APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: The acute-duration inhalation data were not considered adequate for derivation of an acute-duration inhalation MRL for NDMA.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. Available animal data consist of acute lethality studies in rats, mice, and dogs exposed once for 4 hours (all reported by Jacobson et al. 1955). These authors reported LC_{50} values of 57 ppm in mice and 78 ppm in rats; in dogs, the lowest concentration tested (16 ppm) was lethal to two of three exposed animals. These data are not adequate for derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: The intermediate-duration inhalation data were not considered adequate for derivation of an intermediate-duration inhalation MRL for NDMA.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: The chronic-duration inhalation data were not considered adequate for derivation of a chronic-duration inhalation MRL for NDMA.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. Three chronic inhalation cancer bioassays in rats (Druckrey et al. 1967; Klein et al. 1989, 1991; Moiseev and Benemanski 1975) and one in mice (Moiseev and Benemanski 1975) are available, but the only nonneoplastic endpoints evaluated (by Klein et al. [1989, 1991] only) were survival and body weight, so these data were not adequate for MRL derivation.

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.00001 ($1x10^{-5}$) mg/kg/day (0.01 µg/kg/day)
Critical Effect: Liver effect causing decreased total blood iron binding capacity
References: Moniuszko-Jakoniuk et al. 1999; Roszczenko et al. 1996a, 1996b
Point of Departure: $BMDL_{1SD}$ of 0.0014 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 18
Species: Rat

MRL Summary: An oral MRL of 0.00001 ($1x10^{-5}$) mg/kg/day (0.01 µg/kg/day) was derived based on the 95% lower confidence limit of a benchmark dose ($BMDL_{1SD}$) of 0.0014 mg/kg/day for a liver effect resulting in decreased total blood iron binding capacity in rats exposed to NDMA in drinking water for 10 days. An uncertainty factor (UF) of 100 (10 for animal to human and 10 for human variability) was applied to the BMDL to derive the acute-duration oral MRL.

Selection of the Critical Effect: No dose-response data are available for humans. Abundant data indicate that the liver is the most sensitive endpoint for toxic effects following oral exposure to NDMA after all durations. In every species tested (including rats, mice, hamsters, monkeys, dogs, cats, guinea pigs, and mink), oral exposure to NDMA induced severe damage to the liver (see, for example, Anderson et al. 1992a; Carter et al. 1969; Khanna and Puri 1966; Maduagwu and Bassir 1980; Nishie 1983; Ungar 1984). The liver effects, mediated by reactive metabolites of NDMA, are typically characterized by hemorrhagic necrosis, followed (if the animal survives) by fibrosis, cirrhosis, and portal hypertension. These effects have been seen after acute-, intermediate-, and chronic-duration exposures. Many of the studies of animals exposed orally to NDMA identified serious LOAELs for hepatic effects without NOAELs.

Table A-1 shows the studies reporting effects at the lowest oral doses in acute-duration studies. Effects observed at the lowest dose (0.0016–0.002 mg/kg/day) included altered iron parameters (Roszczenko et al. 1996b) and increased serum AST, ALT, ALP, and GGT (Roszczenko et al. 1996a). Thus, these studies indicate effects on the circulation of iron in the blood and concurrently on the liver. The liver plays an important role in maintaining iron levels (production of proteins that regulate iron; storage of excess iron; and mobilization of iron to systemic circulation as needed), and perturbations of iron circulation, with concomitant hematological abnormalities, frequently accompany liver disease (reviewed by Anderson and Shah 2013 and Gkamprela et al. 2017). NDMA treatment in dogs and rats has been used as a model for human liver fibrosis (and its sequelae of cirrhosis, portal hypertension, and hepatocellular carcinoma) for nearly 40 years. Hepatic effects have been observed in animals and humans after NDMA exposure. Therefore, it is possible that the decrements in iron binding parameters at the low doses used by Roszczenko et al. (1996b) are related to the early liver effects (increases in serum hepatic enzyme levels) observed at comparable doses in the study by Roszczenko et al. (1996a). Although data demonstrating a clear mechanistic linkage between the iron binding and hepatic changes are not available, it is clear that the decreases in iron circulation parameters are adverse: inadequate circulating iron in humans leads to symptoms of anemia including fatigue, weakness, and difficulty concentrating, as well as effects on growth and development in infants and children. Furthermore, the identification of a LOAEL at this dose (0.0016 mg/kg/day; Roszczenko et al. 1996b) is supported by the LOAEL for adverse hepatic effects at a comparable dose (0.002 mg/kg/day) (Roszczenko et al. 1996a).

