APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-butyl ether (MTBE)
CAS Numbers: 1634-04-4
Date: September 2023
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 2 ppm
Critical Effect: Neurobehavior (altered gait)
Reference: Daughtrey et al. 1997; Gill 1989
Point of Departure: $BMCL_{10}$ of 454 ppm ($BMCL_{HEC}$ of 70.1 ppm)
Uncertainty Factor: 30
LSE Graph Key: 8
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 2 ppm was derived for MTBE based on neurological effects in female rats exposed to concentrations ≥4,000 ppm for 6 hours/day; a NOAEL of 800 ppm was identified (Daughtrey et al. 1997; Gill 1989). The MRL is based on a $BMCL_{10}$ (95% lower confidence limit on the benchmark concentration [BMC; subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk]) of 454 ppm for increased incidence of altered gait in female rats. The $BMCL_{10}$ was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 70.1 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available acute-duration inhalation studies report numerous MTBE-related effects at lowest-observed-adverse-effect levels (LOAELs) in the range of 1,000–4,000 ppm, including neurological effects in rats and mice, hepatic effects in female mice, and decreased fetal weights in mouse offspring (see Table A-1). Renal effects in male rats were also observed at exposure levels ≥1,500 ppm; however, these effects were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Therefore, only neurological, respiratory, hepatic, and developmental effects were considered for MRL derivation.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Inhalation MRL to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Fischer-344 rat	13 days 6 hours/day	ND	2,000	Hypoactivity	Dodd and Kintigh 1989
CD-1 mouse	13 days 6 hours/day	ND	2,000	Hypoactivity	Dodd and Kintigh 1989
CD-1 mouse	2 days 6 hours/day	400	3,000	Hypoactivity, decreased startle response	Vergnes and Chun 1994

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Inhalation MRL to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Fischer-344 rat	6 hours	800	4,000	Altered gait and decreased limb strength in females	Daughtrey et al. 1997; Gill 1989
Respiratory effects					
Sprague-Dawley rat	9 days 5 days/week 6 hours/day	ND	1,000	Inflammation of nasal mucosa and trachea	Texaco Inc. 1981
Hepatic effects					
CD-1 mouse	13 days 6 hours/day	ND	2,000	Increased relative liver weight in females	Dodd and Kintigh 1989
Developmental effects					
CD-1 mouse	10 days (GDs 6–15) 6 hours/day	1,000	4,000	Decreased fetal weights	Bevan et al. 1997a

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

In order to identify the most sensitive POD, benchmark dose (BMD) modeling was attempted for critical neurological, respiratory, hepatic, and developmental endpoints in Table A-1 when data were amenable to modeling. The data were fit to all available dichotomous or continuous models in EPA's Benchmark Dose Software (BMDS; version 3.2) using a benchmark response (BMR) of 1 standard deviation (grip strength, liver weight), 10% extra risk (altered gait incidence), or 5% relative deviation (developmental body weight). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% lower confidence limit on the benchmark concentration (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen.

The datasets used for BMD modeling are presented in Tables A-2, A-3, and A-4. Neurological data from Dodd and Kintigh (1989) and Vergnes and Chun (1994) were inadequate for BMD modeling (incidence data not reported), and nasal and tracheal inflammation data from Texaco Inc. (1981) were inadequate for BMD modeling because the endpoint was only evaluated in control and high-exposure animals.

Table A-2. Neurological Endpoints in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours

	Concentration (ppm)			
	0	800	4,000	8,000
Altered gait Incidence (percent incidence)	1/8 (13%)	2/8 (25%)	6/8[a] (75%)	8/8[b] (100%)
Hind limb grip strength (kg) Mean±SD (n)	0.40±0.079 (8)	0.38±0.082 (8)	0.35±0.051[a] (8)	0.28±0.084[b] (8)

[a]p<0.05.
[b]p<0.01.

(n) = number of animals; SD = standard deviation

Source: Gill 1989 (unpublished report associated with published study by Daughtrey et al. 1997)

Table A-3. Fetal Weights in Mouse Offspring Following Maternal Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) on GDs 6–15 (6 Hours/Day)

	Concentration (ppm)			
	0	1,000	4,000	8,000
Fetal body weight/litter (%) Mean±SD (n)	1.4±0.1 (27)	1.4±0.1 (29)	1.3±0.1[a] (26)	1.1±0.1[a] (26)

[a]p<0.01.

GD = gestation day; (n) = number of animals; SD = standard deviation

Source: Bevan et al. 1997a

Table A-4. Liver Weights in Female Mice Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 13 Days (6 Hours/Day)

	Concentration (ppm)			
	0	2,000	4,000	8,000
Relative liver weight (percent body weight) Mean±SD (n)	5.830±0.4339 (5)	6.719±0.2502[a] (5)	6.644±0.1258[a] (5)	7.141±0.1970[a] (5)

[a]p<0.01.

(n) = number of animals per group; SD = standard deviation

Source: Dodd and Kintigh 1989

Details of the modeling results for the model predictions for altered gait in female rats are in Table A-5. In accordance with the selection criteria mentioned above, the Probit model, a frequentist, unrestricted model, was selected for altered gait.

Table A-5. Model Predictions for Increased Incidence of Altered Gait in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Daughtrey et al. 1997; Gill 1989)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Dichotomous Hill	3,257.91	176.07	0.52	30.44	0.45	-0.0001
Gamma[d]	886.04	180.30	0.56	30.50	0.25	-0.32
Log-Logistic[e]	3,288.52	176.07	0.52	30.44	0.45	-4.19×10^{-05}
Multistage Degree 3[f]	635.33	189.94	0.88	30.06	-0.04	0.07
Multistage Degree 2[f]	757.08	186.31	0.72	30.21	-0.08	0.15
Multistage Degree 1[f]	287.81	168.16	0.68	29.18	0.23	-0.48
Weibull[d]	1,027.72	184.48	0.64	30.30	0.30	-0.18
Logistic	772.71	446.91	0.92	28.29	-0.07	0.18
Log-Probit	2,873.77	181.50	0.52	30.44	0.45	-0.0001
Probit[g]	**732.29**	**453.69**	**0.96**	**28.14**	**-0.07**	**0.14**

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

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

Details of the modeling results for the model predictions in female rats for hindlimb strength and in mice for decreased fetal weights are in Tables A-6 and A-7, respectively. In accordance with the selection criteria mentioned above, the constant variance, frequentist, restricted 3-degree polynomial model was selected for hindlimb strength and constant variance, frequentist, restricted 2-degree polynomial model was selected for decreased fetal weights. An adequate model was not identified for increased relative liver weight in mice because models failed to meet conventional goodness-of-fit criteria.

Table A-6. Results from Benchmark Dose (BMD) Analysis (Constant Variance) for Decreased Hindlimb Grip Strength in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Daughtrey et al. 1997; Gill 1989)

Model	BMC_{1SD}[a] (ppm)	$BMCL_{1SD}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Exponential (model 2)[d]	4,673.41	2,881.26	0.84	-72.71	0.48	-0.25
Exponential (model 3)[d]	5,470.26	2,915.30	0.65	-70.86	0.13	-0.04
Exponential (model 4)[d]	4,673.42	2,881.26	0.84	-72.71	0.48	-0.25
Exponential (model 5)[d]	5,470.26	2,915.30	0.65	-70.86	0.13	-0.04
Hill[e]	4,263.15	3,835.68	0.57	-70.74	2.78×10^{-7}	1.57×10^{-5}
Polynomial (3-degree)[e,f]	**5,613.07**	**3,311.80**	**0.95**	**-72.95**	**0.07**	**-0.01**
Polynomial (2-degree)[e]	5,512.37	3,307.32	0.94	-72.93	0.10	-0.02
Power	5,441.54	3,298.56	0.68	-70.89	0.15	-0.04
Linear	4,932.20	3,286.39	0.89	-72.83	0.36	-0.15

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. The constant variance model provided an adequate fit to the data. All models provided adequate fits to the means. The BMCLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (3-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., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation from the control)

Table A-7. Results from Benchmark Dose (BMD) Analysis (Constant Variance) for Decreased Fetal Weights in Mouse Offspring Following Maternal Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) on GDs 6–15 (6 Hours/Day) (Bevan et al. 1997a)

					Scaled residuals[c]	
Model	BMC_{RD5}[a] (ppm)	$BMCL_{RD5}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]			0.03	-181.89	0.77	1.73
Exponential (model 3)[d]	3,171.81	2,196.77	0.69	-186.78	0.31	-0.10
Exponential (model 4)[d]			0.03	-181.89	0.77	1.73
Exponential (model 5)[d]			NA	-184.78	0.30	-0.09
Hill[e]	3,891.22	3,786.64	1.00	-186.94	-0.0003	-0.0008
Polynomial (3-degree)[e]	3,108.92	2,020.52	0.80	-188.51	0.51	-0.23
Polynomial (2-degree)[e,f]	**3,108.92**	**2,055.83**	**0.80**	**-188.51**	**0.51**	**-0.23**
Power	3,141.84	2,142.12	0.64	-186.73	0.35	-0.12
Linear			0.07	-183.73	0.68	1.47

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. The constant variance model provided an adequate fit to the data. All models provided adequate fits to the means except for the Exponential models 2, 4, and 5 and the linear model. The BMCLs of the adequately fitting models were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (2-degree polynomial). While it appears that the 2- and 3-degree polynomial models have the same AIC due to rounding, if you go out 10 decimal places, the 2-degree is slightly lower; therefore, it is the selected model.

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., RD5 = dose associated with a 5% relative deviation); GD = gestation day; NA = not applicable

The candidate PODs for neurological, respiratory, hepatic, and developmental effects are summarized in Table A-8. The lowest PODs were identified for neurological effects, with adjusted BMCL/NOAEL values of 100–114 ppm. Therefore, neurological effects were selected as the critical effect.

Table A-8. Summary of Candidate Effects and POD Values Considered for Derivation of an Acute-Duration Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference
Neurological effects					
Fischer-344 rat	13 days 6 hours/day	Hypoactivity	500	$LOAEL_{ADJ}$	Dodd and Kintigh 1989
CD-1 mouse	13 days 6 hours/day	Hypoactivity	500	$LOAEL_{ADJ}$	Dodd and Kintigh 1989

Table A-8. Summary of Candidate Effects and POD Values Considered for Derivation of an Acute-Duration Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference
CD-1 mouse	2 days 6 hours/day	Hypoactivity, decreased startle response	100	$NOAEL_{ADJ}$	Vergnes and Chun 1994
Fischer-344 rat	6 hours	Altered gait in females	114	$BMCL_{ADJ}$	Daughtrey et al. 1997; Gill 1989[a]
Fischer-344 rat	6 hours	Decreased limb strength in females	828	$BMCL_{ADJ}$	Daughtrey et al. 1997; Gill 1989[a]
Respiratory effects					
Sprague-Dawley rat	9 days 5 days/week 6 hours/day	Inflammation of nasal mucosa and trachea	179	$LOAEL_{ADJ}$	Texaco Inc. 1981
Hepatic effects					
CD-1 mouse	13 days 6 hours/day	Increased relative liver weight in females	500	$LOAEL_{ADJ}$	Dodd and Kintigh 1989
Developmental effects					
CD-1 mouse	10 days (GDs 6–15) 6 hours/day	Decreased fetal weights	514	$BMCL_{ADJ}$	Bevan et al. 1997a

[a]Gill (1989) is the unpublished report associated with Daughtrey et al. (1997). Raw data for benchmark dose modeling was acquired from Gill (1989) (not available in published report).

