APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene Oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 0.4 ppm
Critical Effect: Depressed fetal weight
Reference: Snellings et al. 1982a
Point of Departure: $BMCL_{RD05}$ of 45.50 ppm ($BMCL_{HEC}$ of 11.38 ppm)
Uncertainty Factor: 30
LSE Graph Key: 11
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 0.4 ppm has been derived for ethylene oxide based on depressed mean male fetal weight following exposure of pregnant Fischer 344 rats to ethylene oxide vapor for 6 hours/day during gestation days 6–15 (Snellings et al. 1982a). The $BMCL_{05}$ of 45.50 ppm was adjusted for intermittent exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 11.38 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No adequate exposure-response human data are available. Two rat studies were designed to evaluate acute lethality following single 1- or 4-hour exposure (Jacobson et al. 1956; Snellings et al. 2011). NTP (1987) evaluated the effects of repeated inhalation exposure of rats and mice for 2 weeks or up to 2 weeks during 14-week studies. Several studies were designed to evaluate the effects of maternal exposure during periods of gestation (Neeper-Bradley and Kubena 1993; NIOSH 1982; Rutledge and Generoso 1989; Saillenfait et al. 1996; Snellings et al. 1982a).

Selected results from the studies that evaluated sublethal effects (potential candidates for MRL derivation) are summarized in Table A-1. Several studies were considered inadequate for the purpose of deriving an acute-duration inhalation MRL for ethylene oxide. NTP (1987) reported a respiratory effect (rhinitis) at an exposure level (71.4 ppm) resulting in 90% mortality during 2 weeks of repeated exposures. The study of Rutledge and Generoso (1989) employed only a single high ethylene oxide exposure concentration (1,200 ppm) for an exposure period of 1.5 hours. The studies of Saillenfait et al. (1996) employed short exposure durations (30 minutes/day or three 30-minute periods/day).

In two developmental toxicity studies, pregnant rats were exposed to ethylene oxide vapors for 6 hours/day during gestation days 6–15. The studies reported fetal weight data as mean of litter means. Sprague-Dawley rats were used in the study of Neeper-Bradley and Kubena (1993); the study identified a NOAEL of 50 ppm and a LOAEL of 125 ppm for 5% depressed mean fetal weight. Fischer 344 rats were used in the study of Snellings et al. (1982a); the study identified a NOAEL of 33 ppm and a LOAEL of 100 ppm for up to 9% depressed mean fetal weight.

Table A-1. Summary of Selected NOAELs and LOAELs from Acute-Duration Studies in Animals Exposed to Ethylene Oxide by Inhalation

Species	Exposure scenario	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$[a] (ppm)	$LOAEL_{ADJ}$[a] (ppm)	Effect	Reference
Respiratory effects							
B6C3F1 mouse	Up to 2 weeks during a 14-week study 5 days/week 6 hours/day	ND	400[b]	ND	71.4	Rhinitis	NTP 1987
Developmental effects							
Fischer 344 rat	GDs 6–15 6 hours/day	33 F	100 F	8.3 F	25 F	Up to 9% depressed mean fetal weight	Snellings et al. 1982a
Sprague-Dawley rat	GDs 6–15 30 minutes/day	800 F	1,200 F	16.7	25 F	Increased incidence of dilation in renal pelvis and ureter of fetuses	Saillenfait et al. 1996
Sprague-Dawley rat	GDs 6–15 6 hours/day	50	125	12.5	31.3	5% depressed mean fetal weight	Neeper-Bradley and Kubena 1993
Sprague-Dawley rat	GDs 7–16 7 hours/day	ND	150 F	ND	43.8 F	5–6% depressed mean fetal weight; decreased crown-rump length; delayed ossification (skull, sternebrae)	NIOSH 1982
Sprague-Dawley rat	GDs 6–15 3x30 minutes/day	ND	800 F	ND	50 F	4–7% depressed mean fetal weight at maternally toxic exposure level	Saillenfait et al. 1996
Hybrid mouse	Once for 1.5 hours	ND	1,200 F	ND	75 F	Selected fetal defects (mostly hydrops and eye defects)	Rutledge and Generoso 1989

[a]Duration-adjusted from intermittent exposure to a continuous exposure scenario.
[b]Lethal exposure level.

ADJ = adjusted; F = female(s); GD = gestation day; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The mean fetal weight data in the developmental toxicity study of Fischer 344 maternal rats (Snellings et al. 1982a) were selected to represent the critical effect of acute-duration inhalation exposure to ethylene oxide because the fetal weight data represent the lowest LOAEL (100 ppm); the corresponding NOAEL was 33 ppm. As shown in Table A-1, duration adjustment (to account for a continuous exposure scenario) of NOAELs and LOAELs from the various studies did not result in a more appropriate principal study or critical effect.

Summary of the Principal Study:

Snellings WM, Maronpot RR, Zelenak JP, et al. 1982a. Teratology study in Fischer 344 rats exposed to ethylene oxide by inhalation. Toxicol Appl Pharmacol 64:476-481.

Groups of 22 pregnant Fischer 344 rats were exposed to 0, 0, 10, 33, or 100 ppm ethylene oxide 6 hours/day on gestation days 6–15 and sacrificed on gestation day 20. Parameters used to assess toxicity included number of implantation sites, viable fetuses, dead fetuses, early resorption sites, and late resorption sites, number of corpora lutea, fetal body weight, sex, crown-to-rump length, external fetal abnormalities, and internal and skeletal abnormalities in both control and 100 ppm groups (examined in 10 and 33 ppm groups if effects were noted at 100 ppm).

No overt signs of toxicity were observed in the dams. No alterations in preimplantation loss or embryo or fetal resorptions were observed. Significant decreases in fetal body weight were observed at 100 ppm (approximately 6–9% in males and 3–6% in females), but there were no differences in crown-rump length. An increase in the occurrence of vertebrae ossification variations was observed at 100 ppm, but the incidence was not significantly different from controls. No other developmental alterations were observed. The fetal weight data are presented in Table A-2. Although there are no established guidelines as to what minimal change in a continuous endpoint such as body weight is biologically significant, a 10% change is generally used for adult body weight. However, because fetal or neonatal organisms may be more susceptible than adults, a ≥5% decrease in fetal body weight relative to controls was selected to represent an adverse effect.

Table A-2. Fetal Weight Data (Mean of Litter Means) for Fetuses of Maternal Fischer 344 Rats Exposed to Ethylene Oxide Vapor for 6 Hours/Day During Gestation Days 6–15

	Ethylene oxide exposure level (ppm)				
	0 (control I)	0 (control II)	10	33	100
Number of litters	21	17	20	21	19
Mean fetal weight (g)	M: 3.4±0.4[a] F: 3.1±0.3	M: 3.3±0.2 F: 3.0±0.2	M: 3.3±0.3 F: 3.0±0.3	M: 3.3±0.3 F: 3.1±0.3	M: 3.1[b]±0.2 F: 2.9[b]±0.1

[a]Mean of litter means ± standard deviation.
[b]Significantly different from each sex-matched control group by Duncan's multiple range test ($p<0.05$).

F = female; M = male

Source: Snellings et al. 1982a

Selection of the Point of Departure for the MRL: A benchmark dose (BMD) approach was applied to derive the acute-duration inhalation MRL for ethylene oxide. Fetal body weight data from Snellings et al. (1982a; Table A-2) were fit to all available continuous variable models in the EPA Benchmark Dose

Software (BMDS, version 3.2) using a benchmark response (BMR) of 5% relative deviation from control and the assumption of constant variance. However, continuous Hill models were not considered viable because the model has five parameters, requiring a minimum of six data points (including control), and these data sets have only four or five data points. For remaining models, adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value ≥0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest BMCL was selected as the point of departure (POD) when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

BMD modeling results for male fetal weight data reported by Snellings et al. (1982a; see Table A-2) are summarized in Table A-3. Data were a fit to constant variance. Among models providing viable results, the 4-degree Polynomial model-predicted $BMCL_{RD05}$ of 45.50 ppm was selected as a potential POD because it provided the lowest AIC.

Table A-3. Results from BMD Analysis (Constant Variance) of Male Fetal Weight Following Maternal Exposure of Fischer 344 Rats to Ethylene Oxide Vapor for 6 Hours/Day During Gestation Days 6–15 (Snellings et al. 1982a)

					Scaled residuals[c]	
Model	BMC_{RD05}[a]	$BMCL_{RD05}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	67.70	43.83	0.81	40.98	0.47	-0.13
Exponential (model 3)[d]	74.58	44.00	0.55	42.91	0.22	-0.03
Exponential (model 4)[d]	67.69	43.83	0.81	40.98	0.47	-0.13
Exponential (model 5)[d]	73.93	44.00	0.55	42.91	0.24	-0.04
Polynomial (2-degree)[e]	76.38	45.43	0.58	42.86	0.19	-0.02
Polynomial (3-degree)[e]	79.24	45.51	0.87	40.84	0.15	-0.01
Polynomial (4-degree)[e,f]	**81.48**	**45.50**	**0.87**	**40.83**	**0.14**	**-0.002**
Linear[e]	68.39	45.14	0.82	40.96	0.45	-0.11
Power	74.61	54.00	0.56	42.90	0.22	-0.03

[a]BMCLs <10 times the lowest non-zero dose and their corresponding BMCs 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]Coefficients restricted to be negative.
[f]Selected model. Using constant variance, all models provided adequate fit. BMCLs for all models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (4-degree Polynominal).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD05 = dose associated with a 5% relative deviation)

Table A-4 summarizes the results of BMD modeling for female fetal weight data reported by Snellings et al. (1982a; see Table A-2). None of the models provided adequate fit to the data using constant variance. Therefore, the data were fit to all models using nonconstant variance. The Power model and Polynomial models (2-, 3-, and 4-degree) provided viable results. Among these models, the 4-degree Polynomial

model-predicted $BMCL_{RD05}$ of 87.00 ppm was selected as a potential POD because the model provided the lowest AIC.