Table A-1. Summary of Acute-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤5 mg/kg/day)

Species (Strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar, male)	10 days, 7 days/week (W)	0.0007	0.0016	Decreased serum total and latent iron binding capacity	Roszczenko et al. 1996b
Rat (Wistar, male)	10 days, 7 days/week (W)	ND	0.002	Increased serum AST, ALT, ALP, and GGT (no other endpoints evaluated)	Roszczenko et al. 1996a
Rat (Wistar, male)	10 days, 7 days/week (W)	0.003	ND	No changes in liver histopathology	Moniuszko-Jakoniuk et al. 1999
Rat (Crl:CD[SD], male)	14 days, 7 days/week (GW)	ND	1	Inflammatory cell infiltration	Hamada et al. 2015; Takashima et al. 2015
Rat (strain NS)	Once (G)	0.7	1.9	Vacuolation	Korsrud et al. 1973
Mouse (Swiss-Webster)	4 days (G)	ND	3.75	Hepatocellular hypertrophy	Nishie et al. 1972
Rat (strain NS)	7–14 days (F)	ND	3.75 (serious LOAEL)	Necrosis	Khanna and Puri 1966
Mouse (CD-1)	14 days, 7 days/week (G)	ND	4	Increased serum ALT and AST	Doolittle et al. 1987
Hamster (Golden)	1–14 days, 7 days/week (W)	ND	4	Increased serum ALT and AST	Ungar 1984
Rat (F344)	14 days, 7 days/week (G)	ND	4 (serious LOAEL)	Necrosis	Asakura et al. 1998
Other (death, cancer)					
Mouse (A/JNCR)	Once (G)	ND	5 (CEL)	Lung tumors at sacrifice 16 weeks after dosing	Anderson et al. 1992a
Cat (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	LD_{50}	Maduagwu and Bassir 1980
Monkey (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	LD_{50}	Maduagwu and Bassir 1980
Rat (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	LD_{50}	Maduagwu and Bassir 1980

Table A-1. Summary of Acute-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤5 mg/kg/day)

Species (Strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Guinea pig (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	Death	Maduagwu and Bassir 1980

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEL = cancer effect level; (F) = feed; (G) = gavage; GGT= gamma-glutamyl transferase; (GW) = gavage in water; LD_{50} = medial lethal dose; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; (W) = water

As Table A-1 shows, effect levels for the studies by Roszczenko et al. (1996 a, 1996b) and Moniuszko-Jakoniuk et al. (1999) were substantially lower than the remaining effect levels (≥1.9 mg/kg/day) (Korsrud et al. 1973); thus, these studies were considered for use in deriving the MRL.

Selection of the Principal Study: The lowest LOAEL was 0.0016 mg/kg/day for altered iron indices in the 10-day study by Roszczenko et al. (1996b); a NOAEL of 0.0007 mg/kg/day was identified for this study. A comparable LOAEL of 0.002 mg/kg/day was identified for increased serum AST, ALT, ALP, and GGT in a parallel single dose study by Roszczenko et al. (1996a). Moniuszko-Jakoniuk et al. (1999) was a multi-dose study for which a NOAEL of 0.003 mg/kg/day was identified for liver histology.

Both of the studies by Roszczenko et al. (1996a, 1996b) examined limited endpoints (serum enzyme and iron indices), and neither included organ weight or histopathology evaluation of the liver. The lack of histopathology data in these studies raises the question of whether the dose of 0.0016 mg/kg/day could be considered a serious LOAEL. However, this same group of investigators conducted a third study (Moniuszko-Jakoniuk et al. 1999) of comparable design in which histopathology was examined in the liver, spleen, and bone marrow. All three studies were conducted in male Wistar rats of approximately the same initial body weight (190–220 g), and in all studies, the rats were administered NDMA in drinking water at concentrations of 0.01–0.05 mg/L for 10 days. In the study by Moniuszko-Jakoniuk et al. (1999), a NOAEL of 0.003 mg/kg/day was identified, based on a lack of histopathology changes in the liver, bone marrow, and spleen after 10 days of exposure. The results of this study provide support for the conclusion that the LOAEL identified for Roszczenko et al. (1996b) is not a serious LOAEL.