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{ADJ}$ = 95% lower confidence limit on the BMC (adjusted for continuous exposure); GD = gestation day; $LOAEL_{ADJ}$ = lowest observed adverse effect level (adjusted for continuous exposure); MRL = Minimal Risk Level; NA = not applicable; ND = not determined; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); POD = point of departure

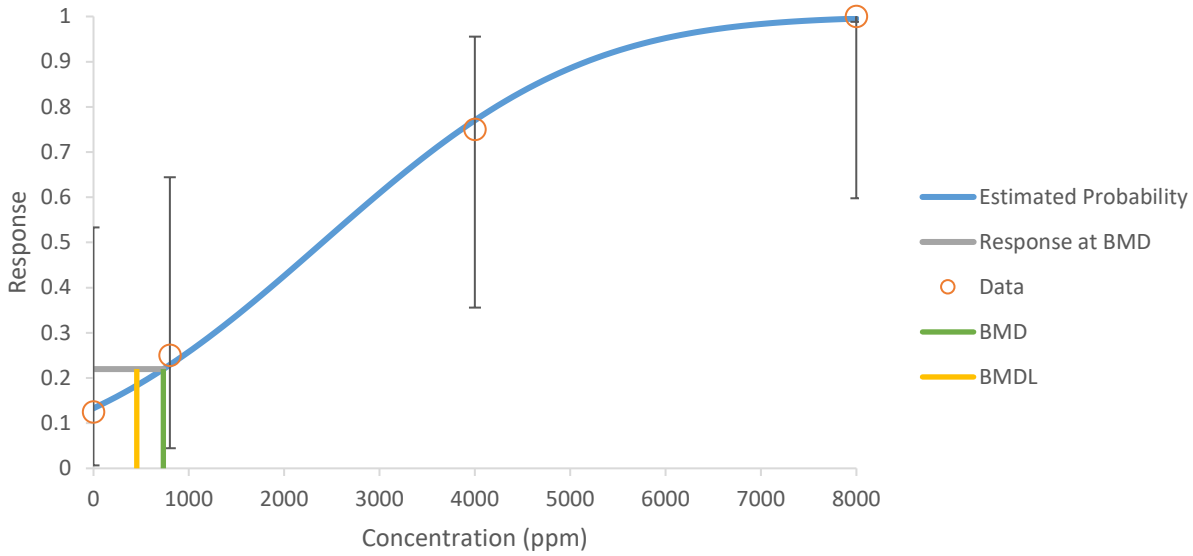
Selection of the Principal Study: Potential PODs for deriving an acute-duration inhalation MRL for MTBE based on neurological effects include:

- $NOAEL_{ADJ}$ of 100 ppm for hypoactivity and decreased startle response in mice (Vergnes and Chun 1994)
- $BMCL_{ADJ}$ of 114 ppm for altered gait in female rats (Daughtrey et al. 1997; Gill 1989)
- $LOAEL_{ADJ}$ of 500 ppm for hypoactivity in rats and mice (Dodd and Kintigh 1989)
- $BMCL_{ADJ}$ of 828 ppm for decreased limb strength in female rats (Daughtrey et al. 1997; Gill 1989)

The $BMCL_{ADJ}$ of 114 ppm for neurological effects (altered gait) in female rats observed by Daughtrey et al. (1997) following a 6-hour exposure to MTBE was selected as the POD for the acute-duration inhalation MRL. Data for this study are also available in the unpublished report by Gill (1989). This POD was selected over the $NOAEL_{ADJ}$ of 100 ppm for neurological effects reported by Vergnes and Chun (1994) because the selected study was designed to examine potential neurological effects following acute-duration inhalation exposure to MTBE, including clinical signs, a functional observation battery (FOB),

and motor activity, while Vergnes and Chun (1994) only evaluated clinical signs in the context of an *in vivo* genotoxicity assay. Additionally, the selected study included more animals per dose than Vergnes and Chun (1994). Therefore, there is higher confidence in the neurological POD from the study by Daughtrey et al. (1997). Additionally, quantitative data adequate for BMD modeling were only available for Daughtrey et al. (1997) (from the associated unpublished report by Gill 1989). Model fit for altered gait is shown in Figure A-1 (Probit model).

Figure A-1. Fit of Probit Model to Incidence Data for Altered Gait in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Gill 1989)



Summary of the Principal Study:

Daughtrey WC, Gill MW, Pritts IM, et al. 1997. Neurotoxicological evaluation of methyl tertiary-butyl ether in rats. J Appl Toxicol 17(Suppl 1):S57-S64.

Gill MW. 1989. Methyl tertiary butyl ether single exposure vapor inhalation neurotoxicity study in rats. Union Carbide Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. 602-823. OTS0528043. 409813440.

Daughtrey et al. (1997) exposed Fischer 344 rats to MTBE vapor for 6 hours at concentrations of 0, 800, 4,000, or 8,000 ppm. Groups were comprised of 22 males and 22 females. Groups of 14 male and 14 female rats were evaluated for motor activity prior to and within 1 hour following a single 6-hour exposure. The length of the test sessions was either 90 minutes (pre-exposure) or 5 hours (post-exposure). The remaining eight rats/sex/group were given an FOB of tests (piloerection, respiratory pattern, gait, urination, startle response, pupil size, pupil response, catatonic pose, fore and hind paw grip strength, treadmill, inclined screen turn, toe pinch, time to tail flick, rectal temperature, and hind leg splay) prior to exposure and at 1, 6, and 24 hours after exposure. Data for this study are also available in the unpublished report by Gill (1989).

No rats died prematurely. No body weight effects were noted. No clinical signs of overt toxicity were observed. In the FOB, evidence of transient CNS depression was observed at the 1-hour observation at

≥4,000 ppm; no effects were observed at the 6- or 24-hour observations. Altered gait (ataxia, duck walk) and decreased body temperature were observed in females at ≥4,000 ppm and males at 8,000 ppm. Decreased grip strength was observed in females only at ≥4,000 ppm. Other significant behavioral findings in males and/or females at 8,000 ppm included decreased muscle tone, decreased treadmill performance, hindlimb splay, and labored respiration. Lacrimation was also observed but was attributed to the irritative nature of MTBE vapors. No significant behavioral observations were found in the 800-ppm group during the FOB. In motor activity testing, a biphasic result was observed in both sexes at 8,000 ppm, with a significant 60–67% reduction in motor activity at 10 minutes followed by significant increases up to 17-fold between 30 and 60 minutes, compared to controls. No significant findings were observed at 4,000 ppm. Significant changes in motor behavior at 800 ppm were observed only at 10 minutes and included a 24% increase in males and a 16% decrease in females. These findings were not considered biologically relevant due to lack of dose-response, low magnitude of effect, and differential findings in males versus females. Motor activity testing during the initial 180 minutes of the dark phase showed a statistically significant decrease in activity during the first hour of darkness only at 8,000 ppm (magnitude of effect not reported by the study authors).

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 454 ppm for neurological effects (altered gait) in female rats was selected as the POD. This value represents the lowest available POD for the critical effect (neurotoxicity) from an acute-duration comprehensive neurological study (Daughtrey et al. 1997). This value was selected over the NOAEL of 400 ppm based on clinical signs in the context of an *in vivo* genotoxicity assay by Vergnes and Chun (1994) due to higher confidence in the value derived from the more comprehensive study by Daughtrey et al. (1997).

Calculations

Intermittent Exposure: The $BMCL_{10}$ of 454 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMCL_{ADJ}$ = 454 ppm x (6 hours/24 hours) = 114 ppm.

Human Equivalent Concentration: While several PBPK models have been developed for MTBE, further refinement is needed to decrease uncertainty in estimated exposure levels, particularly for humans (see Sections 3.1.5 and 6.2 for more details). Therefore, a human equivalent concentration (HEC) for extrarespiratory effects was calculated by multiplying the $BMCL_{ADJ}$ by the ratio of animal:human blood gas partition coefficients, using a reported rat blood gas partition coefficient of 11.5 (Rao and Ginsberg 1997) and the midpoint of the range of human blood gas partition coefficients (17.7–19.6) reported by Rao and Ginsberg (1997) and Kim et al. (2007):

$BMCL_{HEC}$ = $BMCL_{ADJ}$ x ratio of animal:human blood gas partition coefficients
$BMCL_{HEC}$ = 114 ppm x (11.5/18.7)
$BMCL_{HEC}$ = 114 ppm x (0.615)
$BMCL_{HEC}$ = 70.1 ppm

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

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

MRL= $BMCL_{HEC}$ ÷ UF
70.1 ppm ÷ (3 x 10) = 2 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a neurological effect as the critical effect following acute-duration inhalation exposure is supported by consistent observation of CNS depressive effects following inhalation exposure to concentrations ≥2,000 ppm following acute-, intermediate-, and chronic-duration studies (Bevan et al. 1997a, 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; MTBE Committee 1990a; Vergnes and Chun 1994; Vergnes and Morabit 1989). Additionally, some studies have reported effects consistent with transient CNS depression in humans exposed to MTBE in fuel, including headache, nausea or vomiting, dizziness, and a feeling of spaciness or disorientation (Alaska DHSS 1992a, 1992b; CDC 1993a; Moolenaar et al. 1994; Wisconsin DHSS 1995). When using the neurological NOAEL of 400 ppm from Vergnes and Chun (1994), the MRL calculates to the same value.

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-butyl ether (MTBE)
CAS Numbers: 1634-04-4
Date: September 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 1 ppm
Critical Effect: CNS depression and elevated liver weight
Reference: Bevan et al. 1997b; Bird et al. 1997
Point of Departure: NOAEL of 400 ppm ($NOAEL_{HEC}$ of 43.9 ppm)
Uncertainty Factor: 30
LSE Graph Key: 27, 29
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 1 ppm was derived for MTBE based on CNS depression in rats and mice and elevated liver weight in rats exposed to concentrations ≥3,000 ppm for 6 hours/day, 5 days/week for 4–19 weeks; a NOAEL of 400 ppm was identified (Bevan et al. 1997b; Bird et al. 1997). The MRL is based on the NOAEL of 400 ppm, which was adjusted to continuous duration exposure and converted to a $NOAEL_{HEC}$ of 43.9 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration inhalation studies report numerous MTBE-related effects, with NOAEL and LOAEL values of 400 and 3,000 ppm, respectively (see Table A-9). Effects observed at ≥3,000 ppm included neurological effects in rats and mice, hepatic effects in male and female rats and female mice, endocrine (adrenal) effects in rats, and decreased neonatal weights in F1 and F2 rat offspring. Renal effects in male rats were also observed at exposure levels ≥3,000 ppm; however, these effects were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Additionally, the adversity of elevated adrenal gland weight in female rats at ≥3,000 ppm in the absence of histopathological alterations at concentrations up to 8,000 ppm, reported in Bird et al. (1997), is unclear. Only one study reported adrenal lesions in female mice (loss of zona reticularis) at 8,000 ppm, in the absence of altered adrenal weight (Moser et al. 1998); however, no histopathological evidence of damage to the adrenal gland was observed in intermediate-duration inhalation studies in rats at concentrations up to 8,000 ppm (Greenough et al. 1980; Lington et al. 1997). Therefore, only neurological, hepatic, and developmental effects were further considered for MRL derivation.

Table A-9. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Neurological effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	400	3,000 (serious LOAEL)	Ataxia, hypoactivity, loss of startle response, blepharospasm	Bird et al. 1997; Chun and Kintigh 1993

Table A-9. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Sprague-Dawley rat	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	400	3,000	Hypoactivity, blepharospasm, lack of startle response in F0 and F1 adults	Bevan et al. 1997b; Neeper-Bradley 1991
CD-1 mouse	28 days 5 days/week 6 hours/day	400	3,000 (serious LOAEL)	Ataxia, hypoactivity, loss of startle response	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	800	4,000	Transient hypoactivity	Lington et al. 1997
Hepatic effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in males and females	Bird et al. 1997; Chun and Kintigh 1993
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in F1 adult males	Bevan et al. 1997b
CD-1 mouse	28 days 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in females	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	ND	800	Increased relative liver weight in males	Lington et al. 1997
Endocrine effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	400	3,000	Increased relative adrenal gland weight in females	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	800	4,000	Increased relative adrenal gland weight	Lington et al. 1997
Developmental effects					
Sprague-Dawley rat	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	400	3,000	Decreased F1 and F2 offspring body weight during lactation	Bevan et al. 1997b; Neeper-Bradley 1991

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information.

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

In order to identify the most sensitive POD, BMD modeling was attempted for critical neurological and developmental endpoints in Table A-9 when data were amenable to modeling. The data were fit to all

available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 standard deviation (liver weight) or 5% relative deviation (developmental body weight). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMC) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. The datasets used for BMD modeling are presented in Tables A-10, A-11, and A-12. BMD modeling could not be conducted on neurological data because the dataset provides limited information on the dose-response between the extremes of 0% incidence in controls and low-concentration groups and 100% incidence at the LOAEL.

Table A-10. Relative Liver Weights in Rats and Mice Following Inhalation Exposure for 28 Days (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	400	3,000	8,000
Male rat relative liver weight (% BW) Mean±SD (n)	3.756±0.2057 (10)	3.844±0.0959 (10)	4.094±0.2473[a] (10)	4.393±0.2749[a] (10)
Female rat relative liver weight (% BW) Mean±SD (n)	3.556±0.0854 (10)	3.606±0.2525 (10)	3.869±0.1446[a] (10)	3.916±0.1347[b] (10)
Female mouse relative liver weight (% BW) Mean±SD (n)	5.428±0.4886 (10)	5.334±0.4029 (10)	5.895±0.4654[a] (9)	6.120±0.3768[a] (10)

[a]p<0.05.
[b]p<0.01.

