APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 0.02 ppm
Critical Effect: Nasal lesions
Reference: Nitschke and Johnson 1983
Point of Departure: 100 ppm minimal LOAEL ($LOAEL_{HEC}$ of 1.8 ppm)
Uncertainty Factor: 90
LSE Graph Key: 9
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 0.02 ppm was derived for 1,2-dichloropropane based on olfactory mucosal degeneration in rats exposed to concentrations ≥100 ppm for 2 weeks (6 hours/day, 4–5 days/week); a no-observed-adverse-effect level (NOAEL) was not identified for nasal effects (Nitschke and Johnson 1983). The MRL is based on the lowest-observed-adverse-effect level (LOAEL) of 100 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($LOAEL_{HEC}$) of 1.8 ppm for slight olfactory mucosal degeneration and a total uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans after dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: Available data indicate that the upper respiratory system is the most sensitive target for toxic effects following acute-duration inhalation exposure to 1,2-dichloropropane (see Table A-1). Hepatic effects were also considered, but these effects occurred at concentrations 2–4-fold higher than the lowest LOAEL identified for nasal lesions. Of the species evaluated for nasal lesions, the rat was the most sensitive, with a LOAEL of 100 ppm for degeneration of the nasal mucosa (lowest concentrations tested). The LOAEL values for nasal lesions in other species evaluated in this study were higher than the rat LOAEL (300 ppm for mice, 1,000 ppm for rabbits); therefore, the rat is considered the most sensitive species for the critical effect.

Table A-1. Summary of Candidate Critical Effects for Acute Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Nasal effects					
Fischer-344 rat	2 weeks (4–5 days/week; 6 hours/day)	ND	100	Olfactory mucosal degeneration	Nitschke and Johnson 1983
B6C3F1 mouse	2 weeks (4–5 days/week; 6 hours/day)	100	300	Olfactory mucosal degeneration	Nitschke and Johnson 1983
New Zealand rabbit	2 weeks (4–5 days/week; 6 hours/day)	300	1,000	Olfactory mucosal degeneration	Nitschke and Johnson 1983

Table A-1. Summary of Candidate Critical Effects for Acute Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic effects					
BALB/cA mouse	14 days (6 hours/day)	ND	200	Hepatic vacuolation	Zhang et al. 2015
BALB/cA mouse	7 days (8 hours/day)	ND	300	Hepatic vacuolation	Zhang et al. 2015
C57BL/6J mouse	7 days (8 hours/day)	ND	300	Hepatic vacuolation	Zhang et al. 2015
C57BL/6J mice	1–12 days (7 hours/day)	ND	400	Slight fatty degeneration	Heppel et al. 1948
Golden Syrian hamster	14 days (8 hours/day)	200	400	Slight dilation of hepatic sinusoids	Zhang et al. 2015
Golden Syrian hamster	7 days (8 hours/day)	300	ND	ND	Zhang et al. 2015

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The study with the lowest identified LOAEL for the critical effect of nasal lesions was selected as the principal study (Nitschke and Johnson 1983). Of the species tested in this study, the rat was the most sensitive, with a LOAEL of 100 ppm for degeneration of the nasal mucosa (lowest concentrations tested). The LOAEL values for nasal lesions in other species evaluated in this study were 300 ppm for mice and 1,000 ppm for rabbits.

Summary of the Principal Study:

Nitschke KD, Johnson KA. 1983. Propylene dichloride: One day and two week inhalation toxicity in rats. Dow Chemical Company, Midland, MI.

Groups of F344 rats (5/sex) were exposed to 1,2-dichloropropane at concentrations of 0, 100, 300, or 1,000 ppm for 6 hours/day for 9 days over a 2-week period. Animals were observed for signs of toxicity after each exposure period. Body weights were recorded prior to the 1st, 5th, 6th, and 9th exposure. Prior to the 9th exposure, blood was collected for hematology and clinical chemistry. Urine was collected for urinalysis. All surviving animals were sacrificed the day following the final exposure. All animals were examined grossly. The brain, heart, liver, kidneys, thymus, and testes were removed and weighed. The entire respiratory tract (nasal turbinates, larynx, trachea, and lungs), adrenals, liver, kidney, testes, thymus, and bone marrow were examined for histopathological changes.

No deaths or clinical signs of toxicity were observed during the exposure period. All treated rats had significantly reduced body weight gain, which was attributed to reduced food intake by the study authors. No exposure-related hematological effects were observed. Blood chemistry findings were consistent with decreased food intake, and not considered by the study authors to be related to toxicity. Female rats had decreased plasma cholinesterase activities that were not dose related. No effects on urinalysis indices were observed. Relative liver weight was significantly increased by 8–15% in male rats at 1,000 ppm and female rats at 300 and 1,000 ppm; these findings may be exposure related. Other observed organ weight changes were considered secondary to decreased food intake. Olfactory mucosal degeneration was

observed in 100% of rats from all exposure groups, and none of the control rats. The severity of this lesion increased in a dose-related manner, from slight at 100 ppm to severe at 1,000 ppm. Inflammatory and exudative changes were also increased in a dose-related manner in the nasal tissue. No other respiratory tract lesions were observed. Decreased cellularity of bone marrow and thymus observed at 300 and 1,000 ppm is consistent with stress as a result of decreased food intake. The bone marrow changes did not correlate with hematological parameters. Slight hepatocellular hypertrophy in 3/5 female rats exposed to 1,000 ppm is consistent with increased liver weight. No exposure-related histopathologic lesions were observed in kidneys, adrenals, or testes.

Selection of the Point of Departure for the MRL: The LOAEL of 100 ppm for nasal lesions was selected as the POD. This value was considered a minimal LOAEL due to the slight severity of the lesion. The data were not suitable for benchmark dose (BMD) modeling because incidence data went from 0% in the control to 100% in the lowest concentration group.

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

$LOAEL_{ADJ}$ = 100 ppm x (6 hours/24 hours) x (9 days/14 days) = 16 ppm

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted LOAEL by the regional gas dose ratio (RGDR) for the extrathoracic region of the respiratory tract. The $RGDR_{ET}$ of 0.115 was calculated using the following equation:

$$RGDR_{ET} = (V_E/SA_{ET})_A/(V_E/SA_{ET})_H$$

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

V_E = 119 mL/minute and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$RGDR_{ET}$ = (119 mL/minute ÷ 15 cm^2)/(13,800 mL/minute ÷ 200 cm^2) = 0.115

$LOAEL_{HEC} = LOAEL_{ADJ}$ x $RGDR_{ET}$
$LOAEL_{HEC}$ = 16 ppm x 0.115= 1.8 ppm

Uncertainty Factor: The $LOAEL_{HEC}$ is divided by a total uncertainty factor of 90:

- 3 for use of a minimal LOAEL. The dose was considered a minimal LOAEL because the severity of the lesions was graded as slight.
- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

MRL = $LOAEL_{HEC}$ ÷ UFs
MRL = 1.8 ppm ÷ (3 x 3 x 10) = 0.02 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The upper respiratory tract is the most sensitive target following both acute- and intermediate-duration inhalation exposure, and the rat is the most sensitive species tested. Olfactory mucosal degeneration was observed in rats and mice exposed to ≥100 ppm and rabbits at 1,000 ppm for 2 weeks (Nitschke and Johnson 1983). In intermediate-duration studies, nasal cavity lesions were observed in rats exposed to ≥15 ppm (lowest concentration tested), including hyperplasia of the respiratory epithelium at ≥15 ppm, degeneration of the olfactory epithelium at ≥50 ppm, atrophy of the olfactory epithelium at ≥125 ppm, submucosal inflammation at ≥150 ppm, and inflammation of the respiratory epithelium at ≥1,000 ppm (Nitschke et al. 1988; Umeda et al. 2010). Intermediate-duration studies also observed nasal lesions in mice at ≥300 ppm (but not ≤200 ppm) (Matsumoto et al. 2013; Nitschke et al. 1988) and rabbits at 1,000 ppm (but not ≤500 ppm) (Nitschke et al. 1988). In chronic studies, nasal lesions were observed in rats at ≥80 ppm (lowest concentration tested), including atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, hyperplasia of the transitional epithelium, squamous cell hyperplasia, and hyperplasia of the submucosal glands (Umeda et al. 2010) and mice at ≥80 ppm (but not 32 ppm), including atrophy of olfactory epithelium and metaplasia of the olfactory epithelium and submucosal glands (Matsumoto et al. 2013).

Limited evidence from accident reports following chemical spills suggest that inhalation exposure to 1,2-dichloropropane causes respiratory irritation in humans following acute exposure to presumably high concentrations (exposure levels not available) (ACGIH 2014; Rubin 1988).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL 0.002 ppm
Critical Effect: Nasal lesions
Reference: Nitschke et al. 1988
Point of Departure: $BMCL_{10}$ of 2.38 ($BMCL_{HEC}$ of 0.05 ppm)
Uncertainty Factor: 30
LSE Graph Key: 35
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.002 ppm was derived for 1,2-dichloropropane based on hyperplasia of the nasal respiratory epithelium in rats exposed to concentrations ≥15 ppm for 13 weeks (6 hours/day, 5 days/week); a NOAEL was not identified for nasal effects (Nitschke et al. 1988). The MRL is based on the $BMCL_{10}$ of 2.38 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.05 ppm for hyperplastic lesions in male and female rats (combined) and a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available data indicate that the upper respiratory system is the most sensitive target for toxic effects following intermediate-duration inhalation exposure to 1,2-dichloropropane (see Table A-2). Other effects considered (hemolytic anemia, altered estrous cycle) occurred at concentrations 6–10-fold higher than the lowest LOAEL identified for nasal lesions; no NOAEL was identified for nasal lesions.

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects[a]					
F344 rat	13 weeks (6 hours/day, 5 days/week)	ND	15	Hyperplasia of nasal respiratory epithelium	Nitschke et al. 1988
F344 rat	13 weeks (6 hours/day, 5 days/week)	ND	125	Hyperplasia of nasal respiratory epithelium and atrophy of olfactory epithelium	Umeda et al. 2010
B6D2F1/Crlj mouse	13 weeks (6 hours/day, 5 days/week)	200	300	Respiratory metaplasia, atrophy, necrosis, and desquamation of nasal cavity	Matsumoto et al. 2013

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Reproductive effects					
F344 rat	21–24 days (8 hours/day)	50	100	Lengthened estrous cycle	Sekiguchi et al. 2002
Hematological effects					
New Zealand rabbit	13 weeks (6 hours/day, 5 days/week)	ND	150	Hemolytic anemia	Nitschke et al. 1988

[a]Selected critical effect.

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The study with the lowest identified LOAEL for the critical effect of nasal lesions was selected as the principal study (Nitschke et al. 1988).

Summary of the Principal Study:

Nitschke KD, Johnson KA, Wackerle DL, et al. 1988. Final report on propylene dichloride 13-week inhalation toxicity study with rats, mice and rabbits with cover letter dated 032888. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS0000399-1. FYI-OTS-0488-0399.

Groups of F344 rats (10/sex/group) were exposed to 1,2-dichloropropane (99.94% pure) via whole-body inhalation for 13 weeks (5 days/week, 6 hours/day) at concentrations of 0, 15, 50, or 150 ppm. Endpoints examined included mortality, clinical signs, weekly body weight, eyes (fluorescent illumination), hematology, clinical chemistry, organ weights (brain, heart, liver, kidneys, thymus, testes), and histology for complete set of 47 tissues including the respiratory tract (nasal tissues, larynx, trachea, lungs, and organs normally present on sections with these organs) in control and high-exposure groups. The respiratory tract, liver, gallbladder, kidney, and thymus were also examined in the low- and mid-exposure groups.

There were no exposure-related mortalities or overt signs of toxicity. Body weight gain was significantly lower than controls throughout the study in rats exposed to 150 ppm, but body weight decreases >10% were only observed in males. There were no exposure-related effects on hematological, clinical chemistry, or urinalysis parameters or on organ weights. Hyperplasia of nasal mucosa was observed in 0/10, 2/9, 5/10, and 9/10 males and 0/10, 3/10, 7/10, and 9/10 females at 0, 15, 50, and 150 ppm, respectively. Slight degeneration of olfactory mucosa was observed in rats exposed to 50 and 150 ppm, with inflammation of larynx in males exposed to 150 ppm. No other exposure-related histopathologic lesions were observed. The authors considered hyperplasic lesions of nasal mucosa to be protective response of equivocal toxicological significance; ATSDR generally considers hyperplasic lesions to be an adverse effect. Furthermore, additional nasal lesions are observed at higher concentrations and following longer exposure durations (see Umeda et al. 2010). Therefore, the lowest concentration (15 ppm) was identified as a LOAEL for upper respiratory lesions; no NOAEL was identified.

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ value of 2.38 ppm for increased incidence of nasal respiratory epithelium hyperplasia in male and female rats (combined) was selected as the basis of the MRL.

BMD modeling was performed on the incidence of nasal respiratory epithelium hyperplasia in male and female F344 rats, as well as the combined data for both sexes (Table A-3). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2) using a benchmark response (BMR) of 10% extra risk. However, dichotomous Hill models were not considered viable because the model has four parameters, requiring at minimum five data points (including control), and these data sets have only four data points. For remaining models, adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) 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's Information Criterion (AIC) was chosen.

Table A-3. Incidence of Nasal Respiratory Epithelium Hyperplasia in F344 Rats Following Inhalation Exposure to 1,3-Dichloropropane for 13 Weeks

	Concentration (ppm)			
	0	15	50	150
Males	0/10 (0%)	2/9 (22%)	5/10 (50%)	9/10 (90%)
Females	0/10 (0%)	3/10 (30%)	7/10 (70%)	9/10 (90%)
Combined	0/20 (0%)	5/19 (25%)	12/20 (60%)	18/20 (90%)

Source: Nitschke et al. 1988

All models except dichotomous Hill provided adequate fit to the increased incidence of nasal lesions in male rats. BMCLs for models providing adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (Log-Logistic). The frequentist, restricted Log-Logistic model estimated a BMC_{10} and $BMCL_{10}$ of 9.08 and 2.44 ppm, respectively. The results of the BMD modeling are summarized in Table A-4.