Considering the data for the three studies together, Roszczenko et al. (1996b) was chosen as the principal study for the derivation of the acute-duration oral MRL. The study identified the lowest LOAEL, with a corresponding NOAEL. Support for the LOAEL and NOAEL determination for Roszczenko et al. (1996b) is provided by the other studies conducted by the same group of investigators (Moniuszko-Jakoniuk et al. 1999; Roszczenko et al. 1996a).

Summary of the Principal and Supporting Studies:

Roszczenko A, Jabloński J, Moniuszko-Jakoniuk J, et al. 1996b. The influence of low doses of N-nitrosodimethylamine on the chosen parameters of iron balance in rat. Polish J Environ Studies 5(5):37-40.

Roszczenko et al. (1996b) administered NDMA in drinking water to groups of seven male Wistar rats for 10 days at concentrations of 10, 20, and 50 µg/L (0.01, 0.02, or 0.05 mg/L) in a study evaluating iron indices. Exposure concentrations were estimated by the study authors to result in doses of 0.0007, 0.0016, or 0.0035 mg/kg/day, respectively. The animals were sacrificed at the end of the 10-day

exposure. Blood was collected for analysis of hematocrit and hemoglobin concentration. In addition, iron, latent iron binding capacity (portion of the plasma transferrin molecule that is not bound to iron), total iron binding capacity (maximum concentration of iron that can be bound to transferrin), and the percentage transferrin saturation were measured in serum. Iron concentrations in the liver and spleen were analyzed. At the lowest dose, no statistically significant effect on any measured parameter was observed. Significant increases in hemoglobin concentration were seen at doses ≥0.0016 mg/kg/day (8 and 15% at 0.0016 and 0.0035 mg/kg/day, respectively). Hematocrit was not significantly increased at any dose. Serum iron concentration was significantly decreased by 36% at the high dose. Significant decreases in total iron binding capacity[1] were observed at doses ≥0.0016 mg/kg/day (18 and 30% at 0.0016 and 0.0035 mg/kg/day, respectively). Latent (unsaturated) iron binding capacity was significantly decreased by 42% at 0.0016 mg/kg/day, but there was no significant difference at 0.0035 mg/kg/day. There was no significant change in the percent transferrin saturation, despite values that decreased with dose (7% decrease at 0.0016 mg/kg/day and 14% decrease at 0.0035 mg/kg/day). After 10 days of exposure, there were no significant differences in the iron content of the liver or spleen. A NOAEL of 0.0007 mg/kg/day and a LOAEL of 0.0016 mg/kg/day were identified for this study based on the decreases in total and latent (unsaturated) iron binding capacity.

Roszczenko A, Jablonski J, Moniuszko-Jakoniuk J. 1996a. [Effect of n-nitrosodimethylamine (NDMA) on activity of selected enzymes in blood serum of the rat (translation and original document)]. Med Pr 47(1):49-53 (Polish).

Roszczenko et al. (1996a) administered NDMA in drinking water at a concentration of 20 µg/L (0.02 mg/L) to groups of seven male Wistar rats for 10 days, yielding a dose estimated by the authors to be 0.002 mg/kg/day. The only endpoints measured were serum enzymes (AST, ALT, ALP, and GGT) assessed at the end of exposure. Statistically significant increases of ≥2-fold (compared with controls) in all four enzymes were observed: serum AST, ALT, and ALP were doubled, and a 6-fold increase in GGT was measured.

Moniuszko-Jakoniuk J, Roszczenko A, Dzieciol J. 1999. Influence of low concentrations of N-nitrosodimethylamine on the iron level and histopathological picture of rats liver, spleen, and bone marrow. Acta Poloniae Toxicologica 7(2):179-186.