BW = body weight; (n) = number of animals; SD = standard deviation

Source: Chun and Kintigh 1993 (unpublished report associated with published study by Bird et al. 1997)

Table A-11. Relative Liver Weights in Male Rats Following Inhalation Exposure for 13 Weeks (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	800	4,000	8,000
Male rat relative liver weight (% BW) Mean±SD (n)	3.15±0.16 (15)	3.39±0.16 (15)	3.78±0.26[a] (15)	4.37±0.19[a] (15)

[a]p≤0.05.

BW = body weight; (n) = number of animals; SD = standard deviation

Source: Lington et al. 1997

Table A-12. Body and Liver Weights in Rat Offspring in a 2-Generation Inhalation Exposure Study (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	400	3,000	8,000
F1 female body weight on PND 14 (g) Litter mean±SD (n)	25.43±2.808 (22)	25.43±2.456 (22)	22.94±3.452[a] (25)	22.16±2.845[b] (20)
F2 body weight on PND 21 (g) Litter mean±SD (n)	45.67±2.707 (22)	44.25±3.479 (22)	41.29±4.178[b] (22)	38.28±8.844[b] (21)
Adult F1 male relative liver weight (%) Mean±SD (n)	3.42±0.29 (25)	3.49±0.32 (25)	3.76±0.37[b] (25)	4.31±0.42[b] (25)

[a]p<0.05.
[b]p<0.01.

(n) = number of animals; PND = postnatal day; SD = standard deviation

Sources: Bevan et al. 1997b; Neeper-Bradley 1991

Details of the modeling results for the model predictions for relative liver weight in female mice reported by Chun and Kintigh (1993) are in Table A-13. In accordance with the selection criteria mentioned above, the constant variance, frequentist, restricted Exponential 4 model was selected. No adequate models were identified for increased relative liver weight in male or female rats (Bird et al. 1997); quantitative data obtained from unpublished report by Chun and Kintigh 1993) because they failed to meet conventional goodness-of-fit criteria.

Table A-13. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Female Mice Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 28 Days (5 Days/Week, 6 Hours/Day) (Bird et al. 1997; Chun and Kintigh 1993)

					Scaled residuals[c]	
Model	BMC_{1SD}[a] (ppm)	$BMCL_{1SD}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	4,701.60	3,395.20	0.22	50.54	1.39	-0.42
Exponential (model 3)[d]	4,702.65	3,395.19	0.22	50.54	1.39	-0.41
Exponential (model 4)[d,e]	**2,255.57**	**843.27**	**0.30**	**50.60**	**-0.79**	**0.29**
Exponential (model 5)[d]			NA	51.74	-0.34	0.00
Hill[f]			NA	51.74	-0.34	0.00
Polynomial (3-degree)[f]	4,517.82	3,195.00	0.24	50.36	1.33	-0.43
Polynomial (2-degree)[f]	4,517.82	3,195.02	0.24	50.36	1.33	-0.43
Power	4,517.82	3,194.95	0.24	50.36	1.33	-0.43
Linear	4,517.82	3,195.02	0.24	50.36	1.33	-0.43

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. The constant variance model provided an adequate fit to the data. All models except Exponential 5 and Hill models provided adequate fits to the means. The BMCLs differed by >3-fold; therefore, the model with the lowest BMCL was selected (Exponential 4).
[f]Coefficients restricted to be positive.

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., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation from the control); NA = not applicable

Details of modeling results for the model predictions for relative liver weight in male rats reported by Lington et al. (1997) are in Table A-14. In accordance with the selection criteria mentioned above, the constant variance, frequentist, restricted Power model was selected.

Table A-14. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Male Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 13 Weeks (5 Days/Week, 6 Hours/Day) (Lington et al. 1997)

Model	BMC_{1SD}[a] (ppm)	$BMCL_{1SD}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Exponential (model 2)[d]	1,541.55	1,320.87	0.13	-18.79	1.30	0.41
Exponential (model 3)[d]	1,541.79	1,320.87	0.13	-18.79	1.30	0.41
Exponential (model 4)[d]			0.08	-17.94	1.32	-0.59
Exponential (model 5)[d]			0.08	-17.95	1.33	-0.50
Hill[e]			NA	-8.04	2.23	0.0002
Polynomial (3-degree)[e]	1,338.81	1,136.63	0.21	-19.80	1.34	-0.18
Polynomial (2-degree)[e]	1,338.81	1,136.63	0.21	-19.80	1.34	-0.18
Power[f]	**1,338.80**	**1,136.64**	**0.21**	**-19.80**	**1.34**	**-0.18**
Linear	1,338.81	1,136.63	0.21	-19.80	1.34	-0.18

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. The constant variance model provided an adequate fit to the data. All models except Exponential 4 and 5 and Hill models provided adequate fits to the means. The BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Power). While it appears that the several models have the same AIC due to rounding, if you go out 7 decimal places, the Power model is slightly lower; therefore, it is the selected model.

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., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation from the control); NA = not applicable

Details of modeling results for the model predictions for F1 female body weight on PND 14, F2 body weight on PND 21, and adult F1 male relative liver weight in mice reported by Bevan et al. (1997b) and Neeper-Bradley (1991) are in Table A-15, A-16, and A-17, respectively. In accordance with the selection criteria mentioned above, the constant variance, frequentist, restricted Exponential 4 model was selected for F1 female body weight; the nonconstant variance, frequentist, restricted Exponential 2 model was selected for F2 body weight; and the constant variance, frequentist, unrestricted Linear model was selected for F1 male relative liver weight.

Table A-15. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Decreased F1 Body Weights in Female Rat Offspring on PND 14 Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Bevan et al. 1997a; Neeper-Bradley 1991)

Model	BMC_{RD5}[a] (ppm)	$BMCL_{RD5}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Exponential (model 2)[d]	2,756.74	1965.74	0.18	449.55	0.65	-1.54
Exponential (model 3)[d]	2,756.44	1970.12	0.18	449.55	0.65	-1.54
Exponential (model 4)[d,e]	**1,056.04**	**368.70**	**0.49**	**448.58**	**0.52**	**-0.21**
Exponential (model 5)[d]			NA	450.11	0.01	0.00
Hill[f]			NA	450.11	0.03	0.00
Polynomial (3-degree)[f]	2,936.57	2148.57	0.15	449.85	0.69	-1.61
Polynomial (2-degree)[f]	2,936.57	2148.42	0.15	449.85	0.69	-1.61
Power	2,936.57	2151.93	0.15	449.85	0.69	-1.61
Linear	2,936.57	2148.31	0.15	449.85	0.69	-1.61

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. The constant variance model provided an adequate fit to the data. All models except Exponential 5 and Hill models provided adequate fits to the means. The BMCLs differed by >3-fold; therefore, the model with the lowest BMCL was selected (Exponential 4).
[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., RD5 = dose associated with a 5% relative deviation); NA = not applicable; PND = postnatal day

Table A-16. Results from Benchmark Dose (BMD) Analysis (Nonconstant Variance) of Decreased F2 Body Weights in Rat Offspring on PND 21 Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Bevan et al. 1997a; Neeper-Bradley 1991)

Model	BMC_{RD5}[a] (ppm)	$BMCL_{RD5}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Exponential (model 2)[d,e]	**2,065.98**	**1,492.44**	**0.33**	**507.064**	**-0.67**	**-0.65**
Exponential (model 3)[d]	2,063.24	1,492.32	0.33	507.065	-0.67	-0.65
Exponential (model 4)[d]	1,687.78	902.49	0.19	508.576	-0.69	-0.24
Exponential (model 5)[d]	1,692.17	902.85	0.19	508.573	-0.69	-0.25
Hill[f]	1,645.17	709.17	0.20	508.526	-0.67	-0.22
Polynomial (3-degree)[f]	2,214.69	1,633.73	0.28	507.389	-0.65	-0.81
Polynomial (2-degree)[f]	2,212.30	1,633.80	0.28	507.389	-0.65	-0.80
Power	2,214.97	1,698.40	0.28	507.389	-0.65	-0.81
Linear	2,214.56	1,633.72	0.28	507.389	-0.65	-0.80

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. The constant variance did not provide an adequate fit to the data. With nonconstant variance applied, all models provided adequate fit to the means. The BMDLs were sufficiently close (<3-fold), so the model with the lowest AIC was selected (Exponential 2 model).
[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., RD5 = dose associated with a 5% relative deviation); PND = postnatal day

Table A-17. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Adult F1 Male Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Bevan et al. 1997b)

					Scaled residuals[c]	
Model	BMC_{1SD}[a] (ppm)	$BMCL_{1SD}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	3,388.81	2,869.25	0.92	77.88	0.21	-0.08
Exponential (model 3)[d]	3,388.81	2,869.25	0.92	77.88	0.21	-0.08
Exponential (model 4)[d]	3,127.92	2,591.78	0.79	79.79	-0.05	0.01
Exponential (model 5)[d]	3,135.01	2,606.18	0.79	79.79	-0.04	0.01
Hill[e]			NA	82.23	-7.3×10^{-5}	0.0007
Polynomial (3-degree)[e]	3,157.23	2,629.08	0.96	77.79	-0.02	-0.002
Polynomial (2-degree)[e]	3,157.23	2,629.08	0.96	77.79	-0.02	-0.002
Power	3,157.23	2,629.07	0.96	77.79	-0.02	-0.002
Linear[f]	**3,157.23**	**2,629.08**	**0.96**	**77.79**	**-0.02**	**-0.002**

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. The constant variance model provided an adequate fit to the data. All models except the Hill model provided adequate fits to the means. The BMDLs were sufficiently close (<3-fold). Several models had the same lowest AIC value (Linear, Power, Polynomial 2 and 3), and the Polynomial models converged upon the Linear model. Between the Power and the Linear model, the model with the (slightly) lower BMCL was selected (Linear).

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., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation from the control); NA = not applicable

The candidate PODs are summarized in Table A-18. The most sensitive candidate PODs for all three critical effects (neurological, hepatic, developmental) were comparable (adjusted NOAEL/BMCL values of 65.9–71.4 ppm). Based on consistent evidence across several studies, neurological and hepatic effects were selected as co-critical effects. Decreased PND 14 F1 body weight in females (Bevan et al. 1997b) was not selected as a co-critical effect due to inconsistent findings across postnatal time periods and sexes; additionally, the BMCL for the F2 generation was much higher, further suggesting inconsistencies in the data.

Table A-18. Summary of Candidate Effects and POD Values Considered for Derivation of an Intermediate-Duration Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference[a]
Neurological effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	Ataxia, hypoactivity, loss of startle response, blepharospasm[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Sprague-Dawley rat	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	Hypoactivity, blepharospasm, loss of startle response in F0 and F1 adults[b]	71.4	$NOAEL_{ADJ}$	Bevan et al. 1997b; Neeper-Bradley 1991
CD-1 mouse	28 days 5 days/week 6 hours/day	Ataxia, hypoactivity, loss of startle response[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	Transient hypoactivity at ≥4,000 ppm; ataxia at 8,000 ppm	143	$NOAEL_{ADJ}$	Lington et al. 1997
Hepatic effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	Increased relative liver weight in males and females[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	Increased relative liver weight in F1 adult males	469	$BMCL_{ADJ}$	Bevan et al. 1997b
CD-1 mouse	28 days 5 days/week 6 hours/day	Increased relative liver weight in females	151	$BMCL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	Increased relative liver weight in males	203	$BMCL_{ADJ}$	Lington et al. 1997
Developmental effects					
Sprague-Dawley rat	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	Decreased body weight in F1 females on PND 14	65.9	$BMCL_{ADJ}$	Bevan et al. 1997b; Neeper-Bradley 1991

Table A-18. Summary of Candidate Effects and POD Values Considered for Derivation of an Intermediate-Duration Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference[a]
Sprague-Dawley rat	2 generations ~14–19 weeks/generation 5 days/week 6 hours/day	Decreased body weight in F2 pups on PND 21	266	$BMCL_{ADJ}$	Bevan et al. 1997b; Neeper-Bradley 1991

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information and/or raw data for benchmark dose modeling.
[b]Selected studies/endpoints for derivation of intermediate-duration inhalation MRL.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{ADJ}$ = 95% lower confidence limit on the BMC (adjusted for continuous exposure); MRL = Minimal Risk Level; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); PND = postnatal day; POD = point of departure

Selection of the Principal Studies: The 2-generation study in rats (Bevan et al. 1997b; Neeper-Bradley 1991) and the 28-day day studies in rats and mice (Bird et al. 1997; Chun and Kintigh 1993) were selected as co-principal studies based on identical PODs ($NOAEL_{ADJ}$ of 71.4 ppm) for CNS depression and elevated liver weight.