Table A-4. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

					Scaled residuals[c]	
Model	BMC_{10}[a] (mg/kg/day)	$BMCL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Dose near BMC	Dose near control
Dichotomous Hill			0.55	36.27	0.273	-3.90×10^{-4}
Gamma[d]	7.05	4.54	1.00	31.96	-3.90×10^{-4}	-3.90×10^{-4}
Log-Logistic[e,f]	**9.08**	**2.44**	**0.83**	**34.27**	**0.273**	**-3.90×10^{-4}**
Log-Probit[e]	11.59	7.44	0.76	34.41	0.577	-3.90×10^{-4}
Multistage (3-degree)[g]	7.21	4.54	0.97	33.95	-3.90×10^{-4}	-3.90×10^{-4}
Multistage (2-degree)[g]	7.17	4.54	0.97	33.95	-3.90×10^{-4}	-3.90×10^{-4}

Table A-4. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

Model	BMC_{10}[a] (mg/kg/day)	$BMCL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Dose near control
Multistage (1-degree)[g]	7.05	4.54	1.00	31.96	-3.90×10^{-4}	-3.90×10^{-4}
Weibull[d]	7.05	4.54	0.97	33.96	-3.94x10-4	-3.94×10^{-4}
Logistic	21.20	13.30	0.32	37.21	0.399	-1.13
Probit	20.89	13.84	0.32	37.19	0.422	-1.11

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

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

For increased incidence of nasal lesions in female rats, six frequentist, restricted models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Multistage 1-, 2-, and 3-degree). The Multistage models, which all converged on the 1-degree model, estimated a BMC_{10} and $BMCL_{10}$ of 5.28 and 3.45 ppm, respectively. The results of the BMD modeling are summarized in Table A-5.

Table A-5. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Female F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

Model	BMC_{10}[a] (mg/kg/day)	$BMCL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Dose near control
Dichotomous Hill			NA	38.94	-4.04×10^{-4}	-4.04×10^{-4}
Gamma[d]	5.28	3.45	0.67	35.64	-3.92×10^{-4}	-3.92×10^{-4}
Log-Logistic[e]			0.99	34.95	-3.90×10^{-4}	-3.90×10^{-4}
Log-Probit[e]	8.31	5.32	0.74	35.44	0.405	-3.90×10^{-4}
Multistage (3-degree)[f]	5.28	3.45	0.85	33.64	-3.90×10^{-4}	-3.90×10^{-4}
Multistage (2-degree)[f]	5.28	3.45	0.85	33.64	-3.90×10^{-4}	-3.90×10^{-4}
Multistage (1-degree)[f,g]	**5.28**	**3.45**	**0.85**	**33.64**	**-3.90×10^{-4}**	**-3.90×10^{-4}**
Weibull[d]	5.28	3.45	0.67	35.64	-8.25×10^{-3}	-8.25×10^{-3}
Logistic			0.09	41.09	0.366	-0.142
Probit			0.08	41.47	0.361	-0.145

[a]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models except the LogLogistic, Logistic, Probit, and dichotomous Hill models provided adequate fit to the data (the Weibull and 2- and 3-degree Multistage 2- and 3-degree models converged onto the 1-degree Multistage model). BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (1-Degree Multistage).

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

For nasal lesions in male and female rats (combined), seven frequentist, restricted models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by 3-fold), so the lowest BMCL was selected (Log-Logistic). The Log-Logistic model estimated a BMC_{10} and $BMCL_{10}$ of 6.78 and 2.38 ppm, respectively. The results of the BMD modeling are summarized in Table A-6.

Table A-6. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male and Female F344 Rats exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

Model	BMC_{10}[a] (mg/kg/day)	$BMDC_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Dose near control
Dichotomous Hill			0.70	67.98	-5.52×10^{-4}	-5.52×10^{-4}
Gamma[d]	6.10	4.48	0.84	66.16	-5.57×10^{-4}	-5.57×10^{-4}
Log-Logistic[e,f]	**6.76**	**2.38**	**0.70**	**67.98**	**-5.52×10^{-4}**	**-5.52×10^{-4}**
Log-Probit[e]	9.80	7.17	0.84	64.62	0.737	-5.52×10^{-4}
Multistage (3-degree)[g]	6.10	4.48	0.95	64.16	-5.52×10^{-4}	-5.52×10^{-4}
Multistage (2-degree)[g]	6.10	4.48	0.95	64.16	-5.52×10^{-4}	-5.52×10^{-4}
Multistage (1-degree)[g]	6.10	4.48	0.84	66.16	-5.52×10^{-4}	-5.52×10^{-4}
Weibull[d]	6.10	4.48	0.95	64.16	-5.52×10^{-4}	-5.52×10^{-4}
Logistic			0.04	74.98	0.550	-1.82
Probit			0.03	75.27	0.565	-1.82

[a]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. All models except the Logistic, Probit, and dichotomous Hill models provided adequate fit to the data. BMCLs for remaining models providing adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (Log-Logistic).
[g]Betas restricted to ≥0.

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

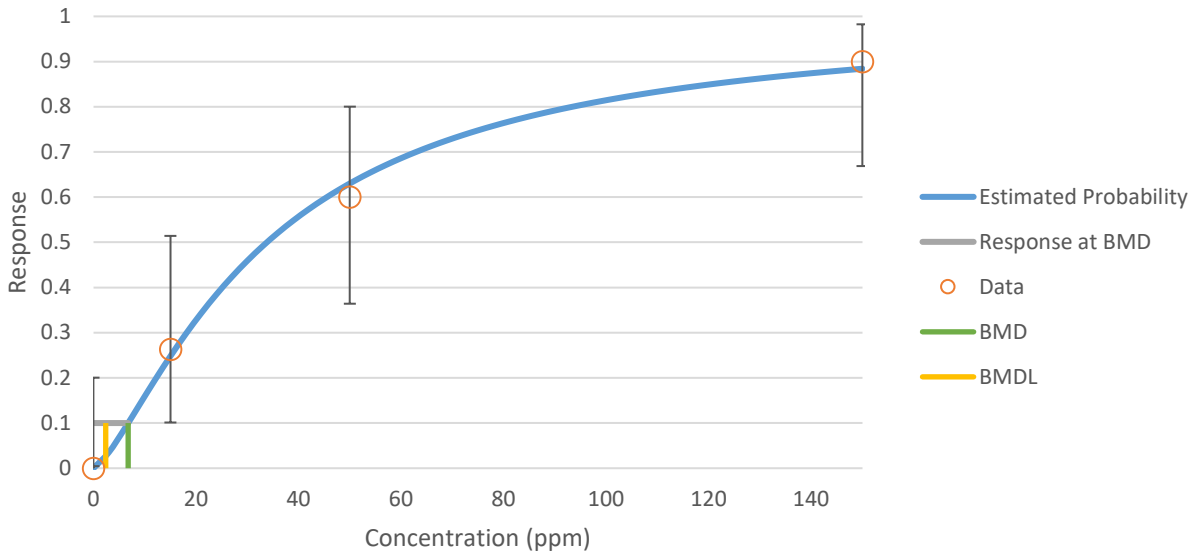
Table A-7 summarizes the potential candidate PODs for the intermediate-duration inhalation MRL for 1,2-dichloropropane. While the female data have the lowest BMC, the BMCL of 2.38 ppm from the combined male and female data was selected as the POD for the MRL derivation because it has the highest statistical power. The Log-Logistic model fit to the nasal respiratory epithelium hyperplasia in the male and female rats presented in Figure A-1.

Table A-7. Candidate Points of Departure 1,2-Dichloropropane Intermediate-Duration Inhalation MRL

Endpoint	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Increased incidence of nasal lesions in males	9.08	2.44
Increased incidence of nasal lesions in females	5.28	3.45
Increased incidence of nasal lesions in males and females (combined)	6.76	2.38

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC; MRL = Minimal Risk Level

Figure A-1. Fit of Log-Logistic Model to Data for Combined Incidence of Nasal Respiratory Epithelium Hyperplasia in Male and Female F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks



Adjustment for Intermittent Exposure: The $BMCL_{10}$ of 2.38 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMCL_{ADJ}$ = 2.38 ppm x (6 hours/24 hours) x (5 days/7 days) = 0.43 ppm

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted BMCL by the regional gas dose ratio (RGDR) for the extrathoracic region of the respiratory tract. The $RGDR_{ET}$ of 0.115 was calculated using the following equation:

$$RGDR_{ET} = (V_E/SA_{ET})_A/(V_E/SA_{ET})_H$$

where:

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

V_E = 119 mL/minute and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$RGDR_{ET}$ = (119 mL/minute ÷ 15 cm^2)/(13,800 mL/minute ÷ 200 cm^2) = 0.115

$BMCL_{HEC} = BMCL_{ADJ}$ x $RGDR_{ET}$
$BMCL_{HEC}$ = 0.43 ppm x 0.115 = 0.05 ppm

Uncertainty Factor: The $BMCL_{10[HEC]}$ is divided by a total uncertainty factor of 30:

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

MRL = $BMCL_{10[HEC]}$ ÷ UFs
MRL = 0.05 ppm ÷ (3 x 10) = 0.002 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The upper respiratory tract is the most sensitive target following both acute- and intermediate-duration inhalation exposure, and the rat is the most sensitive species tested. As discussed in the acute-duration inhalation MRL worksheet, olfactory mucosal degeneration was observed in rats and mice exposed to ≥100 ppm and rabbits at 1,000 ppm for 2 weeks (Nitschke and Johnson 1983). In intermediate-duration studies, nasal cavity lesions were observed in rats exposed to ≥15 ppm (lowest concentration tested), including hyperplasia of the respiratory epithelium at ≥15 ppm, degeneration of the olfactory epithelium at ≥50 ppm, atrophy of the olfactory epithelium at ≥125 ppm, submucosal inflammation at ≥150 ppm, and inflammation of the respiratory epithelium at ≥1,000 ppm (Nitschke et al. 1988; Umeda et al. 2010). Intermediate-duration studies also observed nasal lesions in mice at ≥300 ppm (but not ≤200 ppm) (Matsumoto et al. 2013; Nitschke et al. 1988) and rabbits at 1,000 ppm (but not ≤500 ppm) (Nitschke et al. 1988). In chronic studies, nasal lesions were observed in rats at ≥80 ppm (lowest concentration tested), including atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, hyperplasia of the transitional epithelium, squamous cell hyperplasia, and hyperplasia of the submucosal glands (Umeda et al. 2010) and mice at ≥80 ppm (but not 32 ppm), including atrophy of olfactory epithelium and metaplasia of the olfactory epithelium and submucosal glands (Matsumoto et al. 2013).

Limited evidence from accident reports following chemical spills suggest that inhalation exposure to 1,2-dichloropropane causes respiratory irritation in humans following acute exposure to presumably high concentrations (exposure levels not available) (ACGIH 2014; Rubin 1988).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration inhalation MRL was not derived due to lack of adequate low-concentration data for the critical effect. As a result, there is too much uncertainty in the chronic database to support derivation of an MRL based on chronic data. It is not considered appropriate to use the intermediate-duration data for derivation of a chronic MRL because there is evidence that the severity of nasal lesions increases with longer durations of exposure. Therefore, we cannot be sure that the intermediate MRL would be protective for chronic exposure. Two chronic-duration inhalation studies evaluating comprehensive endpoints in rats and mice are available (Matsumoto et al. 2013; Umeda et al. 2010); the results of these studies are summarized in Table A-8. The most sensitive effect identified in rats was nasal lesions at ≥80 ppm (lowest concentration tested); the lesions included atrophy of the olfactory epithelium, inflammation and squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium (Umeda et al. 2010). In mice, the most sensitive effect was basophilic changes and cortical mineralization in the kidney of male mice at ≥32 ppm (lowest concentration tested) and atrophy of the olfactory epithelium at ≥80 ppm (Matsumoto et al. 2013). While the LOAEL identified for renal effects was lower than the LOAEL identified for nasal lesions, renal effects were not selected as critical effects because there is a lack of consistent evidence for renal effects in exposed animals and the systematic review of renal toxicity determined that data are inadequate to determine if kidney toxicity will be observed in humans exposed to 1,2-dichloropropane. Therefore, the lowest LOAEL for the critical effect of nasal lesions was 80 ppm. This LOAEL is >5-fold higher than the LOAEL observed for nasal lesions following intermediate-duration exposure (15 ppm; Nitschke et al. 1988). Therefore, available chronic studies are inadequate to characterize low-concentration effects of chronic 1,2-dichloropropane inhalation exposure.

Table A-8. Summary of Candidate Critical Effects for Chronic Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects					
F344 rat	104 weeks (6 hours/day, 5 days/week)	ND	80	Atrophy of olfactory epithelium, inflammation and squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium	Umeda et al. 2010
B6D2F1/Crlj mouse	104 weeks (6 hours/day, 5 days/week)	32	80	Atrophy of olfactory epithelium	Matsumoto et al. 2013

Table A-8. Summary of Candidate Critical Effects for Chronic Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Renal effects					
B6D2F1/Crlj mouse	104 weeks (6 hours/day, 5 days/week)	ND	32	Basophilic changes and cortical mineralization in kidney; males only	Matsumoto et al. 2013

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Oral
Duration: Acute
MRL 0.3 mg/kg/day
Critical Effect: Maternal anemia
Reference: Berdasco et al. 1988 and Kirk et al. 1995
Point of Departure: $BMDL_{1SD}$ of 30 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 17, 18
Species: Rabbit

MRL Summary: An acute-duration oral MRL of 0.3 mg/kg/day was derived for 1,2-dichloropropane based on evidence of maternal anemia in rabbits exposed to doses ≥100 mg/kg/day on gestation days 7–19 (Berdasco et al. 1988; Kirk et al. 1995). The MRL is based on the $BMDL_{1SD}$ of 30 mg/kg/day for increased maternal reticulocyte counts relative to control animals and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the toxicity of 1,2-dichloropropane following acute-duration oral exposure. The most sensitive effects identified in acute oral studies included hematological, developmental, neurological, and body weight effects; see Table A-9. Since all of these adverse effects occurred at similar doses, all were considered for MRL derivation.