In the study by Moniuszko-Jakoniuk et al. (1999) groups of eight male Wistar rats were exposed to NDMA concentrations of 30 or 45 µg/L (0.03 or 0.045 mg/L) in drinking water for 10 days. The study authors did not estimate doses; based on the ratio of dose to concentration (0.0035 mg/kg/day for 0.05 mg/L) reported by Roszczenko et al. (1996b), the concentrations in the Moniuszko-Jakoniuk et al. (1999) study (0.03 and 0.045 mg/L) were estimated to result in doses of approximately 0.002 and 0.003 mg/kg/day, respectively. The control group (n=24) received drinking water without added NDMA. When sacrificed at the end of the exposure period, iron content of the liver and spleen was measured, and histopathology was evaluated in the liver, bone marrow, and spleen. There was no effect on the iron content of the liver or spleen, and there were no histopathological changes observed in the liver, bone marrow, or spleen in either dose group after 10 days of exposure.

Selection of the Point of Departure for the MRL: BMD modeling was performed for each of the iron indices evaluated by Roszczenko et al. (1996b), as shown in Table A-2.

[1]Total iron binding capacity refers to the sum of serum iron and serum unsaturated (latent) iron-binding capacity. Percentage transferrin saturation is calculated by dividing the serum iron concentration by the total iron binding capacity and multiplying by 100.

Table A-2. Changes in Iron Indices in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days

	Exposure dose (mg/kg/day)			
	0	0.0007	0.0016	0.0035
Number of animals	7	7	7	7
Total iron binding capacity (µmol/L)	**138.94±22.74**	**120.13±10.04 (-14%)**	**114.12±13.97[b] (-18%)**	**96.94±4.93[c] (-30%)**
Hematocrit (%)	26.27±1.65[a]	26.1±1.21 (-1%)	27.31±1.58 (4%)	27.3±2.34 (4%)
Hemoglobin (g/L)	11.91±0.73	13.01±1.02 (9%)	12.88±0.74[b] (8%)	13.69±1.27[b] (15%)
Latent iron binding capacity (µmol/L)	100.62±17.56	101.26±10.02 (1%)	57.93±7.28[b] (-42%)	87.14±6.86 (-13%)
Percent transferrin saturation (%)	47.34±6.05	51.16±7.62 (8%)	43.83±6.94 (-7%)	40.52±5.90 (-14%)
Serum iron (µmol/L)	65.88±10.05	66.78±8.09 (1%)	59.21±6.59 (-10%)	41.95±2.41[b] (-36%)

[a]Mean±standard deviation.
[b]Statistically significantly ($p<0.05$) different from controls.
[c]Statistically significantly ($p<0.001$) different from controls.

Source: Roszczenko et al. 1996b

The data for iron indices shown in Table A-2 were fit to continuous models in EPA's Benchmark Dose Software (BMDS; version 3.1.2) using a benchmark response (BMR) of 1 standard deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the point of departure (POD) when the difference between the BMDLs estimated from these models was ≥3 fold; otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) was chosen. All continuous models were applied to the data and considered for the derivation of a POD except for the Hill model; the continuous Hill model has five parameters and requires a dataset with a minimum of six datapoints (including control).

For latent iron binding capacity (µmol/L), none of the models provided an adequate fit to the variance data with or without the variance model applied.

For total iron binding capacity, constant variance models did not provide adequate fit to the variance data. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means for total iron binding capacity. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Polynomial models and Power model converged on the form of the linear model. The Linear model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.0021 and 0.0014 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-3.

Table A-3. Model Predictions (Non-Constant Variance) for Total Iron Binding Capacity (µmol/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	Scaled residuals[c]		
				AIC	Dose near BMD	Dose near control
Exponential (model 2)[d]	0.0014	0.0010	0.14	223.62	-0.23	0.69
Exponential (model 3)[d]	0.0014	0.0010	0.14	223.62	-0.23	0.69
Exponential (model 4)[d]	0.0010	0.0006	0.10	224.73	-0.90	0.18
Exponential (model 5)[d]	0.0010	0.0006	0.10	224.74	-0.88	0.24
Polynomial (3-degree)[e]	0.0021	0.0014	0.21	223.28	-0.31	1.03
Polynomial (2-degree)[e]	0.0021	0.0014	0.21	223.28	-0.31	1.03
Power[d]	0.0021	0.0014	0.21	223.28	-0.31	1.03
Linear[e,f]	**0.0021**	**0.0014**	**0.21**	**223.28**	**-0.31**	**1.03**

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

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

For hematocrit, constant variance models provided adequate fit to the variance data; however, the upper bound on the benchmark dose (BMDU) was infinite (unbounded) for all models. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means. The BMDUs for the Exponential 2, Exponential 3, Exponential 4, and Power models could not be determined (infinity); therefore, these models were not considered. The BMD computation failed for the Exponential 5 model; therefore, the BMD and BMDL could not be estimated. Visual inspection of the remaining dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the remaining models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The BMD of the selected model was slightly higher (0.0036 mg/kg/day) than the maximum dose tested (0.0035 mg/kg/day). The Linear model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.0036 and 0.0015 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-4.

