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 S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	1,2-Dichloroethane
CAS Numbers:	107-06-2
Date:	July 2024
Profile Status:	Final
Route:	Inhalation
Duration:	Acute
MRL:	0.1 ppm (0.4 mg/m^3)
Critical Effect:	Degeneration, with necrosis, olfactory epithelium
Reference:	Hotchkiss et al. 2010
Point of Departure:	$BMCL_{10}$ of 57.62 ppm ($BMCL_{HEC}$ of 3.84 ppm)
Uncertainty Factor:	30
LSE Graph Key:	5
Species:	Rat

MRL Summary: An acute-duration inhalation MRL of 0.1 ppm was derived for 1,2-dichloroethane based on an increased incidence of nasal epithelium degeneration/necrosis in rats administered 1,2-dichloroethane via inhalation (Hotchkiss et al. 2010). The MRL is based on a $BMCL_{10}$ of 57.62 ppm converted to human equivalent concentration ($BMCL_{HEC}$) of 3.84 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of 1,2-dichloroethane following acute-duration inhalation exposure; these studies examine a wide range of endpoints including neurotoxicity (Heppel et al. 1945; Hotchkiss et al. 2010; Jin et al. 2018a, 2018b; Niu et al. 2009; Wang et al. 2013, 2014, 2018; Zhang et al. 2011; Zhou et al. 2016), liver and kidney effects (Hotchkiss et al. 2010; Spencer et al. 1951), respiratory effects (Chan et al. 2002; Hotchkiss et al. 2010), immunotoxicity (Sherwood et al. 1987), developmental toxicity (Schlacter et al. 1979), reproductive toxicity (Zhang et al. 2017), gastrointestinal toxicity (Heppel et al. 1945), and hematotoxicity (Spencer et al. 1951). The LOAELs for these studies range from 50 to 3,000 ppm; a summary of the lowest NOAEL and LOAEL values is presented in Table A-1. To provide a consistent basis for comparison across species, the NOAELs and LOAELs were adjusted for intermittent exposure and converted to human equivalent concentrations (HECs) following EPA (1994a) methodology. For systemic (extrarespiratory) effects, the HEC is calculated by multiplying the duration-adjusted animal NOAEL or LOAEL by the ratio of the blood:gas partition coefficients in animals and humans. Gargas et al. (1989) estimated a blood:air partition coefficient of 19.5±0.7 for 1,2-dichloroethane in humans; however, a blood:air partition coefficient for mice was not located. The default value of 1 was used for the ratio in calculating the HEC values for reduced locomotor activity in mice (Wang et al. 2013). For effects on the respiratory tract, the regional gas dose ratio (RGDR) corresponding to the part of the respiratory tract that is affected was used. Thus, the RGDR for extrathoracic effects was used for nasal lesions and the $RGDR_{ET}$ (extrathoracic) value for rats (0.20) was calculated as follows:

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h}$$

where:

V_{E_a} = ventilation rate for male and female F344 rats = 0.211 L/minute (EPA 1994a)
SA_a = surface area of the extrathoracic region in rats = 15 cm^2 (EPA 1994a)

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

Species	Duration	NOAEL (ppm)	LOAEL or SLOAEL (ppm)	$NOAEL_{ADJ}$ (ppm)[a]	$LOAEL_{ADJ}$ (ppm)[a]	$NOAEL_{HEC}$ (ppm)	$LOAEL_{HEC}$ (ppm)	Effect	Reference
Respiratory effects									
Rat/ Fischer 344	8 hours	50	100	17	33	3.3	6.6	Olfactory epithelium degeneration/necrosis	Hotchkiss et al. 2010
Neurological effects									
Mouse/ Albino	3.5 hours/day 10 days	56	111	8.2	16.2	8.2	16.2	Reduced locomotor activity	Wang et al. 2013
Reproductive effects									
Mouse (Swiss-Webster)	6 hours/day, 7 days	25	86 (SLOAEL)	6.25	NA	6.25	NA	Increased abnormal sperm[b]	Zhang et al. 2017

[a]NOAEL and LOAEL values were adjusted from intermittent daily exposures to the equivalent of 24-hour continuous exposure. The duration adjusted values were calculated as:

$$Adjusted\ daily\ dose = Intermittent\ dose \times \frac{hours\ per\ day\ exposed}{24\ hours} \times \frac{days\ per\ week\ exposed}{7\ days}$$

[b]Histopathological effects at 86 ppm (vacuolar degeneration of germ cells in the seminiferous tubules and sloughing of spermatogenic cells into the lumen of the testes) are considered to be serious adverse effects.

LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NA = not applicable (MRLs cannot be based on exposure levels that produce serious adverse effects); NOAEL = no-observed-adverse-effect level; $NOAEL_{ADJ}$ = NOAEL adjusted to continuous exposure; $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ converted to human equivalent concentration (HEC; see text); SLOAEL = serious lowest-observed-adverse-effect level

V_{E_h} = ventilation rate for humans = 13.8 L/minute (EPA 1994a)
SA_h = surface area of the extrathoracic region in humans = 200 cm^2 (EPA 1994a)

As Table A-1 shows, the lowest $LOAEL_{HEC}$ and $NOAEL_{HEC}$ values were 6.6 and 3.3 ppm, respectively, for nasal epithelial degeneration and necrosis.

Selection of the Principal Study: Hotchkiss et al. (2010) conducted studies evaluating neurological and toxicological effects of 1,2-dichloroethane inhalation in rats. Hotchkiss et al. (2010) demonstrated a dose-response relationship between 1,2-dichloroethane exposure and degeneration of the nasal tissue. The $LOAEL_{HEC}$ and $NOAEL_{HEC}$ values for nasal lesions in the Hotchkiss et al. (2010) study were the lowest among the studies evaluating acute-duration exposure.

Summary of the Principal Study:

Hotchkiss JA, Andrus AK, Johnson KA, et al. 2010. Acute toxicologic and neurotoxic effects of inhaled 1,2-dichloroethane in adult Fischer 344 rats. Food Chem Toxicol 48(2):470-481. http://doi.org/10.1016/j.fct.2009.10.039.

Fischer 344 rats were exposed to 0, 200, 600, or 2,000 ppm (or 0.0, 196.4, 607.8, and 2,029 ppm as analytically measured mean concentrations delivered) 1,2-dichloroethane for 4 hours or 0, 50, 100, or 150 ppm (or 0.0, 52.8, 107.5, and 155.8 ppm as analytically measured mean concentrations delivered) for 8 hours. Neurobehavioral and neuropathological effects were assessed using a functional observational battery and by light microscopy, respectively. Acute toxicological effects were assessed by bronchoalveolar lavage and histopathology of the respiratory tract and selected target organs. Neurobehavioral effects consistent with central nervous system depression were observed on day 1, but not at subsequent times (days 8 or 15). No neuropathological changes were reported. Degeneration/ necrosis of the olfactory epithelium was reported at an exposure of 107.5 ppm for 8 hours. Nasal regeneration occurred at 196.4 ppm (4-hour exposure). A decrease in adrenal, kidney, and liver weights occurred at an exposure concentration of 2,029 ppm for 4 hours.

Selection of the Point of Departure for the MRL: Benchmark dose (BMD) modeling was conducted to identify a point of departure (POD) using the data for degeneration/necrosis of nasal epithelium in rats administered 1,2-dichloroethane via inhalation for 8 hours. Combined male and female rat incidence data for nasal degeneration/necrosis were selected for BMD analysis (Table A-2) as the male and female data were deemed to be similar in their response. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.2.0.1) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMC (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 was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen. BMDS recommended the Multistage-3 model for nasal epithelium degeneration/ necrosis; however, this model yielded a BMCL (36.28 ppm) that was less than the experimental NOAEL (52.88 ppm) and three of four Multistage-3 model parameters were bounded. Evaluation of viable alternate models showed that the Log-Probit model derived a BMCL (57.62 ppm), similar to the experimental NOAEL (52.8 ppm), and provided a better fit than the Multistage 3-degree model with lower residuals near the BMC; therefore, the Log-Probit model was selected as the basis for estimating this MRL. The BMC/BMCL values considered for MRL derivation are presented in Table A-3 and the fit of the selected model is presented in Figure A-1.