Table A-4. Results from BMD Analysis (Nonconstant Variance) of Female Fetal Weight Following Maternal Exposure of Fischer 344 Rats to Ethylene Oxide Vapor for 6 Hours/Day During Gestation Days 6–15 (Snellings et al. 1982a)

					Scaled residuals[c]	
Model	BMC_{RD05}[a]	$BMCL_{RD05}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]			0.01	5.97	1.46	0.41
Exponential (model 3)[d]			0.03	2.00	0.40	0.93
Exponential (model 4)[d]			0.01	5.97	1.46	0.41
Exponential (model 5)[d]			0.03	2.00	0.40	0.93
Polynomial (2-degree)[e]	97.62	82.74	0.31	-2.54	1.00	-0.02
Polynomial (3-degree)[e]	96.02	84.98	0.68	-5.37	0.68	0.28
Polynomial (4-degree)[e,f]	**99.07**	**87.00**	**0.83**	**-6.00**	**0.75**	**0.07**
Linear[e]			0.01	4.41	1.59	-0.23
Power	99.98	98.35	0.39	-2.14	0.76	0.003

[a]BMCLs <10 times the lowest non-zero dose and their corresponding BMCs 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]Coefficients restricted to be negative.
[f]Selected model. Using nonconstant variance, the polynomial and power models provided adequate fit to the data. BMCLs for these models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (4-degree Polynomial).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD05 = dose associated with a 5% relative deviation)

Fetal weight data (per litter) reported by Neeper-Bradley and Kubena (1993; see Table A-5) were also modeled for comparison. Table A-6 summarize the results of BMD modeling for this data set. Data were a fit to constant variance. All models provided adequate fit to the data. The Exponential model 3 was selected as the best-fitting model (lowest AIC) and provided a $BMCL_{RD05}$ of 92.09 ppm.

Table A-5. Fetal Weight per Litter Following Maternal Exposure of Sprague-Dawley Rats to Ethylene Oxide Vapor for 6 Hours/Day on Gestation Days 6–15

	Ethylene oxide concentration (ppm)			
	0	50	125	225
Number of litters	23	20	20	24
Fetal weight per litter (g)	5.161±0.2480[a]	4.972±0.2766[b]	4.891±0.2745[b]	4.644±0.2899[c]

[a]Mean ± standard deviation.
[b]Significantly different from control group by t- test ($p<0.05$).
[c]Significantly different from control group by t- test ($p<0.01$).

Source: Neeper-Bradley and Kubena 1993

Table A-6. Fetal Weight per Litter Following Maternal Exposure of Sprague-Dawley Rats to Ethylene Oxide Vapor for 6 Hours/Day on Gestation Days 6–15 (Neeper-Bradley and Kubena 1993)

					Scaled residuals[c]	
Model	BMC_{RD05}[a]	$BMCL_{RD05}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	115.38	92.07	0.54	23.92	-0.88	0.52
Exponential (model 3)[e]	**115.38**	**92.09**	**0.54**	**23.92**	**-0.88**	**0.52**
Exponential (model 4)[d]	112.35	59.62	0.27	25.91	-0.85	0.58
Exponential (model 5)[d]	115.38	59.50	0.27	25.92	-0.88	0.52
Polynomial (2-degree)[f]	118.32	95.58	0.53	23.95	-0.91	0.46
Polynomial (3-degree)[f]	118.32	95.58	0.53	23.95	-0.91	0.46
Linear[f]	118.32	95.58	0.53	23.95	-0.91	0.46
Power[d]	118.32	95.59	0.53	23.95	-0.91	0.46

[a]BMCLs <10 times the lowest non-zero dose and their corresponding BMCs 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]Selected model. Using constant variance, all models provided adequate fit. BMCLs for all models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential model 3).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD05 = dose associated with a 5% relative deviation)

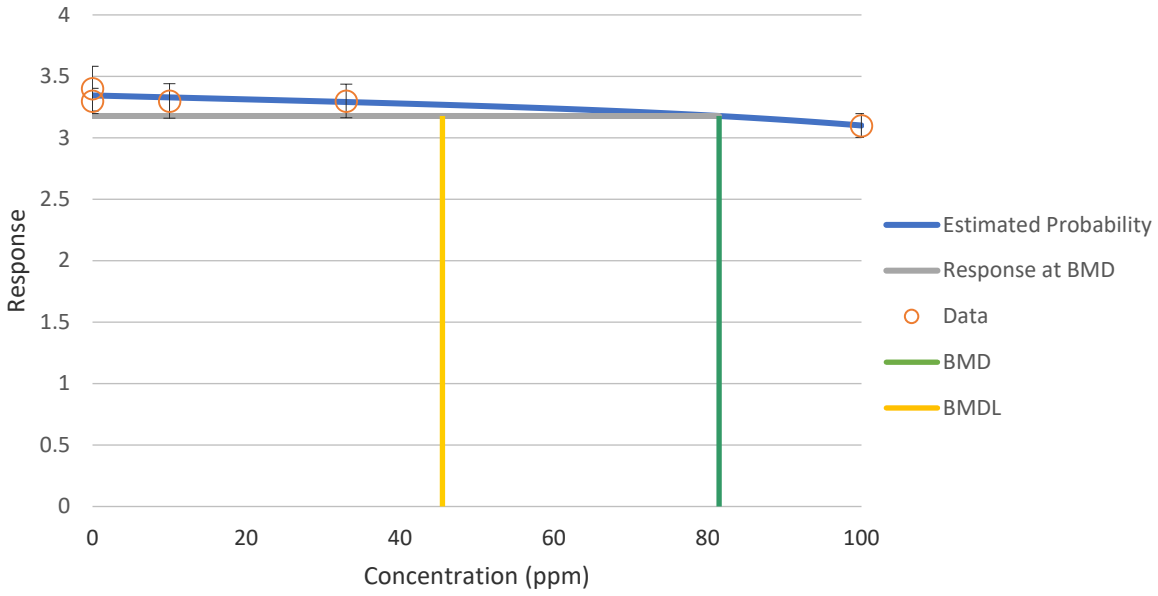
Potential PODs for deriving an acute-duration inhalation MRL for ethylene oxide include:

- $BMCL_{RD05}$ of 92.09 ppm from the fetal weight data of Neeper-Bradley and Kubena (1993)
- $BMCL_{RD05}$ of 87.00 ppm from the female fetal weight data of Snellings et al. (1982a)
- $BMCL_{RD05}$ of 45.50 ppm from the male fetal weight data of Snellings et al. (1982a)

The $BMCL_{RD05}$ of 45.50 ppm from the male fetal weight data of Snellings et al. (1982a) was selected as the POD for deriving an acute-duration inhalation MRL for ethylene oxide because it represents the most

conservative (health-protective) POD. The 4-degree Polynomial model fit to the male fetal weight data is presented in Figure A-1.

Figure A-1. Fit of 4-Degree Polynominal Model to Data on Male Fetal Weight Following Maternal Exposure of Fischer 344 Rats to Ethylene Oxide Vapor



Calculations

Intermittent Exposure: The $BMCL_{RD05}$ of 45.50 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMCL_{ADJ}$ = $BMCL_{RD05}$ of 45.50 ppm x (6 hours/24 hours) = 11.38 ppm

Human Equivalent Concentration: A PBPK modeling approach was initially considered to calculate a human equivalent to the rat $BMCL_{ADJ}$. However, a PBPK modeling approach was rejected due to a lack of experimental data regarding the proper dose metric (proximate toxicant) for ethylene oxide-induced developmental toxicity. Therefore, a human equivalent concentration was calculated by multiplying the duration adjusted BMCL by the regional gas dose ratio (RGDR). The RGDR for extrarespiratory tract effects is the ratio of animal to human blood:gas partition coefficients:

$BMCL_{HEC}$ = $BMCL_{ADJ}$ x $RGDR_{ER}$
$BMCL_{HEC}$ = $BMCL_{ADJ}$ x ($[H_{b/g}]_A/[H_{b/g}]_H$)

$[H_{b/g}]_A$ = animal blood/air partition coefficient = 64.1 for rats (Krishnan et al. 1992)
$[H_{b/g}]_H$ = human blood/air partition coefficient = 61 for humans (Csanady et al. 2000)

A default value of 1 is used for the ratio of blood/air partition coefficients because the animal value is greater than the human value.

$BMCL_{HEC}$ = 11.38 ppm x 1 = 11.38 ppm

Uncertainty Factor: The $BMCL_{HEC}$ of 11.38 ppm was divided by a total uncertainty factor (UF) of 30:

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

$MRL = BMCL_{HEC} \div UF$
$MRL = 11.38 \text{ ppm} \div (3 \times 10) = 0.379 \text{ ppm} \approx 0.4 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Other acute-duration developmental toxicity studies in rats identified fetal body weight effects as well (Neeper-Bradley and Kubena 1993; NIOSH 1982; Saillenfait et al. 1996), although LOAELs were higher than the LOAEL of Snellings et al. (1982a). Reduced fetal body weight was also observed in rats exposed to inhaled ethylene oxide for intermediate exposure durations (EPA 1994; NIOSH 1982)

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene Oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.07 ppm
Critical Effect: Decreased pup body weight
Reference: EPA 1994
Point of Departure: NOAEL of 10 ppm ($NOAEL_{HEC}$ of 2.1ppm)
Uncertainty Factor: 30
LSE Graph Key: 22
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.07 ppm has been derived based on decreased body weight in F1 male pups on postnatal day (PND) 21 in CD rats exposed to ethylene oxide vapor for 6 hours/day, 5.85 days/week in a 2-generation reproduction study (EPA 1994). The MRL is based on a NOAEL of 10 ppm that was adjusted to continuous exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 2.1 ppm, divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No adequate exposure-response human data are available. Case studies of workers have reported a number of neurological effects including headache, neuropathy, impaired hand-eye coordination, hand numbness, cognitive dysfunction, and memory loss (Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Zampollo et al. 1984). These effects were seen at estimated average exposure levels as low as 3 ppm; however, short-term exposures may have been as high as 700 ppm for some of these workers. These case studies are insufficient to establish a causal relationship between exposure to ethylene oxide and neurological effects in humans.