Table A-4. Model Predictions (Non-Constant Variance) for Hematocrit (%) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]			0.50	112.44	-0.46	0.20
Exponential (model 3)[d]			0.50	112.44	-0.46	0.20
Exponential (model 4)[d]			0.32	114.38	-0.38	0.31
Exponential (model 5)[d]			0.26	115.35	-9999	0.23
Polynomial (3-degree)[e]	0.0035	0.0015	0.22	115.62	-0.33	0.09
Polynomial (2-degree)[e]	0.0036	0.0015	0.22	115.62	-0.29	0.05
Power[d]			0.23	115.56	-0.33	0.01
Linear[e,f]	**0.0036**	**0.0015**	**0.46**	**113.63**	**-0.28**	**0.12**

[a]BMD and BMDL values for models that do not provide adequate fit, for models that failed to calculate BMDLs, and for models with infinite BMDUs are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data; however, the BMDU was infinity for all models. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means. The BMD computation failed for the Exponential 5 model; therefore, the BMD and BMDL could not be estimated. The BMDUs for the Exponential 2, Exponential 3, Exponential 4, and Power models could not be determined (infinity); therefore, these models were not selected. BMDLs for the remaining models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear).

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

For hemoglobin, all applicable constant variance models provided adequate fit to the variance data. The BMDU for the Exponential 4 and 5 models could not be determined (infinity) so these models were not selected. Visual inspection of the remaining dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the remaining models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Polynomial 2-degree, polynomial 3-degree and power models converged on the form of the linear model. The Linear model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 0.0022 and 0.0014 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-5.

Table A-5. Model Predictions (Constant Variance) for Hemoglobin Concentration (g/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	0.0023	0.0015	0.24	82.08	-0.12	-0.99
Exponential (model 3)[d]	0.0023	0.0015	0.24	82.08	-0.12	-0.99
Exponential (model 4)[d]			0.18	83.04	0.87	-0.26
Exponential (model 5)[d]			0.18	83.04	0.87	-0.26
Polynomial (3-degree)[e]	0.0022	0.0014	0.25	81.99	-0.16	-0.95
Polynomial (2-degree)[e]	0.0022	0.0014	0.25	81.99	-0.16	-0.95
Power[d]	0.0022	0.0014	0.25	81.99	-0.16	-0.95
Linear[e,f]	**0.0022**	**0.0014**	**0.25**	**81.99**	**-0.16**	**-0.95**

[a]BMD and BMDL values for models that do not provide adequate fit and for models with infinite BMDUs are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. The 95% upper bounds for the Exponential 4 and 5 models were infinity. BMDLs for the remaining models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Polynomial 2-degree, polynomial 3-degree and power models converged on the form of the linear model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear).

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

For percent transferrin saturation, all applicable constant variance models provided adequate fit to the variance data. Only the Exponential 2 and Linear models provided adequate fit to the means. Visual inspection of the dose-response curves for these models suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Linear model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 0.0026 and 0.0016 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-6.

Table A-6. Model Predictions (Constant Variance) for Percent Transferrin Saturation in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	0.0025	0.0014	0.19	190.72	-0.56	-0.85
Exponential (model 3)[d]			0.09	192.32	0.16	-0.62
Exponential (model 4)[d]			0.07	192.72	-0.56	-0.85
Exponential (model 5)[d]			NA	192.67	0.00	-0.80
Polynomial (3-degree)[e]			0.08	192.52	0.13	-0.61
Polynomial (2-degree)[e]			0.08	192.52	0.13	-0.61
Power[d]			0.08	192.37	0.15	-0.61
Linear[e,f]	**0.0026**	**0.0016**	**0.19**	**190.66**	**-0.01**	**-0.82**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. Constant variance models provided adequate fit to the variance data. Only the Exponential 2 and Linear models provided an adequate fit to the means. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear).