Summary of the Principal Studies:

Bevan C, Neeper-Bradley TL, Tyl RW, et al. 1997b. Two-generation reproductive toxicity study of methyl tertiary-butyl ether (MTBE) in rats. J Appl Toxicol 17(Suppl 1):S13-S19.

Neeper-Bradley TL. 1991. Two-generation reproduction study of inhaled methyl tert-butyl ether in CD (Sprague-Dawley) rats (final report) with attachments and cover letter dated 081691. MTBE Task Force. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0534056. 40-9113465. 42098 G8-2. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0540108.xhtml. January 17, 2020.

Bevan et al. (1997b) exposed Sprague-Dawley rats (25/sex/group) to MTBE at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for 10 weeks prior to mating. Exposure continued through the 21-day mating period (males were then randomly allocated to co-house with one female for 7 days maximum until mating was confirmed; after a 7-day period, unmated females were placed with a different male for the remainder of the 21-day mating period). Day of copulation was designated as GD 0. Male exposure continued until the last litter they sired was delivered, at which point they were sacrificed. Females were exposed during the mating period, gestation, lactation (GD 5), and weaning on PND 21. Females were sacrificed after the weaning of their offspring. The total exposure period was 16 weeks in F0 males and 17–19 weeks in F0 females. Birth was recorded as PND 0. On PND 28, at least one F1 rat/sex/litter was selected at random to continue exposure for up to 8 weeks prior to mating for generation of the F2 litter. Mating, exposure, and sacrifice schedule for F1 parental animals followed the same schedule as F0 parental animals. Parental rats were observed for viability twice daily and for clinical signs once daily. Male body weights were recorded weekly. Female body weights were recorded weekly prior to mating and then on GDs 0, 7, 14, and 20 after mating. Food

consumption was recorded weekly for both sexes. After mating, female food consumption was recorded at 3–4-day intervals throughout gestation. All parental adults were examined grossly. Reproductive endpoints evaluated in both generations included number of sperm-positive females, number pregnant, number of live litters, gestation length, male and female mating indices, male and female fertility indices, and gestational index. At necropsy, the liver was weighed in F1 parental animals. Histopathological examination was conduction on the following tissues in F0 control and 8,000-ppm groups: pituitary, testes, epididymides, prostate and seminal vesicles, vagina, uterus, ovaries, respiratory tract (with nasal turbinates), and gross lesions. Only the livers from control and 8,000-ppm groups were examined for histopathological changes in F1 parental animals. Litters were examined twice a day for general appearance and any deaths. Offspring were counted, sexed, weighed, and examined for abnormalities on PNDs 0, 1, 4, 7, 14, 21, and 28. Live birth and survival indices were calculated. On PND 4, each litter was reduced to four females and four males via random selection. Culled pups were euthanized and examined for external malformations. Those with observed abnormalities were given a gross postmortem examination. Data for this study are also available in the unpublished report by Neeper-Bradley (1991).

All F0 parental animals survived until scheduled sacrifice. Hypoactivity, blepharospasms, and lack of startle response were observed at ≥3,000 ppm; ataxia was observed at 8,000 ppm. Periocular encrustation and ocular discharge were observed at 8,000 ppm as well (attributed to irritative nature of vapor; see dermal entry). There were no clinical signs of toxicity observed in the 400-ppm group. Body weight was significantly reduced throughout the 10-week premating exposure period for F0 males at 8,000 ppm group, with a 12% reduction the end of the premating period. Body weight gain was also decreased in F0 males at 8,000 ppm from week 1 to 7 of premating exposure (magnitude not reported), and an 8–13% decrease in food consumption was observed from week 1 to 3. Body weights for F0 males were not reported once mating began. In F0 females, body weights were similar to controls prior to mating, during mating, and during gestation. During lactation, a significant 2-fold increase in body weight gain was observed at 8,000 ppm; the biological significance of this increase is unclear especially since food consumption was significantly reduced in this group from PND 7 to 14. No exposure-related changes were observed in reproductive parameters. No exposure-related changes in gross or microscopic histology were observed in the F0 generation.

All F1 parental animals survived until scheduled sacrifice. Hypoactivity, blepharospasms, and lack of startle response were observed at ≥3,000 ppm; ataxia was observed at 8,000 ppm. Periocular encrustation and ocular discharge were observed at 8,000 ppm as well (attributed to irritative nature of vapor). There were no clinical signs of toxicity observed in the 400-ppm group. Body weight gain was reduced throughout the 8-week premating exposure period for F1 males at 8,000 ppm group, with a significant 13–14% decrease during weeks 1 and 2. Final body weight was significantly reduced by 11%. While body weights were significantly reduced for F1 females during the premating exposure period, body weights were lower at the beginning of the exposure period and body weight gains were comparable across groups. Similar to F0 dams, a significant 4-fold increase in body weight gain was observed at 8,000 ppm; the biological significance of this increase is unclear, especially since food consumption was significantly reduced in this group from PND 7 to 14. No exposure-related changes were observed in reproductive parameters. Absolute liver weight was significantly increased at 8,000 ppm in F1 males and females by 12 and 27%, respectively. Relative liver weight was also significantly increased at 8,000 ppm in F1 males and females by 26%. Relative liver weight was significantly increased in F1 males by 10% at 3,000 ppm as well. No exposure-related changes were observed at gross necropsy, and no exposure-related liver lesions were noted.

No exposure-related changes were observed in litter survival parameters for F1 or F2 generations. Exposure-related changes in F1 pups included decreased weights at 8,000 ppm from PND 14 to 28 in both sexes and at 3,000 ppm on PND 14 in females. In addition, body weight gain was reduced in the 3,000- and 8,000-ppm exposed groups on PNDs 7–14 and 14–21. In F2 pups, body weights were

significantly reduced at 8,000 ppm from PND 7 to 28 in both sexes and at 3,000 ppm in males from PND 14 to 28. No exposure-related changes were observed at gross necropsy of pups.

Bird MG, Burleigh-Flayer HD, Chun JS, et al. 1997. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol 17(Suppl 1):S45-S55.

Chun JS, Kintigh WJ. 1993. Methyl tertiary butyl ether: Twenty-eight day vapor inhalation study in rats and mice. Union Carbide. Submitted to the MTBE Health Effects Testing Task Force. BRRC Report 93N1241.

Bird et al. (1997) exposed groups of Fischer-344 rats (10/sex/group) to MTBE at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for at least 4 weeks for 23 or 24 exposures (main experiment). Additional groups of rats (5/sex/group) were similarly exposed to 0 or 8,000 ppm for 24 exposures and maintained for 19 days following the last exposure (recovery experiment) or were exposed to 0, 400, 3,000, or 8,000 ppm for 23 exposures to evaluate cell proliferation in the renal tubules (cell proliferation experiment). All rats were examined for clinical signs of toxicity and body weight changes during the study. Clinical blood chemistry parameters (urea nitrogen, creatinine, calcium, phosphorus, sodium, potassium, and chloride) were evaluated only in the 0 or 8,000 ppm groups prior to sacrifice. Urine samples from all exposure groups were evaluated for osmolality, pH, total volume, lactate dehydrogenase, ALP, N-acetyl-beta-D-glucosaminidase, total protein, and protein fraction. Complete necropsy, organ weight determinations (liver, kidneys, uterus, lungs, brain, spleen, thyroid, and adrenals), and measurement of the length and width of the brain were performed on all rats except those in the cell proliferation experiment. Histological examinations were limited to the liver and kidneys. The livers were examined microscopically in the 0 and 8,000 ppm groups only, while the kidneys were examined microscopically in all groups. In addition, slides from all male rat kidneys were examined for protein accumulation in the tubular epithelial cells by Mallory's Heidenhain technique and for α2u-globulin accumulation using immunostaining with an antibody to α2u-globulin. Data are also available for this study in the unpublished report by Chun and Kintigh (1993).

No exposure-related mortality was observed. Clinical signs consisted of ataxia, hypoactivity, lack of startle response, and blepharospasm in rats during exposures to 3,000 and 8,000 ppm, and ataxia in rats following exposures to 8,000 ppm. Body weight loss (about 2%) occurred in male rats exposed to 8,000 ppm during the first week. Decreased body weight gain was seen throughout the study in male rats exposed to 8,000 ppm, with percentages of decreased body weight gain of 24–35% from exposure days 1–19 to 1–33. Decreased body weight gain was observed in female rats exposed to 8,000 ppm only during the first 2 weeks of exposure. No exposure-related effects on clinical chemistry parameters were found in rats. Urinalysis and urine chemistry evaluations revealed increased urine volume and decreased urinary pH in male and female rats at 8,000 ppm, but there was no other indication of renal damage. Exposure-related organ weight changes were observed in the kidneys, liver, adrenal glands, and spleen. Statistically significant organ weight changes in male rats at 3,000 ppm were limited to an 8 and 13% increase in absolute and relative liver weight, respectively. At 8,000 ppm, statistically significant organ weight changes included a 10% increase in absolute and relative liver weight; an 8% decrease in relative kidney weight; 45 and 53% increases in absolute and relative adrenal weight, respectively; and 18 and 13% decreases in absolute and relative spleen weight, respectively. In females, statistically significant organ weight changes at 3,000 ppm included 9 and 8% increases in absolute and relative liver weight, respectively; 11 and 8% increases in absolute and relative kidney weight, respectively; and 14 and 8% increases in absolute and relative adrenal weight, respectively. At 8,000 ppm, statistically significant organ weight changes in female rats included 17 and 10% increases in absolute and relative liver weight, respectively; a 4% increase in relative kidney weight; 21 and 23% increases in absolute and relative adrenal weight, respectively; and a 6% decrease in relative spleen weight. No gross or histopathological effects were noted in the organs and tissues examined. Although more protein accumulation in male rats

exposed to 3,000 and 8,000 ppm was observed, no evidence of α2u-globulin accumulation was found. These results suggest that a mechanism other than α2u-globlin accumulation (perhaps the accumulation of another protein unique to male rats) may be responsible for increased susceptibility in male rats.

Bird et al. (1997) also exposed groups of CD-1 mice (10/sex/group) to MTBE at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for at least 4 weeks for 20 or 21 exposures (main experiment). Additional groups (5/sex/group) were similarly exposed to 0 or 8,000 ppm for 23 exposures and maintained for 21 days following the last exposure (recovery experiment). Animals were evaluated for body weight and clinical signs of toxicity. Select organ weights were recorded (liver, brain, spleen, thyroid). Histopathological evaluations were conducted on liver, kidney, and thyroid. At the end of the exposure period, brains from all male and female mice of the main experiment were homogenized to determine the levels of calcium and magnesium. Special blood chemistry evaluation of total T3, total T4, TSH, total bile acid, and estradiol were conducted. Data are also available for this study in the unpublished report by Chun and Kintigh (1993).

No exposure-related mortality was observed. Clinical signs consisted of ataxia, hypoactivity, and lack of startle response during exposures to 3,000 and 8,000 ppm and ataxia following exposures to 8,000 ppm. No exposure-related clinical signs were observed during the recovery period. No body weight effects were noted. Absolute and relative liver weights were elevated in females at ≥3,000 ppm, and centrilobular hypertrophy was observed in males at 8,000 ppm. Decreased absolute and relative spleen weight was observed in females at 8,000 ppm. However, the spleen was not examined histologically. No exposure-related effects on brain weight were found. No exposure-related effects on brain calcium and magnesium levels were found. Special blood chemistry evaluation of total T3, total T4, TSH, total bile acid, and estradiol revealed that an increase in total T4 and TSH occurred in male mice at 8,000 ppm. However, these increases were not considered to be biologically significant due to the absence of histological evidence of thyroid lesions.

Selection of the Point of Departure for the MRL: The NOAEL of 400 ppm for CNS depression and elevated liver weights in rats and mice was selected as the POD because it is the identified lowest POD for the critical effects (neurotoxicity, hepatotoxicity) identified in the co-principal studies.