Table A-9. Summary of Candidate Critical Effects for Acute Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
New Zealand rabbit	GDs 7–19 (GO)	25	100	Maternal anemia	Berdasco et al. 1988
New Zealand rabbit	GDs 7–19 (GO)	50	150	Maternal anemia	Kirk et al. 1995
Developmental effects					
Sprague-Dawley rat	GDs 6–15 (GO)	30	125	Delayed skull ossification	Kirk et al. 1995
New Zealand rabbit	GDs 7–19 (GO)	50	150	Delayed skull ossification	Kirk et al. 1995
Neurological effects					
Sprague-Dawley rat	1–10 days (GO)	ND	100	CNS depression	Bruckner et al. 1989
Sprague-Dawley rat	GDs 6–15 (GO)	30	125	Clinical signs of neurotoxicity in dams	Kirk et al. 1995
Wistar rat	Once (G)	ND	145	CNS depression	Shell Oil Co.1982

Table A-9. Summary of Candidate Critical Effects for Acute Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
Sprague-Dawley rat	GDs 6–15 (GO)	30	125	Decreased maternal body weight gain	Kirk et al. 1995

CNS = central nervous system; G = gavage (no vehicle); GD = gestation day; GO = gavage (oil vehicle); LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; ND = not determined

In order to identify the most sensitive endpoint, BMD modeling was attempted for candidate critical endpoints in Table A-9 when data were amenable to modeling. Data modeled included maternal anemia in rabbits, delayed ossification in rabbits and rats, and decreased maternal body weight gain in rats (see Tables A-10, A-11, and A-12); data for neurological effects were not adequate for modeling due to qualitative and/or incomplete quantitative reporting. The data were fit to all available dichotomous or continuous models in EPA's BMDS (version 3.1.2) using a BMR of 1 standard deviation (hematological data), 10% relative deviation (body weight data), or 5% extra risk (developmental endpoints). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) 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.

Table A-10. Maternal Anemia in New Zealand Rabbits Following Gavage Administration of 1,2-Dichloropropane on GDs 7–19

	Dose (mg/kg/day)			
	0	25	100	250
Maternal reticulocyte counts Mean ± SD (N)	2.1±1.2 (4)	2.5±0.4 (3)	4.5±1 (5)	7.8±1.5 (3)

GD = gestation day; N = number; SD = standard deviation

Source: Berdasco et al. 1988

Table A-11. Maternal Anemia and Incidence of Delayed Ossification in New Zealand Rabbits Following Gavage Administration of 1,2-Dichloropropane on GDs 7–19

	Dose (mg/kg/day)			
	0	15	50	150
Maternal reticulocyte counts Mean ± SD (N)	3.2±0.6 (18)	3.6±0.7 (16)	3.8±0.9 (17)	6.7±1.7 (15)
Delayed ossification Litter incidence (% incidence)	0/18 (0%)	0/16 (0%)	2/17 (12%)	6/15 (40%)

GD = gestation day; N = number; SD = standard deviation

Source: Kirk et al. 1995

Table A-12. Maternal Body Weight Gain and Incidence of Delayed Ossification in Sprague-Dawley Rats Following Gavage Administration of 1,2-Dichloropropane on GDs 6–15

	Dose (mg/kg/day)			
	0	10	30	125
Maternal body weight gain (g) Mean ± SD (N)	189.2±30 (25)	188.8±23.7 (28)	188.7±23.5 (28)	170.5±23.7 (30)
Delayed ossification Litter incidence (% incidence)	8/25 (32%)	8/28 (29%)	10/28 (36%)	16/30 (53%)

GD = gestation day; N = number; SD = standard deviation

Source: Kirk et al. 1995

Suitable models were not identified for delayed ossification data in rabbits or rats (Kirk et al. 1995). Models produced questionable results, providing BMDL values that were inconsistent with empirical data (values of 5.6 and 10 mg/kg/day, respectively, were substantially lower than two no-effect dose levels in both studies). Therefore, ATSDR used the NOAEL/LOAEL approach for this endpoint.

For maternal anemia in rabbits reported by Berdasco et al. (1998), seven frequentist, constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The unrestricted Linear model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 41 and 30 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-13.

Table A-13. Model Predictions (Constant Variance) for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on GDs 7–19 (Berdasco et al. 1988)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Exponential (model 2)[d]	74	57	0.29	49.09	1.16	-0.78
Exponential (model 3)[d]	74	57	0.29	49.09	1.16	-0.78
Exponential (model 4)[d]	38	22	0.74	48.69	-0.28	0.16
Exponential (model 5)[d]			NA	50.58	0.00	0.00
Hill[d]			NA	50.58	0.00	0.00
Polynomial (3-degree)[e]	41	30	0.92	46.75	-0.29	0.05
Polynomial (2-degree)[e]	41	30	0.92	46.75	-0.29	0.05
Power[d]	41	30	0.92	46.75	-0.29	0.05
Linear[e,f]	**41**	**30**	**0.92**	**46.75**	**-0.29**	**0.05**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e] Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. With constant variance model applied, all models except the Exponential 5 and the Hill models provided adequate fit to the means (the Exponential 3 model converged on Exponential model 2, and Power and Polynomial models all converged upon the Linear model). BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear model)

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = exposure dose associated with a 1 standard deviation change in outcome); GD = gestation day; NA = not applicable (goodness of fit test cannot be calculated)

For maternal anemia in rabbits reported by Kirk et al. (1995), six frequentist, non-constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 2). The restricted Exponential 2 model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 37 and 30 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-14.

Table A-14. Model Predictions (Non-constant Variance) for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on GDs 7–19 (Kirk et al. 1995)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Exponential (model 2)[d,e]	**37**	**30**	**0.35**	**176.44**	**-1.25**	**-0.04**
Exponential (model 3)[d]	47	30	0.19	178.05	-0.76	-0.43
Exponential (model 4)[d]			0.04	180.61	0.71	0.21
Exponential (model 5)[d]			NA	180.48	-0.69	-0.60

Table A-14. Model Predictions (Non-constant Variance) for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on GDs 7–19 (Kirk et al. 1995)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Hill[d]			NA	180.50	-0.74	-0.57
Polynomial (3-degree)[f]	49	27	0.28	177.52	-0.57	-0.41
Polynomial (2-degree)[f]	48	27	0.21	177.93	-0.71	-0.44
Power[d]	50	25	0.14	178.48	-0.69	-0.60
Linear[f]	29	22	0.12	178.60	0.71	0.23

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model did not fit the variance data, but non-constant variance model did. With nonconstant variance model applied, all models except for Exponential models 4 and 5, and the Hill model, provided adequate fit to means. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential model 2).
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = exposure dose associated with a 1 standard deviation change in outcome); GD = gestation day; NA = not applicable (goodness of fit test cannot be calculated)

For decreased maternal body weight gain reported by Kirk et al. (1995), seven frequentist, non-constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (2-degree Polynomial). The restricted 2-degree Polynomial model estimated a BMD_{RD10} and $BMDL_{RD10}$ of 126 and 84 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-15.

Table A-15. Model Predictions (Constant Variance) for Reduced Body Weight Gain in Female Sprague-Dawley Rats Orally Administered 1,2-Dichloropropane on GDs 6–15 (Kirk et al. 1995)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Exponential (model 2)[d]	120	80	0.78	1,033.8	-0.14	-0.35
Exponential (model 3)[d]	126	83	0.95	1,035.3	0.00	0.03
Exponential (model 4)[d]	120	80	0.78	1,033.8	-0.14	-0.35
Exponential (model 5)[d]			NA	1,037.3	0.00	0.04
Hill[d]			NA	1,037.3	-9,999.00	0.04
Polynomial (3-degree)[e]	126	85	0.95	1,035.3	0.00	0.02
Polynomial (2-degree)[e,f]	**126**	**84**	**0.99**	**1,033.3**	**-0.01**	**-0.02**

Table A-15. Model Predictions (Constant Variance) for Reduced Body Weight Gain in Female Sprague-Dawley Rats Orally Administered 1,2-Dichloropropane on GDs 6–15 (Kirk et al. 1995)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Power[d]	126	85	0.95	1,035.3	0.00	0.03
Linear[e]	120	82	0.80	1,033.8	-0.12	-0.34

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. With constant variance model applied, all models provided adequate fit to the means, except for the Hill and Exponential 5 models. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (2-degree Polynomial).

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{RD10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., RD10 = exposure dose associated with a 10% change in outcome); GD = gestation day; NA = not applicable (goodness of fit test cannot be calculated)

Table A-16 summarized the potential candidate PODs for the acute-duration oral MRL for 1,2-dichloropropane. The lowest BMD value of 37 mg/kg/day is based on maternal anemia in rabbits (Kirk et al. 1995); this value is lower than BMD/LOAEL values associated with developmental, neurological, or body weight effects. Maternal anemia reported in the Kirk et al. (1995) and Berdasco et al. (1988) studies and delayed skull ossification in rats (Kirk et al. 1995) provided the same POD based on BMDL or NOAEL values, respectively (30 mg/kg/day). Based on adequate BMD modeling and consistency of results from two studies, maternal anemia was selected as the critical effect. For the Kirk et al. (1995) study, the Exponential 2 model fit to the hematological data in maternal rabbits is presented in Figure A-3. For the Berdasco et al. (1998) study, the Linear model fit to the hematological data in maternal rabbits is presented in Figure A-2; the 2- and 3-Degree Polynomial and Power models converge on the Linear model.

Table A-16. Candidate Points of Departure for 1,2-Dichloropropane Acute-Duration Oral MRL

Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Maternal anemia (Kirk et al. 1995)			37	30
Maternal anemia (Berdasco et al. 1988)			41	30
Delayed skull ossification (rat)	30	125		
Delayed skull ossification (rabbit)	50	150		
CNS depression (Sprague-Dawley rat)	ND	100		
Clinical signs of neurotoxicity	30	125		
CNS depression (Wistar rat)	ND	145		
Decreased maternal body weight gain			126	84

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; CNS = central nervous system; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Figure A-2. Fit of Exponential Model 2 to Data for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on Gestational Days 7–19 (Kirk et al. 1995)

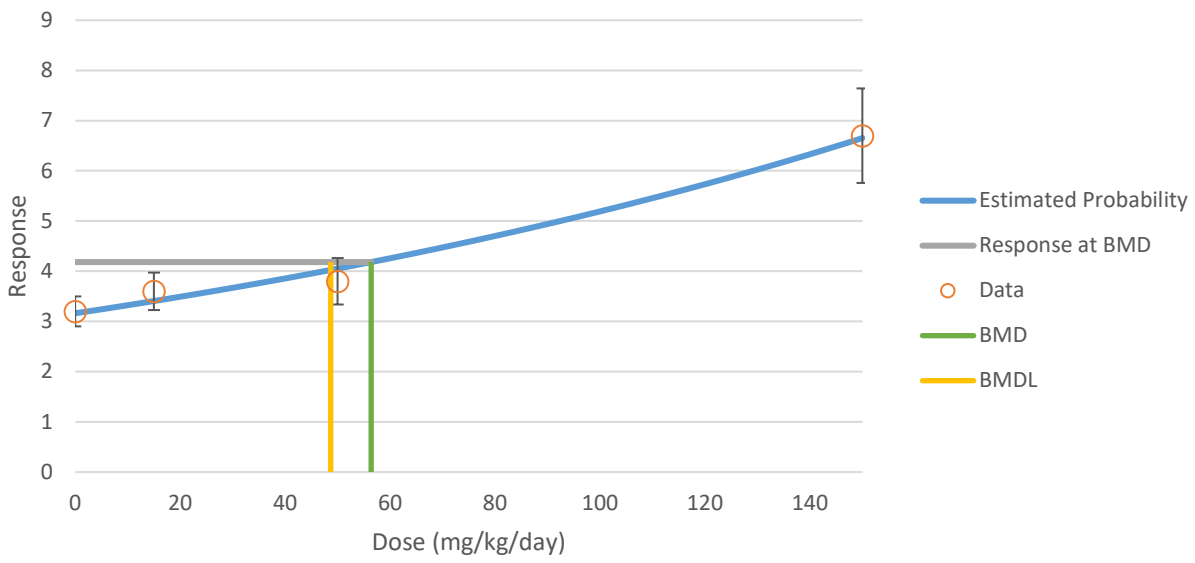
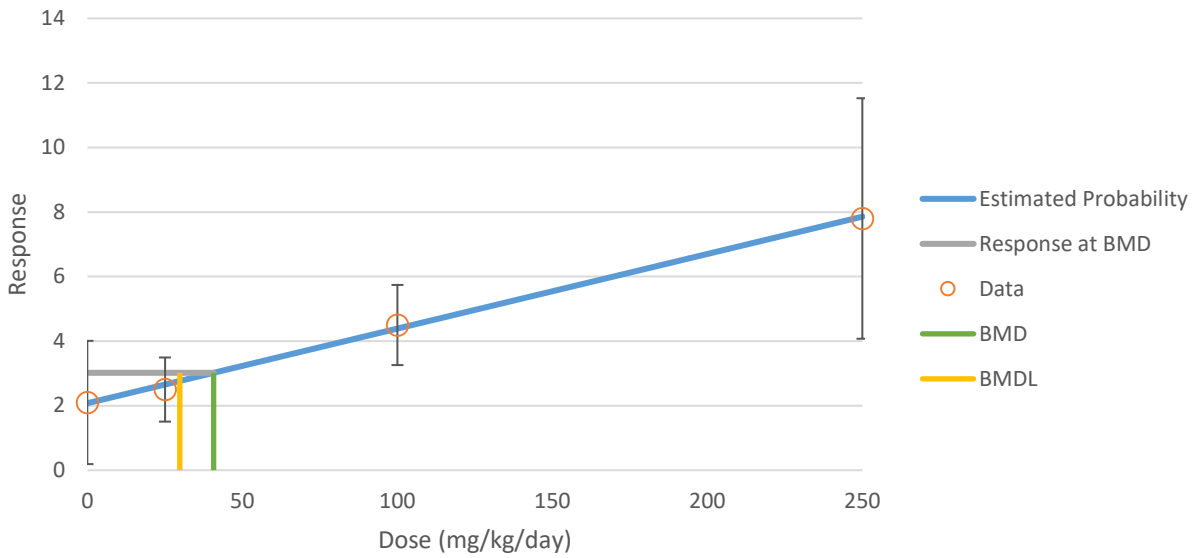


Figure A-3. Fit of Linear Model to Data for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on Gestational Days 7–19 (Berdasco et al. 1988)



Selection of the Principal Study: The two studies that provided identical BMCL values for the critical effect of maternal anemia were selected as co-principal studies for derivation of the acute oral MRL (Berdasco et al. 1988; Kirk et al. 1995).