Table A-2. Results from an 8-Hour Exposure to 1,2-Dichloroethane Via Inhalation and Subsequent Incidence of Nasal Epithelium Degeneration/Necrosis

Analytically measured mean concentration delivered (ppm)	Number (males and females)	Incidence of nasal epithelium degeneration/necrosis	
		Males	Females
0.0	10	0/5	0/5
52.8	10	0/5	0/5
107.5	10	1/5	3/5
155.8	10	4/5	5/5

Source: Hotchkiss et al. (2010)

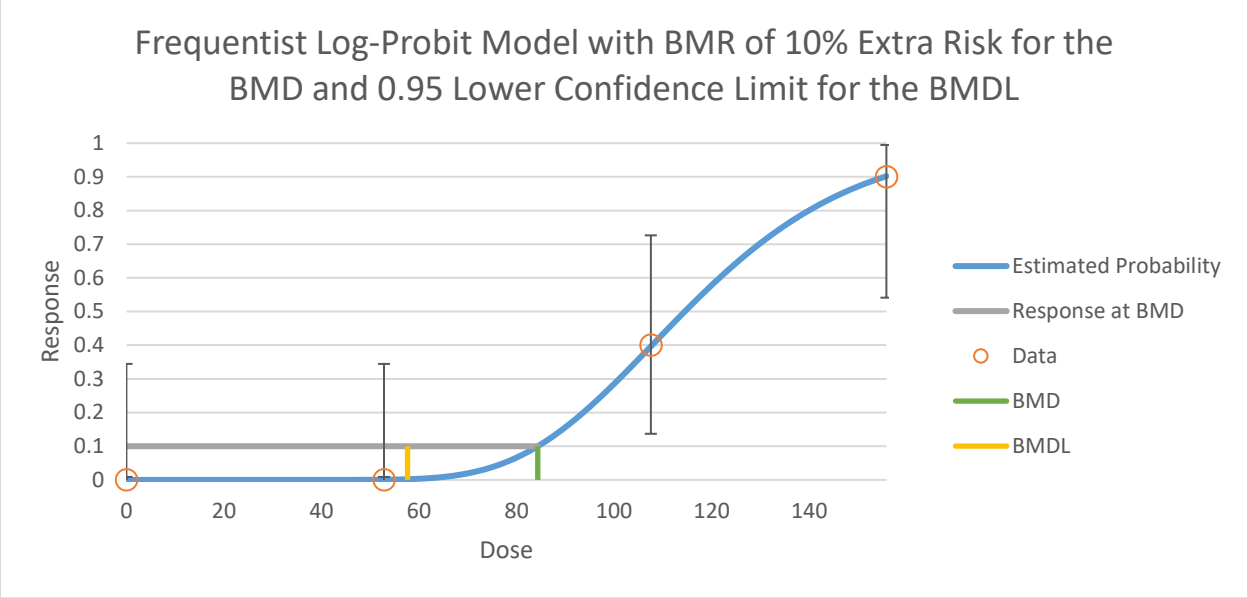
Table A-3. Model Predictions for Increased Incidence of Nasal Epithelium Degeneration/Necrosis in Male and Female (Combined) Rats Following Inhalation Exposure to 1,2-Dichloroethane for 8 Hours (Hotchkiss et al. 2010)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Dichotomous Hill			NA	27.96	-0.01	8.68×10^{-5}
Gamma[d]	83.06	55.73	0.98	24.01	-0.15	0.07
Log-Logistic[e]	84.68	57.42	0.83	26.04	-0.19	0.07
Multistage Degree 3[f]	60.32	36.28	0.77	23.80	-0.86	-0.31
Multistage Degree 2[f]	42.87	25.40	0.36	26.87	-0.0004	-1.32
Multistage Degree 1[f]			0.02	34.86	-0.0004	-1.96
Weibull[d]	78.44	50.57	0.61	26.39	-0.42	0.27
Logistic	81.81	53.84	0.85	24.46	-0.42	0.26
Log-Probit[g]	**84.32**	**57.62**	**0.997**	**23.97**	**-0.08**	**0.02**
Probit	81.49	52.26	0.91	24.26	-0.33	0.24

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]All models provided an adequate fit to the data except for the Dichotomous Hill and Multistage 1-degree models. BMCLs were sufficiently close (differed by <3-fold). The BMDS recommended the model with the lowest AIC (3-degree Multistage); however, three of the four parameters were bounded and the resulting BMCL (36.28) was lower than the experimental NOAEL (52.8 ppm). The Log-Probit model derived a BMCL value (57.62 ppm) similar to the experimental NOAEL and provided a better fit near the BMC with lower residuals; therefore, the Log-Probit model was selected.

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); BMDS = Benchmark Dose Software

Figure A-1. Fit of Log-Probit Model to Data on Incidence of Nasal Degeneration/Necrosis in Male and Female Rats (Combined) Administered 1,2-Dichloroethane via Inhalation for 8 Hours



Adjustment for Intermittent Exposure: The rats from the Hotchkiss et al. (2010) study were exposed for a total of 8 hours in a single day. Therefore, the $BMCL_{10}$ was adjusted for intermittent exposure as follows:

$$BMCL_{10ADJ} = BMCL_{10} \times \frac{8\ hours}{24\ hours} = 57.62\ ppm \times \frac{8\ hours}{24\ hours} = 19.21\ ppm$$

Human Equivalent Concentration: The $BMCL_{10ADJ}$ was converted to a HEC by multiplying the $BMCL_{10}$ by the rat-specific regional gas dose ratio that corresponds with the extrathoracic region ($RGDR_{ET}$), as nasal epithelium degeneration/necrosis is a localized-portal of entry effect (EPA 2012b). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994a):

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h}$$

where:
V_{E_a} = ventilation rate for male and female F344 rats = 0.211 L/minute (EPA 1994a)
SA_a = surface area of the extrathoracic region in rats = 15 cm^2 (EPA 1994a)
V_{E_h} = ventilation rate for humans = 13.8 L/minute (EPA 1994a)
SA_h = surface area of the extrathoracic region in humans = 200 cm^2 (EPA 1994a)

Applying this equation results in an RGDR of 0.20 and the HEC was calculated as:

$$BMCL_{10HEC} = BMCL_{10ADJ} \times RGDR = 3.84\ ppm$$

Uncertainty Factor: The $BMCL_{HEC}$ is divided by a total uncertainty factor (UF) of 30:

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

This resulted in the following MRL:

$$MRL = \frac{BMCL_{HEC}}{UFs} = \frac{3.84\ ppm}{30} = 0.13\ ppm, which\ rounds\ to\ 0.1\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Few studies of animals exposed to 1,3-dichloroethane by inhalation evaluated histopathology of the nasal turbinates. A chronic-duration study in rats exposed to 1,2-dichloroethane via inhalation also observed a NOAEL of 50 ppm for respiratory toxicity (Cheever et al. 1990). No histological alterations were observed in respiratory tracts, including nasal turbinates, of rats in this study. In another chronic-duration study, Nagano et al. (2006) evaluated a wide range of endpoints including clinical chemistry, hematology, gross pathology, organ weights, and histopathology; however, the publication does not specify the tissues examined for histopathology. The observation that the NOAELs were identical after acute- and chronic-duration exposure suggests that the nasal lesions may occur when exposure exceeds a concentration threshold.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: July 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.1 ppm (0.40 mg/m^3)
Critical Effect: Neurobehavioral changes (altered performance in open field test)
Reference: Zhong et al. 2022
Point of Departure: $BBMCL_{1SD}$ of 14.8 ppm ($BBMCL_{HEC}$ of 3.70 ppm)
Uncertainty Factor: 30
LSE Graph Key: 51
Species: Mouse

MRL Summary: An intermediate-duration inhalation MRL of 0.1 ppm was derived for 1,2-dichloroethane based on altered performance in an open field test of male mice. Mice were exposed to ≤173 ppm 1,2-dichloroethane for 28 days at 6 hours/day, 7 days/week (Zhong et al. 2022). The MRL is based on a Bayesian benchmark response of 1 standard deviation ($BBMCL_{1SD}$) of 14.8 ppm, which was adjusted to continuous duration exposure (6 hour/24 hour) and converted to a $BBMCL_{1SD\text{-}HEC}$ of 3.70 ppm. The $BBMCL_{1SD\text{-}HEC}$ of 3.70 ppm was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Review of the intermediate-duration inhalation database shows that the exposure level of 86 ppm is a serious LOAEL for neurological (Zhong et al. 2022) and male reproductive effects (Zhang et al. 2017). Therefore, to determine the critical effect for the intermediate-duration inhalation MRL, the POD must be <86 ppm. Studies with data meeting this criterion were considered for the critical effect (Table A-4).

The lowest exposure level evaluated in the intermediate-duration inhalation database was 25 ppm; this value is a NOAEL for both neurological effects and male reproductive effects. Neurological effects have been evaluated in numerous studies, identifying the neurological system as a target organ for 1,2-dichloroethane toxicity (details provided in Section 2.15). In contrast, male reproductive effects have only been evaluated in a single study (Zhang et al. 2017). Although results of the Zhang et al. (2017) show that 1,2-dichloroethane can produce serious effects to the testes, these findings have not been corroborated. Therefore, neurological effects, with the more extensive database, were identified as the critical effects for the intermediate-duration inhalation MRL (Liang et al. 2021; Zhong et al. 2022). Given that NOAELs for reproductive and neurological effect are the same (25 ppm), an MRL based on neurological effects should be protective of reproductive effects.