Calculations

Intermittent Exposure: The NOAEL of 400 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = 400 ppm x 6 hours/24 hours x 5 days/7 days = 71.4 ppm

Human Equivalent Concentration: While several PBPK models have been developed for MTBE, further refinement is needed to decrease uncertainty in estimated exposure levels, particularly for humans (see Sections 3.1.5 and 6.2 for more details). Therefore, HEC values for extrarespiratory effects were calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of animal:human blood gas partition coefficients. For rats, the reported rat blood gas partition coefficient of 11.5 (Rao and Ginsberg 1997) and the midpoint of the range of human blood gas partition coefficients (17.7–19.6) reported by Rao and Ginsberg (1997) and Kim et al. (2007) were used:

Rat $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x ratio of rat:human blood gas partition coefficients
Rat $NOAEL_{HECP}$ = 71.4 ppm x (11.5/18.7)
Rat $NOAEL_{HEC}$ = 71.4 ppm x 0.615 = 43.9 ppm

For mice, the default the animal:human blood gas partition coefficient of 1 was used (mouse blood gas partition coefficient is unknown):

Mouse $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x ratio of mouse:human blood gas partition coefficients
Mouse $NOAEL_{HEC}$ = 71.4 ppm x 1 (default value) = 71.4 ppm

Uncertainty Factor: The rat $NOAEL_{HEC}$ (most conservative HEC value) is divided by a total uncertainty factor (UF) of 30.

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

MRL = $NOAEL_{HEC}$ ÷ UFs
43.9 ppm ÷ (3 x 10) = 1 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a neurological effect as a co-critical effect following intermediate-duration inhalation exposure is supported by consistent observation of CNS-depressive effects following inhalation exposure to concentrations ≥2,000 ppm following acute-, intermediate-, and chronic-duration studies (Bevan et al. 1997a, 1997b; MTBE Committee 1990a; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; Vergnes and Chun 1994; Vergnes and Morabit 1989). Results from epidemiological studies also support CNS depression as a co-critical effect. Taxi drivers and health care workers who routinely traveled via motor vehicles experience greater incidence of MTBE-related symptoms, including headache, spaciness, and nausea, compared to a lesser exposed referent group (exposure levels not reported) (Alaska DHSS 1992a). Workers exposed to automobile exhaust (median MTBE blood concentrations were 0.05 and 0.08 µg/L for nonsmokers and smokers, respectively) experienced a greater incidence of dizziness and headaches compared to controls who were not occupationally exposed to MTBE (MTBE blood concentrations were below the limit of detection for control smokers and nonsmokers) (CDC 1993a). Ecological studies show that residents in areas participating in oxyfuel programs had increased risk of symptoms associated with MTBE exposure compared to those living in areas not participating in the oxyfuel program (Moolenaar et al. 1994; Wisconsin DHSS 1995). Some studies did not show an association between MTBE and neurological effects. For instance, healthy males exposed to up to 50 ppm of MTBE while performing light physical activity did not self-report any neurological effects (Johanson et al. 1995); however, this exposure scenario and population may not be representative of the general population. For more information, see Section 2.15.

Selection of elevated liver weight as a co-critical effect following intermediate-duration inhalation exposure is supported by consistent observation of elevated liver weights in rats and mice following inhalation exposure to concentrations ≥2,000 ppm following acute-, intermediate-, and chronic-duration studies (Bevan et al. 1997a, 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996), with evidence of centrilobular hypertrophy in mice at 8,000 ppm (Bird et al. 1997; Moser et al. 1996).

Agency Contacts (Chemical Managers): Gaston Casillas

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-butyl ether (MTBE)
CAS Numbers: 1634-04-4
Date: September 2023
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL: 1 ppm
Critical Effect: Renal effects
Reference: Bird et al. 1997; Chun et al. 1992
Point of Departure: NOAEL of 400 ppm ($NOAEL_{HEC}$ of 43.9 ppm)
Uncertainty Factor: 30
LSE Graph Key: 42
Species: Rat

MRL Summary: A chronic-duration inhalation MRL of 1 ppm was derived for MTBE based on renal effects (increased kidney weight and increased incidence and severity of chronic progressive nephropathy) in female rats exposed to concentrations ≥3,000 ppm for 6 hours/day, 5 days/week for 24 months; a NOAEL of 400 ppm was identified (Bird et al. 1997). The MRL is based on the NOAEL of 400 ppm, which was adjusted to continuous duration exposure and converted to a $NOAEL_{HEC}$ of 43.9 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available chronic-duration inhalation studies report relevant MTBE-related effects at 3,000 ppm (renal effects in female rats, hepatic effects in rats and mice) and 8,000 ppm (CNS effects) (see Table A-19). Renal effects were also observed in male rats at ≥400 ppm; however, the higher incidence and greater severity of chronic progressive nephropathy at lower exposure concentrations in male rats compared with female rats may be due to the exacerbation of this syndrome by the accumulation of α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Because enhancement of chronic progressive nephropathy, which led to increased mortality and decreased survival time in males, is associated with α2u-globulin accumulation in male rats only, these endpoints in male rats are not considered for MRL derivation. However, since female rats also had enhanced chronic progressive nephropathy not associated with α2u-globulin accumulation, renal effects in female rats were considered relevant. Therefore, hepatic and female rat renal effects were further considered for MRL derivation.

Table A-19. Summary of NOAEL and LOAEL Values Following Chronic-Duration Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Neurological effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	3,000	8,000 (serious LOAEL)	Ataxia, prostration, salivation	Bird et al. 1997; Chun et al. 1992

Table A-19. Summary of NOAEL and LOAEL Values Following Chronic-Duration Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Renal effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	400	3,000	Increased relative kidney weight and incidence and severity of CPN in females	Bird et al. 1997; Chun et al. 1992
Hepatic effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in females	Bird et al. 1997; Chun et al. 1992

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information

CPN = chronic progressive nephropathy; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level

In order to identify the most sensitive POD, BMD modeling was attempted for critical hepatic and female rat renal endpoints in Table A-19 when data were amenable to modeling. The data were fit to all available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 standard deviation for continuous data or 10% extra risk for dichotomous data. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMC) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. The datasets used for BMD modeling are presented in Table A-20. Incidence data for lesions associated with chronic progressive nephropathy in female rats were not suitable for BMD modeling due to non-monotonic responses and/or high incidence in controls (e.g., tubular proteinosis, glomerulosclerosis, interstitial nephritis, and fibrosis). Therefore, ATSDR used the NOAEL/LOAEL approach for the renal endpoints.

Table A-20. Relative Liver and Kidney Weights in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 24 Months (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	400	3,000	8,000
Relative liver weight (% BW) Mean±SD (n)	3.867±0.6629 (30)	3.725±0.5096 (27)	4.654±0.6379[a] (23)	5.508±1.3994[a] (25)
Relative kidney weight (% BW) Mean±SD (n)	0.907±0.2578 (30)	0.827±0.1427 (27)	1.072±0.2354[b] (23)	1.168±0.2564[a] (25)

[a]p<0.01.
[b]p<0.05.

BW = body weight; (n) = number of animals; SD = standard deviation

Source: Chun et al. 1992 (unpublished report associated with published study by Bird et al. 1997)

Details of the modeling results for the model predictions for relative liver weight in female rats reported by Chun et al. (1992) are in Table A-21. No adequate model fits were observed with the full data set; however, with the highest concentration dropped, the constant variance, frequentist, restricted 2-Degree Polynomial model was selected in accordance with the selection criteria mentioned above. No adequate models were identified for increased relative kidney weight in female rats (Bird et al. 1997; quantitative data obtained from unpublished report by Chun et al. 1992) because they failed to meet conventional goodness-of-fit criteria.

Table A-21. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 24 Months (5 Days/Week, 6 Hours/Day); Highest Dose Dropped (Bird et al. 1997; Chun et al. 1992)

					Scaled residuals[c]	
Model	BMC_{1SD}[a] (ppm)	$BMCL_{1SD}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	2,130.70	1,659.47	0.12	152.78	-1.19	0.14
Exponential (model 3)[d]			NA	153.12	-0.65	$1.4x10^{-7}$
Exponential (model 4)[d]	2,072.04	1,571.16	0.10	153.00	-1.25	0.18
Exponential (model 5)[d]			65,535	155.12	-0.65	$9.8x10^{-7}$
Hill[e]			65,535	155.12	-0.65	$3.66x10^{-6}$
Polynomial (2-degree)[e,f]	**2,507.18**	**1,730.39**	**0.61**	**149.30**	**-0.72**	**0.01**
Power			NA	153.12	-0.65	$-3.1x10^{-8}$
Linear	2,072.63	1,564.59	0.10	153.00	-1.25	0.18

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. The constant variance model did not provide an adequate fit to the full dataset. With nonconstant variance applied, none of the models provided an adequate fit to the means. With the highest dose dropped, the constant variance model provided an adequate fit the data. Only the Exponential 2, Exponential 4, Polynomial 2, and Linear models provided an adequate fit to the means. BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (2nd 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., 1SD = exposure dose associated with a change of 1 standard deviation from the control); NA = not applicable

The candidate PODs are summarized in Table A-22. The lowest POD was identified for renal effects in female rats, with a NOAEL value of 400 ppm. Therefore, renal effects in female rats were selected as the critical effect.

Table A-22. Summary of Candidate Effects and POD Values Considered for Derivation of a Chronic-Duration Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference[a]
Renal effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	Increased relative kidney weight and incidence and severity of CPN in females[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun et al. 1992
Hepatic effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	Increased relative liver weight in females	309	$BMCL_{ADJ}$	Bird et al. 1997; Chun et al. 1992

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information and/or raw data for benchmark dose modeling.
[b]Selected study/endpoint for derivation of chronic-duration inhalation MRL.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{ADJ}$ = 95% lower confidence limit on the BMC (adjusted for continuous exposure); MRL = Minimal Risk Level; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); POD = point of departure

Selection of the Principal Study: The 24-month study in rats by Bird et al. (1997) is selected as the principal study based on renal effects in female rats because this study provides the lowest POD for the identified critical effect. Data are also available for this study in the unpublished report by Chun et al. (1992).

Summary of the Principal Study:

Bird MG, Burleigh-Flayer HD, Chun JS, et al. 1997. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol 17(Suppl 1):S45-S55.

Chun JS, Burleigh-Flayer HD, Kintigh WJ. 1992. Final report, methyl tertiary butyl ether: Vapor inhalation oncogenicity study in Fischer 344 rats, with cover letter dated 11/19/92. MTBE Task Force. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0558686. 42098 G9-3. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0558686.xhtml. January 20, 2020.

Bird et al. (1997) exposed groups of Fischer 344 rats (50/sex/group) to MTBE vapor at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for 24 months. Animals were observed individually for mortality and clinical signs of toxicity every day. Body weights were measured weekly up to week 13 and then measured every other week. Blood was collected at 12 months and prior to sacrifice for hematology and serum chemistry analyses in rats from the control and 8,000-ppm groups. In female rats, corticosterone levels were measured in 10 rats/group at sacrifice. In male rats, corticosterone levels were measured from 10 animals each in the control and 8,000-ppm groups at week 81, 10 animals from the 3,000-ppm group at week 94, and 10 animals from the 400-ppm group at week 104. Urinalysis was conducted at termination. Gross necropsy was carried out for all animals after 24 months of exposure, including those that had died prematurely. The brain, liver, kidneys, lungs, spleen, adrenal glands, and testes were weighed. Tissues of all major organ systems were collected for histopathological evaluation from control and 8,000-ppm exposed rats, as well as all rats that died or were

sacrificed moribund. In males, the liver, kidneys, testes, and gross lesions were also examined microscopically in the 400- and 3,000-ppm groups. For females, the liver and gross lesions of the 400- and 3,000-ppm groups were examined. Data are also available for this study in the unpublished report by Chun et al. (1992).