Summary of the Co-Principal Studies:

Berdasco NM, Johnson KA, Hanley TRJ. 1988. Propylene dichloride: Oral teratology probe study in New Zealand white rabbits with cover letter dated 100188. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0516583. 86890000004.

Kirk HD, Berdasco NM, Breslin WJ, et al. 1995. Developmental toxicity of 1,2-dichloropropane (PDC) in rats and rabbits following oral gavage. Fundam Appl Toxicol 28(1):18-26.

Berdasco et al. (1988) administered 1,2-dichloroporpane (99.9% pure) to groups of artificially-inseminated rabbits via gavage in corn oil at doses of 0, 25, 100, or 250 mg/kg/day on GDs 7–19. Does were sacrificed on GD 20. Maternal toxicity endpoints evaluated included mortality, clinical signs of toxicity, body weight, gross necropsy, hematology (on GD 20), organ weights (kidney, liver, spleen), and eye examination (*in situ*, glass slide technique). Reproductive endpoints included the number of corpora lutea and numbers and positions of implantations and resorptions.

In the high-dose group, 2/7 does died; the cause of death was undetermined. Two additional high-dose animals showed weight loss and complete litter loss. Overall body weights did not differ between control and exposed animals and the resorption rates were not significantly different between groups. There were no exposure-related changes in organ weights or gross necropsy. Several changes were observed in hematological parameters, indicating regenerative anemia, including: 22–24% decreases in erythrocyte count, hemoglobin, and hematocrit at 500 mg/kg/day; a 2–3.7-fold increase in the percentage of reticulocytes at ≥100 mg/kg/day; increased slight-to-moderate polychromasia in red blood cells at ≥100 mg/kg/day; and increased slight-to-moderate anisocytosis in red blood cells at 250 mg/kg/day.

Kirk et al. (1995) administered 1,2-dichloropropane (99.9% pure) to groups of artificially inseminated rabbits via gavage in corn oil at doses of 0, 15, 50, or 150 mg/kg/day on GDs 7–19 (18 rabbits/group). Does were sacrificed on GD 28. Maternal toxicity endpoints evaluated included mortality, clinical signs, body weight, hematology (on GD 19), and organ weights (liver, kidney, spleen, gravid uterus). Reproductive and developmental endpoints included number of corpora lutea, number and position of implantations, resorptions, and live or dead fetuses, sex and body weight of each fetus, and external, visceral, and skeletal malformations.

In the high-dose group, 2/18 does died (one due to intubation error; cause of death not reported in second doe). Intermittent anorexia was observed in 17/18 does in the high-dose group during dosing. Significantly lowered weight gains were observed in high dose rabbits during dosing (GDs 7–20), but no significant differences were observed in absolute body weight compared to controls. Evidence of regenerative anemia was observed at the high dose (decreased erythrocyte counts, hemoglobin concentration, and hematocrit and increased platelet, leukocyte, and reticulocyte counts; slight-to-moderate anisocytosis, poikilocytosis, and/or polychromasia of red blood cells observed microscopically). No organ weight changes were observed. No exposure-related changes in the number of litters or pregnancy outcomes were observed. The litter incidence of delayed ossification of the skull was significantly elevated at 150 mg/kg/day (6/15 litters, 6/140 fetuses) and non-significantly elevated at 50 mg/kg/day (2/17 litters, 2/142 fetuses), compared with controls (0/18 litters, 0/149 fetuses).

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 30 mg/kg/day for increased maternal reticulocyte counts (from both studies) was selected as the POD.

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

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

$MRL = BMDL_{1SD} \div UFs$
$MRL = 30 \text{ mg/kg/day} \div (10 \times 10) = 0.3 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As detailed in Appendix C, hematological effects are a presumed health effect for humans. Several human case studies reported hematological effects, including hemolytic anemia, following accidental or intentional oral exposure to high levels of 1,2-dichloropropane (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985). In addition to the findings in maternal rabbits by Berdasco et al. (1988) and Kirk et al. (1995) following acute exposure, hemolytic anemia has also been reported following oral exposure in rats at an acute dose of 2,000 mg/kg/day (Imberti et al. 1990) and intermediate-duration doses as low as 100 mg/kg/day (Bruckner et al. 1989; Kirk et al. 1990). Evidence of hemolytic anemia was also observed in rats, mice, and rabbits following intermediate-duration inhalation exposure to concentrations as low as 150 ppm (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.07 mg/kg/day
Critical Effect: Hemolytic anemia
Reference: Bruckner et al. 1989
Point of Departure: LOAEL of 100 mg/kg/day ($LOAEL_{ADJ}$ of 71 mg/kg/day)
Uncertainty Factor: 1,000
LSE Graph Key: 19
Species: Rabbit

MRL Summary: An intermediate-duration oral MRL of 0.07 mg/kg/day was derived for 1,2-dichloropropane based on evidence of hemolytic anemia in rats exposed to doses ≥100 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 1989). The MRL is based on the LOAEL of 100 mg/kg/day, which was adjusted to a continuous exposure ($LOAEL_{ADJ}$) of 71 mg/kg/day for increased serum bilirubin, hemosiderosis in the spleen, and erythropoietic hyperplasia and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the toxicity of 1,2-dichloropropane following intermediate-duration oral exposure. The most sensitive effects identified in intermediate oral studies included hematological, hepatic, and body weight effects; see Table A-17. Since all of these adverse effects occurred at similar doses, all were considered for MRL derivation.

Table A-17. Summary of Candidate Critical Effects for Intermediate Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
B6C3F1 mouse	4 weeks 5 days/week (GO)	ND	125	Increased absolute liver weight	Gi et al. 2015a
B6C3F1 mouse	4 weeks 5 days/week (GO)	ND	125	Increased relative liver weight	Gi et al. 2015a
B6C3F1 mouse	4 weeks 5 days/week (GO)	ND	125	Mild fatty change	Gi et al. 2015a
Body weight effects					
F344 rat	13 weeks 5 days/week (GO)	65	200	Decreased body weight in males	Johnson and Gorzinski 1988

Table A-17. Summary of Candidate Critical Effects for Intermediate Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
Sprague-Dawley rat	13 weeks 5 days/week (GO)	ND	100	Hemolytic anemia	Bruckner et al. 1989

GO = gavage (oil vehicle); LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

In order to identify the most sensitive endpoint, BMD modeling was attempted for candidate critical endpoints listed in Table A-17 when data were amenable to modeling. Data modeled included increased absolute and relative liver weight in mice and decreased body weight in rats (see Tables A-18 and A-19). The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a BMR of 10% relative deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) 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. Histological effects in the liver were not amenable for modeling because the incidence increased from 0% in controls to 100% in the lowest dose tested (Gi et al. 2015a). Hematological data for rats were inadequate for modeling because exact animal number per group was not reported (Bruckner et al. 1989). Therefore, a NOAEL/LOAEL approach was used for these studies.

Table A-18. Body Weight in Male F344 Rats Following Gavage Administration of 1,2-Dichloropropane for 13 Weeks

	Dose (mg/kg/day)			
	0	20	65	200
Terminal body weight; mean±SD (N)	341.7±11.2 (15)	334.9±13.7 (15)	331.0±25.7 (15)	308.0±14.8 (15)

N = number; SD = standard deviation

Source: Johnson and Grozinski 1988

Table A-19. Liver Weight in B6C3F1 Mice Following Gavage Administration of 1,2-Dichloropropane for 4 Weeks (Gi et al. 2015a)

	Dose (mg/kg/day)		
	0	125	250
Absolute liver weight; mean±SD (N)	0.93±0.05 (5)	1.04±0.03 (5)	1.09±0.06 (5)
Relative liver weight; mean±SD (N)	3.67±0.16 (5)	4.03±0.20 (5)	4.2±0.14 (5)

N = number; SD = standard deviation

Source: Gi et al. 2015a

None of the BMD models (with constant variance or nonconstant variance) provided adequate fit to the decreased body weight in male rats. Therefore, a NOAEL/LOAEL approach was used for this endpoint.

For absolute liver weight, five frequentist, constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear); the 2-Degree Polynomial and Power models converged on the Linear model. The unrestricted Linear model estimated a BMD_{RD10} and $BMDL_{RD10}$ of 147 and 109 ppm, respectively. The results of the BMD modeling are summarized in Table A-20.

Table A-20. Model Predictions (Constant Variance) for Absolute Liver Weight in Male B6C3F1 Mice Orally Administered 1,2-Dichloropropane 5 Days/Week for 5 Weeks (Gi et al. 2015a)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	153	117	0.18	-43.85	1.07	-0.58
Exponential (model 3)[d]	153	117	0.18	-43.85	1.07	-0.58
Exponential (model 4)[d]			NA	-43.69	0.00	0.00
Exponential (model 5)[d]			<0.0001	-41.69	0.00	0.00
Hill[d]			<0.0001	-41.69	0.00	0.00
Polynomial (2-degree)[e]	147	109	0.22	-44.16	0.98	-0.49
Power[d]	147	109	0.22	-44.16	0.98	-0.49
Linear[e,f]	**147**	**109**	**0.22**	**-44.16**	**0.98**	**-0.49**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. With constant variance model applied, all models provided adequate fit to the means except for the Hill and Exponential 4 and 5 models (Exponential 3 converged upon Exponential 2 and the power and 2-degree polynomial models converged upon the linear model). BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure concentration associated with a 10% change in outcome); NA = not applicable (Goodness of fit test cannot be calculated); RD = relative deviation

For relative liver weight, five frequentist, constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear); the 2-Degree Polynomial and Power models converged on the Linear model. The unrestricted Linear model estimated a BMD_{RD10} and $BMDL_{RD10}$ of 175 and 129 ppm, respectively. The results of the BMD modeling are summarized in Table A-21.

Table A-21. Model Predictions (Constant Variance) for Relative Liver Weight in Male B6C3F1 Mice Orally Administered 1,2-Dichloropropane 5 Days/Week for 5 Weeks (Gi et al. 2015a)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	180	135	0.22	-6.70	0.97	-0.52
Exponential (model 3)[d]	180	135	0.22	-6.70	0.97	-0.52
Exponential (model 4)[d]			NA	-6.20	0.00	0.00
Exponential (model 5)[d]			NA	-6.20	0.00	0.00
Hill[d]			<0.0001	-4.20	0.00	0.00

Table A-21. Model Predictions (Constant Variance) for Relative Liver Weight in Male B6C3F1 Mice Orally Administered 1,2-Dichloropropane 5 Days/Week for 5 Weeks (Gi et al. 2015a)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	Scaled residuals[c]		
				AIC	Dose near BMD	Dose near control
Polynomial (2-degree)[e]	175	129	0.26	-6.93	0.90	-0.45
Power[d]	175	129	0.26	-6.93	0.90	-0.45
Linear[e,f]	**175**	**129**	**0.26**	**-6.93**	**0.90**	**-0.45**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance model provided adequate fit to the variance data. With constant variance model applied, all models except Exponential 4, provided adequate fit to means (Exponential 3 converged upon Exponential 2 and the power and 2-degree polynomial models converged upon the linear model). BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure concentration associated with a 10% change in outcome); NA = not applicable (Goodness of fit test cannot be calculated); RD = relative deviation

Table A-22 summarizes the potential candidate PODs for the intermediate-duration oral MRL for 1,2-dichloropropane. Based on the lowest available PODs, hematological effects (hemolytic anemia) were identified as the critical effect for following intermediate-duration oral exposure to 1,2-dichloropropane.

Table A-22. Candidate Points of Departure 1,2-Dichloropropane Acute-Duration Oral MRL

Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Increased absolute liver weight			145	109
Increased relative liver weight			175	129
Mild fatty liver change	ND	125		
Decreased body weight	65	200		
Hemolytic anemia	ND	100		

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level;

Selection of the Principal Study: The study with the lowest identified LOAEL for the critical effect of hemolytic anemia was selected as the principal study (Bruckner et al. 1989).

Summary of the Principal Study:

Bruckner JV, MacKenzie WF, Ramanathan R, et al. 1989. Oral toxicity of 1,2-dichloropropane: Acute, short-term, and long-term studies in rats. Fundam Appl Toxicol 12(4):713-730.

Groups of Sprague-Dawley rats were administered 1,2-dichloropropane (99% pure) via gavage in corn oil at doses of 0, 100, 250, 500, or 750 mg/kg/day for 13 weeks (5 days/week). Endpoints evaluated included mortality, clinical signs, body weight, serum chemistry, urinalysis, liver and kidney weight, and histology (liver, kidneys, lungs, brain, adrenals, spleen, stomach, testis, epididymis).