Table A-4. Summary of Possible Critical Effect for Derivation of the Intermediate-Duration Inhalation Exposure MRL for 1,2-Dichloroethane

Reference	Species	Exposure	Effect	NOAEL/LOAEL/SLOAEL
Liang et al. 2021	Mouse	28 days, 7 days/week, 6 hours/day (WB) 0, 25, 86, 173 ppm	Neurological: vacuolization in the cerebral cortex[a]	NOAEL: 25 ppm LOAEL: 86 ppm

Table A-4. Summary of Possible Critical Effect for Derivation of the Intermediate-Duration Inhalation Exposure MRL for 1,2-Dichloroethane

Reference	Species	Exposure	Effect	NOAEL/LOAEL/SLOAEL
Zhong et al. 2022	Mouse	28 days, 7 days/week, 6 hours/day (WB) 0, 25, 86, 173 ppm	Neurological: altered behavior in open field (decreased distance and time in central area); vacuolization and demyelination in the cerebral cortex	NOAEL: 25 ppm SLOAEL: 86 ppm
Zhang et al. 2017	Mouse	28 days, 7 days/week, 6 hours/day (WB) 0, 25, 86, 173 ppm	Reproductive SLOAEL: histopathological alterations to the testes and dose-related increases in abnormal sperm	NOAEL: 25 ppm SLOAEL: 86 ppm

[a]Behavioral effects and demyelination were not assessed.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level; WB = whole-body exposure

Selection of the Principal Study: Neurological effects following intermediate-duration inhalation exposure to 1,2-dichloroethane were observed in studies by Zhong et al. (2022) and Liang et al. (2021), both with the same NOAEL value of 25 ppm. Results of open field tests by Zhong et al. (2022) showed decreased central distance/total distance (%) and decreased time in the central area of the test site; histopathological evaluations showed vacuolization and demyelination in the cerebral cortex at a concentration of 86 ppm. Taken together, these effects were considered to be a serious LOAEL. However, no neurological effects were observed at 25 ppm. Liang et al. (2021) reported increased vacuolization in the cerebral cortex at 86 ppm, with no effects at 25 ppm; neurobehavior was not evaluated in this study. Endpoints from both studies were further evaluated to determine the basis of the MRL. As discussed below, further analyses identified the lowest POD for central distance/total distance (%). Therefore, Zhong et al. (2022) was selected as the principal study.

Summary of the Principal Study:

Zhong, Y, Liang, B, Meng H, et al. 2022. 1,2-Dichloroethane induces cortex demyelination by depressing myelin basic protein via inhibiting aquaporin 4 in mice. Ecotoxicol Environ Saf 231:113180.

Groups of 20 male CD-1 mice were exposed to 0, 25, 86, and 173 ppm 1,2-dichloroethane (whole body) for 6 hours/day for 28 consecutive days. In addition to CD-1 mice, the experiments also included aquaporin 4 knock-out mice to provide mechanistic data (not discussed in this summary). After the last exposure, mice were evaluated in open field tests for total distance traveled, distance traveled in the central area relative to the total distance traveled (%), time spent in the central area, and mean speed. Additional assessments included histopathological examination of the cerebral cortex and brain-water content measurement from five additional mice exposed under the same conditions.

Results of open field tests showed dose-dependent decreases in the distance traveled in the central area relative to the total distance traveled and time spent in the central area in mice exposed to 86 and 173 ppm; no decreases were observed relative to control at 25 ppm. The total distance traveled was decreased in mice exposed to 173 ppm, but not at 25 or 86 ppm. Mean speed was similar between

controls and the three treatment groups. Histopathological examination of the cerebral cortex found dose-related increases in vacuolization and demyelination in mice exposed to 86 and 173 ppm. Brain water content was increased in the 173-ppm group. Based on results of this study, the NOAEL and SLOAEL were identified as 25 and 86 ppm, respectively.

Selection of the Point of Departure for the MRL: Neurological effects data from the Zhong et al. (2022) and Liang et al. (2021) studies were considered as the possible basis for derivation of the intermediate-duration inhalation MRL. Data sets for distance traveled in the central area relative to the total distance traveled, mean time in the central area, and vacuolization in the cerebral cortex are summarized in Table A-5. All data were presented graphically; therefore, GrabIt® software was used to convert graphic data to numeric data.

Table A-5. Data Considered as the Critical Effect for the Intermediate-Duration Inhalation MRL

			Exposure concentration (ppm)			
Reference	Endpoint	Number	0	25	86	173
Liang et. al 2021	Vacuolization area cerebral cortex (%)	5	21.39±1.18[a]	21.98±0.59	29.11±1.19[b]	34.46±0.59[b]
Zhong et al. 2022	Central distance/total distance (%)	20	18.71±7.74	12.9±5.81	9.35±5.81[b]	6.13±3.71[b]
Zhong et al. 2022	Mean time in the central area (seconds)	20	36.99±23.23	25.81±12.9	13.76±15.49[b]	9.46±4.3[b]
Zhong et al. 2022	Vacuolization area cerebral cortex (%)	5	1.81±0.82	2.13±0.89	5.00±1.07[b]	5.6±1.09[b]

[a]Values are mean±standard deviation; estimated from graphically presented data using GrabIt! or DigitizeIt 2.5.9 Software.
[b]ANOVA and LSD multiple comparison test, $p<0.05$.

ANOVA = analysis of variance; LSD = least significant difference

All data sets were modeled using EPA's Benchmark Dose Software (BMDS, version 3.2.0.1). None of the models for these endpoints provided adequate fit. Therefore, data were run using the Bayesian Benchmark Dose (BBMD) modeling online software [Bayesian BMD (benchmarkdose.com)]. Data for distance/total distance and mean time in central area were fitted to all continuous models using a $BBMCL_{1SD}$. Data for vacuolization were also fitted to all continuous models but used a Bayesian benchmark response of 10% relative deviation ($BBMCL_{10\%RD}$). To obtain a model averages, Bayesian benchmark concentration (BBMC) weighted the Exponential 2, Exponential 3, Exponential 4, Exponential 5, Hill, Power, Michaelis-Menten, and linear models equally (i.e., 12.5% each) as recommended by EPA (2020b). The resulting average $BBMCL_{1SD}$ values for distance/total distance and mean time in central area were 14.763 and 20.073 ppm, respectively, and the $BBMCL_{10\%RD}$ for vacuolization data obtained for Liang et al. (2021) was 15.523 ppm. Vacuolization data from Zhong et al. (2022) could not be appropriately modeled because of the wide uncertainty on each of the dose groups which was due to the small response, small sample size (n=5), and high variability between the animals. ATSDR considered the NOAEL of 25 ppm for Zhong et al. (2022) vacuolization data for a potential POD. However, the lowest model-averaged BBMCL value of 14.763 ppm for central distance/total distance (%) was selected as the POD. The posterior model probabilities were 0.318, 0.0.83, 0.284,

0.052, 0.069, 0.016, 0.110, and 0.07 for the Exponential 2, Exponential 3, Exponential 4, Exponential 5, Hill, Power, Michaelis-Menten, and linear models, respectively (Table A-6). Model results are presented graphical in Figure A-2.

Adjustment for Intermittent Exposure: Mice in the Zhong et al. (2022) study were exposed for 6 hours/day for 28 consecutive days. Therefore, the $BBMCL_{1SD}$ was adjusted for intermittent exposure as follows:

$$BBMCL_{ADJ} = BBMCL_{1SD} \times \frac{6\ hours}{24\ hours} = 14.8\ \text{ppm} \times \frac{6\ \text{hours}}{24\ hours} = 3.70\ ppm$$

Human Equivalent Concentration: For systemic (extrarespiratory) effects, the HEC is calculated by multiplying the duration-adjusted animal $BBMCL_{ADJ}$ by the ratio of the blood:gas partition coefficients in animals and humans. Gargas et al. (1989) estimated a blood:air partition coefficient of 19.5±0.7 for 1,2-dichloroethane in humans; however, a blood:air partition coefficient for mice was not located. Therefore, the default value of 1 was used for the ratio, resulting in the $BBMCL_{HEC}$ of 3.70 ppm.