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

For serum iron concentration (μmol/L), constant variance models did not provide adequate fit to the variance data. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means, except for the Exponential 4 and 3-degree polynomial models. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 3). The Exponential 3 model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 0.0017 and 0.0011 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-7.

Table A-7. Model Predictions (Non-Constant Variance) for Serum Iron Concentration (µmol/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	0.0011	0.0008	0.18	186.63	0.54	-1.58
Exponential (model 3)[d,e]	**0.0017**	**0.0011**	**0.85**	**184.13**	**-0.16**	**-0.44**
Exponential (model 4)[d]			0.09	188.63	0.53	-1.60
Exponential (model 5)[d]	0.0017	0.0011	0.72	185.92	-0.01	-0.24
Polynomial (3-degree)[f]			NA	188.36	-0.25	-0.50
Polynomial (2-degree)[f]	0.0018	0.0011	0.54	186.17	-0.24	-0.40
Power[d]	0.0018	0.0011	0.61	186.04	-0.18	-0.39
Linear[f]	0.0013	0.0009	0.31	186.15	0.69	-1.25

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

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

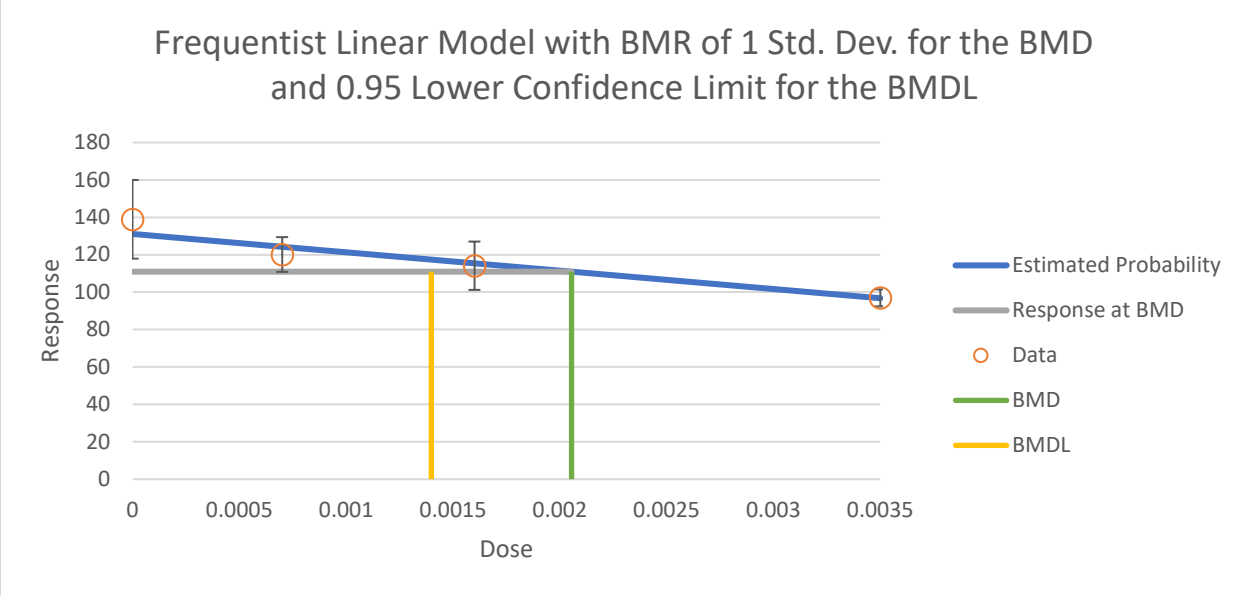
Table A-8 summarizes the potential candidate PODs for the acute-duration oral MRL for NDMA. The BMDL values were similar among the candidate endpoints (0.0011–0.0016 mg/kg/day). The $BMDL_{1SD}$ value of 0.0014 mg/kg/day for decreased total iron binding capacity was selected as the critical effect following acute-duration oral exposure to NDMA, as it is the most sensitive effect showing a monotonic change (Table A-2). Modeling results for the other candidate endpoints provide strong support for the selected POD. The Linear model fit to the total iron binding capacity data is presented in Figure A-1.