High mortality was observed in the 750 mg/kg/day group, with ~55% mortality within 10 days. The remaining animals were sacrificed moribund. By the end of the 13-week exposure period, >50% of the rats treated with 500 mg/kg/day had died. Survival was at least 90% in remaining groups. The 500 mg/kg/day group showed pronounced CNS depression, but no brain lesions were observed in any groups. Body weight gain was significantly decreased in a dose-related manner in all treatment groups throughout the study. Liver effects were seen only at 500 mg/kg/day and included periportal vacuolization and active fibroplasia. Evidence of hemolytic anemia was seen at all doses and was dose-related in severity. At 100 mg/kg/day, serum bilirubin was increased, and hemosiderosis in the spleen and erythropoietic hyperplasia were seen. At 250 mg/kg/day, hemosiderosis in the liver and kidney was also observed. Increased fat storage in the adrenal cortex was observed at 500 mg/kg/day; vacuolization of the adrenal medulla and lipidosis of the adrenal cortex were also observed in high-dose animals sacrificed moribund on day 10. Testicular effects seen at 500 mg/kg/day included degeneration, reduced sperm production, accumulation of spermatid giant cells, increased number of degenerate spermatogonia, and reduced number of sperm in epididymides. No such effects were observed at 100 or 250 mg/kg/day.

Selection of the Point of Departure for the MRL: The LOAEL of 100 mg/kg/day for hemolytic anemia was selected as the POD.

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

$LOAEL_{ADJ}$ = 100 mg/kg/day x 5 days/7 days = 71 mg/kg/day

Uncertainty Factor: $LOAEL_{ADJ}$ is divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $LOAEL_{ADJ}$ ÷ UFs
MRL = 71 mg/kg/day ÷ (10 x 10 x 10) = 0.07 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As discussed in the acute oral MRL worksheet, hemolytic anemia has been reported in several human case reports (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985) and following inhalation and oral exposure in laboratory animals (Berdasco et al. 1988, Bruckner et al. 1989; Imberti et al. 1990; Kirk et al. 1990, 1995; Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). Systematic review of available data indicates that hematological effects are a presumed health effect for humans (see Appendix C).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration oral MRL was not derived due to lack of adequate data for the critical effect of anemia (identified in acute- and intermediate-duration oral studies). Available chronic studies did not assess hematological parameters. Derivation of a chronic-duration oral MRL based on the lowest LOAEL identified in the available chronic studies (body weight effects) results in an MRL that is higher than the intermediate-duration oral MRL based on hematological effects and may not be protective of hematological effects. Thus, the chronic database was not considered adequate for derivation of a chronic oral MRL. Since it is unknown if hematological effects would occur at lower doses with longer exposure durations, it is considered inappropriate to base the chronic MRL on intermediate-duration data. Therefore, we cannot be sure that the intermediate MRL would be protective for chronic exposure.

Two studies evaluated the toxicity of 1,2-dichloropropane following chronic-duration oral exposure: one in rats and one in mice. The most sensitive effects identified in these studies included hepatic effects, hemosiderosis of the spleen, and body weight effects (see Table A-23). The data for these effects were not suitable for modeling. The lowest LOAEL identified was 125 mg/kg/day for body weight effects in male rats (NTP 1986); the associated NOAEL of 65 mg/kg/day would be the most sensitive POD.

After adjustment for intermittent exposure (65 mg/kg/day x 5 days/7 days), the $NOAEL_{ADJ}$ of 46 mg/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) would result in a chronic MRL of 0.5 mg/kg/day. This candidate MRL is almost 10-fold higher than the MRL derived for intermediate-duration oral exposure.

Table A-23. Summary of Candidate Critical Effects for Chronic Oral MRL for 1,2-Dichloropropane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
F344 rat	104 weeks 5 days/week (GO)	62	125	Decreased body weight in males	NTP 1986
Hepatic effects					
F344 rat	104 weeks 5 days/week (GO)	125	250	Clear cell foci and necrosis	NTP 1986

Table A-23. Summary of Candidate Critical Effects for Chronic Oral MRL for 1,2-Dichloropropane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
B6C3F1 mouse	104 weeks 5 days/week (GO)	125	250	Hepato-cytomegaly and necrosis in males	NTP 1986
Hematological effects					
F344 rat	104 weeks 5 days/week (GO)	125	250	Slight hemosiderosis of the spleen in females (blood hematological parameters not evaluated)	NTP 1986

GO = gavage (oil vehicle); LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Carolyn Harper

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

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-dichloropropane.

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 1,2-dichloropropane. 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 1,2-dichloropropane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dichloropropane 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 1,2-dichloropropane released for public comment in 2019; thus, the literature search was restricted to studies published between December 2015 and June 2020. The following main databases were searched in June 2020:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,2-dichloropropane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to 1,2-dichloropropane were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2020	("propylene dichloride"[nm] OR 78-87-5[rn] OR "1,2-DCP"[tw] OR "1,2-Dichloropropane"[tw] OR "1,2-Dichloropropane"[tw] OR "alpha,beta-Dichloropropane"[tw] OR "alpha,beta-Propylene dichloride"[tw] OR "D-D Mixture"[tw] OR "D-D Pilfume"[tw] OR "Dichloro-1,2 propane"[tw] OR "Dichloropropane, 1,2-"[tw] OR "Dorlone"[tw] OR "Dow-421"[tw] OR "Dowfume NC"[tw] OR "EP-201"[tw] OR "Nemex"[tw] OR "New Fieldfume"[tw] OR "Propane, 1,2-dichloro-"[tw] OR "Propylene chloride"[tw] OR "PROPYLENE DICHLORIDE"[tw] OR "Propylenedichloride"[tw] OR "R 270da"[tw] OR "Terr-o-cide"[tw] OR "Terr-o-gas"[tw] OR "Vidden D"[tw] OR "Vorlex"[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 ("Dichloropropanes"[tw] AND 1987:3000[dp]) "dichloropropane"[tw] OR "Propane dichloride"[tw] OR "Propane, dichloro-"[tw]
NTRL	
06/2020	Limits: Date Published 2015 to 2020 "1,2-DCP" OR "1,2-Dichloro-propane" OR "1,2-Dichloropropane" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "D-D Mixture" OR "D-D Pilfume" OR "Dichloro-1,2 propane" OR "Dichloropropane, 1,2-" OR "Dorlone" OR "Dow-421" OR "Dowfume NC" OR "EP-201" OR "Nemex" OR "New Fieldfume" OR "Propane, 1,2-dichloro-" OR "Propylene chloride" OR "PROPYLENE DICHLORIDE" OR "Propylenedichloride" OR "R 270da" OR "Terr-o-cide" OR "Terr-o-gas" OR "Vidden D" OR "Vorlex" OR "Dichloropropanes" OR "Dichloropropane" OR "Propane dichloride" OR "Propane, dichloro"
Toxcenter	
06/2020	FILE 'TOXCENTER' ENTERED AT 13:09:33 ON 29 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 2285 SEA FILE=TOXCENTER 78-87-5 L2 0 SEA FILE=TOXCENTER 26198-63-0 L6 2106 SEA FILE=TOXCENTER L1 NOT PATENT/DT L8 186 SEA FILE=TOXCENTER L6 AND ED>=20151201 ACT TOXQUERY/Q --------- L10 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L11 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,

Table B-2. Database Query Strings

Database search date	Query string
	IT)
	L12 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L13 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L14 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L15 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L16 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L17 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L18 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L19 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L20 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L21 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L22 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L23 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L24 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L25 QUE (ENDOCRIN? AND DISRUPT?)
	L26 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L27 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L28 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L29 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L30 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L31 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L32 QUE (NEPHROTOX? OR HEPATOTOX?)
	L33 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L34 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L35 QUE 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 OR L33 OR L34
	L36 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
	L37 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L38 QUE L35 OR L36 OR L37 L39 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L40 QUE L38 OR L39 --------- L41 100 SEA FILE=TOXCENTER L8 AND L40 D SCAN L41 69: FILE 'TOXCENTER' ENTERED AT 09:42:29 ON 30 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 157 SEA FILE=TOXCENTER 26638-19-7 NOT 78-87-5 L2 115 SEA FILE=TOXCENTER L1 NOT (PATENT/DT OR TSCATS/FS) ACT TOXQUERY/Q --------- L3 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L4 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L5 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L6 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L7 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L8 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L9 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L10 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L11 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L12 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L13 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L14 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L15 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L16 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L17 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L18 QUE (ENDOCRIN? AND DISRUPT?)

Table B-2. Database Query Strings

Database search date	Query string
	L19 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L20 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L21 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L22 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L23 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L24 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L25 QUE (NEPHROTOX? OR HEPATOTOX?) L26 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L27 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L28 QUE L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 L29 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?) L30 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L31 QUE L28 OR L29 OR L30 L32 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L33 QUE L31 OR L32 --------- L34 69 SEA FILE=TOXCENTER L2 AND L33 D SCAN L34

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2020	Compounds searched: 78-87-5; 26198-63-0; 26638-19-7
NTP	
06/2020	Limited 2015-present 78-87-5 26198-63-0 "1,2-DCP" "1,2-Dichloro-propane" "1,2-Dichloropropane" "alpha,beta-Dichloropropane" "alpha,beta-Propylene dichloride" "D-D Mixture" "D-D Pilfume" "Dichloro-1,2 propane" "Dichloropropane, 1,2-" "Dorlone" "Dow-421" "Dowfume NC" "EP-201" "Nemex" "New Fieldfume" "Propane, 1,2-dichloro-" "Propylene chloride" "PROPYLENE DICHLORIDE" "Propylenedichloride" "R 270da" "Terr-o-cide" "Terr-o-gas" "Vidden D" "Vorlex" "Dichloropropanes" "Dichloropropane" "26638-19-7" "Propane dichloride" "Propane, dichloro-"
NPIRS	
06/2020	PC Codes searched: 29002; 600030
Regulations.gov	
06/2020	78-87-5; 26198-63-0; 26638-19-7
NIH RePORTER	
10/2020	Search Criteria: Text Search: "1,2-DCP" OR "1,2-Dichloro-propane" OR "1,2-Dichloropropane" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "D-D Pilfume" OR "Dichloro-1,2 propane" OR "Dichloropropane, 1,2-" OR "Dorlone" OR "Dow-421" OR "Dowfume NC" OR "EP-201" OR "Nemex" OR "New Fieldfume" OR "Propane, 1,2-dichloro-" OR "Propylene chloride" OR "PROPYLENE DICHLORIDE" OR "Propylenedichloride" OR "R 270da" OR "Terr-o-cide" OR "Terr-o-gas" OR "Vidden D" OR "Vorlex" OR "Dichloropropanes" OR Dichloropropane (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): 340
- Number of records identified from other strategies: 28
- Total number of records to undergo literature screening: 368

B.1.2 Literature Screening

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

- 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.

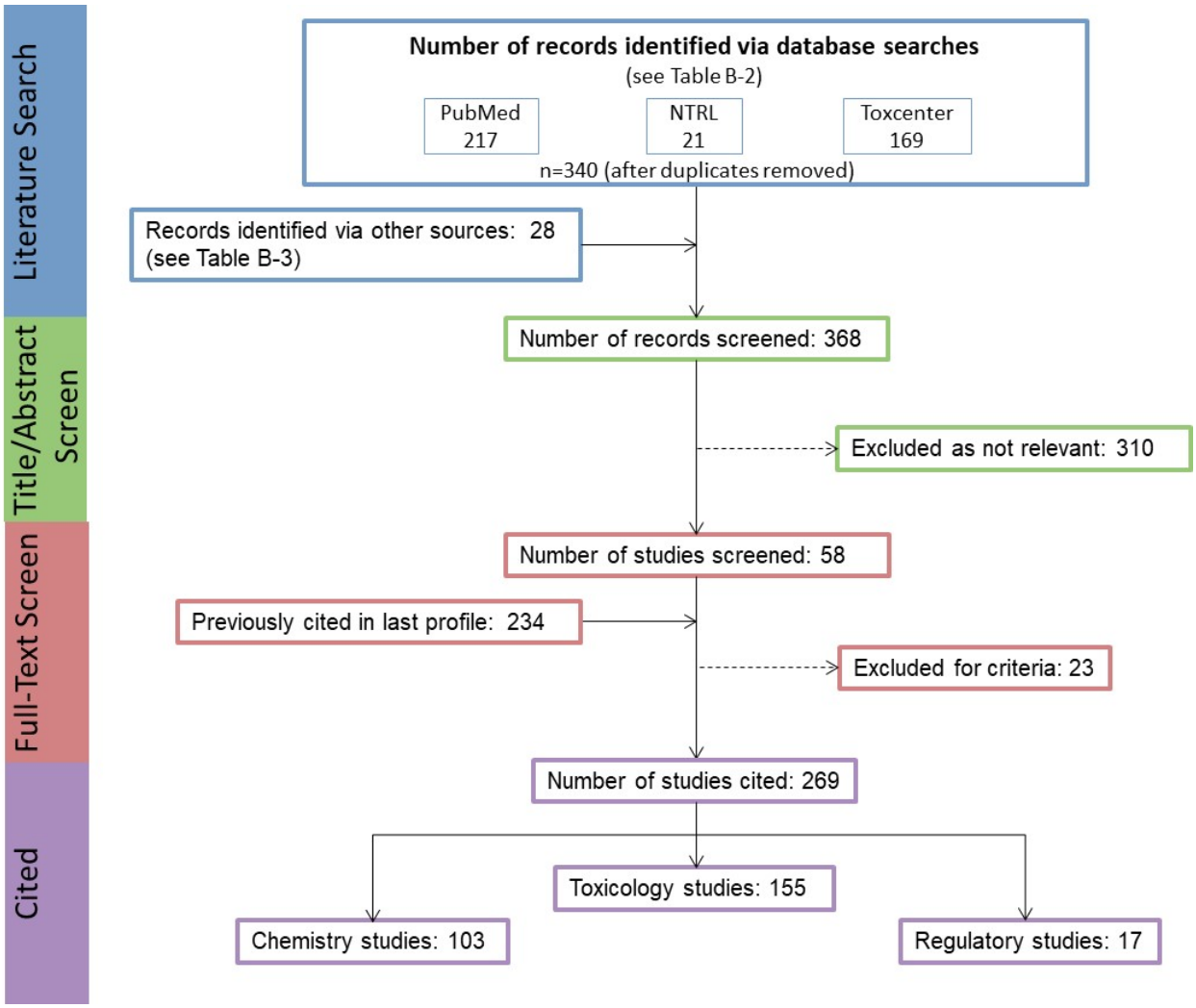
- Number of titles and abstracts screened: 368
- Number of studies considered relevant and moved to the next step: 58

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: 58
- Number of studies cited in the pre-public draft of the toxicological profile: 234
- Total number of studies cited in the profile: 269

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

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



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

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to 1,2-dichloropropane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to 1,2-dichloropropane:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-dichloropropane. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dichloropropane 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 1,2-dichloropropane. 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 1,2-dichloropropane released for public comment in 2019. See Appendix B for the databases searched and the search strategy.