Uncertainty Factor: The $BBMCL_{HEC}$ was divided by a total uncertainty factor (UF) of 30:

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

This results in the following MRL:

$$\text{MRL} = \frac{BBMCL_{HEC}}{\text{UFs}} = \frac{3.70\ \text{ppm}}{30} = 0.123\ \text{ppm, which rounds to } 0.1\ \text{ppm}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The intermediate-duration inhalation oral MRL is based on neurological effects identified in open field tests. ATSDR considers results of open field and maze tests to be valid indicators of adverse neurological effects and has used results from these tests to derive MRLs for other chemicals (e.g., 1-bromopropane, bromomethane, cypermethrin, permethrin, and fuel oil #2). Studies in humans and animals identify the neurological system as a target for inhaled 1,2-dichloroethane. In animals, acute- and intermediate-duration inhalation exposure studies have observed neurological effects. Acute effects of inhalation exposure have been observed at concentrations of 111–1,235 ppm; effects include decreased motor activity and response to stimuli (Hotchkiss et al. 2010; Wang et al. 2013; Yang et al. 2021), tremor (Jin et al. 2018a, 2018b, 2019), cerebral edema (Jin et al. 2019; Zhang et al. 2011), vacuolization in the cerebral cortex (Zhong et al. 2020), and brain lesions (Zhou et al. 2016). For intermediate-duration exposure, in addition to neurological effects observed at 86 ppm (Liang et al. 2021; Zhong et al. 2022), damage to cerebellar granular cells (shrunken and hypereosinophilic cytoplasm, nuclear pyknosis, apoptosis) was observed at approximately 180 ppm (Huang et al. 2020).

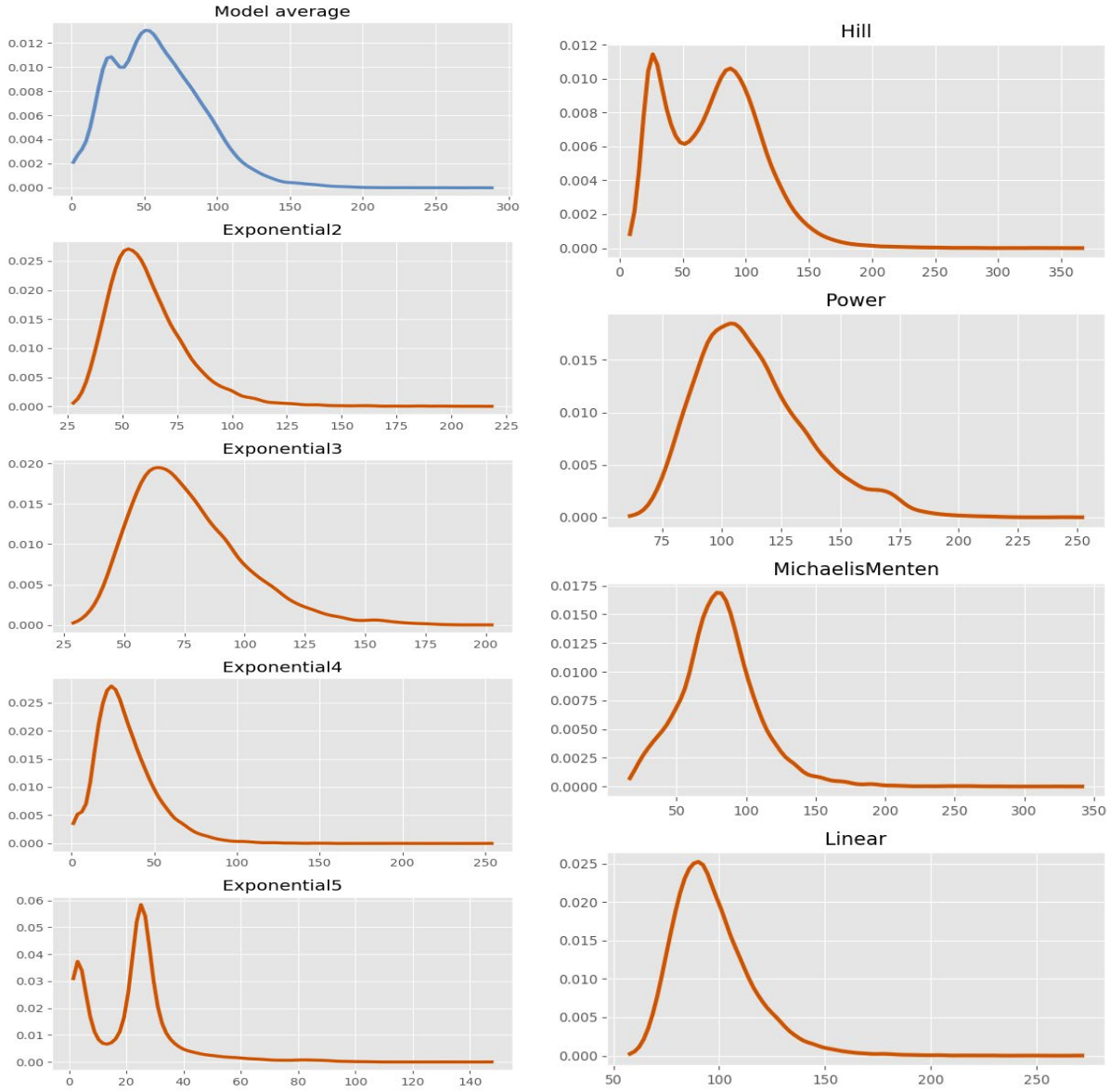
Relevance of neurological effects observed in animals to humans is supported by numerous case reports of individuals who inhaled 1,2-dichloroethane (Chen et al. 2015, Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011). Effects included drowsiness, delirium, and headache; tremors; slow response to verbal commands; encephalopathy and cerebral edema; and neuronal necrosis and white matter demyelination. Autopsies of individuals who died following exposure showed morphological alterations in the nervous system including vascular disorders, diffuse changes in cerebellar cells, parenchymatous changes in the brain and spinal cord, myelin degeneration, and hyperemia, swelling, edema, and hemorrhage of the brain (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951). An occupational

Table A-6. BBMD Model Predictions for Central Distance/Total Distance (%) in Male Mice Following 28-Day Inhalation Exposure to 1,2-Dichloroethane (Zhong et al. 2022)

Statistic	Model average	Exponential 2	Exponential 3	Exponential 4	Exponential 5	Hill	Power	Michaelis Menten	Linear
Prior model weight	N/A	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Posterior model weight	N/A	0.312	0.080	0.284	0.053	0.065	0.015	0.126	0.065
Fraction with BMDs	99.7%	100.0%	100.0%	99.5%	97.0%	99.6%	100.0%	100.0%	100.0%
BMD (median)	55.814	58.347	72.517	29.552	24.197	75.847	109.656	79.796	93.986
BMDL (5^{th} percentile)	14.763	38.897	46.033	9.588	2.105	21.876	81.229	35.408	72.990
25^{th} percentile	34.964	49.106	59.691	20.606	6.994	39.699	96.090	63.696	84.162
Mean (SD)	59.101 (32.913)	61.845 (18.584)	76.768 (23.704)	33.172 (19.079)	22.044 (15.871)	74.517 (39.174)	113.655 (24.152)	81.165 (29.207)	97.483 (19.388)
75^{th} percentile	79.044	70.683	89.736	42.112	27.497	100.076	127.109	96.015	107.108
95^{th} percentile	114.375	96.155	121.097	67.658	49.466	136.830	161.300	130.349	132.593

BBMD = Bayesian benchmark dose; BMD = benchmark dose; BMDL = lower confidence limit on the BMD; SD = standard deviation

Figure A-2. Bayesian Benchmark Dose (BBMD) Model Predictions for Central Distance/Total Distance (%) in Male Mice Following 28-Day Inhalation Exposure to 1,2-Dichloroethane (Zhong et al. 2022)



exposure study in 221 workers reported impaired attention, nonverbal processing speed, verbal memory and learning, and motor strength and speed (Bowler et al. 2003). Reliable exposure estimates for 1,2-dichloroethane in humans were not reported.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: July 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL. The two available studies identified effect levels (LOAELs and NOAELs) for noncancer effects that are higher than both the POD for the acute-duration inhalation MRL (36.28 ppm) and the serious LOAEL for intermediate-duration inhalation exposure (25 ppm), precluding derivation of an MRL.

Rationale for Not Deriving an MRL: An MRL has not been derived for chronic-duration inhalation exposure to 1,2-dichloroethane. As summarized in Table A-7, there are only two studies that investigate the effects of chronic-duration inhalation exposure to 1,2-dichloroethane. Cheever et al. (1990) monitored for a number of health effects in rats exposed to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week, for 2 years. No increased cancer incidences were observed, and the only noncancer effect noted was an increased incidence of unspecified testicular lesions (24 versus 10% in controls) observed at gross necropsy. Histopathology examination did not show increased incidences of testicular lesions. Nagano et al. (2006) found significantly increased tumor incidences in rats and mice exposed to 1,2-dichloroethane for 6 hours/day, 5 days/week, for 104 weeks, but did not report any noncancer effects, resulting in freestanding noncancer NOAELs of 160 and 90 ppm in rats and mice, respectively. All of the available effect levels are higher than the POD used for derivation of the acute-duration inhalation MRL (36.28 ppm) and the serious LOAEL of 25 ppm for sperm abnormalities in mice exposed for 4 weeks (Zhang et al. 2017). Neither Cheever et al. (1990) nor Nagano et al. (2006) evaluated sperm parameters. Therefore, a chronic-duration MRL could not be derived.

