: Hepatic effects			
Human studies	Moderate	None	Moderate
Animal studies	High	+1 consistency in findings	High
Outcome: Renal effects			
Human studies	Moderate	None	Moderate
Animal studies	High	+1 consistency in findings	High

Table C-17. Confidence in the Body of Evidence for 1,1-Dichloroethene

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

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

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

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

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

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

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

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

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

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

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

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

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

Upgrade one confidence level if there is a high degree of consistency in the database

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

In the seventh step of the systematic review of the health effects data for 1,1-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 1,1-dichloroethene is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for 1,1-Dichloroethene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	Moderate	No effect	Inadequate
Renal effects	Moderate	No effect	Inadequate
Animal studies			
Respiratory effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Renal effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

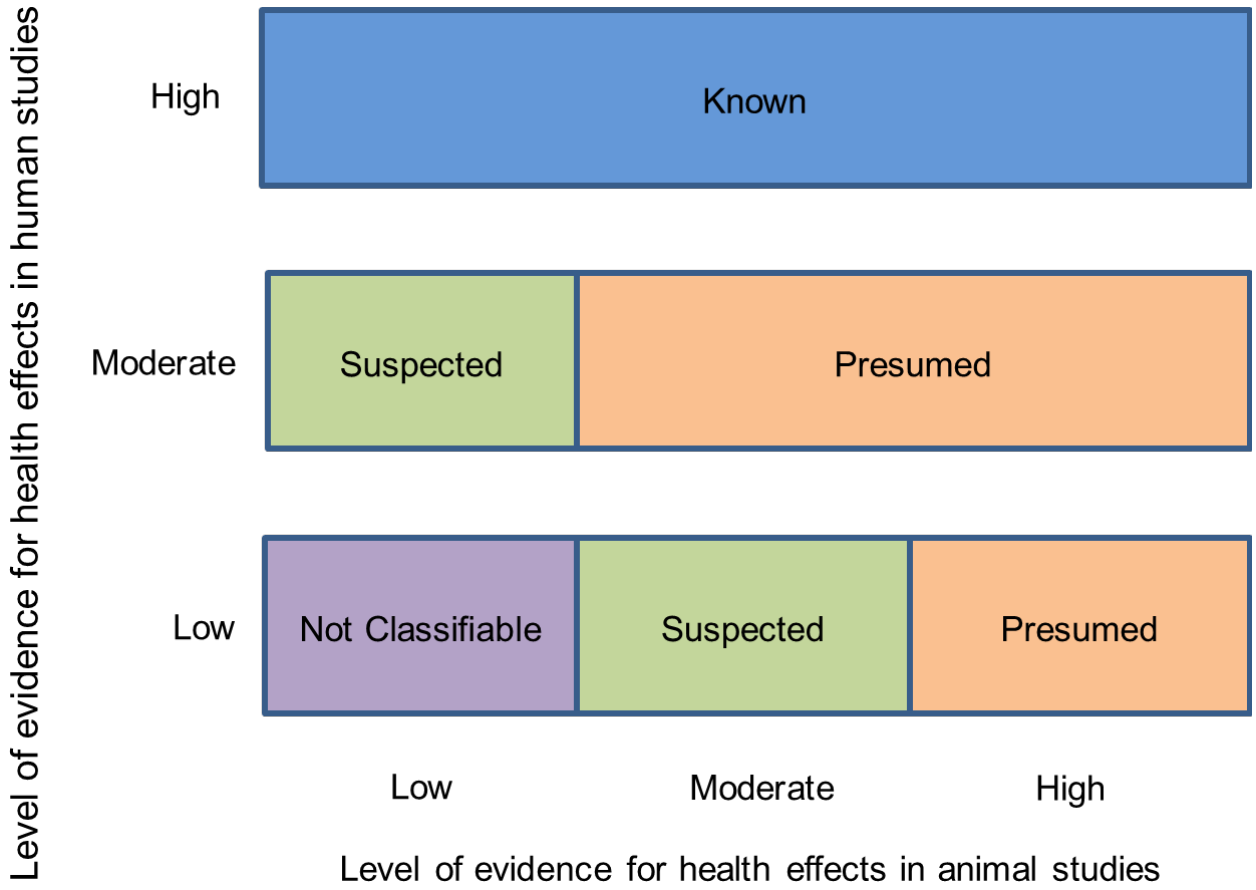
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

The hazard identification conclusions for 1,1-dichloroethene are listed below and summarized in Table C-19.