Table A-8. Candidate Points of Departure for the Acute-Duration Oral MRL

Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ mg/kg/day)
Total iron binding capacity			**0.0021**	**0.0014**
Percent hematocrit			0.0036	0.0015
Hemoglobin			0.0022	0.0014
Latent iron binding capacity	0.0007	0.0016	No model fit	
Percent transferrin saturation			0.0026	0.0016
Serum iron			0.0017	0.0011

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

Figure A-1. Fit of Linear Model (Non-constant Variance) to Total Iron Binding Capacity (µmol/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)



Uncertainty Factor: The $BMDL_{1SD}$ was divided by a total uncertainty factor (UF) of 100:

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

MRL = $BMDL_{1SD}$ ÷ (UF)
0.0014 mg/kg/day ÷ (10 x 10) ≈ 0.00001 mg/kg/day ($1x10^{-5}$ mg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this: As discussed above, the studies by Roszczenko et al. (1996a) and Moniuszko-Jakoniuk et al. (1999) provide support for the effect level determinations by Roszczenko et al. (1996b). Examples of other studies that demonstrate liver

toxicity, often severe, after oral exposure to higher doses of NDMA in rats, mice, hamsters, monkeys, dogs, cats, guinea pigs, and mink include: Anderson et al. (1992a); Carter et al. (1969); Hamada et al. 2015; Khanna and Puri (1966); Maduagwu and Bassir (1980); Nishie (1983); Takashima et al. 2015; and Ungar (1984).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-9 summarizes results from candidate intermediate-duration oral studies in laboratory animals.

Table A-9. Summary of Intermediate-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤1.5 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.0016 (severity unknown)	Altered iron indices after 30 days	Roszczenko et al. 1996b
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.002 (severity unknown)	Increased serum AST, ALT, ALP, and GGT after 30 days	Roszczenko et al. 1996a
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.002 (serious LOAEL)	Degeneration, argyrophilic and collagenic fibers, and inflammatory infiltrations near portal biliary tract after 30 days; steatosis and parenchymatosis after 90 days	Moniuszko-Jakoniuk et al. 1999
Mink	122 days, 7 days/week (F)	0.08	0.13	Venopathy	Koppang and Rimeslatten 1976
Rabbit (New Zealand)	12 weeks, 7 days/week (GW)	ND	0.5 (serious LOAEL)	Necrosis; vascular degeneration; central vein congestion	Sheweita et al. 2017
Dog (Beagles)	24 weeks, 2 days/week at 2 mg/kg (C)	ND	0.6 (serious LOAEL)	Severe hepatic effects including histopathology; elevated serum enzyme levels; and ascites	Boothe et al. 1992
Dog (Mongrel)	4 weeks, 2 days/week at 2.51 mg/kg (C)	ND	0.72 (serious LOAEL)	Necrosis; fibrosis; increased serum AST and ALT	Hashimoto et al. 1989

Table A-9. Summary of Intermediate-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤1.5 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Dog (Mongrel)	4 weeks, 2 days/week at 2.51 mg/kg (C)	ND	0.72 (serious LOAEL)	Necrosis; fibrosis; increased serum AST, ALT, ALP, and bilirubin; ascites	Madden et al. 1970
Rat (strain NS)	30 days, 1 time/day (G)	ND	1	Vacuolation and congestion	Maduagwu and Bassir 1980
Monkeys and guinea pigs (species NS)	30 days, 1 time/day (G)	ND	1 (serious LOAEL)	Necrosis	Maduagwu and Bassir 1980
Rat (Crl:CD[SD], male)	28 days, 7 days/week (G)	1	2	Inflammatory cell infiltration	Hamada et al. 2015; Takashima et al. 2015
Rat (Sprague-Dawley)	15 days, 1 time/day (GW)	0.5	2 (serious LOAEL)	Hepatocyte degeneration and fibrosis	Rothfuss et al. 2010
Hematology effects					
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.002 (serious LOAEL)	Bone marrow histopathology changes after 90 days: focal necrosis; edema, degeneration; decrease in megakaryocytes and migration to vascular sinus; myelosclerosis	Moniuszko-Jakoniuk et al. 1999
Developmental effects					
Mouse (CD-1)	75 days prior to mating and through pregnancy until weaning (W)	ND	0.026 (serious LOAEL)	Perinatal death (stillborn and within 2 days of birth)	Anderson et al. 1978
Reproductive effects					
Rabbit (New Zealand)	12 weeks, 7 days/week (GW)	ND	0.5 (serious LOAEL)	Histopathology changes in testes	Sheweita et al. 2017
Immune system effects					
Mouse (C57BL/6)	13 weeks, 7 days/week (W)	0.26	1.3	Immunosuppression	Desjardins et al. 1992
Other (death, cancer)					
Mouse (A/JNCr)	16–48 weeks, 7 days/week (W)	ND	0.25 (CEL)	Lung tumors	Anderson et al. 1992a
Mink	23–34 days, 7 days/week (F)	ND	0.32 (serious LOAEL)	Death	Carter et al. 1969
Rat (MRC)	30 weeks, 5 days/week (W)	ND	0.4 (CEL)	Liver tumors	Keefer et al. 1973