Table A-7. Summary of Relevant NOAEL and LOAEL Values Following Chronic-Duration Inhalation Exposure to 1,2-Dichloroethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$)[a] (ppm)	LOAEL ($LOAEL_{ADJ}$)[a] (ppm)	Effect	Reference
Rat Sprague-Dawley	7 hours/day 5 days/week 2 years		50 (10)	Increased testicular lesions (not further specified)	Cheever et al. 1990
Rat Fischer 344	6 hours/day 5 days/week 104 weeks	160 (28.6)		NOAEL without LOAEL	Nagano et al. 2006
Mouse B6D2F1	6 hours/day 5 days/week 104 weeks	90 (16)		NOAEL without LOAEL	Nagano et al. 2006

[a]Adjusted daily dose = $Intermittent\ dose \times \frac{Exposure\ hours}{24\ hours} \times \frac{Exposure\ days}{7\ days}$

ADJ = adjusted; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: July 2024
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: The available data are insufficient for derivation of an acute-duration oral MRL for 1,2-dichloroethane.

Rationale for not deriving an MRL: The database of acute-duration oral toxicity studies of 1,2-dichloroethane consists of one 14-day study in rats (van Esch et al. 1977), one 14-day study in mice (Munson et al. 1982), one 14-day developmental toxicity study in rats (Payan et al. 1995), one 10-day study in rats (Daniel et al. 1994), and two lethality studies (McCollister et al. 1956; Munson et al. 1982). With limited data reporting, the lethality studies were excluded from consideration. All of the remaining studies used gavage administration. van Esch et al. (1977) identified hepatic effects of fatty degeneration in rats at 300 mg/kg/day, the same dose at which 100% mortality occurred. In the study by Daniel et al. (1994), due to high mortality in the 300 mg/kg/day group, the highest dose evaluated was 100 mg/kg/day. Inflammation of the forestomach was observed at 100 mg/kg/day. No other effects were reported in Daniel et al. (1994). In the developmental toxicity study (Payan et al. 1995), a LOAEL of 198 mg/kg/day was identified for decreased maternal weight gain. The lowest dose from an acute-duration study was in Munson et al. (1982). Mice were administered doses of 0, 4.9, or 49 mg/kg/day for 14 days. The lowest dose at which an effect was observed was a LOAEL of 4.9 mg/kg/day based on reduced humoral and cell-mediated immune responses (Munson et al. 1982). As the LOAEL was the lowest dose tested, no NOAEL was determined. Male mice had a dose-related reduction in humoral immune response (IgM response to sheep erythrocytes). The number of antibody-forming cells (AFCs) were reduced in a dose-related manner, significant at both doses, and adjusted AFC/10^6 cells were reduced in a dose-related manner, significant at 49 mg/kg/day. Cell-mediated immune response (delayed-type hypersensitivity response to sheep erythrocytes) was significantly reduced in both dose groups but was not dose-related. Decreased serum leukocytes were observed at 49 mg/kg/day.

As Munson et al. (1982) was a gavage study, it is important to emphasize that there is a notable difference in toxicokinetics between gavage and drinking water administration (see Section 3.1). With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity. In an intermediate-duration, 90-day study by the same study authors, mice administered up to 189 mg/kg/day 1,2-dichloroethane in the drinking water did not exhibit immune suppression (Munson et al. 1982). As the critical effect from the acute-duration gavage study was not observed at higher doses in the drinking water, it is not appropriate to derive an acute-duration oral MRL.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: July 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.7 mg/kg/day
Critical Effect: Kidney tubule regeneration, increased kidney weight
References: Morgan et al. 1990; NTP 1991
Point of Departure: $BMDL_{10}$ 70.08 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 10
Species: Rat

***MRL Summary*:** An intermediate-duration oral MRL of 0.7 mg/kg/day was derived for 1,2-dichloroethane based on an increase in kidney lesions (tubule regeneration) in rats administered 1,2-dichloroethane via drinking water (Morgan et al. 1990; NTP 1991). The MRL is based on a $BMDL_{10}$ of 70.08 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of 1,2-dichloroethane following intermediate-duration oral exposure; these studies examined a wide range of endpoints including kidney and liver effects (Alumot et al. 1976; Cottalasso et al. 2002; Daniel et al. 1994; Morgan et al. 1990; Munson et al. 1982; NTP 1991; van Esch et al. 1977), neurotoxicity (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977), gastrointestinal toxicity (Morgan et al. 1990; NTP 1991; van Esch et al. 1977), hematotoxicity (Daniel et al. 1994; Morgan et al. 1990; Munson et al. 1982; NTP 1991; van Esch et al. 1977), and reproductive toxicity (Charlap 2015; Daniel et al. 1994; Lane et al. 1982; Morgan et al. 1990; NTP 1991; van Esch et al. 1977). The LOAELs for these studies range from 75 to 448 mg/kg/day.

The available data suggest that nephrotoxicity is the most sensitive endpoint following intermediate-duration oral exposure. The lowest LOAELs and NOAELs for renal effects are shown in Table A-8. In female F344/N rats exposed via drinking water, increased absolute and relative kidney weights and renal tubule degeneration were observed at doses >102 mg/kg/day (Morgan et al. 1990; NTP 1991). Increased relative kidney weight was also seen in rats treated with 75 or 90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; NTP 1991; van Esch et al. 1977); however, it is important to emphasize that there is a notable difference in toxicokinetics between gavage and drinking water administration (see Section 3.1). With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity. Renal effects (e.g., increased kidney weight and/or histopathological lesions) were also found in in mice exposed via drinking water at doses $\geq$448 mg/kg/day and in rats following acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; Hotchkiss et al. 2010; Morgan et al. 1990; NTP 1991; Spencer et al. 1951).

Table A-8. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Drinking Water Exposure to 1,2-Dichloroethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Renal effects					
F344 rat	13 weeks 7 days/week	58 F	102 F	Tubular regeneration, increase in absolute and relative kidney weight	Morgan et al. 1990; NTP 1991
CD-1 mouse	90 days	189	ND	None	Munson et al. 1982
B6C3F1 mouse	13 weeks 7 d/week	249	448	Tubular regeneration, increased absolute and relative kidney weight	Morgan et al. 1990; NTP 1991
Sprague-Dawley rat	1-generation (90–120 days) 7 days/week	300	ND	None	Charlap 2015
Sprague-Dawley rat	13 weeks 7 days/week	531	ND	None	Morgan et al. 1990; NTP 1991
Osborne-Mendel rat	13 weeks 7 days/week	727	ND	None	Morgan et al. 1990; NTP 1991
Body weight effects					
Osborne-Mendel rat	13 weeks 7 days/week	126 M	266 M	12% decrease in terminal body weight of males	Morgan et al. 1990; NTP 1991
Sprague-Dawley rat	1-generation (90–120 days)	150 M	300 M	Decreased body weight by 10%	Charlap 2015
Sprague-Dawley rat	13 weeks 7 days/week	531	ND	None	Morgan et al. 1990; NTP 1991
F344 rat	13 weeks 7 days/week	601	ND	None	Morgan et al. 1990; NTP 1991
B6C3F1 mouse	13 weeks 7 days/week	2,710 M	4,207 M	16% decrease in terminal body weight	Morgan et al. 1990; NTP 1991

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

Alumot et al. (1976) reported increased fat content in the livers of rats exposed via feed at a dose of 80 mg/kg/day for 7 weeks. However no hepatic effects were seen in rats or mice at much higher doses and for longer durations in the remaining studies (Charlap 2015; Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977; Munson et al. 1982); thus, hepatic effects were not considered for use in MRL derivation.

Body weight effects were reported in several drinking water studies of 1,2-dichloroethane, as shown in Table A-9. The lowest LOAEL for body weight effects in a drinking water study was 266 mg/kg/day in the 13-week study of Osborne-Mendel rats (Morgan et al. 1990; NTP 1991). This LOAEL is higher than the LOAEL of 102 mg/kg/day for renal effects in F344 rats exposed by drinking water; therefore, renal effects were selected as the critical effect.

Selection of the Principal Study: F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice were exposed to drinking water containing 1,2-dichloroethane (Morgan et al. 1990; NTP 1991). Dose-related effects on the kidney (i.e., increased weight and renal tubule regeneration) were observed in female F344/N rats and male B6C3F1 mice only. Rats were more sensitive to these effects than mice, with significantly lower NOAEL and LOAEL values; therefore, the drinking water experiment in F344/N rats was selected as the principal study.