Male rats in the 3,000- and 8,000-ppm exposed groups had increased mortality rates and decreased mean survival times with the major cause of death being chronic progressive nephropathy. Due to this, male rats in the 3,000- and 8,000-ppm exposed groups were terminated early at weeks 97 and 82, respectively. Slight, but not significant, increases in mortality and/or decreases in survival time were also observed in males at 400 ppm and females at 3,000 and 8,000 ppm; these were also attributed to chronic progressive nephropathy. Bird et al. (1997) qualitatively reported an increase in clinical signs of neurotoxicity such as blepharospasm, hypoactivity, ataxia, and lack of startle response at 3,000 and 8,000 ppm, with increased salivation in males of these groups, and prostration at 8,000 ppm. However, statistics performed for this review (Fisher's Exact Probability Test) of incidence data provided by Chun et al. (1992) for rats showing blepharospasm, hypoactivity, salivation, ataxia, and prostration at least once during the chronic-duration study indicate that statistically significant changes were limited to prostration in females at 3,000 ppm (but not 8,000 ppm), increased incidence of ataxia in males and females at 8,000 ppm, and increased prostration and salivation in males at 8,000 ppm. Due to lack of dose-response, it is unclear if prostration observed in females is exposure-related. Quantitative startle response data could not be located for independent statistical review. The only non-neurological clinical sign noted was swollen periocular tissue in male rats at ≥3,000 ppm, which was attributed to irritative effect of direct vapor exposure rather than systemic toxicity. Based on statistics performed for this review (Fisher's Exact Probability Test) of incidence data provided by Chun et al. (1992), statistically significant increases were observed at 3,000 and 8,000 ppm. Body weight and body weight gain decreased in the 8,000-ppm group throughout the study. Upon termination of males from the 8,000-ppm group at 82 weeks, body weight and body weight gain were decreased by 19 and 29%, respectively, compared to controls. At terminal sacrifice at 104 weeks, body weight and body weight gain in females from the 8,000-ppm group were reduced by 13 and 22%, respectively, compared to controls. No abnormalities were observed in hematological parameters of any MTBE exposed group. Serum corticosterone levels were increased by 2-fold in males from the 3,000-ppm group at week 97, but a 61% decrease was observed in males of the 8,000-ppm group at week 81. No other exposure-related changes were reported for clinical chemistry parameters. Statistical analysis for organ weights was not conducted for males exposed to 3,000 or 8,000 ppm due to early termination. In females, exposure-related and statistically significant changes in organ weight included a 20–45% increase in absolute and relative liver weights at ≥3,000 ppm and a 22–33% increase in relative kidney weight at ≥3,000 ppm.

Histopathological examination confirmed increased incidence and severity of changes associated with chronic progressive nephropathy in males at ≥400 ppm and females at ≥3,000 ppm, including glomerulosclerosis, tubular proteinosis, interstitial nephritis, and interstitial fibrosis. The most severe lesions were observed in male rats at 8,000 ppm. Additional lesions were observed in males, and considered secondary to nephropathy, including fibrous osteodystrophy, parathyroid hyperplasia, and mineralization within numerous tissues. Neoplastic lesions were observed in both the kidneys and testes. The incidence of renal tubular cell tumors was increased in male rats at ≥3,000 ppm, with a significant increase in combined incidence of adenomas and carcinomas for the 3,000-ppm group (8/50) compared to controls (1/50). Early mortality may have contributed to lack of significant increase at 8,000 ppm (3/50). No renal tubular cell tumors were found in males at 400 ppm. The incidence of testicular interstitial cell adenomas was increased significantly in at 3,000 ppm (41/50) and 8,000 ppm (47/50), compared to controls (32/50). However, observed incidences in the exposure groups were within historical controls and the control incidence was low compared to historical data. Since testicular tumors are the most common tumor in this strain of rat, and findings were within historical controls, these tumors were not considered exposure related.

Selection of the Point of Departure for the MRL: The NOAEL of 400 ppm for renal effects in female rats was selected as the POD, as it represents the lowest candidate POD. This POD is protective of local irritative effects on the eyes observed at ≥3,000 ppm and non-dose-related female prostration observed at 3,000 ppm only.

Calculations

Intermittent Exposure: The NOAEL of 400 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = 400 ppm x 6 hours/24 hours x 5 days/7 days = 71.4 ppm.

Human Equivalent Concentration: While several PBPK models have been developed for MTBE, further refinement is needed to decrease uncertainty in estimated exposure levels, particularly for humans (see Sections 3.1.5 and 6.2 for more details). Therefore, a HEC value for extrarespiratory effects was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of animal:human blood gas partition coefficients, using reported rat blood gas partition coefficient of 11.5 (Rao and Ginsberg (1997) and the midpoint of the range of human blood gas partition coefficients (17.7–19.6) reported by Rao and Ginsberg (1997) and Kim et al. (2007):

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x ratio of animal:human blood gas partition coefficients
$NOAEL_{HEC}$ = 71.4 ppm x (11.5/18.7)
$NOAEL_{HEC}$ = 71.4 ppm x (0.615) = 43.9 ppm

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

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

MRL = $NOAEL_{HEC}$ ÷ UFs
43.9 ppm ÷ (3 x 10) = 1 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a renal effect in female rats as the critical effect following chronic-duration inhalation exposure is supported by evidence of elevated kidney weights in female rats following exposure to ≥4,000 ppm for 13 weeks (Lington et al. 1997), and female mice following exposure to 8,000 ppm for 18 months (Bird et al. 1997).

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-butyl ether (MTBE)
CAS Numbers: 1634-04-4
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data to support derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: Available acute-duration oral studies report MTBE-related effects at LOAELs in the range of 400–450 mg/kg/day, including neurological and male reproductive effects in rats (see Table A-23). Gastrointestinal effects were observed at ≥357 mg/kg/day, but effects are limited to qualitatively reported diarrhea, which may be due to irritative portal-of-entry effects associated with bolus gavage. This is supported by evidence of gastrointestinal effects only in gavage studies (Amoco 1992; Robinson et al. 1990) and not in drinking water studies, even after chronic-duration exposure (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013). Therefore, diarrhea was not considered for MRL derivation because it may not be a relevant endpoint for humans who are predominantly exposed via drinking water.

Of the candidate endpoints in Table A-23, none were considered adequate for MRL derivation. Reports of neurological effects at ≥400 mg/kg/day had limited qualitative and quantitative reporting, precluding use of these studies as the basis for the MRL. For male reproductive effects, adversity of decreased testes weight and increased serum LH in the absence of other testicular effects is unclear, particularly because neither of these effects were observed after 4 weeks of exposure using the same protocols at doses up to 1,600 mg/kg/day (Dong-mei et al. 2009; Li et al. 2008). Uncertainties in male reproductive effects following acute-duration oral exposure preclude the use of these endpoints as the basis for the MRL.

Table A-23. Summary of NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Fischer 344 rat	Once	40	400	Drowsiness	MTBE Committee 1990b
Sprague-Dawley rat	2 weeks	ND	450	Lethargy; transient ataxia in some animals	de Peyster et al. 2014
Male reproductive effects					
Sprague-Dawley rat	2 weeks	ND	400	Transient decreases in testes weight (not observed at 4 weeks)	Dong-mei et al. 2009

Table A-23. Summary of NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sprague-Dawley rat	2 weeks	ND	400	Transient increased serum LH (not observed at 4 weeks)	Li et al. 2008

LH = luteinizing hormone; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Gaston Casillas

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-butyl ether (MTBE)
CAS Numbers: 1634-04-4
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.4 mg/kg/day
Critical Effect: Altered male reproductive development (decreased serum testosterone)
Reference: Zhu et al. 2022
Point of Departure: $BMDL_{1SD}$ of 36 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 32
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.4 mg/kg/day was derived for MTBE based on developmental reproductive effects (decrease serum testosterone) in rats exposed to doses ≥300 mg/kg/day for 21 days (PNDs 35–56); a NOAEL was not identified (Zhu et al. 2022). The MRL is based on the BMDL of 36 mg/kg/day, which was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration oral studies report the most sensitive MTBE-related effects at LOAELs in the range of 300–440 mg/kg/day, including neurological effects in rats (CNS depression), reproductive effects in adult male rats (sperm effects and changes to seminiferous tubules), and developmental reproductive effects in male rats exposed prior to puberty (decreased serum testosterone) (see Table A-24). Neurological, male reproductive, and developmental effects were all considered for MRL derivation.

Table A-24. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Sprague-Dawley rat	4 weeks 5 days/week	90	440	Transient hypoactivity	Amoco 1992
Reproductive effects					
Sprague-Dawley rat	4 weeks	ND	400	Increased abnormal sperm	Li et al. 2008
Sprague-Dawley rat	30 days	ND	400	Seminiferous tubule changes	Gholami et al. 2015
Developmental effects					
Sprague-Dawley rat	21 days PNDs 35–56	ND	300	50% reduction in serum testosterone	Zhu et al. 2022

LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Gastrointestinal effects were also observed in intermediate-duration oral studies at doses ≥100 mg/kg/day, but effects are limited to qualitatively reported diarrhea, which may be due to irritative portal-of-entry effects associated with bolus gavage. This is supported by evidence of gastrointestinal effects only in gavage studies (Amoco 1992; Robinson et al. 1990) and not in drinking water studies, even after chronic-duration exposure (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013). Therefore, diarrhea was not considered for MRL derivation because it may not be a relevant endpoint for humans who are predominantly exposed via drinking water. One study reported mild hepatic effects (elevated serum cholesterol) in rats following exposure to ≥100 mg/kg/day for 90 days (Robinson et al. 1990); this effect was not considered for MRL derivation due to unclear adversity in the absence of associated hepatic lesions (e.g., fatty liver). Renal effects in male rats were also observed at ≥209 mg/kg/day; however, renal effects in male rats were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). One low-dose study reported altered zinc and glucose homeostasis at drinking water doses ≥0.15 mg/kg/day (Saeedi et al. 2017); however, this study evaluated a limited number of endpoints and other studies evaluating serum glucose levels at much higher doses report inconsistent findings (Robinson et al. 1990). Due to unknown adversity of the findings by Saeedi et al. (2017), this study was not considered for MRL derivation.

In order to identify the most sensitive POD, BMD modeling was attempted for critical neurological, male reproductive, and developmental endpoints listed in Table A-24 when data were amenable to modeling. Data modeled for hypoactivity, sperm effects, and developmental reproductive effects (decreased serum testosterone) in male rats are shown in Tables A-25, A-26, and A-27, respectively. Data reporting for changes in the seminiferous tubules were inadequate for modeling because incidence data were not reported by Gholami et al. (2015). The data were fit to all available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 standard deviation (sperm deformity ratio, serum testosterone) or 10% extra risk (hypoactivity). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen.

Table A-25. Neurological Effects in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks (5 Days/Week)

	Dose (mg/kg/day)			
	0	90	440	1,750
Hypoactivity Incidence (percent incidence)	0/10 (0%)	0/10 (0%)	4/10[a] (40%)	4/10[a] (40%)

[a]p<0.05.

Source: Amoco 1992

Table A-26. Sperm Effects in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks

	Dose (mg/kg/day)			
	0	400	800	1,600
Sperm deformity ratio (percent) Mean±SD (n)	12.1±3.3 (8)	18.5±4.9[a] (7)	19.5±2.8[a] (9)	29.1±4.5[b] (9)

[a]p<0.05.
[b]p<0.01.

(n) = number of animals; SD = standard deviation

Source: Li et al. 2008

Table A-27. Serum Testosterone Levels[a] in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) on PNDs 35–56

	Dose (mg/kg/day)			
	0	300	600	1,200
Serum testosterone (ng/mL) Mean±SD (n)	0.98±0.42 (6)	0.46±0.20[b] (6)	0.47±0.20[b] (6)	0.41±0.29[b] (6)

[a]Estimated from graphically presented data using GrabIt! Software.
[b]p<0.05.

(n) = number of animals; SD = standard deviation

Source: Zhu et al. 2022

Details of the modeling results for male rats are in Table A-28 for hypoactivity, Table A-29 for sperm effects, and Table A-30 for serum testosterone. In accordance with the selection criteria mentioned above, the Log-Logistic model was selected for hypoactivity, the Polynomial 3 model was selected for sperm effects, and the Exponential 4 model was selected for serum testosterone. All selected models were frequentist, restricted models.

Table A-28. Results from Benchmark Dose (BMD) Analysis of Hypoactivity in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks (5 Days/Week) (Amoco 1992)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	238.95	82.11	0.98	32.92	-0.01	0.01
Gamma[d,e]	236.28	137.76	0.21	33.23	-0.64	1.83
Log-Logistic[e,f]	**174.53**	**83.54**	**0.37**	**32.34**	**-0.0004**	**-0.76**
Multistage Degree 3[g]	236.28	137.75	0.21	33.23	-0.64	1.83
Multistage Degree 2[g]	236.28	137.75	0.21	33.23	-0.64	1.83
Multistage Degree 1[g]	236.28	137.75	0.10	35.23	-0.64	1.83
Weibull[d]	236.28	137.76	0.21	33.23	-0.64	1.83
Logistic			0.03	38.90	2.25	-0.37
Log-Probit[h]			0.11	35.90	-0.82	1.23
Probit			0.03	38.67	2.26	-0.42

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model (lowest AIC). The Hill, Gamma, Log-Logistic, Multistage, and Weibul models provided adequate fit to the means. Of these models, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Log-Logistic).
[g]Betas restricted to ≥0.
[h]BMDL 10 times lower than lowest non-zero dose; BMD/BMDL ratio >20.