Table C-19. Hazard Identification Conclusions for 1,1-Dichloroethene

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Hepatic effects	Presumed health effect
Renal effects	Presumed health effect

Presumed Health Effects

- Respiratory effects
  - No human data
  - High level of evidence of nasal lesions in rats and mice following intermediate- and chronic-duration inhalation exposure (NTP 2015a)
- Hepatic effects
  - Inadequate human data; one study did not find evidence of hepatotoxicity in a cohort of workers exposed to 1,1-dichloroethene (Ott et al. 1976).
  - High level of evidence from inhalation or oral exposure of laboratory animals (e.g., Henck et al. 1979; NTP 1982, 2015a; Prendergast et al. 1967; Quast et al. 1983; Short et al. 1977a, 1977b).
  - 1,1-Dichloroethene was significantly more toxic to the kidney of rats that were fasted prior to exposure.
- Renal effects
  - Inadequate human data; one study did not find evidence of renal toxicity in a cohort of workers exposed to 1,1-dichloroethene (Ott et al. 1976).
  - High level of evidence from inhalation exposure of laboratory animals (e.g., Henck et al. 1979; Maltoni et al. 1985; NTP 2015a; Prendergast et al. 1967; Short et al. 1977a, 1977b).
  - 1,1-Dichloroethene was significantly more toxic to the kidney of mice than rats.

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 C-5)

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

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

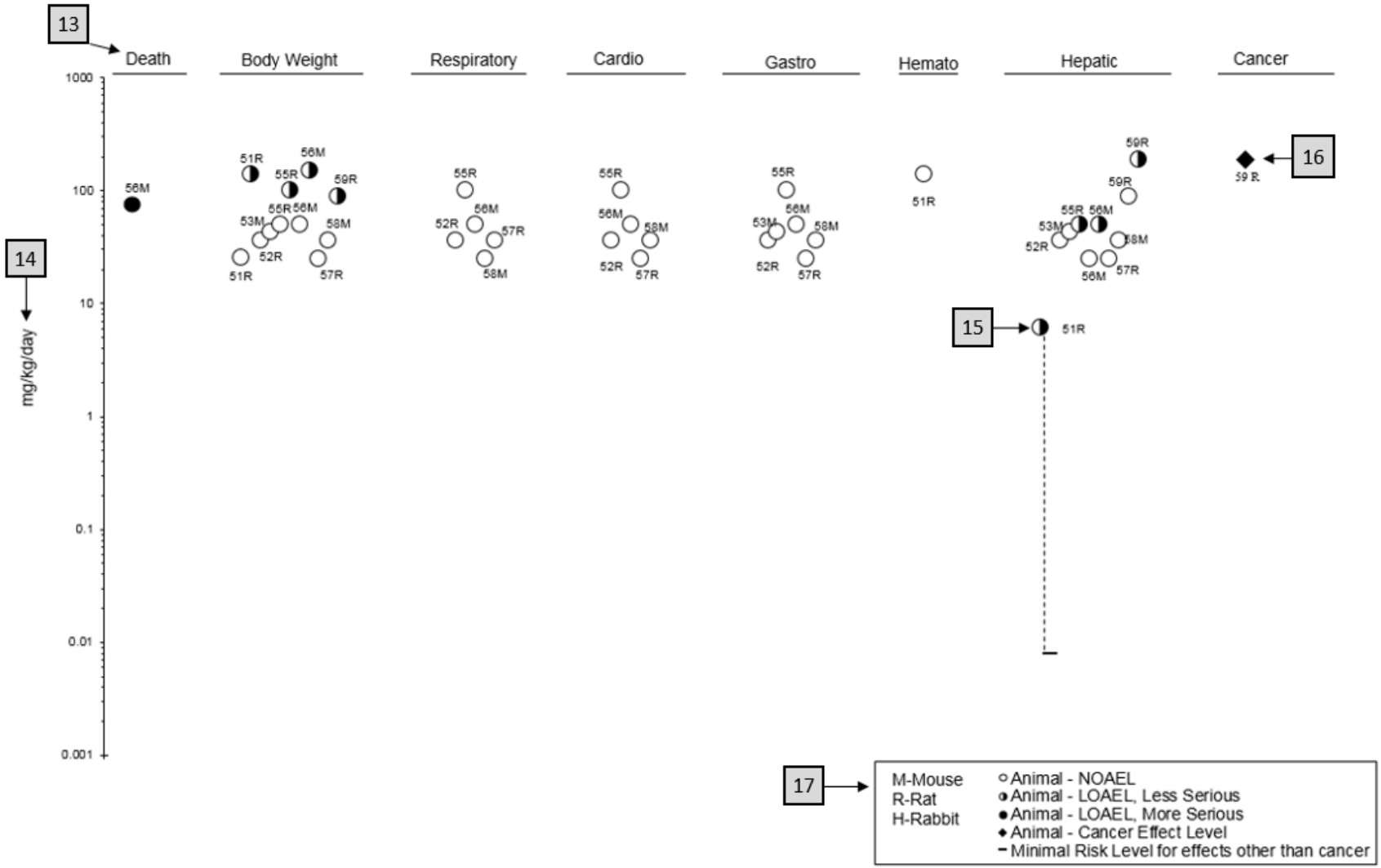
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

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

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

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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