Summary of the Principal Studies:

Morgan DL, Bucher JR, Elwell MR. 1990. Comparative toxicity of ethylene dichloride in F344/N, Sprague-Dawley and Osborne-Mendel rats. Food Chem Toxicol 28(12):839-845.

NTP. 1991. NTP technical report on the toxicity studies of 1,2-dichloroethane (ethylene dichloride) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (drinking water and gavage studies) (CAS No. 107-06-2). Research Triangle Park, NC: National Toxicology Program. NTP Tox 4. NIH Publication No. 91-3123.

Groups of F344/N rats (10 /sex) were exposed to drinking water containing 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm of 1,2-dichloroethane for 13 weeks. The high concentration was close to the solubility limit for 1,2-dichloroethane in water. Reported estimates of intake from the water were 0, 49, 86, 147, 259, and 515 mg/kg/day in male rats and 0, 58, 102, 182, 320, and 601 mg/kg/day in female rats. Signs of toxicity, body weight, food and water consumption, hematology, and serum chemistry were evaluated throughout the study, and comprehensive gross and histological examinations were performed at the end of the exposure period.

Dose-related decreased water consumption occurred in both sexes. There was >10% reduction in body weight gain at 259 mg/kg/day in male F344/N rats. There were no significant reductions in body weight gain in female rats. In female rats, absolute and relative kidney weights were increased at doses >102 mg/kg/day. Renal tubular regeneration, described as one or more foci of basophilic-staining tubules lined by closely packed tubular epithelium in the cortex or outer medulla (minimal-to-mild in severity), was observed in female rats administered 601 mg/kg/day. Thus, dose-related changes in kidney weight were not correlated with renal lesions. Absolute and relative kidney weight increases were also observed in male rats at doses >86 mg/kg/day; however, the dose-related change in organ weight was not correlated with renal lesions, which occurred in 9/10 rats in all groups including controls. No effects were observed in other organs of male or female rats.

***Selection of the Point of Departure for the MRL*:** BMD modeling was conducted to identify a POD using the kidney weight and histopathological lesion data from female rats in the drinking water study (see Table A-9).

Table A-9. Kidney Weights and Incidence of Tubule Regeneration in Female F344 Rats Exposed to 1,2-Dichloroethane in Drinking Water for 13 Weeks

Dose (mg/kg/day)	0	58	102	182	320	601
Body weight (% of control)		101	102	99	97	93
Water intake (g/day)	19	18	16	14	12	11
Absolute kidney weight[a] (mg)	739±26	814±16[b] (↑10)	885±16[c] (↑20)	845±17[c] (↑14)	932±15[c] (↑26)	923±15[c] (↑25)
Relative kidney weight[a] (%)	3.8±0.13	4.1±0.07 (↑8%)	4.2±0.17[b] (↑11%)	4.3±0.07[c] (↑13%)	4.8±0.09[c] (↑26%)	5.0±0.04[c] (↑32%)
Tubule regeneration[d]	0/10	0/10	1/10	2/10	3/10	9/10[c]

[a]Organ weights reported as mean±standard error; n=10.
[b]p<0.5.
[c]p<0.01.
[d]Tubule regeneration was characterized as one or more foci of basophilic-staining tubules lined by closely packed tubular epithelium in the cortex or outer medulla of the kidney of minimal-to-mild severity.

Source; NTP (1991)

BMD modeling of dichotomous data (renal lesions in Female F344 rats) was conducted with EPA's BMDS (version 3.2.0.1). For these data, the Dichotomous Hill, Gamma, Logistic, Log Logistic, Log Probit, Multistage, Probit, and Weibull dichotomous models available within the software were fit using a BMR of 10% extra risk. Adequacy of model fit was judged by four criteria: the $\chi 2$ goodness-of-fit p-value (p>0.1), magnitude of scaled residuals for the dose group nearest to the BMD (absolute value <2.0), BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest AIC is selected as a potential POD if the BMDLs are sufficiently close (<3-fold); if the BMDLs are not sufficiently close (>3-fold), model-dependence is indicated, and the model with the lowest reliable BMDL is selected. All models provided an adequate fit to the data ($\chi 2$ goodness-of-fit p-value >0.1). The BMDLs were marginally over the 3-fold difference (~3.1-fold) suggested rule; therefore, the model with the lowest BMDL (1-degree Multistage model) was recommended by the BMDS. Visual inspection of the dose-response of the 1-degree Multistage model, however, indicates that there is a poor visual fit in the low-dose region of the predicted curve. A poorer fit is also indicated by the scaled residual near the BMD of -1.03, which is higher when compared to the viable alternative models. Because the difference in BMDLs was marginally close and because there was a relatively poor visual fit of the 1-degree Multistage model in the low-dose region of the curve, the model with the lowest AIC was chosen as a viable alternative (2-degree Multistage). The predicted BMD_{10} and $BMDL_{10}$ values for this dataset are 139.26 and 70.08 mg/kg-day, respectively (see Table A-10 and Figure A-3).

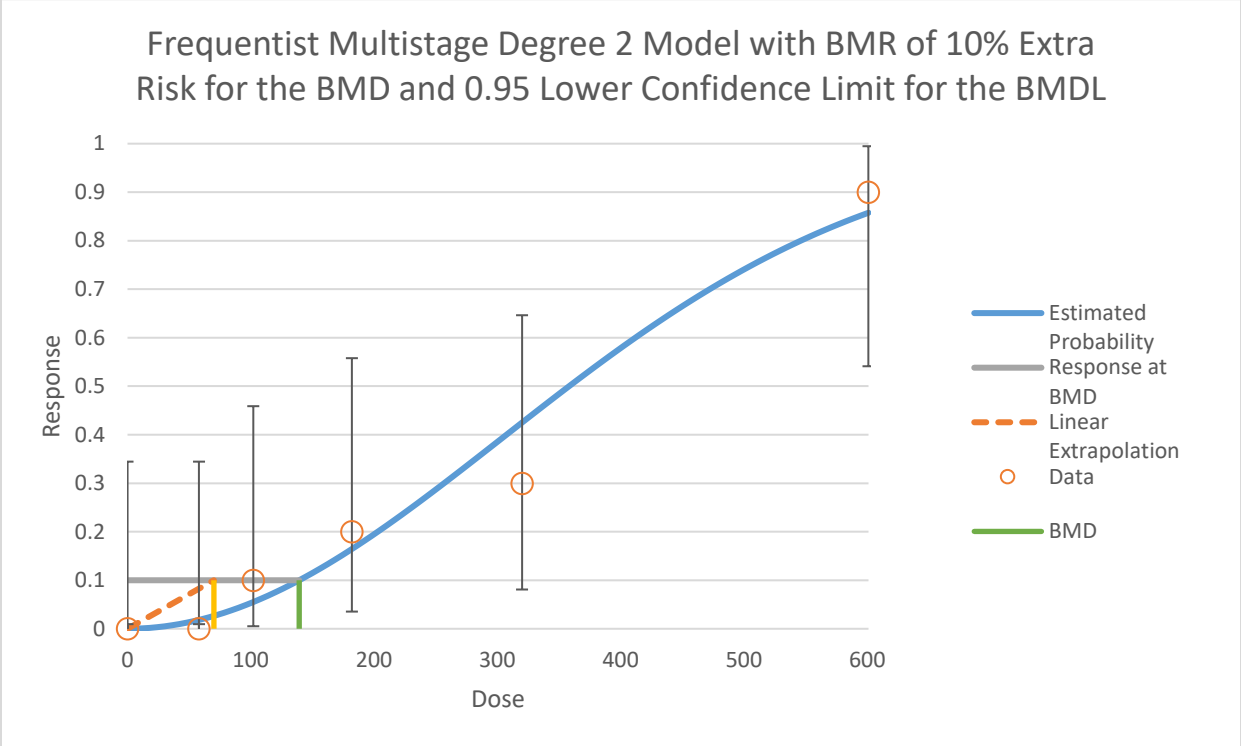
Table A-10. Model Predictions for Increased Incidence of Renal Lesions in Female F344 Rats Following Exposure to 1,2-Dichloroethane in Drinking Water for 13 Weeks (NTP 1991)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	142.02	80.55	0.29	45.75	0.81	0.24
Gamma[d,e]	138.68	75.97	0.75	41.23	0.72	0.21
Log-Logistic[e]	142.02	80.55	0.66	41.75	0.81	0.24
Multistage Degree 5[f]	131.14	59.37	0.86	42.34	0.32	0.42
Multistage Degree 4[f]	132.74	61.03	0.84	42.42	0.33	0.45
Multistage Degree 3[f]	137.24	64.48	0.80	42.55	0.39	0.46
Multistage Degree 2[f,g]	**139.26**	**70.08**	**0.83**	**40.83**	**0.62**	**0.30**
Multistage Degree 1[f]	61.10	40.50	0.28	45.91	-1.03	-0.53
Weibull[d]	142.44	77.67	0.68	42.82	0.69	0.35
Logistic	178.79	124.15	0.81	41.34	0.52	0.73
Log-Probit	135.39	81.04	0.45	43.90	0.82	0.04
Probit	166.93	115.93	0.84	41.08	0.57	0.64

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. All models provided adequate fit to the data. The BMDLs were marginally >3-fold; however, the model with the lowest BMDL (1-degree Multistage) provided a relatively poor fit to the low-dose region of the curve. After exclusion of the 1-degree Multistage model, the remaining BMDLs were within 3-fold; therefore, the model with the lowest AIC was selected (2-degree Multistage).