A total of 368 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 1,2-dichloropropane.

Title and Abstract Screen. In the Title and Abstract Screen step, 368 records were reviewed; 8 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 72 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 72 documents, 121 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted from Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for 1,2-dichloropropane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in 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 2-2, 2-3, and 2-4, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,2-dichloropropane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The only available human studies evaluating noncancer effects are limited to case reports of accidental or intentional exposure. However, when evaluated together, these studies indicate that hematological, hepatic, renal, and neurological systems are susceptible to 1,2-dichloropropane toxicity. Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin irritation, and skin sensitization. Respiratory, hematological, hepatic, renal, neurological, and developmental effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 121 studies (published in 72 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 Substance 1,2-Dichloropropane 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												5 5
Case control												1					
Population																	
Case series/reports		1 1		2 2	2 2		3 3	1 1		1 1			2 2	1 1			11 11
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series/reports			3 3		3 3		5 5	2 2					2 2				
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series/reports			1 1	1 1	1 1	1 1	1 1	1 1	3 3			2 2					

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

APPENDIX C

Table C-4. Overview of the Health Outcomes for 1,2-Dichloropropane 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	9	5	5		5		27	16		1	10	3	9	3			
	3	5			3		17	8		1	5	1	8				
Intermediate-duration	10	5	12	5	12	3	14	12	3	3	7	5	6	6			1
	6	4	2	1	10		8	3			3		1	1			1
Chronic-duration	2	2	2	2	2		2	2	1		2	2	2	2			2
	2				1												2
Oral studies																	
Acute-duration	10	3		2	8		13	12			1		8	6	2		
	7			1	4		8						7	2	2		
Intermediate-duration	7	5	2	3	6	2	6	6	2	1	3	2	4	4	1		1
	4				2	2	5				1		1	1	1		
Chronic-duration	2	2	2	2	2	2	2	2	2		2	2	2	2			2
	1			1			2										2
Dermal studies																	
Acute-duration	2								4			1					
									4			1					
Intermediate-duration																	
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for human observational studies and animal experimental studies are presented in Tables C-8 and C-9, respectively.

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 1,2-Dichloropropane —Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	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 exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	
Outcome: Upper respiratory effects							
Inhalation—case reports							
Rubin 1988	– –	– –	–	– –	+	–	Third
Outcome: Hematological Effects							
Inhalation – retrospective cohort							
Kumagai et al. 2013, 2014	++	–	+	– –	**+**	++	Third
Inhalation—case reports							
Lucantoni et al. 1991, 1992	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	
Oral—case reports							
Di Nucci et al. 1988	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Dermal—case reports							
Fiaccadori et al. 2003	– –	– –	–	– –	+	–	Third
Outcome: Hepatic Effects							
Inhalation—case reports							
Lucantoni et al. 1991, 1992	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Kubo et al. 2015	– –	– –	–	– –	+	–	Third
Oral—case reports							Third
Chiappino and Secchi 1968	– –	– –	–	– –	+	–	Third
Di Nucci et al. 1988	– –	– –	–	– –	+	–	Third
Larcan et al. 1977	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 1,2-Dichloropropane —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 exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Secchi and Alessio 1968	– –	– –	–	– –	+	–	Third
Thorel et al. 1986	– –	– –	–	– –	+	–	Third
Dermal—case reports							
Fiaccadori et al. 2003	– –	– –	–	– –	+	–	Third
Outcome: Renal Effects							
Inhalation—case reports							
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Oral—case reports							
Di Nucci et al. 1988	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Dermal—case reports							
Fiaccadori et al. 2003	– –	– –	–	– –	+	–	Third
Outcome: CNS Depression							
Inhalation—case reports							
Kwack et al. 2018	– –	– –	+	–	+	+	Third
Rubin 1988	– –	– –	–	– –	+	–	Third
Oral—case reports							
Larcan et al. 1977	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third

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

Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Upper Respiratory Effects										
Inhalation acute exposure										
Nitschke and Johnson 1983 (rat; 2 weeks)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke and Johnson 1983 (mouse; 2 weeks)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke and Johnson 1983 (rabbit; 2 weeks)	++	+	++	+	++	++	**++**	++	NA	First
Inhalation intermediate exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	**++**	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	**++**	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Outcome: Hematological Effects										
Inhalation acute exposure										
Heppel et al. 1946b (rat; 5–8 days)	–	+	++	+	+	–	**–**	+	NA	Second
Heppel et al. 1946a (guinea pig; 5 days)	–	+	++	+	+	–	**–**	+	NA	Second
Heppel et al. 1946a (rabbit; 2–8 days)	–	+	++	+	+	–	**–**	+	NA	Second
Nitschke and Johnson 1983 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke and Johnson 1983 (mouse)	++	+	++	+	++	++	**++**	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation intermediate exposure										
Heppel et al. 1946b (dog)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946b (rat)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (dog)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Oral acute exposure										
Berdasco et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gorzinski and Johnson 1989 (rat)	+	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Imberti et al. 1990 (rat)	–	–	– –	–	+	++	–	+	NA	Third
Kirk et al. 1989 (rat)	++	+	++	+	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster)	–	+	++	+	++	++	++	++	NA	First
Kirk et al. 1990 (rat)	++	+	++	+	++	++	++	++	NA	First
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Oral chronic exposure										
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Outcome: Hepatic Effects										
Inhalation acute exposure										
Di Nucci et al. 1990 (rat)	–	+	+	+	++	–	–	++	NA	Second
Drew et al. 1978 (rat)	–	+	+	+	++	+	–	++	NA	Second
Heppel et al. 1946a (rat; 7 hours)	– –	– –	– –	– –	+	–	– –	+	NA	Third
Heppel et al. 1946a (rat; 5–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (mouse; 2–7 hours)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit; 2–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig; 5 days)	–	+	++	+	+	–	–	+	NA	Second

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (rat; 5 days)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 7 hours)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 2–3 days)	–	+	+	+	+	–	–	+	NA	Second
Nitschke and Johnson 1983 (rat; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rat; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rabbit; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Toyooka et al. 2017 (mouse)	–	+	++	+	++	++	+	++	NA	First
Wang et al. 2019 (mouse, up to 4 hours)	–	+	++	+	++	+	++	+	NA	First
Wang et al. 2019 (mouse, 6 hours)	–	+	++	+	++	+	++	+	NA	First
Zhang et al. 2015 (rat, 7 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (C57BL/6 mouse; 7 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (BALB mouse; 7 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (mouse; 14 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (hamster; 7 days)	–	+	+	+	+	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Zhang et al. 2015 (hamster; 14 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (guinea pig; 7 days)	–	+	+	+	+	++	++	++	NA	First
Inhalation intermediate exposure										
Heppel et al. 1946a (dog)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946a (rat)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (dog)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Zhang et al. 2018 (mouse)	+	+	++	++	++	++	++	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Oral acute exposure										
Berdasco et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Di Nucci et al. 1988 (rat)	–	+	+	+	++	–	–	++	NA	Second
Gi et al. 2015a (mouse; once)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; once)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gorzinski and Johnson 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Imberti et al. 1990 (rat)	–	–	– –	–	+	++	–	+	NA	Third
Kirk et al. 1988 (rabbit)	–	–	++	–	++	++	+	++	NA	First
Kirk et al. 1989 (rat)	++	+	++	+	++	++	++	++	NA	First
Kirk et al. 1995 (rat)	++	++	++	++	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster)	–	+	++	+	++	++	++	++	NA	First
Kirk et al. 1990 (rat)	++	+	++	+	++	++	++	++	NA	First
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Oral chronic exposure										
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Renal Effects										
Inhalation acute exposure										
Heppel et al. 1946a (rat; 5–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (mouse; 2–7 hours)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit; 2–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig; 5 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (rat; 5 days)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 7 hours)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 2–3 days)	–	+	+	+	+	–	–	+	NA	Second
Nitschke and Johnson 1983 (rat; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rat; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rabbit; 2 weeks)	++	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation intermediate exposure										
Heppel et al. 1946a (dog)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946a (rat)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (dog)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rabbit)	–	+	+	+	+	–	–	+	NA	Second
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Oral acute exposure										
Berdasco et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; 4 days)	–	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Gorzinski and Johnson 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Imberti et al. 1990 (rat)	–	–	– –	–	+	++	–	+	NA	Third
Kirk et al. 1988 (rabbit)	–	–	++	–	++	++	+	++	NA	First
Kirk et al. 1989 (rat)	++	+	++	+	++	++	++	++	NA	First
Kirk et al. 1995 (rat)	++	++	++	++	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (rat)	+	+	++	+	++	++	++	+	NA	First
NTP 1986 (mouse)	+	+	++	+	++	++	++	+	NA	First
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster)	–	+	++	+	++	++	++	++	NA	First
Kirk et al. 1990 (rat)	++	+	++	+	++	++	++	++	NA	First
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Oral chronic exposure										
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Outcome: CNS Depression										
Inhalation acute exposure										
Heppel et al. 1946a (rat; 7 hours)	– –	– –	– –	– –	+	–	–	+	NA	Third
Heppel et al. 1946a (rat; 5–8 days)	–	–	++	–	+	–	–	+	NA	Third

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Heppel et al. 1946a (mouse; 2–7 hours)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946a (guinea pig; 5 days)	–	–	++	–	+	–	–	+	NA	Third
Nitschke and Johnson 1983 (rat; 6 hours)	++	+	++	+	+	++	++	+	NA	First
Nitschke and Johnson 1983 (mouse; 6 hours)	++	+	++	+	+	++	++	+	NA	First
Sidorenko et al. 1979 (rat)	–	–	–	–	–	–	–	–	NA	Third
Sidorenko et al. 1976 (mouse)	–	–	–	–	–	–	–	–	NA	Third
Inhalation intermediate exposure										
Sidorenko et al. 1979 (rat)	–	–	–	–	–	–	–	–	NA	Third
Oral acute exposure										
Bruckner et al. 1989 (rat)	+	–	++	–	++	++	++	++	NA	First
Exxon 1981a (rat)	++	–	++	–	–	++	+	++	NA	First
Gorzinski and Johnson 1989 (rat)	+	–	++	–	++	++	++	++	NA	First
Kirk et al. 1988 (rabbit)	–	–	++	–	++	++	+	++	NA	First
Kirk et al. 1989 (rat)	++	–	++	–	++	++	++	++	NA	First
Kirk et al. 1995 (rat)	++	++	++	++	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
Shell Oil Co. 1982 (rat)	–	–	++	–	++	–	+	++	NA	Second
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	–	++	–	++	++	++	++	NA	First
Johnson and Gorzinski 1988 (rat)	++	++	++	++	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Developmental Effects										
Oral acute exposure										
Kirk et al. 1995 (rat)	++	++	++	++	++	++	**++**	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	**++**	++	NA	First
Oral intermediate exposure										
Kirk et al. 1990 (rat)	++	+	++	+	++	++	**++**	++	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 1,2-dichloropropane 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 1,2-dichloropropane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-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 upper respiratory, hematological, hepatic, renal, neurological, and developmental effects observed in human observational studies 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.

Table C-13. Presence of Key Features of Study Design for 1,2-Dichloropropane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Upper respiratory effects					
Inhalation—case reports					
Rubin 1988	No	Yes	Yes	No	Low
Outcome: Hematological Effects					
Inhalation—retrospective cohort					
Kumagai et al. 2013, 2014	No	Yes	Yes	Yes	Moderate
Inhalation—case reports					
Lucantoni et al. 1991, 1992	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Oral—case reports					
Di Nucci et al. 1988	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Dermal—case reports					
Fiaccadori et al. 2003	No	Yes	Yes	No	Low
Outcome: Hepatic Effects					
Inhalation—case reports					
Lucantoni et al. 1991, 1992	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Kubo et al. 2015	No	Yes	Yes	No	Low
Oral—case reports					
Chiappino and Secchi 1968	No	Yes	Yes	No	Low
Di Nucci et al. 1988	No	Yes	Yes	No	Low
Larcan et al. 1977	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Secchi and Alessio 1968	No	Yes	Yes	No	Low
Thorel et al. 1986	No	Yes	Yes	No	Low
Dermal—case reports					
Fiaccadori et al. 2003	No	Yes	Yes	No	Low
Outcome: Renal Effects					
Inhalation—case reports					
Pozzi et al. 1985	No	Yes	Yes	No	Low
Oral—case reports					
Di Nucci et al. 1988	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low

Table C-13. Presence of Key Features of Study Design for 1,2-Dichloropropane—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Dermal—case reports					
Fiaccadori et al. 2003	No	Yes	Yes	No	Low
Outcome: CNS Depression					
Inhalation—case reports					
Kwack et al. 2018	No	Yes	Yes	No	Low
Rubin 1988	No	Yes	Yes	No	Low
Oral—case reports					
Larcan et al. 1977	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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: Upper Respiratory Effects					
Inhalation acute exposure					
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Hematological Effects					
Inhalation acute exposure					
Heppel et al. 1946b (rat; 5–8 days)	No	Yes	No	No	Very Low