Several animal studies evaluated sublethal effects of intermediate-duration inhalation exposure in laboratory animals (EPA 1994, 2005b; Fujishiro et al. 1990; Matsuoka et al. 1990; Mori et al. 1991a, 1991b; NIOSH 1982; NTP 1987; Ohnishi et al. 1985, 1986; Snellings et al. 1982b, 1984a). Adverse effects were observed in the respiratory, hematological, renal, neurological, and reproductive systems, and in the developing fetus; the most sensitive NOAELs and LOAELs for these effects are summarized in Table A-7. EPA (1994) reported the lowest LOAEL of 33 ppm, with a NOAEL of 10 ppm, for developmental effects (decreased PND pup weight in F1 males) and reproductive effects (increased post-implantation loss in F0 rats). For other systems, the lowest LOAELs were as follows: 100 ppm for renal effects (renal tubular degeneration) (NTP 1987); 200 ppm for respiratory effects (rhinitis) (NTP 1987); and 200 ppm for neurological effects (decreased hindlimb strength) (EPA 2005b); and 250 ppm for hematological effects (decreases in hemoglobin, erythrocyte count, packed cell volume, and/or mean corpuscular hemoglobin) (Snellings et al. 1984a)

Table A-7. Summary of Selected NOAELs and LOAELs from Intermediate-Duration Studies in Animals Exposed to Ethylene Oxide by Inhalation

Species	Exposure scenario	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$[a] (ppm)	$LOAEL_{ADJ}$[a] (ppm)	System: effect	Reference
CD rat	10 weeks premating (6 hours/day, 5 days/week) and during mating, gestation, and lactation (6 hours/day, 7 days/week)	10	33	2.1[b]	6.89[b]	***Developmental:*** Decreased pup body weight in F1 males on PND 21	EPA 1994
CD rat	10 weeks premating (6 hours/day, 5 days/week) and during mating, gestation, and lactation (6 hours/day, 7 days/week)	10	33 (SLOAEL)	2.1[b]	6.89[b]	***Reproductive:*** Increased post-implantation loss in F0 rats	EPA 1994
B6C3F1 mouse	Up to 14 weeks (6 hours/day, 5 days/week)	NR M 100 F	100 M 200 F	ND M 17.9 F	17.9 M 35.7 F	***Renal:*** Renal tubular degeneration	NTP 1987
Sprague-Dawley rat	14 weeks (6 hours/day, 5 days/week)	100	200	17.8	35.7	***Neurological:*** Decreased hindlimb grip strength	EPA 2005b
B6C3F1 mouse	Up to 14 weeks (6 hours/day, 5 days/week)	100	200	17.9	35.7	***Respiratory:*** Rhinitis	NTP 1987
B6C3F1 mouse	10–11 weeks (6 hours/day, 5 days/week)	100	250	17.9	44.6	***Hematological:*** Decreases in hemoglobin, erythrocyte count, packed cell volume, and/or mean corpuscular hemoglobin	Snellings et al. 1984a

[a]Duration-adjusted from intermittent exposure to a continuous exposure scenario.
[b]Duration-adjusted to continuous exposure using the time-weighted average for the exposure frequency (5.85 days/week, 6 hours/day).

ADJ = adjusted; F = female(s); LOAEL = lowest observed adverse effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NR = not reported; PND = postnatal day; SLOAEL = serious LOAEL

Selection of the Principal Study: Among available intermediate-duration inhalation studies in laboratory animals, EPA (1994) identified the lowest NOAEL and LOAEL of 10 and 33 ppm, respectively. Therefore, EPA (1994) was selected as the principal study for derivation of the intermediate-duration inhalation MRL.

Summary of the Principal Study:

EPA. 1994. Data evaluation report: Ethylene oxide (EtO): Range-finding/developmental studies in rats (MRID #427977-01 and -02). D192811. Two generation reproduction study in rats (MRID #427881-01). D192453 (Previous 189547). Washington, DC: U.S. Environmental Protection Agency.

Groups CD rats (28/sex/group) were exposed by inhalation (whole body) to 0, 10, 33, or 100 ppm of ethylene oxide for 10 weeks premating (6 hours/day, 5 days/week), and during mating (2 weeks), gestation days 0–21, and lactation days 5–28 (6 hours/day, 7 days/week). The time-weighted exposure frequency for the study is 5.85 days/week for 6 hours/day. Parental animals were evaluated mortality, clinical signs, body weight, food consumption, organ weights (liver and lung), gross pathology, and histopathology, including reproductive organs. Uteri were examined to determine the total number of implantation sites. Litters were examined for numbers of live and stillborn pups, number of live and dead pups, sex, external anomalies, and pup body weight.

In F0 and F1 parents, no mortality or clinical signs were observed. Significant decreases in body weight gain were observed in F0 males in the 100 ppm group during the first 3 weeks of the pre-mating period (13–23%) and in F1 males in the 100 ppm group during the first (13%) and fifth (24%) weeks in the pre-mating period. A decrease in body weight was also reported in F1 males (7–11%) in the 33 ppm group "throughout study," but data were not provided. No consistent treatment-related alterations in body weight gain were observed in the F0 or F1 females during the pre-mating period. Significant decreases in body weight gain were observed in F0 and F1 females in the 100 ppm group during gestation; the decreases in body weight in the F1 group were considered to be due to the reduced litter size in this group. Decreases in food consumption were observed in F0 and F1 lactating females. No treatment-related effects were observed for organ weights, or on gross pathological or histopathological examinations in males or females.

Reproductive and developmental effects were observed in F0 parents and F1 offspring at 33 and 100 ppm and in F1 parents and F2 offspring at 100 ppm. In F0 parents, post-implantation loss was increased to 14 and 41% in the 33 and 100 ppm groups respectively, compared to 7% in controls. The mean number of live births per litter was decreased by 36% in the 100 ppm group, compared to control. In F1 offspring, pup body weight on PND 21 was decreased by 7 and 13% in males in the 33 and 100 ppm groups, respectively. In female pups, body weight on PND 21 was decreased by 13% in the 100 ppm group. In F1 parents, post-implantation loss was increased to 42% in the 100 ppm group, compared to 11% in controls. The mean number of live births per litter were also decreased by 45% in the 100 ppm group, compared to control. In the 100 ppm group, alterations in F2 pup body weight were observed on PNDs 1 and 21. On PND 1, male and female body weights were increased by 10 and 9%, respectively, compared to controls; this was attributed to reduced litter size. In contrast, on PND 21, male and female body weights were decreased by 11%.

Selection of the Point of Departure for the MRL: Among intermediate-duration inhalation studies in laboratory animals, the 2-generation reproduction study in rats summarized by EPA (1994) identified the lowest LOAEL of 33 ppm for decreased F1 pup body weight in males on PND 21; data are presented in Table A-8. As noted in discussions above, post-implantation loss exposed to 33 and 100 ppm was also observed in this study. However, in a companion gestation-only exposure study (conducted by the same researchers using the same strain of rats with daily exposures on gestation days 6–15), post-implantation

loss was not observed at exposure levels up to 250 ppm (EPA 1994). Additionally, the reproductive NOAEL and LOAEL values in a 1-generation study in F-344 rats were 33 and 100 ppm, respectively, based on a significant decrease in the ratio of the number of fetuses born per number of implantation sites (Snellings et al. 1982b). Due to observed discrepancies regarding the LOAEL for post-implantation loss, this endpoint was not selected as a co-critical effect for the intermediate-duration inhalation MRL. Data for pup body weight was not amenable to BMD analysis because measures of variance (e.g., standard deviation or standard error) for pup body weights were not reported. Therefore, the NOAEL of 10 ppm was selected as the POD.

Table A-8. Male Pup Body Weight in F1 Offspring of CD Rats Exposed to Ethylene Oxide in a 2-Generation Reproduction Study

	Ethylene oxide exposure level (ppm)			
Effect	0	10	33	100
Body weight PND 21 (g)	40.8	41.7[a] (↑ 2.2%)	38.0[b] (↓6.9%)	35.3[c] (↓13.5%)

↑ = increase; ↓ = decrease; PND = postnatal day

[a]Values are means (% change from control)
[b]Significantly different from control ($p<0.05$)
[c]Significantly different from control ($p<0.01$)

Source: EPA 1994

Calculations

Intermittent Exposure: The NOAEL of 10 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = NOAEL of 10 ppm x (6 hours/24 hours) x (5.85 days/7 days) = 2.1 ppm.

Human Equivalent Concentration: A PBPK modeling approach was initially considered to calculate a human equivalent to the rat $NOAEL_{ADJ}$. Available PBPK models for ethylene oxide are described in Section 3.1.5. However, a PBPK modeling approach was rejected due to a lack of experimental data regarding the proper dose metric (proximate toxicant) for ethylene oxide-induced developmental effects. Therefore, a human equivalent concentration was calculated by multiplying the duration adjusted BMDL by the RGDR. The RGDR for extrarespiratory tract effects is the ratio of animal to human blood:gas partition coefficients.

$NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ER}$
$NOAEL_{HEC} = NOAEL_{ADJ} \times ([H_{b/g}]_A/[H_{b/g}]_H)$

$[H_{b/g}]_A$ = andecreaseimal blood/air partition coefficient = 64.1 for rats (Krishnan et al. 1992)
$[H_{b/g}]_H$ = human blood/air partition coefficient = 61 for humans (Csanady et al. 2000)

A default value of 1 for the ratio of blood/air partition coefficients for rats and humans was used because the rat blood/air partition coefficient was greater than the value for humans.