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

Figure A-3. Fit of 2-Degree Multistage Model to Incidence Data for Renal Lesions in Female F344 Rats Following Exposure to 1,2-Dichloroethane in Drinking Water for 13 Weeks (NTP 1991)



BMD modeling of continuous data (absolute and relative kidney weight) was conducted with the EPA's BMDS (version 3.2.0.1). For these data, the Exponential, Hill, Linear, Polynomial, and Power continuous models available within the software were fit employing a BMR of 1 standard deviation (SD). An adequate fit was judged based on the $\chi 2$ goodness-of-fit p value ($p>0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2; p-value >0.1), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (p-value <0.1), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3; p-value <0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied >3-fold; otherwise, the BMDL from the model with the lowest AIC was selected. For absolute kidney weight, the constant variance model provided an adequate fit to the full dataset; however, none of the models provided adequate fit to the means (p-value <0.1). For relative kidney weight, neither the constant variance nor the nonconstant variance model provided an adequate fit to the variance data. Therefore, the kidney weight datasets were not amenable to BMD modeling.

The selected POD for intermediate-duration oral exposure was the $BMDL_{10}$ value of 70.08 mg/kg/day for renal lesions (tubule regeneration) in female rats.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMLD_{10}$ of 70.08 mg/kg/day was divided by a total uncertainty factor (UF) of 100 (10 for human variability and 10 for extrapolation from animals to humans.

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

This resulted in the following MRL:

$MRL = BMLD_{10} \div UF$
$MRL = 70.08 \text{ mg/kg/day} \div (10x10) = 0.7 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information: Renal effects (e.g., increased kidney weight and/or tubular epithelial regeneration) were also found in mice exposed via drinking water at doses >448 mg/kg/day and in animals following acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; Hotchkiss et al. 2010; Spencer et al. 1951) and intermediate-duration dermal exposure (Suguro et al. 2017).

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: July 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The available data are insufficient for derivation of a chronic-duration oral MRL for 1,2-Dichloroethane.

Rationale for not deriving an MRL: The database of chronic-duration oral toxicity studies for 1,2-dichloroethane consists of one 2-year dietary study in rats (Alumot et al. 1976) and one 78-week gavage study in rats and mice (NCI 1978). Alumot et al. (1976) administered doses of 0, 12.5, or 25 mg/kg/day in feed to rats for 2 years. No effects were observed for any endpoint. This study had several significant limitations including unknown purity of the compound, unclear concentrations of 1,2-dichloroethane in the mash diet and dose consumed, and absence of gross or histological examination of organs or tissues. NCI (1978) administered 1,2-dichloroethane to Osborne-Mendel rats at doses of 0, 47, and 95 mg/kg/day and B6C3F1 mice at doses of 0, 97, and 195 (males) and 0, 149, and 299 mg/kg/day (females) via gavage on 5 days/week for 78 weeks. There was high mortality at the high dose in rats of both sexes and in female mice. The only other health effect observed was cancer. Limitations of the NCI (1978) study include dosage adjustments throughout the exposure period, high mortality, and fewer control animals (20/sex) than exposed (50/sex). Both available studies are via the gavage route, and it is important to emphasize that there is a notable difference in toxicokinetics between gavage and drinking water administration (see Section 3.1). With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity. Due to the limitations, route, and the fact that the only observed effects were death and cancer, available data were not considered adequate for use in deriving an MRL.

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

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

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-dichloroethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,2-dichloroethane. 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-dichloroethane 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-dichloroethane 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-dichloroethane released for public comment in 2022; thus, the literature search was restricted to studies published between January 2019 and June 2022. The following main databases were searched in June 2022:

- 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-dichloroethane. 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-dichloroethane 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	
06/2022	(107-06-2[rn] OR "ethylene dichloride"[nm] OR "Ethylene Dichlorides"[mh] OR "1,2-Bichloroethane"[tw] OR "1,2-DCA"[tw] OR "1,2-Dichlorethane"[tw] OR "1,2-Dichloroethane"[tw] OR "1,2-Ethylene dichloride"[tw] OR "1,2-Ethylidene dichloride"[tw] OR "alpha,beta-Dichloroethane"[tw] OR "Dichloro-1,2-ethane"[tw] OR "dichloroethane"[tw] OR "dichloroethanes"[tw] OR "EDC (halocarbon)"[tw] OR "Ethane dichloride"[tw] OR "Ethane, 1,2-dichloro-"[tw] OR "Ethylene chloride"[tw] OR "Ethylene dichloride"[tw] OR "Ethylenedichloride"[tw] OR "Glycol dichloride"[tw] OR "sym-Bichloroethane"[tw] OR "sym-Dichloroethane"[tw] OR "α,β-Dichloroethane"[tw] OR "Borer sol"[tw] OR "Brocide"[tw] OR "Di-chlor-mulsion"[tw] OR "Dichlor-Mulsion"[tw] OR "Dichloremulsion"[tw] OR "Dutch liquid"[tw] OR "Dutch oil"[tw] OR "Freon 150"[tw] OR "HCC 150"[tw]) AND (2019/01/01:3000[mhda] OR 2019/01/01:3000[crdat] OR 2019/01/01:3000[edat] OR 2018:3000[dp])
NTRL	
06/2022	Date Published 2018 to 2022 "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "alpha,beta-Dichloroethane" OR "Dichloro-1,2-ethane" OR "dichloroethanes" OR "EDC (halocarbon)" OR "Ethane dichloride" OR "Ethane, 1,2-dichloro-" OR "Ethylene chloride" OR "Ethylene dichloride" OR "Ethylenedichloride" OR "Glycol dichloride" OR "sym-Bichloroethane" OR "sym-Dichloroethane" OR "α,β-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Di-chlor-mulsion" OR "Dichlor-Mulsion" OR "Dichloremulsion" OR "Dutch liquid" OR "Dutch oil" OR "Freon 150" OR "HCC 150" OR "Dichloroethane"
Toxcenter	
06/2022	FILE 'TOXCENTER' ENTERED AT 19:14:00 ON 13 JUN 2022 L1 8364 SEA FILE=TOXCENTER 107-06-2 L2 8140 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 6930 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 740 SEA FILE=TOXCENTER L3 AND PY>2017 L5 647 SEA FILE=TOXCENTER L3 AND ED>=20190101 L6 797 SEA FILE=TOXCENTER L4 OR L5 ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE

Table B-2. Database Query Strings

Database search date	Query string
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (NONHUMAN MAMMALS)/ORGN
	L37 QUE L35 OR L36
	L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L39 QUE L37 OR L38

	L40 360 SEA FILE=TOXCENTER L6 AND L39
	L41 25 SEA FILE=TOXCENTER L40 AND MEDLINE/FS
	L42 341 DUP REM L40 (19 DUPLICATES REMOVED)
	D SCAN L42

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2022	Compounds searched: 107-06-2
NTP	
06/2022	"107-06-2" "1,2-Dichloroethane" "Dichloroethane" "Ethylene dichloride" "1,2-DCA" "dichloroethanes" "Ethane dichloride" "Ethylene chloride" "Ethylenedichloride" "sym-Dichloroethane" Years 2010-2019, 2020-2022
Regulations.gov	
06/2022	"107-06-2" dichloroethane "ethylene dichloride" Posted date 01/01/2018-06/14/2022; Docket and EPA notices
NIH RePORTER	
02/2024	Fiscal Year: Active ProjectsText Search: "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "alpha,beta-Dichloroethane" OR "Dichloro-1,2-ethane" OR "dichloroethanes" OR "EDC (halocarbon)" OR "Ethane dichloride" OR "Ethane, 1,2-dichloro-" OR "Glycol dichloride" OR "sym-Bichloroethane" OR "sym-Dichloroethane" OR "α,β-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Di-chlor-mulsion" OR "Dichlor-Mulsion" OR "Dichloremulsion" OR "Dutch liquid" OR "Dutch oil" OR "Freon 150" OR "HCC 150" (advanced)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 613
- Number of records identified from other strategies: 74
- Total number of records to undergo literature screening: 687

B.1.2 Literature Screening

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

- 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.