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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	
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	No	No	Very Low
Heppel et al. 1946a (rabbit; 2–8 days)	No	No	No	No	Very Low
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	Yes	High
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Heppel et al. 1946b (dog)	Yes	No	Yes	No	Low
Heppel et al. 1946b (rat)	Yes	Yes	No	No	Low
Heppel et al. 1946a (rabbit)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (dog)	Yes	Yes	No	No	Low
Heppel et al. 1948 (rat)	Yes	Yes	No	No	Low
Heppel et al. 1948 (mouse)	Yes	Yes	No	No	Low
Heppel et al. 1946a (guinea pig)	Yes	Yes	No	No	Low
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	No	Moderate
Umeda et al. 2010 (rat)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Berdasco et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Gi et al. 2015a (rat)	Yes	Yes	No	Yes	Moderate
Gi et al. 2015a (hamster)	Yes	Yes	No	Yes	Moderate
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Imberti et al. 1990 (rat)	No	Yes	Yes	No	Low
Kirk et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1995 (rabbit)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (mouse)	Yes	Yes	No	Yes	Moderate
Gi et al. 2015a (hamster)	Yes	Yes	Yes	Yes	High
Kirk et al. 1990 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1986 (mouse)	Yes	Yes	No	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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					
NTP 1986 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1986 (mouse)	Yes	Yes	No	Yes	Moderate
Outcome: Hepatic Effects					
Inhalation acute exposure					
Di Nucci et al. 1990 (rat)	Yes	Yes	No	No	Low
Drew et al. 1978 (rat)	Yes	Yes	No	No	Low
Heppel et al. 1946a (rat; 7 hours)	No	No	Yes	No	Very Low
Heppel et al. 1946a (rat; 5–8 days)	No	Yes	Yes	No	Low
Heppel et al. 1946a (mouse; 2–7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (rabbit; 2–8 days)	No	No	Yes	No	Very Low
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	Yes	No	Low
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (guinea pig)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (rat; 5 days)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 7 hours)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 2–3 days)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Yes	Yes	Yes	No	Moderate
Toyooka et al. 2017	Yes	NR	No	No	Very Low
Wang et al. 2019 (mouse, up to 4 hours)	Yes	Yes	Yes	Yes	High
Wang et al. 2019 (mouse, 6 hours)	Yes	Yes	Yes	Yes	High
Zhang et al. 2015 (rat; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (C57BL/6 mouse; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (BALB mouse; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (mouse; 14 days)	Yes	Yes	Yes	No	Moderate
Zhang et al. 2015 (hamster; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (hamster; 14 days)	Yes	Yes	Yes	No	Moderate
Zhang et al. 2015 (guinea pig; 7 days)	Yes	No	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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
Inhalation intermediate exposure					
Heppel et al. 1946a (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rabbit)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (guinea pig)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Zhang et al. 2018 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Berdasco et al. 1988 (rabbit)	Yes	Yes	No	Yes	Moderate
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Di Nucci et al. 1990 (rat)	Yes	Yes	No	Yes	Moderate
Gi et al. 2015a (mouse; once)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (mouse; 4 days)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster; once)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster; 4 days)	Yes	Yes	Yes	Yes	High
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Imberti et al. 1990 (rat)	No	Yes	No	No	Very Low
Kirk et al. 1988 (rabbit)	Yes	No	Yes	Yes	Moderate
Kirk et al. 1989 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rabbit)	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (mouse)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster)	Yes	Yes	Yes	Yes	High
Kirk et al. 1990 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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	
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Renal Effects					
Inhalation acute exposure					
Heppel et al. 1946a (rat; 5–8 days)	No	Yes	Yes	No	Low
Heppel et al. 1946a (mouse; 2–7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (rabbit; 2–8 days)	No	No	Yes	No	Very Low
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	Yes	No	Low
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (guinea pig)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (rat; 5 days)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 7 hours)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 2–3 days)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Heppel et al. 1946a (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rabbit)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (guinea pig)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (guinea pig)	Yes	Yes	Yes	No	Moderate
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Berdasco et al. 1988 (rabbit)	Yes	Yes	No	Yes	Moderate
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Gi et al. 2015a (mouse; 4 days)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster; 4 days)	Yes	Yes	Yes	Yes	High
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Imberti et al. 1990 (rat)	No	Yes	No	No	Very Low
Kirk et al. 1988 (rabbit)	Yes	No	Yes	Yes	Moderate
Kirk et al. 1989 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rabbit)	Yes	Yes	No	Yes	Moderate
NTP 1986 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1986 (mouse)	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Gi et al. 2015a (mouse)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster)	Yes	Yes	Yes	Yes	High
Kirk et al. 1990 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: CNS Depression					
Inhalation acute exposure					
Heppel et al. 1946a (rat; 7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (rat; 5–8 days)	No	Yes	Yes	No	Low
Heppel et al. 1946a (mouse; 2–7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	Yes	No	Low
Nitschke and Johnson 1983 (rat; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 6 hours)	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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	
Sidorenko et al. 1979 (rat)	Yes	NR	NR	No	Very low
Sidorenko et al. 1976 (mouse)	No	NR	Yes	No	Very low
Inhalation intermediate exposure					
Sidorenko et al. 1979 (rat)	Yes	NR	NR	No	Very low
Oral acute exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Exxon 1981a (rat)	No	Yes	Yes	No	Low
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1988 (rabbit)	Yes	No	Yes	Yes	Moderate
Kirk et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1995 (rat)	Yes	Yes	Yes	No	Moderate
Kirk et al. 1995 (rabbit)	Yes	Yes	Yes	No	Moderate
Shell Oil Co. 1982 (rat)	No	Yes	Yes	Yes	Moderate
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Johnson and Gorzinski 1988 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Developmental Effects					
Oral acute exposure					
Kirk et al. 1995 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1995 (rabbit)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Kirk et al. 1990 (rat)	Yes	Yes	No	Yes	Moderate

NR = not reported

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Upper Respiratory Effects		
Inhalation acute exposure		
Human studies		
Rubin 1988	Low	Low
Inhalation acute exposure		
Nitschke and Johnson 1983 (rat; 2 weeks)	Moderate	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Inhalation chronic exposure		
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Outcome: Hematological Effects		
Inhalation acute exposure		
Human Studies		
Lucantoni et al. 1991, 1992	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Heppel et al. 1946b (rat; 5–8 days)	Very Low	High
Heppel et al. 1946a (guinea pig; 5 days)	Very Low	
Heppel et al. 1946a (rabbit; 2–8 days)	Very Low	
Nitschke and Johnson 1983 (rat; 2 weeks)	High	
Nitschke and Johnson 1983 (mouse; 2 weeks)	High	
Inhalation intermediate exposure		
Animal studies		
Heppel et al. 1946b (dog)	Low	High
Heppel et al. 1946b (rat)	Low	
Heppel et al. 1946a (rabbit)	Moderate	
Heppel et al. 1948 (dog)	Low	
Heppel et al. 1948 (rat)	Low	
Heppel et al. 1948 (mouse)	Low	
Heppel et al. 1946a (guinea pig)	Low	
Matsumoto et al. 2013 (mouse)	High	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Inhalation chronic exposure		
Human studies		
Kumagai et al. 2013, 2014	Moderate	Moderate
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Oral acute exposure		
Human studies		
Di Nucci et al. 1988	Low	
Perbellini et al. 1985	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Berdasco et al. 1988 (rabbit)	High	
Bruckner et al. 1989 (rat)	Moderate	
Gi et al. 2015a (rat)	Moderate	
Gi et al. 2015a (hamster)	Moderate	High
Gorzinski and Johnson 1989 (rat)	High	
Imberti et al. 1990 (rat)	Low	
Kirk et al. 1989 (rat)	High	
Kirk et al. 1995 (rabbit)	High	
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	High	
Gi et al. 2015a (mouse)	Moderate	
Gi et al. 2015a (hamster)	High	High
Kirk et al. 1990 (rat)	High	
NTP 1986 (rat)	Moderate	
NTP 1986 (mouse)	Moderate	
Oral chronic exposure		
Animal studies		
NTP 1986 (rat)	Moderate	Moderate
NTP 1986 (mouse)	Moderate	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Dermal acute exposure		
Human studies		
Fiaccadori et al. 2003	Low	Low
Outcome: Hepatic Effects		
Inhalation acute exposure		
Human studies		
Lucantoni et al. 1991, 1992	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Di Nucci et al. 1990 (rat)	Low	Moderate
Drew et al. 1978 (rat)	Low	
Heppel et al. 1946a (rat; 7 hours)	Very Low	
Heppel et al. 1946a (rat; 5–8 days)	Low	
Heppel et al. 1946a (mouse; 2–7 hours)	Low	
Heppel et al. 1946a (rabbit; 2–8 days)	Very Low	
Heppel et al. 1946a (guinea pig; 5 days)	Low	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (guinea pig)	Moderate	
Highman and Heppel 1946 (rat; 5 days)	Moderate	
Highman and Heppel 1946 (guinea pig; 7 hours)	Moderate	
Highman and Heppel 1946 (guinea pig; 2–3 days)	Moderate	
Nitschke and Johnson 1983 (rat; 6 hours)	Moderate	
Nitschke and Johnson 1983 (rat; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (mouse; 6 hours)	Moderate	
Nitschke and Johnson 1983 (mouse; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Moderate	
Toyooka et al. 2017	Very Low	
Wang et al. 2019 (mouse, up to 4 hours)	High	
Wang et al. 2019 (mouse, 6 hours)	High	
Zhang et al. 2015 (rat; 7 days)	Low	
Zhang et al. 2015 (C57BL/6 mouse; 7 days)	Low	
Zhang et al. 2015 (BALB mouse; 7 days)	Low	
Zhang et al. 2015 (mouse; 14 days)	Moderate	
Zhang et al. 2015 (hamster; 7 days)	Low	
Zhang et al. 2015 (hamster; 14 days)	Moderate	
Zhang et al. 2015 (guinea pig;7 days)	Low	
Inhalation intermediate exposure		
Animal studies		
Heppel et al. 1946a (dog)	Moderate	High

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Heppel et al. 1946a (rat)	Moderate	
Heppel et al. 1946a (rabbit)	Moderate	
Heppel et al. 1946a (guinea pig)	Moderate	
Heppel et al. 1948 (dog)	Moderate	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (rabbit)	Moderate	
Matsumoto et al. 2013 (mouse)	High	
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Zhang et al. 2018 (mouse)	High	
Inhalation chronic exposure		
Human studies		
Kubo et al. 2015	Low	Low
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Oral acute exposure		
Human studies		
Chiappino and Secchi 1968	Low	
Di Nucci et al. 1988	Low	
Larcan et al. 1977	Low	
Perbellini et al. 1985	Low	Low
Pozzi et al. 1985	Low	
Secchi and Alessio 1968	Low	
Thorel et al. 1986	Low	
Animal studies		
Berdasco et al. 1988 (rabbit)	Moderate	
Bruckner et al. 1989 (rat)	High	
Di Nucci et al. 1988 (rat)	Moderate	
Gi et al. 2015a (mouse; once)	High	
Gi et al. 2015a (mouse; 4 days)	High	
Gi et al. 2015a (hamster; once)	High	High
Gi et al. 2015a (hamster; 4 days)	High	
Gorzinski and Johnson 1989 (rat)	High	
Imberti et al. 1990 (rat)	Very Low	
Kirk et al. 1988 (rabbit)	Moderate	
Kirk et al. 1989 (rat)	Moderate	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Kirk et al. 1995 (rat)	Moderate	
Kirk et al. 1995 (rabbit)	Moderate	
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	High	
Gi et al. 2015a (mouse)	High	
Gi et al. 2015a (hamster)	High	High
Kirk et al. 1990 (rat)	High	
NTP 1986 (rat)	High	
NTP 1986 (mouse)	High	
Oral chronic exposure		
Animal studies		
NTP 1986 (rat)	High	High
NTP 1986 (mouse)	High	
Dermal acute exposure		
Human studies		
Fiaccadori et al. 2003	Low	Low
Outcome: Renal Effects		
Inhalation acute exposure		
Human studies		
Pozzi et al. 1985	Low	Low
Animal studies		
Heppel et al. 1946a (rat; 5–8 days)	Low	
Heppel et al. 1946a (mouse; 2–7 hours)	Low	
Heppel et al. 1946a (rabbit; 2–8 days)	Very Low	
Heppel et al. 1946a (guinea pig; 5 days)	Low	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (guinea pig)	Moderate	
Highman and Heppel 1946 (rat; 5 days)	Moderate	Moderate
Highman and Heppel 1946 (guinea pig; 7 hours)	Moderate	
Highman and Heppel 1946 (guinea pig; 2–3 days)	Moderate	
Nitschke and Johnson 1983 (rat; 6 hours)	Moderate	
Nitschke and Johnson 1983 (rat; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (mouse; 6 hours)	Moderate	
Nitschke and Johnson 1983 (mouse; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Heppel et al. 1946a (dog)	Moderate	High

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Heppel et al. 1946a (rat)	Moderate	
Heppel et al. 1946a (rabbit)	Moderate	
Heppel et al. 1946a (guinea pig)	Moderate	
Heppel et al. 1948 (dog)	Moderate	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (guinea pig)	Moderate	
Matsumoto et al. 2013 (mouse)	High	
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Inhalation chronic exposure		
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Oral acute exposure		
Human studies		
Di Nucci et al. 1988	Low	
Perbellini et al. 1985	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Berdasco et al. 1988 (rabbit)	Moderate	
Bruckner et al. 1989 (rat)	Moderate	
Gi et al. 2015a (mouse; 4 days)	High	
Gi et al. 2015a (hamster; 4 days)	High	
Gorzinski and Johnson 1989 (rat)	High	
Imberti et al. 1990 (rat)	Very Low	
Kirk et al. 1988 (rabbit)	Moderate	High
Kirk et al. 1989 (rat)	Moderate	
Kirk et al. 1995 (rat)	Moderate	
Kirk et al. 1995 (rabbit)	Moderate	
NTP 1986 (rat)	Moderate	
NTP 1986 (mouse)	Moderate	
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	Moderate	
Gi et al. 2015a (mouse)	High	High
Gi et al. 2015a (hamster)	High	
Kirk et al. 1990 (rat)	High	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1986 (rat)	High	
NTP 1986 (mouse)	High	
Oral chronic exposure		
Animal studies		
NTP 1986 (rat)	High	High
NTP 1986 (mouse)	High	
Dermal acute exposure		
Human studies		
Fiaccadori et al. 2003	Low	Low
Outcome: CNS Depression		
Inhalation acute exposure		
Human studies		
Kwack et al. 2018	Low	Low
Rubin 1988	Low	
Animal studies		
Heppel et al. 1946a (rat; 7 hours)	Low	Moderate
Heppel et al. 1946a (rat; 5–8 days)	Low	
Heppel et al. 1946a (mouse; 2–7 hours)	Low	
Heppel et al. 1946a (guinea pig; 5 days)	Low	
Nitschke and Johnson 1983 (rat; 6 hours)	Moderate	
Nitschke and Johnson 1983 (mouse; 6 hours)	Moderate	
Sidorenko et al. 1976 (mouse)	Very low	
Sidorenko et al. 1979 (rat)	Very low	
Inhalation intermediate exposure		
Animal studies		
Sidorenko et al. 1979 (rat)	Very low	Very Low
Oral acute exposure		
Human studies		
Larcan et al. 1977	Low	Low
Perbellini et al. 1985	Low	
Animal studies		
Bruckner et al. 1989 (rat)	Moderate	High
Exxon 1981a (rat)	Low	
Gorzinski and Johnson 1989 (rat)	High	
Kirk et al. 1988 (rabbit)	Moderate	
Kirk et al. 1989 (rat)	High	
Kirk et al. 1995 (rat)	Moderate	
Kirk et al. 1995 (rabbit)	Moderate	
Shell Oil Co. 1982 (rat)	Moderate	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	Moderate	High
Johnson and Gorzinski 1988 (rat)	High	
Outcome: Developmental Effects		
Oral acute exposure		
Animal studies		
Kirk et al. 1995 (rat)	High	High
Kirk et al. 1995 (rabbit)	High	
Oral intermediate exposure		
Animal studies		
Kirk et al. 1990 (rat)	Moderate	Moderate

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for upper respiratory, hematological, hepatic, renal, CNS depression, and developmental 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 1,2-dichloropropane exposure is presented in Table C-17.