$NOAEL_{HEC}$ = 2.1 ppm x 1 = 2.1 ppm

Uncertainty Factor and Modifying Factor: The $NOAEL_{HEC}$ of 2.1 ppm was divided by a total uncertainty factor (UF) of 30:

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

$MRL = NOAEL_{HEC} \div UF$
$MRL = 2.1 \text{ ppm} \div (3 \times 10) = 0.07 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Gestational exposure studies in rats provide supporting evidence for developmental effects, specifically decreased pup body weight in dams exposed to inhaled ethylene oxide (Neeper-Bradley and Kubena 1993; NIOSH 1982; Saillenfait et al. 1996; Snellings et al. 1982a). LOAELs in these studies range from 100 ppm (Snellings et al. 1982a) to 800 ppm (Saillenfait et al. 1996).

The pre-public version of the ethylene oxide profile developed a provisional intermediate-duration inhalation MRL based on neurological effects. However, newly available data indicate that developmental effects are more sensitive than neurological effects. Therefore, the final intermediate-duration MRL for ethylene oxide was revised based on these developmental effects. The provisional neurological MRL in the pre-public version applied a modifying factor to address the insufficient assessment of functional neurological endpoints. However, since the endpoints in the developmental study were assessed thoroughly, ATSDR determined that no additional modifying factor was needed.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene Oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: Available chronic-duration inhalation data were not considered adequate for derivation of a chronic-duration inhalation MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Case studies of neurological effects in workers exposed to ethylene oxide have been reported. These studies are insufficient to establish a causal relationship between exposure to ethylene oxide and neurological effects in humans. Neuropathy, impaired hand-eye coordination, cognitive dysfunction, memory loss, headache, and hand numbness were reported after occupational exposure to ethylene oxide (Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Zampollo et al. 1984). Sural nerve biopsies performed on two occupational groups revealed axonal degeneration and regeneration (Kuzuhara et al. 1983; Schröder et al. 1985).

The effects of chronic-duration inhalation exposure studies have been evaluated in monkeys (Lynch et al. 1984a), rats (Lynch et al. 1984a, 1984b; Snellings et al. 1984b), and mice (NTP 1987). Studies in monkeys and mice were not considered as potential principal studies. In cynomolgus monkeys intermittently exposed to ethylene oxide vapor for 2 years, decreased sperm count (28% less than controls) and motility (32% less than controls) were noted at the lowest exposure level tested (50 ppm) (Lynch et al. 1984a). However, evaluation of sperm parameters at cessation of exposures at 24 months included only two monkeys per group. Therefore, data are not adequate for derivation of the chronic-duration MRL. The NTP (1987) study in mice did not identify any noncancer effects at the highest exposure level tested (100 ppm); therefore, data from this study cannot be considered as the basis of the MRL.

The rat studies (Lynch et al. 1984b; Snellings et al. 1984b) were considered as principal studies for derivation of the chronic-duration inhalation MRL; however, ATSDR determined that they are inadequate to support derivation of an MRL. Exposure concentrations in these studies ranged from 10 to 100 ppm. Observed effects included decreased body weight (Lynch et al. 1984b; Snellings et al. 1984b) and alterations in the hematological, musculoskeletal, and endocrine systems (Lynch et al. 1984b). The NOAEL and LOAEL values for these effects are summarized in Table A-9. Lynch et al. (1984b) identified the lowest LOAEL of 50 ppm based on splenic extramedullary hematopoiesis and histopathological changes to the adrenal gland (multifocal vacuolization and hyperplasia). NOAEL values for these effects were not identified. However, ATSDR deemed the study inappropriate for MRL derivation because the rat colony experienced a *Mycoplasma pulmonis* infection during the study period. This infection was treated with antibiotics but did not appear to resolve and resulted in decreased survival. The potential contribution of the infection and stress associated with infection to adverse health effects is unknown, particularly regarding adrenal gland findings. Adrenal findings are further confounded by evidence that administration of antibiotics may induce adrenal hyperplasia in rats (Dickson et al. 1954; Dietz et al. 1991). Therefore, effects reported by Lynch et al. (1984b) at ≥50 ppm are of uncertain toxicological relevance due to concurrent infection. The other available rat study (Snellings et al. 1984b) identified a higher LOAEL of 100 ppm based on decreased body weight. However, potential non-

Table A-9. Summary of Selected NOAELs and LOAELs from Chronic-Duration Studies in Animals Exposed to Ethylene Oxide by Inhalation

Species	Exposure scenario	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$[a] (ppm)	$LOAEL_{ADJ}$[a] (ppm)	Effect	Reference
Body weight effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/day	50	100	10.4	20.8	13% depressed body weight gain	Lynch et al. 1984b
Fischer 344 rat	2 years 5 days/week 6 hours/day	33	100	5.9	17.9	Depressed body weight gain in males (up to 12%) and females (12–18%)	Snellings et al. 1984b
Hematological effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/day	ND	50	ND	10.4	Splenic extramedullary hematopoiesis	Lynch et al. 1984b
Musculoskeletal effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/day	50	100	10.4	20.8	Multifocal myopathy	Lynch et al. 1984b
Endocrine effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/days	ND	50	ND	10.4	Multifocal cortical vacuolation and hyperplasia in adrenal gland	Lynch et al. 1984b

[a]Duration-adjusted from intermittent exposure to a continuous exposure scenario.

ADJ = adjusted; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

neoplastic changes in the spleen may have been masked at 33 ppm due to increased incidence of mononuclear cell leukemia that was associated with marked splenomegaly in these rats. Therefore, an MRL based on body weight effects observed at 100 ppm may not be protective of potential nonneoplastic effects at lower exposure levels.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: Available acute-duration oral data were not considered adequate for derivation of an acute-duration oral MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available animal data are restricted to a single study in which 100% mortality occurred in rats treated with ethylene oxide by single gavage dose at 200 mg/kg; treatment at 100 mg/kg did not affect body weight (Hollingsworth et al. 1956).

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: The intermediate-duration oral data were not considered adequate for derivation of an intermediate-duration oral MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available animal data are restricted to a single study in which gavage dosing of rats at 100 mg/kg/day for 15 or 22 treatments in 15 or 30 days resulted in weight loss, gastric irritation, and slight liver damage (not otherwise described); the NOAEL was 30 mg/kg/day (Hollingsworth et al. 1956). The lack of quantitative data precludes derivation of an intermediate-duration oral MRL for ethylene oxide.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The chronic-duration oral data were not considered adequate for derivation of a chronic-duration oral MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available animal data are restricted to a single study in which gavage dosing at 30 mg/kg/day, 2 times/week for up to 150 weeks resulted in decreased survival; forestomach squamous cell carcinoma (at the application site for oral gavage) was reported at 7.5 mg/kg/day (Dunkelberg 1982).

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ETHYLENE OXIDE

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 ethylene oxide.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for ethylene oxide. 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 ethylene oxide 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 ethylene oxide 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 ethylene oxide released for public comment in 2020; thus, the literature search was restricted to studies published between Month YEAR and Month YEAR. The following main databases were searched in January 2021:

- 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 ethylene oxide. 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 ethylene oxide 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	
01/2021	(75-21-8 [rn] AND (((("ethylene oxide/toxicity"[mh] OR "ethylene oxide/adverse effects"[mh] OR "ethylene oxide/poisoning"[mh] OR "ethylene oxide/pharmacokinetics"[mh] OR "ethylene oxide/blood"[mh] OR "ethylene oxide/cerebrospinal fluid"[mh] OR "ethylene oxide/urine"[mh] OR "ethylene oxide/antagonists & inhibitors"[mh]) OR ("ethylene oxide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh])) OR ("ethylene oxide"[mh] AND toxicokinetics[mh:noexp]) OR ("ethylene oxide"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("ethylene oxide"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("ethylene oxide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("ethylene oxide"[mh] AND cancer[sb]) OR ("ethylene oxide/pharmacology"[majr])) AND (2018:3000[dp] OR 2018:3000[mhda] OR 2018:3000[crdt] OR 2018:3000[edat]))) OR ((("1,2-Epoxyethane"[tw] OR "Amprolene"[tw] OR "Anprolene"[tw] OR "dihydrooxirene"[tw] OR "Epoxyethane"[tw] OR "Ethene oxide"[tw] OR "ethylene oxide"[tw] OR "Ethyleneoxy"[tw] OR "Ethylenoxid"[tw] OR "Merpol"[tw] OR "Oxacyclopropane"[tw] OR "Oxane"[tw] OR "Oxidoethane"[tw] OR "Oxiran"[tw] OR "Oxirane"[tw] OR "Oxyfume"[tw] OR "Anproline"[tw] OR "Dimethylene oxide"[tw] OR "Emulsifier-Ethylene oxide"[tw] OR "Ethylene oxide-ionene copolymer"[tw] OR "Mirror Ox"[tw] OR "1,2,3,4-tetrahydro-1,1,6-trimethyl-Naphthalene polymer with oxirane"[tw] OR "Naphthalene, 1,2,3,4-tetrahydro-1,1,6-trimethyl-, polymer with oxirane"[tw] OR "Oxirane, polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene"[tw] OR "polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene oxirane"[tw] OR "Oxirene, dihydro-"[tw] OR "Oxyfume 12"[tw] OR "Oxyfume 2002"[tw]) NOT medline[sb]) AND (2018:3000[crdt] OR 2018:3000[edat] OR 2018:3000[dp]))