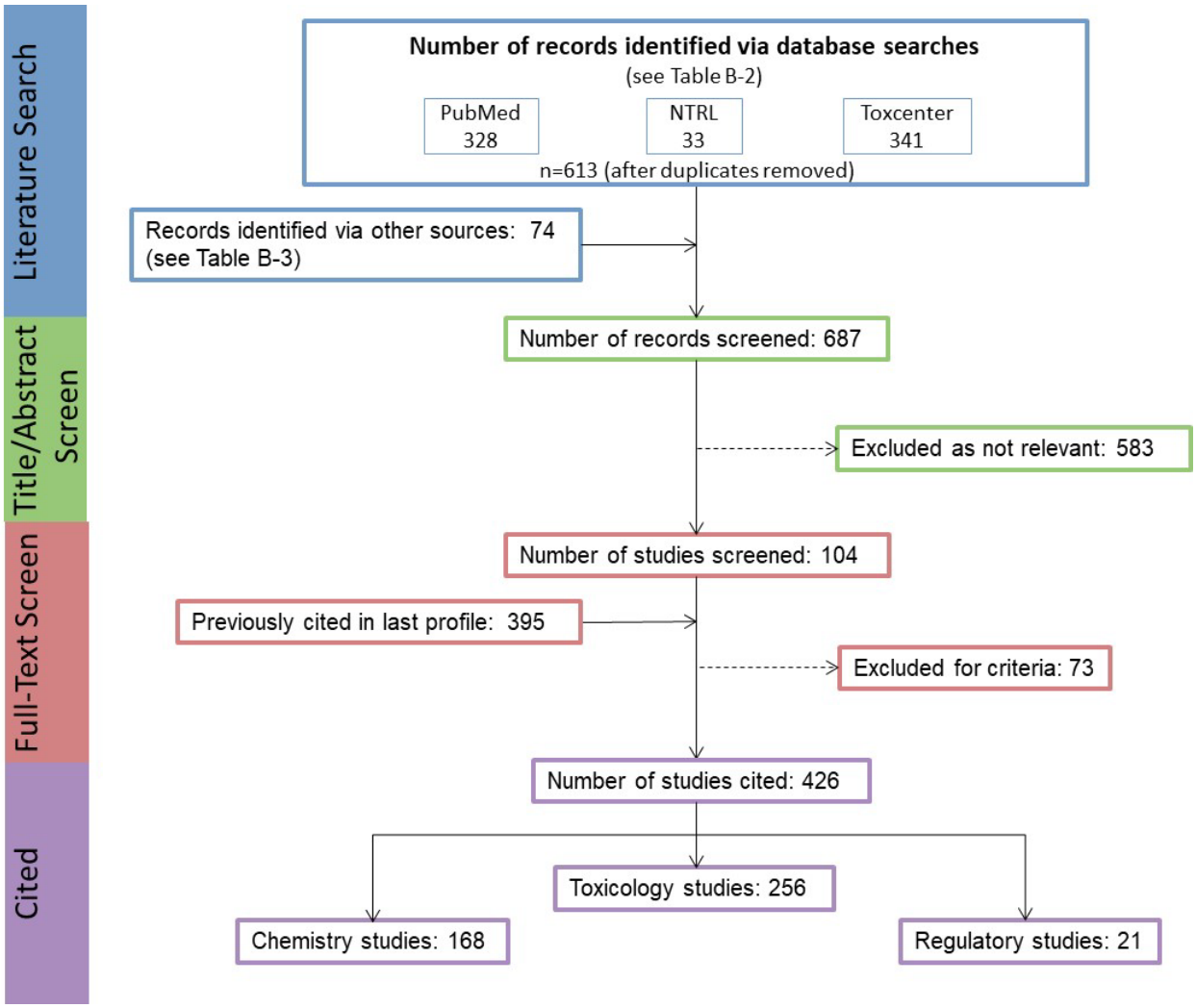
- Number of titles and abstracts screened: 687
- Number of studies considered relevant and moved to the next step: 104

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: 104
- Number of studies cited in the pre-public draft of the toxicological profile: 395
- Total number of studies cited in the profile: 426

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

Figure B-1. June 2022 Literature Search Results and Screen for 1,2-Dichloroethane



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), 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 C-6)

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

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

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

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

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

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

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

APPENDIX C

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

Figure key[a] (4)	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
(2) **CHRONIC EXPOSURE**									
51 (3)	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
(10) **Aida et al. 1992**									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

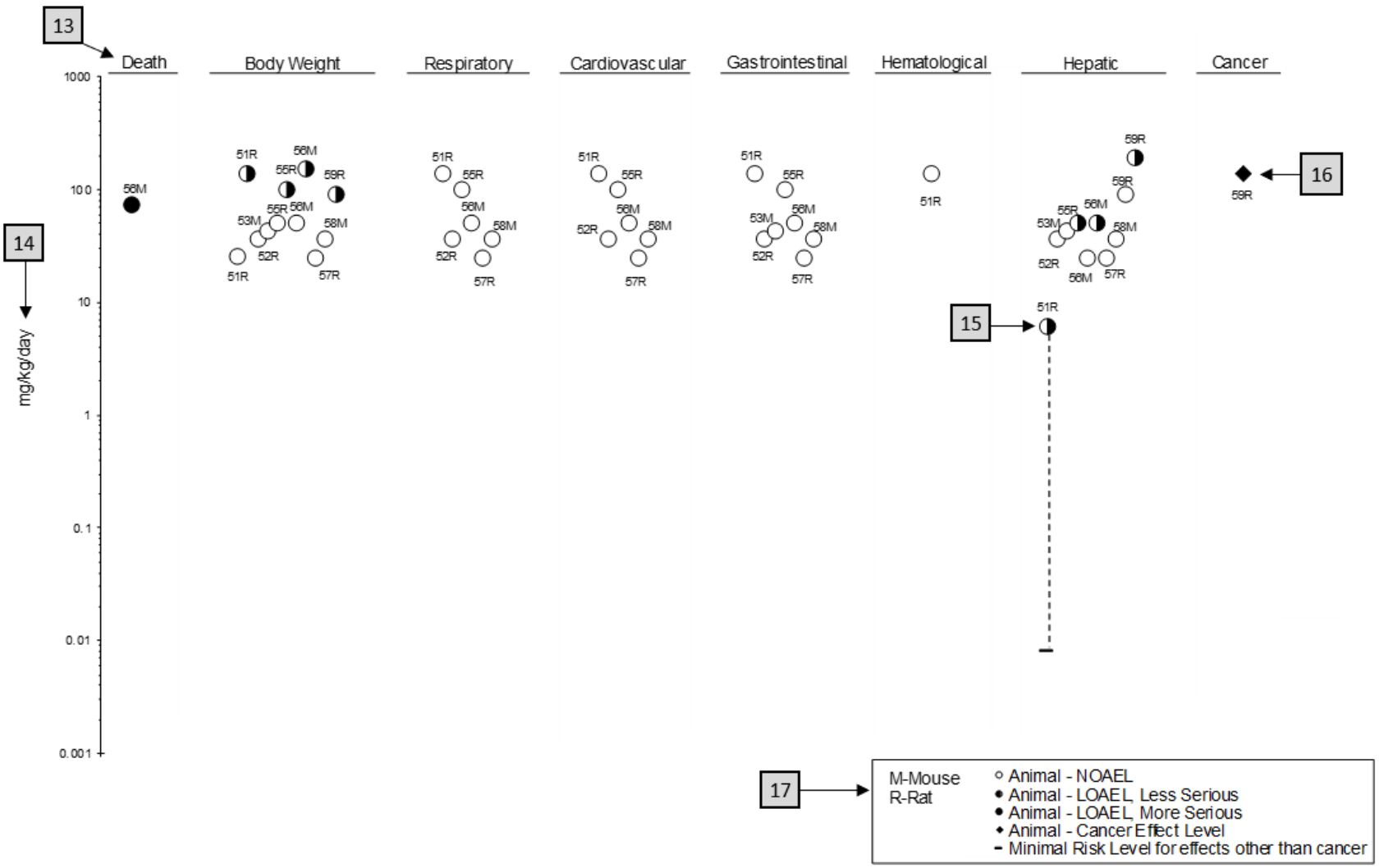
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX C

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

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

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

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

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

APPENDIX D

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 E. 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.

APPENDIX E

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 exposure level 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 exposure level, 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)—A National Institute for Occupational Safety and Health (NIOSH) value to protect workers, most often expressed as time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek. RELs may also be expressed as 8-hour TWAs, short-term exposure limits (STELs), or ceiling limits (a concentration that should never be exceeded).

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) value to protect workers, most often expressed as time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek. RELs may also be expressed as 8-hour TWAs, short-term exposure limits (STELs), or ceiling limits (a concentration that should never be exceeded).

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 F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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