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

Table A-29. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Sperm Deformity Ratio (%) in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks (Li et al. 2008)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential (model 2)[d]	522.19	431.25	0.18	188.92	1.46	-0.28
Exponential (model 3)[d]	522.19	431.24	0.18	188.92	1.46	-0.28
Exponential (model 4)[d]			0.09	190.32	-0.37	1.26
Exponential (model 5)[d]			0.09	190.34	-0.35	1.24
Hill[d]			0.09	190.36	-0.33	1.24
Polynomial (3-degree)[d,e]	**409.32**	**297.57**	**0.26**	**188.22**	**1.33**	**-0.73**
Polynomial (2-degree)[d]	394.28	296.60	0.25	188.30	-0.46	1.31
Power[d]	377.79	296.35	0.24	188.32	-0.38	1.26
Linear	377.79	296.35	0.24	188.32	-0.38	1.26

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model (lowest AIC). The constant variance model provided an adequate fit to the data. The Exponential 2, Exponential 3, 3-degree polynomial, 2-degree polynomial, Power, and Linear models provided adequate fit to the means. Of these models, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Polynomial 3-degree model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation from the control)

Table A-30. BMD Model Predictions (Nonconstant Variance) for Serum Testosterone Levels in Male Sprague-Dawley Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 21 Days (PNDs 35 to 56) (Zhu et al. 2022)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential (model 2)[d]			0.02	16.93	-0.41	0.85
Exponential (model 3)[d]			0.02	16.93	-0.41	0.85
Exponential (model 4)[d,e]	**83.53**	**35.67**	**0.87**	**11.30**	**-0.001**	**0.11**
Exponential (model 5)[d]			NA	13.29	$3.56x10^{-5}$	0.15
Hill[d]			NA	13.29	$-9.43x10^{-7}$	0.15
Polynomial (3-degree)[d]			0.01	18.51	-0.70	0.48
Polynomial (2-degree)[d]			0.01	18.51	-0.70	0.48
Power[d]			0.01	18.51	-0.70	0.48
Linear			0.01	18.51	-0.70	0.48

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model (lowest AIC; only adequate fitting model). The constant variance model provided an adequate fit to the data. Only the Exponential 4 model provided adequate fit to the means and calculated a BMDL; however, the BMDL for this model was 10 times lower than the lowest non-zero dose and is considered an inadequate fit to the data (data not shown). The nonconstant variance model also provided an adequate fit to the data. Only the Exponential 4 model provided adequate fit to the means. Therefore, the model with the lowest AIC and the only model with an adequate fit to the means was selected (Exponential 4).

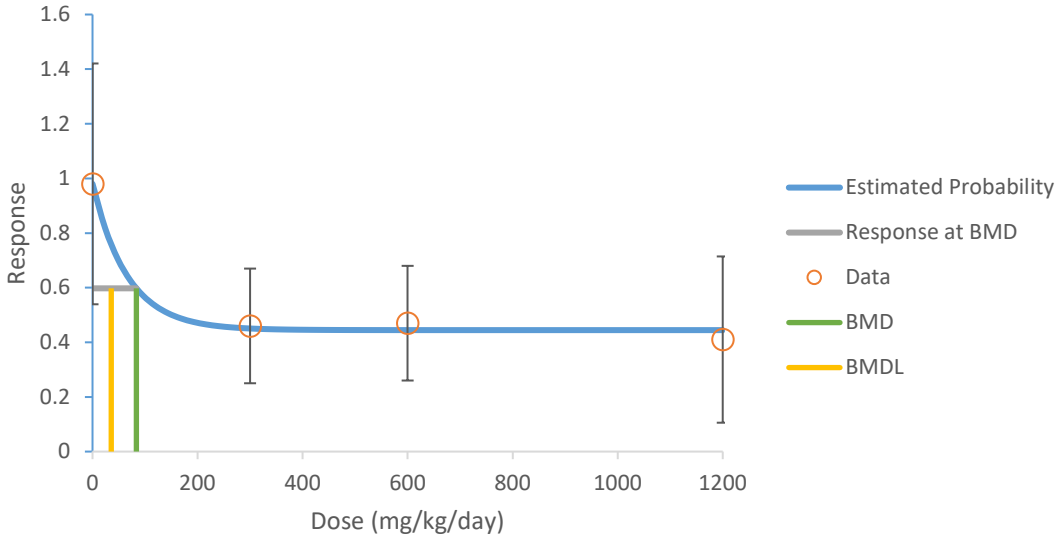
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation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

Potential PODs for deriving an intermediate-duration oral MRL for MTBE include:

- $BMDL_{1SD}$ of 36 mg/kg/day based on decreased serum testosterone in rats following early postnatal exposure (Zhu et al. 2022)
- $BMDL_{ADJ}$ of 60 mg/kg/day based on transient hypoactivity in rats (Amoco 1992)
- $BMDL_{1SD}$ of 298 mg/kg/day based on increased abnormal sperm in rats (Li et al. 2008)
- LOAEL of 400 mg/kg/day based on seminiferous tubule changes in rats (Gholami et al. 2015)

The $BMDL_{1SD}$ of 36 mg/kg/day for decreased serum testosterone following developmental exposure was selected as the POD for deriving an intermediate-duration oral MRL for MTBE because it represents the more conservative (health-protective) POD. Model fit for decreased serum testosterone is shown in Figure A-2 (Exponential 4 Model); no alternative models were identified.

Figure A-2. Fit of the Exponential 4 Model (Nonconstant Variance) to Data for Methyl tert-Butyl Ether (MTBE), Serum Testosterone Levels in Male Sprague-Dawley Rats (Zhu et al. 2022)



Selection of the Principal Study: The 21-day prepubertal study in rats by Zhu et al. (2022) was selected as the principal studies because it provided the lowest POD (BMDL = 36 mg/kg/day) for the critical effect (developmental toxicity).

Summary of the Principal Study:

Zhu Q, Zhu S, Li Q, et al. 2022. Methyl tert-butyl ether inhibits pubertal development of Leydig cells in male rats by inducing mitophagy and apoptosis. Ecotoxicol Environ Saf 232:113282

Groups of juvenile male rats (6/group) were exposed to 0, 300, 600, or 1,200 mg/kg/day via gavage in corn oil from PND 35 to 56, a time frame that covers late puberty. Body weights were recorded at the beginning and end of the exposure period. After the exposure period, rats were sacrificed. Blood was collected for analysis of testosterone, LH, and FSH levels. The testes and epididymides were removed and weighed. The number and volume of Sertoli and Leydig cells was determined. Biomarkers for Sertoli and Leydig cells were SOX9 and CYP11A1, respectively. Cell proliferation and apoptosis was determined. Protein and RNA were isolated from testicular tissue for expression analysis.

No changes in body or testicular weights were noted. Serum testosterone was significantly decreased by ≥50% at all tested dose levels. No changes in serum LH or FSH were observed. No changes in the number of Sertoli cells were noted; however, the number Leydig cells were significantly decreased by ~20% at 1,200 mg/kg/day, compared to control. Analysis showed that overall cell size and cytoplasmic size of Leydig cells were decreased, while nuclear size was unchanged. The study authors interpreted these findings to indicate a delayed maturation of Leydig cells in high-dose males. Tunnel assay showed that decreased Leydig cell number was, in part, due to a significant increase in Leydig cell apoptosis at ≥600 mg/kg/day. Gene analysis showed reduced messenger RNA (mRNA) levels of cell cycle-related genes, and protein analysis showed alterations in proteins involved in apoptosis and autophagy. *In vitro* data published with the *in vivo* study supported inhibition of testosterone synthesis by cultured Leydig cells via reactive oxygen species generation, mitophagy, and apoptosis.

Selection of the Point of Departure for the MRL: The BMDL of 36 mg/kg/day developmental reproductive toxicity (decreased serum testosterone following prepubertal exposure) in rats reported by Zhu et al. (2022) was selected as the POD because it represents the lowest available POD for the critical effect (developmental toxicity).

Intermittent Exposure: Exposure was daily; therefore, no adjustment for intermittent exposure was necessary.

Uncertainty Factor: The BMDL is divided by a total uncertainty factor (UF) of 100:

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

$$MRL = BMDL_{1SD} \div (UFs \times MF)$$
$$36 \text{ mg/kg/day} \div (10 \times 10) = 0.36 \text{ mg/kg/day} \approx 0.4 \text{ mg/kg/day}$$

***Other Additional Studies or Pertinent Information that Lend Support to this MRL*:** Selection of a reduced serum testosterone as the critical effect following intermediate-duration oral exposure during development is supported by progression to decreased Leydig cell number and size at higher doses (Zhu et al. 2022). Studies in adult rats also provide some evidence of adverse male reproductive effects following oral exposure, although there are some inconsistencies across study and exposure durations. Regarding the critical effect, decreased serum testosterone was observed at acute- and intermediate-duration doses ≥800 mg/kg/day in several studies (de Peyster et al. 2003; Khalili et al. 2015; Li et al. 2008; Williams et al. 2000); however, one study did not observe exposure-related changes in serum or testicular testosterone levels in rats at gavage doses as high as 1,200 mg/kg/day for 2 weeks (de Peyster et al. 2014). There is some evidence of testicular damage, including damage to sperm/germ cells, after acute-duration exposure to 1,600 mg/kg/day or intermediate-duration exposure to doses ≥400 mg/kg/day (Gholami et al. 2015; Li et al. 2008). However, other studies in rats reported no non-neoplastic alterations in the testes following acute-duration exposure to ≤1,428 mg/kg/day (Bermudez et al. 2012; Robinson et al. 1990), intermediate-duration exposure to ≤1,750 mg/kg/day (Amoco 1992; Bermudez et al. 2012; Robinson et al. 1990; Williams et al. 2000), or chronic-duration exposure to ≤1,000 mg/kg/day (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013).

Despite inconsistencies in the oral database, available data suggest that the male reproductive system may be a sensitive target of MTBE toxicity. This is supported by mechanistic data attributing observed male reproductive effects to direct toxic effects of MTBE on testicular cells, which may be mediated via oxidative stress (Li and Han 2006; Li et al. 2007, 2009). Additionally, mechanistic data provide support for inhibition of testosterone synthesis via toxicity to Leydig cells (Zhu et al. 2022).

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-butyl ether (MTBE)
CAS Numbers: 1634-04-4
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: Serious effects (death and cancer) were observed at ≥250 mg/kg/day, along with dysplastic proliferation of lymphoreticular tissue (possibly preneoplastic). The only adverse effects observed at doses below this serious LOAEL value are renal effects in male rats at drinking water doses ≥29 mg/kg/day (Bermudez et al. 2012); however, these effects were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Renal effects in female rats were not observed until chronic-duration doses 4-fold higher than the identified serious LOAEL (1,042 mg/kg/day; Dodd et al. 2013). Therefore, a chronic-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MTBE

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 MTBE.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for MTBE. 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 MTBE 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 MTBE 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
    - Other noncancer effects

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

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 MTBE released for public comment in 2022; thus, the literature search was restricted to studies published between January 2019 and June 2022. The following main databases were searched in June 2022:

- PubMed
- National Library of Medicine's TOXLINE
- 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 MTBE. 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 MTBE were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2022	(1634-04-4[rn] OR (("2-Methoxy-2-methylpropane"[tw] OR "Methyl t-butyl ether"[tw] OR "Methyl tert butyl ether"[tw] OR "Methyl tertiary butyl ether"[tw] OR "MTBE"[tw] OR "t-Butyl methyl ether"[tw] OR "tert-Butyl methyl ether"[tw] OR "(tert-Butyl)methylether"[tw] OR "1,1-Dimethylethyl methyl ether"[tw] OR "2-Methoxy-2-methyl propane"[tw] OR "2-Methyl-2-methoxypropane"[tw] OR "Ether, methyl tert-butyl"[tw] OR "Ether, tert-butyl methyl"[tw] OR "Methyl 1,1-dimethylethyl ether"[tw] OR "Methyl-1,1-dimethylethyl ether"[tw] OR "Propane, 2-methoxy-2-methyl"[tw] OR "tert-Butoxymethane"[tw] OR "tert-Butyl-methyl-aether"[tw]) AND ("Methyl Ethers/toxicity"[mh] OR "Methyl Ethers/adverse effects"[mh] OR "Methyl Ethers/poisoning"[mh] OR "Methyl Ethers/pharmacokinetics"[mh] OR ("Methyl Ethers"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "occupational groups"[mh])) OR ("Methyl Ethers"[mh] AND toxicokinetics[mh:noexp]) OR ("Methyl Ethers/blood"[mh] OR "Methyl Ethers/cerebrospinal fluid"[mh] OR "Methyl Ethers/urine"[mh]) OR ("Methyl Ethers"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Methyl Ethers"[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 "Methyl Ethers/antagonists and inhibitors"[mh] OR ("Methyl Ethers/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Methyl Ethers/pharmacology"[majr] OR ("Methyl Ethers"[mh] AND ("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))))) OR (("2-Methoxy-2-methylpropane"[tw] OR "Methyl t-butyl ether"[tw] OR "Methyl tert butyl ether"[tw] OR "Methyl tertiary butyl ether"[tw] OR "MTBE"[tw] OR "t-Butyl methyl ether"[tw] OR "tert-Butyl methyl ether"[tw] OR "(tert-Butyl)methylether"[tw] OR "1,1-Dimethylethyl methyl ether"[tw] OR "2-Methoxy-2-methyl

Table B-2. Database Query Strings

Database search date	Query string
	propane"[tw] OR "2-Methyl-2-methoxypropane"[tw] OR "Ether, methyl tert-butyl"[tw] OR "Ether, tert-butyl methyl"[tw] OR "Methyl 1,1-dimethylethyl ether"[tw] OR "Methyl-1,1-dimethylethyl ether"[tw] OR "Propane, 2-methoxy-2-methyl"[tw] OR "tert-Butoxymethane"[tw] OR "tert-Butyl-methyl-aether"[tw]) NOT medline[sb])) AND (2019:3000[dp] OR 2019:3000[mhda] OR 2019:3000[crdt] OR 2019:3000[edat])
NTRL	
06/2022	General search box: "2-Methoxy-2-methylpropane" OR "Methyl t-butyl ether" OR "Methyl tert butyl ether" OR "Methyl tertiary butyl ether" OR "MTBE" OR "t-Butyl methyl ether" OR "tert-Butyl methyl ether" Date published: 2019-2022
Toxcenter	
06/2022	FILE 'TOXCENTER' ENTERED AT 16:15:45 ON 08 JUN 2022 CHARGED TO COST=EH038.12.04.LB.04 L1 6851 SEA FILE=TOXCENTER 1634-04-4 L2 6669 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 5263 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 385 SEA FILE=TOXCENTER L3 AND ED>=20190101 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)

Table B-2. Database Query Strings

Database search date	Query string
	L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (NONHUMAN MAMMALS)/ORGN L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 186 SEA FILE=TOXCENTER L4 AND L37 L39 14 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 172 DUP REM L38 (14 DUPLICATES REMOVED) D SCAN L40

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2022	Compounds searched: 1634-04-4

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NTP	
06/2022	"Methyl t-butyl ether" "Methyl tert butyl ether" "MTBE" "Methyl tertiary butyl ether" "tert-Butyl methyl ether" "t-Butyl methyl ether" "2-Methoxy-2-methylpropane" Date limited 2010-present and not dated
Regulations.gov	
06/2022	“1634-04-4” "MTBE" "Methyl t-butyl ether" "Methyl tert butyl ether" "Methyl tertiary butyl ether" "tert-Butyl methyl ether" "t-Butyl methyl ether" "2-Methoxy-2-methylpropane"
NIH RePORTER	
08/2022	Fiscal Year: Active Projects; Logic:advanced; Limit search to: Project Title, Project Terms, Project Abstracts; Text Search: "2-Methoxy-2-methylpropane" or "Methyl t-butyl ether" or "Methyl tert butyl ether" or "Methyl tertiary butyl ether" or "MTBE" or "t-Butyl methyl ether" or "tert-Butyl methyl ether" or "(tert-Butyl)methylether" or "1,1-Dimethylethyl methyl ether" or "2-Methoxy-2-methyl propane" or "2-Methyl-2-methoxypropane" or "Ether, methyl tert-butyl" or "Ether, tert-butyl methyl" or "Methyl 1,1-dimethylethyl ether" or "Methyl-1,1-dimethylethyl ether" or "Propane, 2-methoxy-2-methyl" or "tert-Butoxymethane" or "tert-Butyl-methyl-aether"
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 255
- Number of records identified from other strategies: 18
- Total number of records to undergo literature screening: 273

B.1.2 Literature Screening

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

- 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.

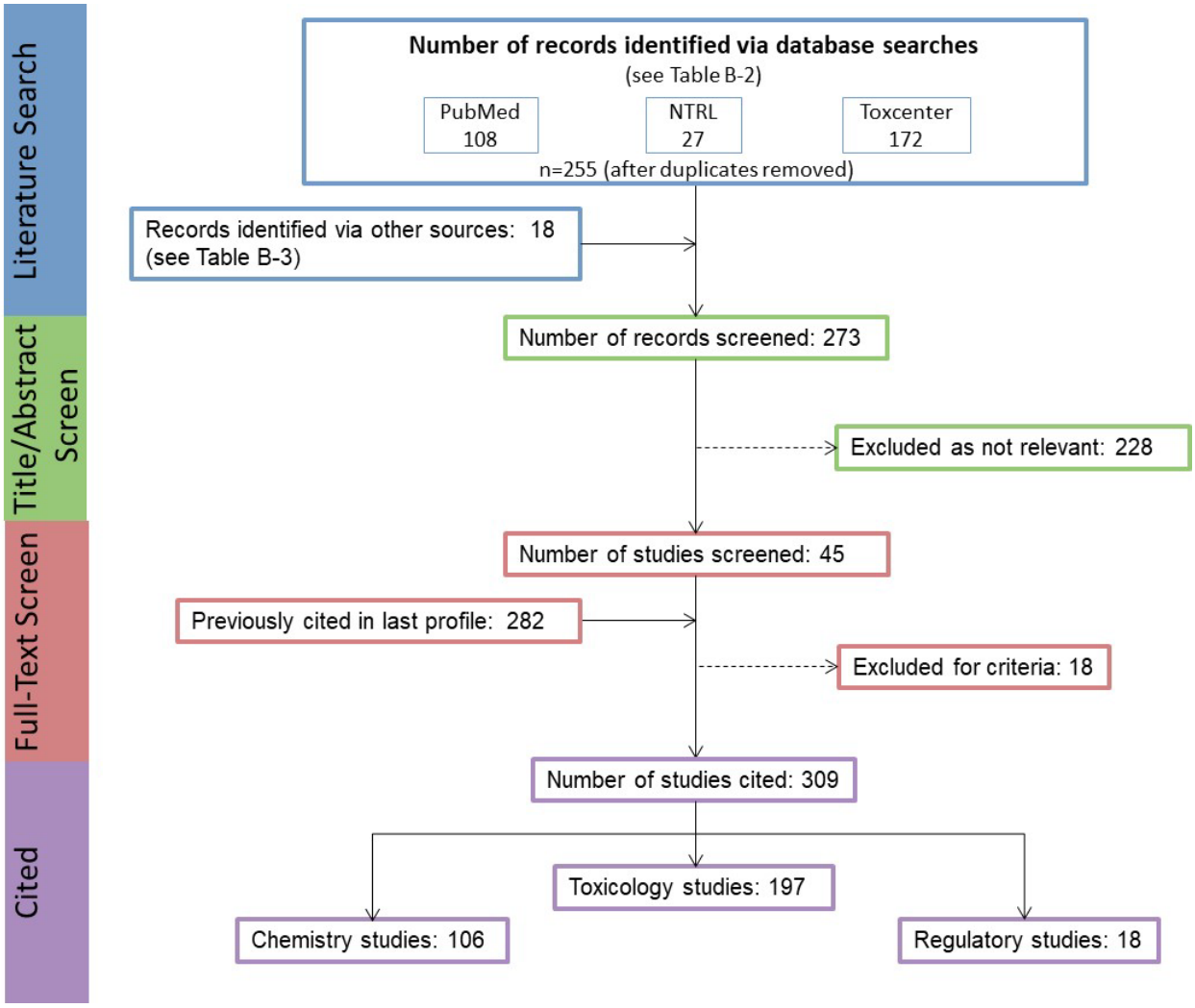
- Number of titles and abstracts screened: 273
- Number of studies considered relevant and moved to the next step: 45

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: 45
- Number of studies cited in the pre-public draft of the toxicological profile: 282
- Total number of studies cited in the profile: 309

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

Figure B-1. June 2022 Literature Search Results and Screen for MTBE



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

APPENDIX C

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

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

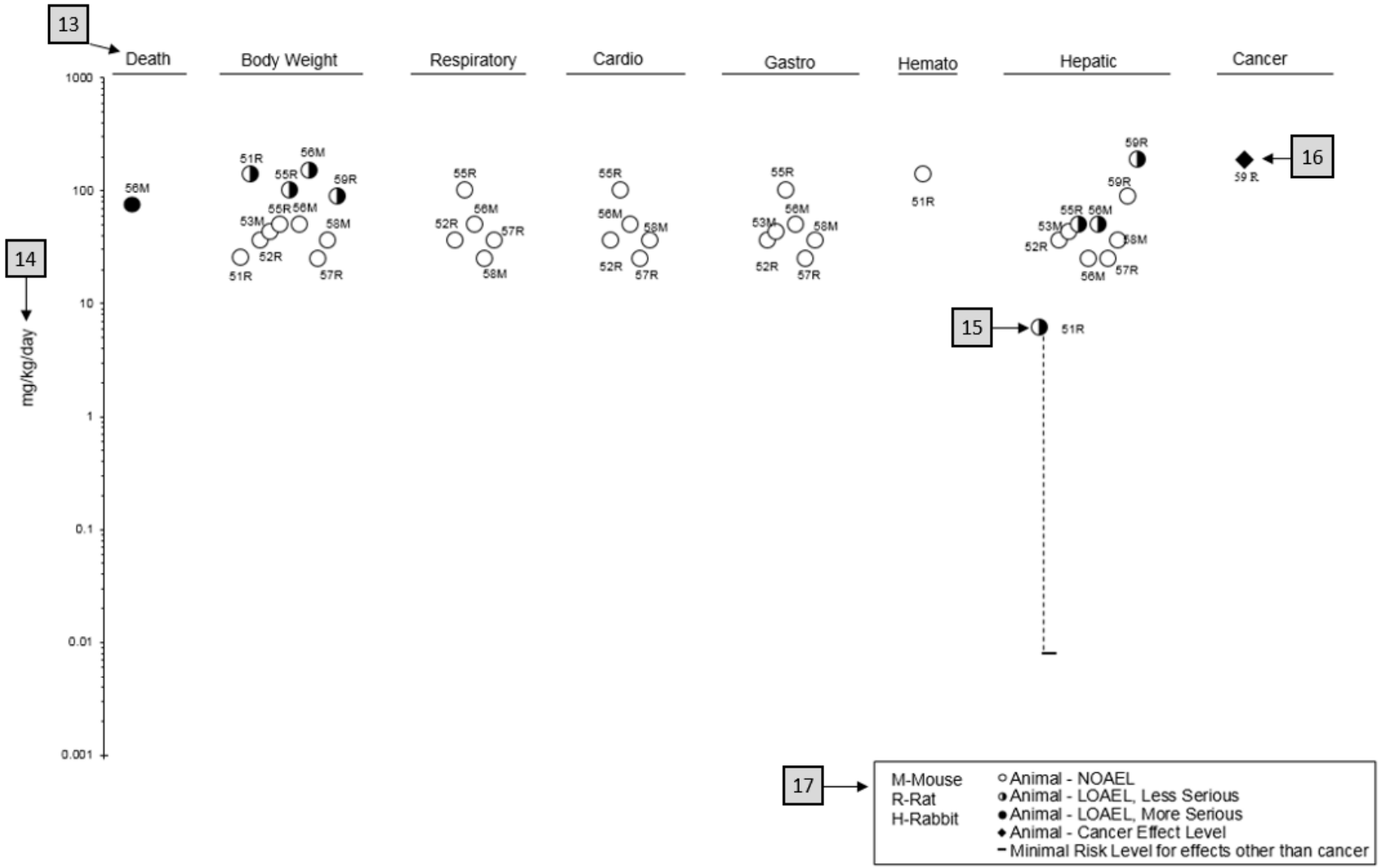
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX C

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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 F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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