Table B-2. Database Query Strings

Database search date	Query string
NTRL	
01/2021	"1,2-Epoxyethane" OR "Amprolene" OR "Anprolene" OR "dihydrooxirene" OR "Epoxyethane" OR "Ethene oxide" OR "ethylene oxide" OR "Ethyleneoxy" OR "Ethylenoxid" OR "Merpol" OR "Oxacyclopropane" OR "Oxane" OR "Oxidoethane" OR "Oxiran" OR "Oxirane" OR "Oxyfume" "Anproline" OR "Dimethylene oxide" OR "Emulsifier-Ethylene oxide" OR "Ethylene oxide-ionene copolymer" OR "Mirror Ox" OR "1,2,3,4-tetrahydro-1,1,6-trimethyl-Naphthalene polymer with oxirane" OR "Naphthalene, 1,2,3,4-tetrahydro-1,1,6-trimethyl-, polymer with oxirane" OR "Oxirane, polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene" OR "polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene oxirane" OR "Oxirene, dihydro-" OR "Oxyfume 12" OR "Oxyfume 2002"
Toxcenter	
01/2021	FILE 'TOXCENTER' ENTERED AT 13:04:37 ON 26 JAN 2021 CHARGED TO COST=EH038.06.01.LB.03 L1 10178 SEA 75-21-8 L2 9971 SEA L1 NOT TSCATS/FS L3 6793 SEA L1 NOT PATENT/DT L4 6586 SEA L2 NOT PATENT/DT L5 283 SEA L4 AND PY>=2018 ACTIVATE TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (NONHUMAN MAMMALS)/ORGN
	L36 QUE L34 OR L35
	L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L38 QUE L36 OR L37

	L39 194 SEA L5 AND L36
	L40 191 SEA L5 AND L31
	L41 27 SEA L40 AND MEDLINE/FS
	L42 29 SEA L40 AND BIOSIS/FS
	L43 132 SEA L40 AND CAPLUS/FS
	L44 3 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L45 169 DUP REM L41 L42 L44 L43 (22 DUPLICATES REMOVED)
	L*** DEL 27 S L40 AND MEDLINE/FS
	L*** DEL 27 S L40 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L46 27 SEA L45 L*** DEL 29 S L40 AND BIOSIS/FS L*** DEL 29 S L40 AND BIOSIS/FS L47 22 SEA L45 L*** DEL 132 S L40 AND CAPLUS/FS L*** DEL 132 S L40 AND CAPLUS/FS L48 117 SEA L45 L*** DEL 3 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 3 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 3 SEA L45 L50 142 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS D SCAN L50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
01/2021	Compounds searched: 75-21-8
NTP	
01/2021	Limited to 2010 – present "Epoxyethane" "Ethene oxide" "ethylene oxide" "Ethyleneoxy" "Oxidoethane" "Oxiran" "Oxirane" "Oxyfume" "75-21-8" "1,2-Epoxyethane" "Amprolene" "Anprolene" "dihydrooxirene" "Ethylenoxid" "Merpol" "Oxacyclopropane" "Oxane"
Regulations.gov	
01/2021	Documents limited to: date 2018-Present; Notice; U.S. EPA 75-21-8 Ethylene oxide Docket limited to: U.S. EPA 75-21-8 Ethylene oxide"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
07/2021	Active projects, Text Search: "1,2-Epoxyethane" OR "Amprolene" OR "Anprolene" OR "dihydrooxirene" OR "Epoxyethane" OR "Ethene oxide" OR "ethylene oxide" OR "Ethyleneoxy" OR "Ethylenoxid" OR "Merpol" OR "Oxacyclopropane" OR "Oxane" OR "Oxidoethane" OR "Oxiran" OR "Oxirane" OR "Oxyfume" OR "Anproline" OR "Dimethylene oxide" OR "Emulsifier-Ethylene oxide" OR "Ethylene oxide-ionene copolymer" OR "Mirror Ox" OR "1,2,3,4-tetrahydro-1,1,6-trimethyl-Naphthalene polymer with oxirane" OR "Naphthalene, 1,2,3,4-tetrahydro-1,1,6-trimethyl-, polymer with oxirane" OR "Oxirane, polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene" OR "polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene oxirane" OR "Oxirene, dihydro-" OR "Oxyfume 12" OR "Oxyfume 2002" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 934
- Number of records identified from other strategies: 22
- Total number of records to undergo literature screening: 956

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on ethylene oxide:

- 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.

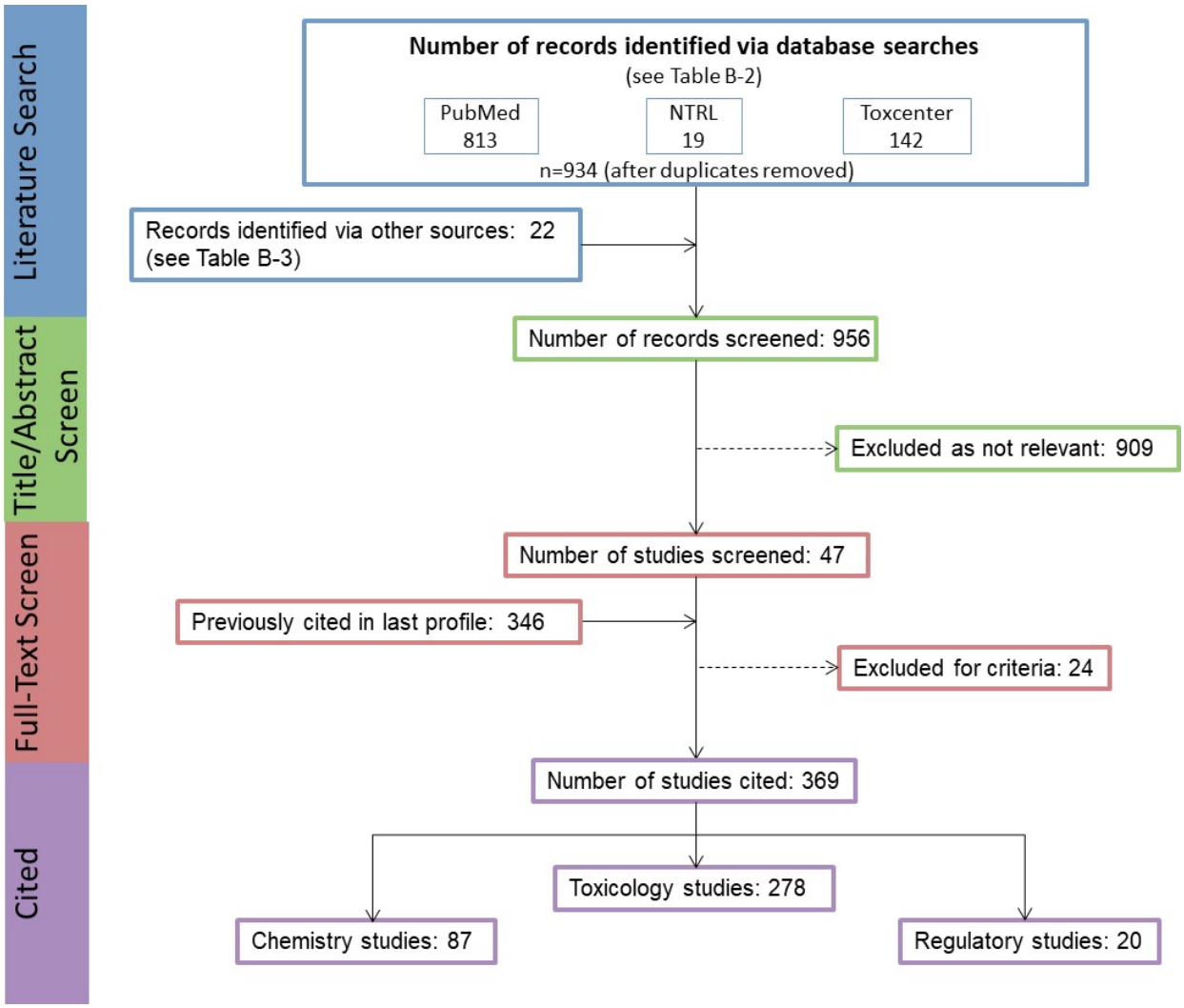
- Number of titles and abstracts screened: 956
- Number of studies considered relevant and moved to the next step: 47

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: 47
- Number of studies cited in the pre-public draft of the toxicological profile: 346
- Total number of studies cited in the profile: 369

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

Figure B-1. January 2021 Literature Search Results and Screen for Ethylene Oxide



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ETHYLENE OXIDE

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

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

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to ethylene oxide. The inclusion criteria used to identify relevant studies examining the health effects of ethylene oxide are presented in Table C-1.

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

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

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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of ethylene oxide. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for ethylene oxide released for public comment in 2020. See Appendix B for the databases searched and the search strategy.

A total of 956 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 956 records were reviewed; 2 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 90 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 90 documents, 127 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for ethylene oxide identified in human and animal studies are presented in Tables C-3 and C-4, respectively. A number of occupational cohorts were evaluated for possible associations between ethylene oxide and risk of death from selected noncancer endpoints; these studies were not included in the systematic review since they did not evaluate specific respiratory endpoints. Animal studies examined a number of endpoints following inhalation exposure. These studies examined most endpoints; the most sensitive endpoints were hematological, endocrine (adrenal gland), and neurological effects.

APPENDIX C

Table C-3. Overview of the Health Outcomes Ethylene Oxide Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		9	10	4	1		1	1	7	4		12		4			23
		2	0	0	0		0	0	7	4		10		4			13
Case control																	
Population																	
Case series													13				
													13				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

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

APPENDIX C

Table C-4. Overview of the Health Outcomes for Ethylene Oxide Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	9 5	6 6					2 2		2 2	1 1	2 2	1 1	1 1		8 6		
Intermediate-duration	26 9	14 6	1 0		4 4	13 6	3 0	1 0			1 0	1 0	19 13	8 7	3 2		1 1
Chronic-duration	3 2	2 1	3 0	2 0	2 1	2 1	2 0	2 0	1 0	1 0	2 1		3 1	3 1			3 3
Oral studies																	
Acute-duration	1 0																
Intermediate-duration	1 1			1 1	1 0		1 1										
Chronic-duration																	1 1
Dermal studies																	
Acute-duration										1 1							
Intermediate-duration																	
Chronic-duration																	1 0

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

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

Studies examining these potential outcomes (as well as respiratory, reproductive, and developmental outcomes) were carried through to Steps 4–8 of the systematic review. Oral data were not available for humans. Animal data were limited to results from a solitary study with limited study details. Gavage dosing of rats at 30 mg/kg/day, 2 times/week for up to 150 weeks resulted in decreased survival; forestomach squamous cell carcinoma (at the application site for oral gavage) was reported at 7.5 mg/kg/day (Dunkelberg 1982). This study was not subjected to systematic review because it could not be used as basis for deriving a chronic-duration oral MRL for ethylene oxide. There were 127 studies (published in 90 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

Table C-6. Risk of Bias Questionnaire for Experimental Animal Studies

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of ethylene oxide health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-7 and C-8, respectively.