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

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Upper Respiratory Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	+1 consistency in findings; +1 large magnitude of effect	High
Outcome: Hematological Effects			
Human studies	Low	-2 risk of bias, +1 consistency in findings	Very Low
Animal studies	High	None	High
Outcome: Hepatic Effects			
Human studies	Low	-2 risk of bias, +1 consistency in findings	Very Low
Animal studies	High	+1 consistency in findings	High
Outcome: Renal Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	-2 inconsistency	Low
Outcome: CNS Depression			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	+1 consistency in findings	High
Outcome: Developmental Effects			
Animals studies	High	None	High

Table C-17. Confidence in the Body of Evidence for 1,2-Dichloropropane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Upper respiratory effects	Very Low	High
Hematological effects	Very Low	High
Hepatic effects	Very Low	High
Renal effects	Very Low	Low
CNS depression	Very Low	High
Developmental effects	No data	High

- **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 1,2-dichloropropane, 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 1,2-dichloropropane is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for 1,2-Dichloropropane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Upper respiratory effects	Very Low	Heath effect	Inadequate
Hematological effects	Very Low	Health effect	Inadequate
Hepatic effects	Very Low	Health effect	Inadequate
Renal effects	Very Low	Health effect	Inadequate
CNS depression	Very Low	Health effect	Inadequate
Developmental effects	No data	No data	Inadequate
Animal studies			
Upper respiratory effects	High	Health effect	High
Hematological effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Renal effects	Low	Mixed	Low
CNS depression	High	Health effect	High
Developmental effects	High	Health effect	High

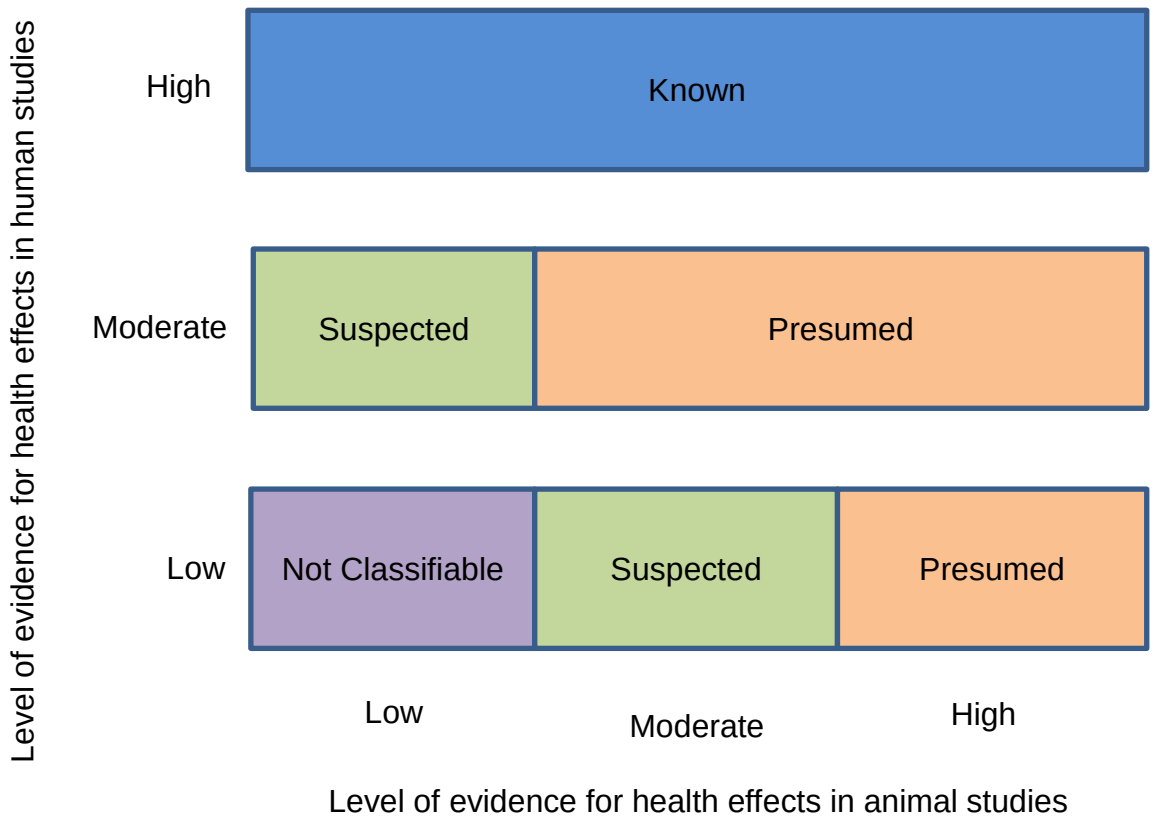
C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

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

The hazard identification conclusions for 1,2-dichloropropane are listed below and summarized in Table C-19.

Table C-19. Hazard Identification Conclusions for 1,2-Dichloropropane

Outcome	Hazard identification
Upper respiratory effects following inhalation exposure	Presumed health effect
Hematological effects	Presumed health effect
Hepatic effects	Presumed health effect
Renal effects	Not classifiable
CNS depression	Presumed health effect
Developmental effects	Presumed health effect

Presumed Health Effects

- Upper respiratory effects
    - Inadequate evidence from case reports of respiratory irritation following accidental industrial spills (Rubin 1988; ACGIH 2014)
    - High level of evidence of nasal lesions in rats, mice, and rabbits following intermediate or chronic inhalation exposure (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).
- Hematological effects
    - Although several case studies report hemolytic anemia and/or disseminating intravascular coagulation following acute inhalation, oral, or dermal exposure to 1,2-dichloropropane at unknown exposure levels (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985), the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
    - High level of evidence for hemolytic anemia in laboratory animals following inhalation or oral exposure (Berdasco et al. 1988; Bruckner et al. 1989; Imberti et al. 1990; Kirk et al. 1990, 1995; Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).
- Hepatic effects
    - Although a number of case reports indicate that the liver is a target of toxicity following inhalation, oral, or dermal exposure to 1,2-dichloropropane at unknown exposure levels (Chiappino and Secchi 1968; Di Nucci et al. 1988; Fiaccadori et al. 2003; Larcan et al. 1977; Lucantoni et al. 1991, 1992; Kubo et al. 2015; Perbellini et al. 1985; Pozzi et al. 1985; Secchi and Alessio 1968; Thorel et al. 1986), the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
    - High level of evidence of hepatic toxicity in laboratory animals following inhalation or oral exposure (Bruckner et al. 1989; Heppel et al. 1946a, 1948; Highman and Heppel

1946; Gorzinski and Johnson 1989; Gi et al. 2015a; Kirk et al. 1990; Matsumoto et al. 2013; NTP 1986; Umeda et al. 2010; Zhang et al. 2015).

- CNS depression
  - Although several case studies report severe CNS depression following acute inhalation or oral exposure to 1,2-dichloropropane at unknown exposure levels (Larcan et al. 1977; Perbellini et al. 1985; see also reviews by ACGIH 2014; EPA 2016a; IARC 2017), the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
  - High level of evidence from acute oral studies in laboratory animals (Bruckner et al. 1989; Exxon 1981a; Gorzinski and Johnson 1989; Kirk et al. 1989; Shell Oil Co. 1982) and low level of evidence from acute inhalation studies (Heppel et al. 1946a).
- Developmental effects
  - No data are available on whether inhalation, oral, or dermal exposure to 1,2-dichloropropane alters human development.
  - High level evidence in oral animal studies based on delayed ossification following gestational exposure in rats and rabbits and decreased neonatal survival and body weight in a 2-generation study in rats at doses associated with maternal toxicity (Kirk et al. 1990, 1995). No data are available on whether inhalation exposure to 1,2-dichloropropane alters animal development.

Not Classifiable Effects

- Renal effects
  - A few case reports indicate that the kidney is a target of toxicity following inhalation or oral exposure to 1,2-dichloropropane at unknown exposure levels (Di Nucci et al. 1988; Perbellini et al. 1985; Pozzi et al. 1985); however, the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
  - Low evidence of renal toxicity in laboratory animals due to inconsistent evidence in inhalation studies (Heppel et al. 1946a, 1948; Highman and Heppel 1946; Matsumoto et al. 2013) and lack of evidence in oral studies (Bruckner et al. 1989; Gi et al. 2015a; Gorzinski and Johnson 1989; Kirk et al. 1990; NTP 1986).

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

APPENDIX D

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

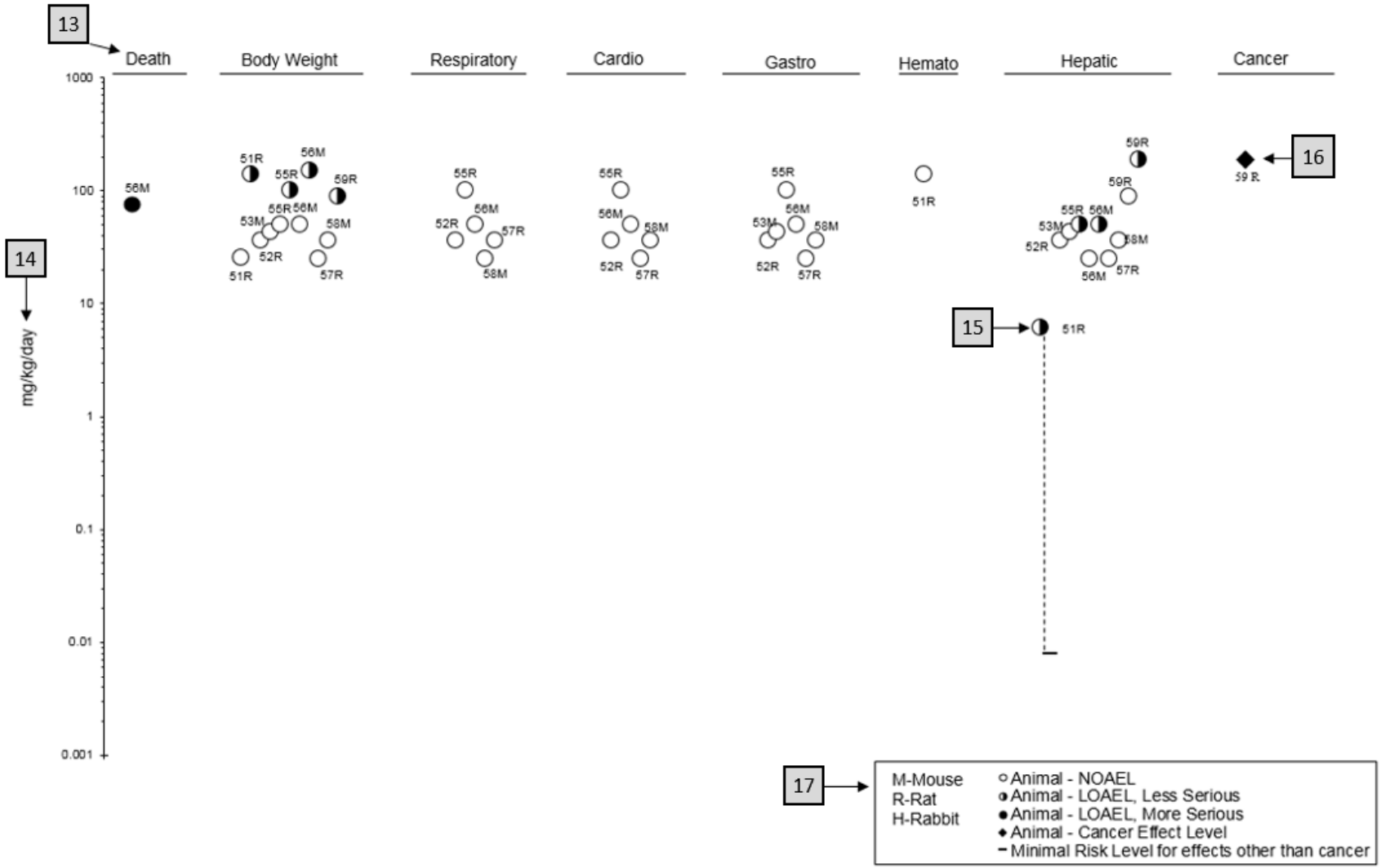
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

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

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

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
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