Table C-7. Summary of Risk of Bias Assessment for Ethylene Oxide—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Respiratory effects							
Case series							
Deschamps et al. 1992	+	–	+	na	–	+	Second
Thiess 1963	+	–	+	na	–	+	Second
Outcome: Neurological effects							
Case series							
Blackwood and Erskine 1938	na	–	+	na	–	+	Third
Brashear et al. 1996	na	–	+	na	–	+	Third
Crystal et al. 1988	na	–	+	na	–	+	Third
Dretchen et al. 1992	na	–	+	na	–	+	Third
Estrin et al. 1987	na	–	+	na	–	+	Third
Finelli et al. 1983	na	–	+	na	–	+	Third
Gross et al. 1979	na	–	+	na	–	+	Third
Kuzuhara et al. 1983	na	–	+	na	–	+	Third
Salinas et al. 1981	na	–	+	na	–	+	Third
Schröder et al. 1985	na	–	+	na	–	+	Third
Sexton and Henson 1949	na	–	+	na	–	+	Third
Von Oettingen 1939	na	–	+	na	–	+	Third
Zampollo et al. 1984	na	–	+	na	–	+	Third

Table C-7. Summary of Risk of Bias Assessment for Ethylene Oxide—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Reproductive effects							
Cohort							
Gresie-Brusin et al. 2007	+	–	+	na	–	+	Second
Hemminki et al. 1982	+	–	+	na	–	+	Second
Rowland et al. 1996	+	–	+	na	–	+	Second

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

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Respiratory effects										
Inhalation acute exposure										
Hollingsworth et al. 1956 (rat, 841 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 357 ppm)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 4-hour)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 2-week)	+	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rabbit, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 406 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 102 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (dog, 292 ppm)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, GDs 1–16)	+	+	+	+	+	+	+	+	+	First

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit, GDs 1–19)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 14-week)	+	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	- -	+	+	Second
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First
Outcome: Hematological effects										
Inhalation intermediate exposure										
Fujishiro et al. 1990 (rat, 500 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 102 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (dog, 292 ppm)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1984a (mouse, 11-week)	++	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984a (monkey, 2-year)	+	+	+	+	+	+	+	+	+	First
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	- -	+	+	Second
Outcome: Endocrine effects										
Inhalation acute exposure										
Hollingsworth et al. 1956 (rat, 841 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig 841 ppm)	+	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	- -	+	+	Second
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Neurological effects										
Inhalation acute exposure										
EPA 2005a	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 4-hour)	+	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
EPA 2005b	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rabbit, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rabbit, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 406 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 102 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (dog, 292 ppm)	+	+	+	+	+	+	+	+	+	First
Kaido et al. 1992 (rat, 500 ppm)	++	+	+	+	+	+	+	+	+	First
Matsuoka et al. 1990 (rat, 500 ppm)	+	+	+	+	+	+	+	+	+	First
Ohnishi et al. 1985 (rat, 13-week)	+	+	+	+	+	+	+	+	+	First

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Ohnishi et al. 1986 (rat, 9-month)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1984a (mouse, 11-week)	++	+	+	+	+	+	-	+	+	Second
Inhalation chronic exposure										
Lynch et al. 1984a (monkey, 2-year)	+	+	+	+	+	+	+	+	+	First
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First
Outcome: Reproductive effects										
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
Kaido et al. 1992 (rat, 13-week)	++	+	+	+	+	+	+	+	+	First
Mori et al. 1991a (rat, 13-week)	+	+	+	+	+	+	+	+	+	First
Mori et al. 1991b (rat, 6-week)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit, GDs 1–19)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1982b (rat, 12-week)	++	+	+	+	+	+	+	+	+	First
Snellings et al. 1984a (mouse, 11-week)	++	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984a (monkey, 2-year)	+	+	+	+	+	+	+	+	+	First
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Developmental effects										
Inhalation acute exposure										
Neeper-Bradley and Kubena 1993 (rat)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit)	+	+	+	+	+	+	+	+	+	First
Rutledge and Generoso 1989 (mouse)	+	+	+	+	+	+	+	+	+	First
Saillenfait et al. 1996 (rat, 400–1,200 ppm)	+	+	+	+	+	+	+	+	+	First
Saillenfait et al. 1996 (rat, 200 or 400 ppm)	+	+	+	+	+	+	+	+	+	First
Saillenfait et al. 1996 (rat, 800 or 1,200 ppm)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1982a (rat, 10–100 ppm)	++	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit, GD 1–19)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1982b (rat, 12-week)	++	+	+	+	+	+	+	+	+	First

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

*Key question used to assign risk of bias tier

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

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to ethylene oxide and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to ethylene oxide and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies and experimental animal studies are presented in Tables C-9 and C-10, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

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

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

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

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

Table C-9. Key Features of Study Design for Observational Epidemiology Studies

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

Table C-10. Key Features of Study Design for Experimental Animal Studies

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

The presence or absence of the key features and the initial confidence levels for studies examining body weight effects, respiratory effects, reproductive effects, and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-11 and C-12, respectively.

Table C-11. Presence of Key Features of Study Design for Ethylene Oxide—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects					
Case series					
Deschamps et al. 1992	No	No	Yes	Yes	Low
Thiess 1963	No	No	Yes	Yes	Low
Outcome: Neurological effects					
Case series					
Blackwood and Erskine 1938	No	No	Yes	No	Very low
Brashear et al. 1996	No	No	Yes	No	Very low
Crystal et al. 1988	No	No	Yes	No	Very low
Dretchen et al. 1992	No	No	Yes	No	Very low
Estrin et al. 1987	No	No	Yes	No	Very low
Finelli et al. 1983	No	No	Yes	No	Very low
Gross et al. 1979	No	No	Yes	No	Very low

Table C-11. Presence of Key Features of Study Design for Ethylene Oxide—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Kuzuhara et al. 1983	No	No	Yes	No	Very low
Salinas et al. 1981	No	No	Yes	No	Very low
Schröder et al. 1985	No	No	Yes	No	Very low
Sexton and Henson 1949	No	No	Yes	No	Very low
Von Oettingen 1939	No	No	Yes	No	Very low
Zampollo et al. 1984	No	No	Yes	No	Very low
Outcome: Reproductive effects					
Cohort					
Gresie-Brusin et al. 2007	No	Yes	Yes	Yes	Moderate
Hemminki et al. 1982	No	Yes	Yes	Yes	Moderate
Rowland et al. 1996	No	Yes	Yes	Yes	Moderate

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
Hollingsworth et al. 1956 (rat, 841 ppm)	Yes	Yes	No	No	Low
Hollingsworth et al. 1956 (rat, 357 ppm)	Yes	Yes	No	No	Low
NIOSH 1982 (rat)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit)	Yes	Yes	No	No	Low
NTP 1987 (mouse, 4-hour)	No	No	Yes	No	Very low
NTP 1987 (mouse, 2-week)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
EPA 1994 (rat)	Yes	Yes	Yes	No	Moderate
Hollingsworth et al. 1956 (4 species, 113 ppm)	Yes	No	No	No	Very low
Hollingsworth et al. 1956 (5 species, 204 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 406 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 102 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (dog, 292 ppm)	Yes	No	No	No	Very low
NIOSH 1982 (rat, GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit, GDs 1–19)	Yes	Yes	No	No	Low
NTP 1987 (mouse, 14-week)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High
Outcome: Hematological effects					
Inhalation intermediate exposure					
Fujishiro et al. 1990 (rat, 500 ppm)	Yes	Yes	Yes	No	Moderate
Jacobson et al. 1956 (rat, 102 ppm)	Yes	Yes	No	No	Low
Jacobson et al. 1956 (dog, 292 ppm)	Yes	No	No	No	Very low
Snellings et al. 1984a (mouse, 11-week)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
Lynch et al. 1984a (monkey, 2-year)	Yes	Yes	Yes	No	Moderate
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
Outcome: Endocrine effects					
Inhalation acute exposure					
Hollingsworth et al. 1956 (2 species, 841 ppm)	Yes	Yes	No	No	Low
Inhalation chronic exposure					
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute exposure					
EPA 2005a	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 4-hour)	No	No	Yes	No	Very low

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
EPA 1994 (rat)	Yes	Yes	No	No	Low
EPA 2005b	Yes	Yes	Yes	Yes	High
Hollingsworth et al. 1956 (monkey, 357 ppm)	Yes	No	No	No	Very low
Hollingsworth et al. 1956 (4 species, 357 ppm)	Yes	No	No	No	Very low
Hollingsworth et al. 1956 (5 species 204 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 406 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 102 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (dog, 292 ppm)	Yes	No	No	No	Very low
Kaido et al. 1992 (rat, 500 ppm)	Yes	No	Yes	No	Low
Matsuoka et al. 1990 (rat, 500 ppm)	Yes	Yes	No	No	Low
Ohnishi et al. 1985 (rat, 13-week)	Yes	No	Yes	Yes	Moderate
Ohnishi et al. 1986 (rat, 9-month)	Yes	No	Yes	Yes	Moderate
Snellings et al. 1984a (mouse, 11-week)	Yes	Yes	No	No	Low
Inhalation chronic exposure					
Lynch et al. 1984a (monkey, 2-year)	Yes	Yes	Yes	No	Moderate
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High
Outcome: Reproductive effects					
Inhalation intermediate exposure					
EPA 1994 (rat)	Yes	Yes	Yes	No	Moderate
Kaido et al. 1992 (rat, 13-week)	Yes	No	Yes	No	Low
Mori et al. 1991a (rat, 13-week)	Yes	No	Yes	Yes	Moderate
Mori et al. 1991b (rat, 6-week)	Yes	Yes	Yes	Yes	High
NIOSH 1982 (rat, GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit, GDs 1–19)	Yes	Yes	No	No	Low
Snellings et al. 1982b (rat, 1-generation)	Yes	Yes	Yes	No	Moderate
Snellings et al. 1984a (mouse, 11-week)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
Lynch et al. 1984a (monkey, 2-year)	Yes	Yes	Yes	No	Moderate
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Developmental effects					
Inhalation acute exposure					
Neeper-Bradley and Kubena 1993 (rat)	Yes	Yes	Yes	Yes	High
NIOSH 1982 (rat)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit)	Yes	Yes	No	No	Low
Rutledge and Generoso 1989 (mouse)	Yes	Yes	Yes	No	Moderate
Saillenfait et al. 1996 (rat, 400–1,200 ppm)	Yes	Yes	Yes	Yes	High
Saillenfait et al. 1996 (rat, 200 or 400 ppm)	Yes	Yes	Yes	Yes	High
Saillenfait et al. 1996 (rat, 800 or 1,200 ppm)	Yes	Yes	Yes	Yes	High
Snellings et al. 1982a (rat, 10–100 ppm)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
EPA 1994 (rat)	Yes	Yes	Yes	No	Moderate
NIOSH 1982 (rat, GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit, GDs 1–19)	Yes	Yes	No	No	Low
Snellings et al. 1982b (rat, 1-generation)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-13. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-13.

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Animal studies		
Hollingsworth et al. 1956 (rat, 841 ppm)	Low	Moderate
Hollingsworth et al. 1956 (rat, 357 ppm)	Low	
NIOSH 1982 (rat)	Low	
NIOSH 1982 (rabbit)	Low	

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1987 (mouse, 4-hour)	Very low	
NTP 1987 (mouse, 2-week)	Moderate	
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Moderate	High
Hollingsworth et al. 1956 (4 species, 113 ppm)	Very low	
Hollingsworth et al. 1956 (5 species, 204 ppm)	Very low	
Jacobson et al. 1956 (rat, 406 ppm)	Very low	
Jacobson et al. 1956 (rat, 102 ppm)	Very low	
Jacobson et al. 1956 (dog, 292 ppm)	Very low	
NIOSH 1982 (rat, GDs 1–16)	Low	
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Low	
NIOSH 1982 (rabbit, GDs 1–19)	Low	
NTP 1987 (mouse, 14-week)	High	
Inhalation chronic exposure		
Human studies (case series)		
Deschamps et al. 1992	Very low	Low
Thiess 1963	Low	
Animal studies		
Lynch et al. 1984b (rat, 2-year)	Moderate	High
NTP 1987 (mouse, 102-week)	High	
Outcome: Hematological effects		
Inhalation intermediate exposure		
Animal studies		
Fujishiro et al. 1990 (rat, 500 ppm)	Moderate	Moderate
Jacobson et al. 1956 (rat, 102 ppm)	Low	
Jacobson et al. 1956 (dog, 292 ppm)	Very low	
Snellings et al. 1984a (mouse, 11-week)	Moderate	
Inhalation chronic exposure		
Animal studies		
Lynch et al. 1984a (monkey, 2-year)	Moderate	Moderate
Lynch et al. 1984b (rat, 2-year)	Moderate	
Outcome: Endocrine effects		
Inhalation acute exposure		
Animal studies		
Hollingsworth et al. 1956 (2 species, 841 ppm)	Low	Low
Inhalation chronic exposure		
Animal studies		
Lynch et al. 1984b (rat, 2-year)	Moderate	High
NTP 1987 (mouse, 102-week)	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Animal studies		
EPA 2005a	High	High

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1987 (mouse, 4-hour)	Very low	
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Low	High
EPA 2005b	High	
Hollingsworth et al. 1956 (monkey, 357 ppm)	Very low	
Hollingsworth et al. 1956 (4 species, 357 ppm)	Very low	
Hollingsworth et al. 1956 (5 species 204 ppm)	Very low	
Jacobson et al. 1956 (rat, 406 ppm)	Very low	
Jacobson et al. 1956 (rat, 102 ppm)	Very low	
Jacobson et al. 1956 (dog, 292 ppm)	Very low	
Kaido et al. 1992 (rat, 500 ppm)	Low	
Matsuoka et al. 1990 (rat, 500 ppm)	Low	
Ohnishi et al. 1985 (rat, 13-week)	Moderate	
Ohnishi et al. 1986 (rat, 9-month)	Moderate	
Snellings et al. 1984a (mouse, 11-week)	Low	
Inhalation chronic exposure		
Human studies		
Blackwood and Erskine 1938	Very low	Very low
Brashear et al. 1996	Very low	
Crystal et al. 1988	Very low	
Dretchen et al. 1992	Very low	
Estrin et al. 1987	Very low	
Finelli et al. 1983	Very low	
Gross et al. 1979	Very low	
Kuzuhara et al. 1983	Very low	
Salinas et al. 1981	Very low	
Schröder et al. 1985	Very low	
Sexton and Henson 1949	Very low	
Von Oettingen 1939	Very low	
Zampollo et al. 1984	Very low	
Animal studies		
Lynch et al. 1984a (monkey, 2-year)	Moderate	High
Lynch et al. 1984b (rat, 2-year)	Moderate	
NTP 1987 (mouse, 102-week)	High	
Outcome: Reproductive effects		
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Moderate	High
Kaido et al. 1992 (rat, 13-week)	Low	
Mori et al. 1991a (rat, 13-week)	Moderate	
Mori et al. 1991b (rat, 6-week)	High	
NIOSH 1982 (rat, GDs 1–16)	Low	
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Low	

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
NIOSH 1982 (rabbit, GDs 1–19)	Low	
NTP 1987 (mouse, 14-week)	High	
Snellings et al. 1982b (rat, 1-generation)	Moderate	
Snellings et al. 1984a (mouse, 11-week)	Moderate	
Inhalation chronic exposure		
Human studies		
Gresie-Brusin et al. 2007	Moderate	
Hemminki et al. 1982	Moderate	Moderate
Rowland et al. 1996	Moderate	
Animal studies		
Lynch et al. 1984a (monkey, 2-year)	Moderate	
Lynch et al. 1984b (rat, 2-year)	Moderate	High
NTP 1987 (mouse, 102-week)	High	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Neeper-Bradley and Kubena 1993 (rat)	High	
NIOSH 1982 (rat)	Low	
NIOSH 1982 (rabbit)	Low	
Rutledge and Generoso 1989 (mouse)	Moderate	High
Saillenfait et al. 1996 (rat, 400–1,200 ppm)	High	
Saillenfait et al. 1996 (rat, 200 or 400 ppm)	High	
Saillenfait et al. 1996 (rat, 800 or 1,200 ppm)	High	
Snellings et al. 1982a (rat, 10–100 ppm)	High	
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Moderate	
NIOSH 1982 (rat, GDs 1–16)	Low	Moderate
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Low	
NIOSH 1982 (rabbit, GDs 1–19)	Low	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, hematological, endocrine, neurological, reproductive, and developmental effects are presented in Table C-14. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with ethylene oxide exposure is presented in Table C-15.

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Human studies	Low	-1 for risk of bias	Very low
Animal studies	High	No adjustments	High
Outcome: Hematological effects			
Animal studies	Moderate	No adjustments	Moderate
Outcome: Endocrine effects			
Animal studies	Moderate	No adjustments	Moderate
Outcome: Neurological effects			
Human studies	Very low	-2 for risk of bias	Very low
Animal studies	High	No adjustments	High
Outcome: Reproductive effects			
Human studies	Moderate	-1 for risk of bias	Low
Animal studies	High	No adjustments	High
Outcome: Developmental effects			
Animal studies	High	No adjustments	High

Table C-15. Confidence in the Body of Evidence for Ethylene Oxide

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	Very low	High
Hematological effects	No data	Moderate
Endocrine effects	No data	Moderate
Neurological effects	Very low	High
Reproductive effects	Low	High
Developmental effects	No data	High

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-7 and C-8). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below

are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:

- No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
- Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
- Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

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

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

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

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

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

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.

  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

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

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

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

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

In the seventh step of the systematic review of the health effects data for ethylene oxide, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for ethylene oxide is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for Ethylene Oxide

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects	Very low	Health effect	Very low
Neurological effects	Very low	Health effect	Very low
Reproductive effects	Low	Health effect	Low
Animal studies			
Respiratory effects	High	Health effect	High
Hematological effects	Moderate	Health effect	Moderate
Endocrine effects	Moderate	Health effect	Moderate
Neurological effects	High	Health effect	High
Reproductive effects	High	Health effect	High
Developmental effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

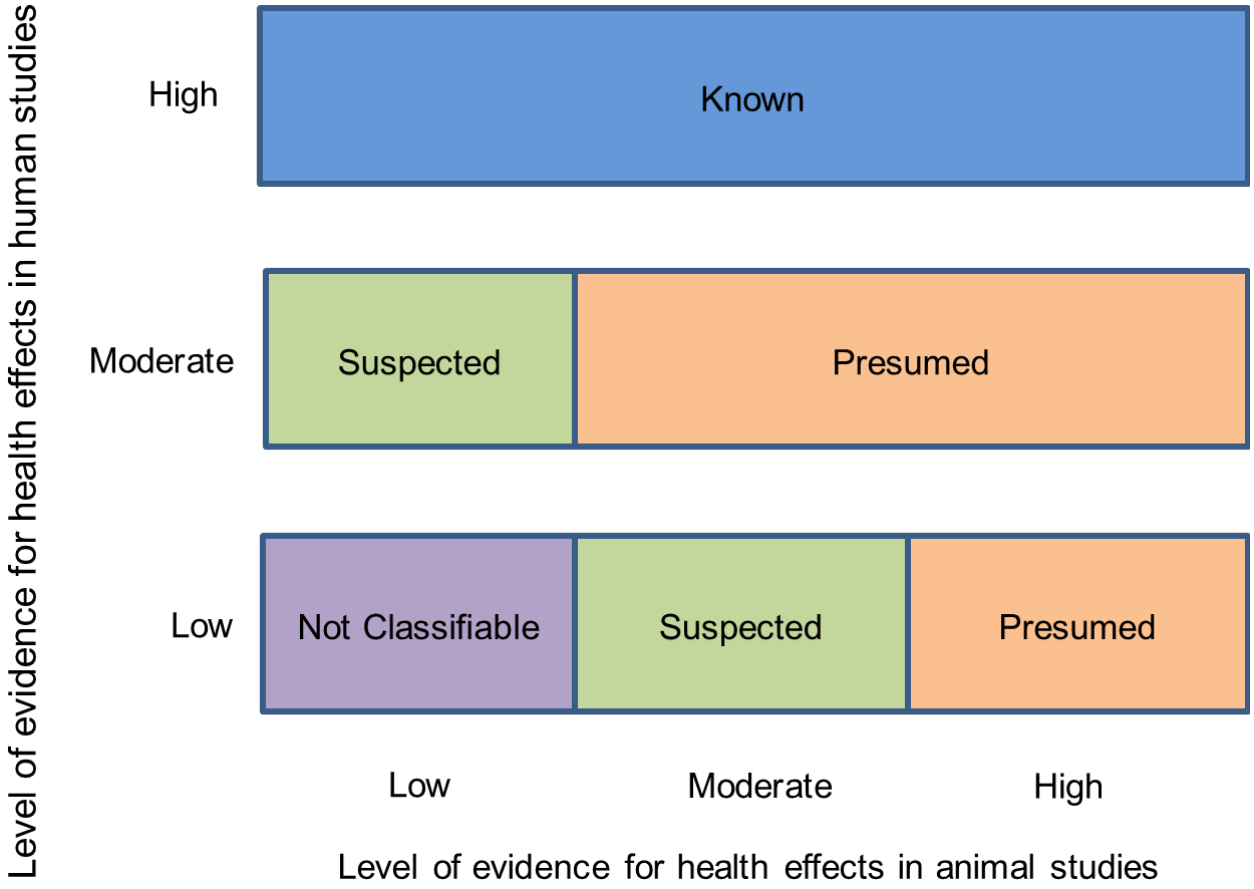
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies

- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



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

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

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

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

The hazard identification conclusions for ethylene oxide are listed below and summarized in Table C-17. Ethylene oxide is a presumed hazard to humans for respiratory effects, neurological effects, reproductive effects, and developmental effects. Ethylene oxide is a suspected hazard to humans for hematological effects and endocrine effects.

Presumed

- Respiratory effects
  - Occupational exposures, presumably to relatively high concentrations in workplace air, have resulted in compromised respiratory function (Deschamps et al. 1992; Thiess 1963).
  - Inhalation exposures of laboratory animals to ethylene oxide vapor concentrations ≥100 ppm have resulted in adverse respiratory effects (Hollingsworth et al. 1956; Jacobson et al. 1956; NTP 1987).

- Neurological effects
  - Clinical signs and symptoms of neurological effects have been reported in occupational exposure scenarios that included estimated ethylene oxide levels as low as 3 ppm, although most reports indicated exposures at much higher levels (Blackwood and Erskine 1938; Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Gross et al. 1979; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Sexton and Henson 1949; von Oettingen 1939; Zampollo et al. 1984).
  - Impaired neurological function and histopathologic lesions have been reported in laboratory animals exposed to ethylene oxide by inhalation at concentrations ≥100 ppm (EPA 2005b; Hollingsworth et al. 1956; Jacobson et al. 1956; Kaido et al. 1992; Lynch et al. 1984b; Matsuoka et al. 1990; NTP 1987; Ohnishi et al. 1985, 1986; Snellings et al. 1984a)

- Reproductive effects
  - Limited human data indicate potential for ethylene oxide-induced reproductive effects among occupationally-exposed persons (Gresie-Brusin et al. 2007; Hemminki et al. 1982).
  - Adverse male reproductive effects have been reported in laboratory animals exposed to ethylene oxide by inhalation at concentrations ≥33 ppm (EPA 1994; Kaido et al. 1992; Lynch et al. 1984b; Mori et al. 1991a, 1991b). Decreased numbers of viable pups have been reported in rats repeatedly exposed to ethylene oxide vapor at 100 ppm prior to mating and throughout gestation and lactation periods (Snellings et al. 1982b).

- Developmental effects
  - No human data are available on the potential for developmental effects of ethylene oxide.
  - Developmental effects such as depressed fetal weight, delayed ossification, dilatation in fetal renal pelvis and ureter, and fetal fluid retention and ocular defects have been associated with inhalation exposure to ethylene oxide by parental laboratory animals at exposure levels ≥33 ppm (EPA 1994; Neeper-Bradley and Kubena 1993; NIOSH 1982; Rutledge and Generoso 1989; Saillenfait et al. 1996; Snellings et al. 1982a).

Suspected

- Hematological effects
  - No human studies have associated ethylene oxide exposure with hematological effects.
  - Inhalation exposure of laboratory animals to ethylene oxide vapor concentrations as low as 50 ppm resulted in splenic histopathology (Lynch et al. 1984a, 1984b); higher

exposure concentrations were associated with changes in selected hematology parameters (Fujishiro et al. 1990; Jacobson et al. 1956; Snellings et al. 1984a).

- Endocrine effects
  - No human data are available regarding ethylene oxide exposure and endocrine effects.
  - Inhalation exposure of laboratory animals to ethylene oxide vapor concentrations as low as 50 ppm resulted in histopathologic lesions in adrenal glands (Lynch et al. 1984a, 1984b).

Table C-17. Hazard Identification Conclusions for Ethylene Oxide

Outcome	Hazard identification
Respiratory effects	Presumed
Hematological effects	Suspected
Endocrine effects	Suspected
Neurological effects	Presumed
Reproductive effects	Presumed
Developmental effects	Presumed

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

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

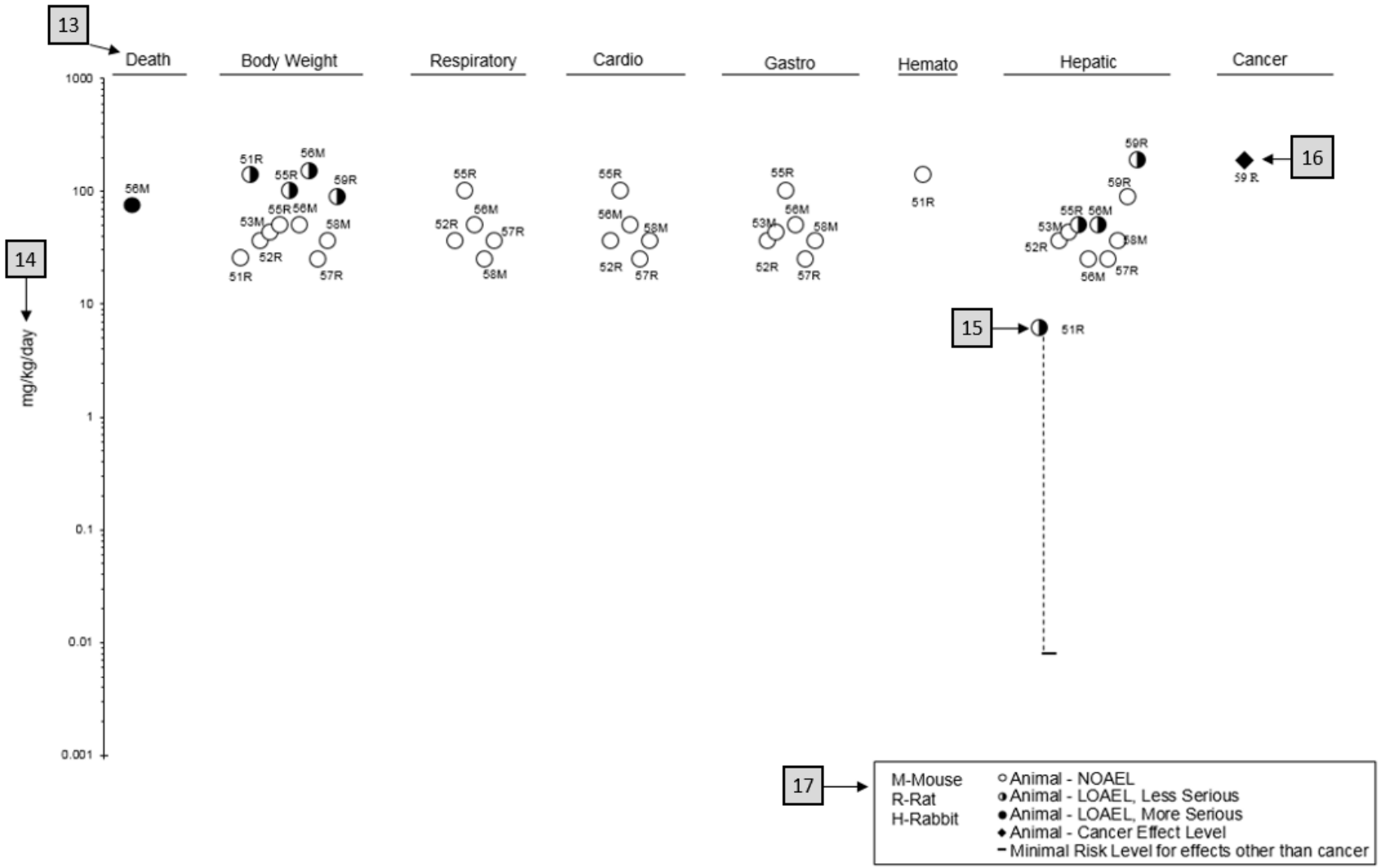
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

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

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

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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