Table A-9. Summary of Intermediate-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤1.5 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Mouse (RF)	32 weeks, 7 days/week (W)	ND	0.4 (CEL)	Lung tumors	Clapp and Toya 1970
Rat (F344)	30 weeks, (5 days/week) (W)	ND	0.75 (serious LOAEL, CEL)	Decreased survival and liver tumors	Lijinsky and Reuber 1984
Cats (strain NS)	30 days, 1 time/day (G)	ND	1 (serious LOAEL)	Death	Maduagwu and Bassir 1980
Mouse (Swiss)	38 weeks, 7 days/week (W)	ND	1 (serious LOAEL, CEL)	Decreased survival and liver, lung, and kidney tumors	Terracini et al. 1966
Hamster (Syrian Golden)	Up to 7 months, 7 days/week (W)	ND	1.1 (serious LOAEL)	Decreased survival and liver tumors	Bosan et al. 1987
Mouse (C3Hf)	13 weeks, 7 days/week (W)	ND	1.2 (serious LOAEL, CEL)	Decreased survival; liver and lung tumors	Den Engelse et al. 1974
Rat (Wistar)	30 weeks, 7 days/week (W)	ND	1.5 (serious LOAEL, CEL)	Decreased survival and liver tumors	Takahashi et al. 2000

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; (C) = capsule; CEL = cancer effect level; (F) = feed; (G) = gavage; GGT= gamma-glutamyl transferase; (GW) = gavage in water; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; (W) = water

Roszczenko et al. (1996b) identified effects at the lowest dose (0.0016 mg/kg/day) tested in any intermediate-duration study. In this study, groups of seven male Wistar rats were exposed to NDMA in drinking water for 30 or 90 days in a study evaluating iron indices. Exposure concentrations of 10 or 20 μg/L (0.01 and 0.02 mg/L) were estimated by the study authors to yield doses of 0.0007 and 0.0016 mg/kg/day, respectively. At sacrifice at the end of exposure, blood was collected for analysis of hematocrit and hemoglobin concentration. Iron, total and latent iron binding capacity, and percentage transferrin saturation in serum were measured. Iron concentration in the liver and spleen were analyzed. At 0.0007 mg/kg/day, no statistically significant effect on any measured parameter was observed. At 0.0016 mg/kg/day, there was a significant 28% increase in hemoglobin concentration, but no effect on hematocrit. Serum iron concentration was not significantly affected by treatment. Latent iron binding capacity was significantly decreased by 51%, and there was a significant, 22% increase in percent transferrin saturation. Total iron binding capacity was lower than controls at 0.0016 mg/kg/day, but the difference (16%) was not statistically significant. Iron content of the liver did not differ significantly from controls in treated animals, but there was a significant and marked 87% increase in iron content of the spleen.

In the related study by Roszczenko et al. (1996a), NDMA was administered in drinking water at a concentration of 20 μg/L (0.02 mg/L) to groups of seven male Wistar rats for 30 or 90 days, yielding a dose of approximately 0.002 mg/kg/day. The only endpoints measured in this study were serum enzymes (AST, ALT, ALP, and GGT). Statistically significant increases in enzymes were observed at all time

points. After 30 days, serum AST was increased by 10% compared to controls; ALT and ALP concentrations were doubled; and a 4-fold increase in GGT was measured. Results at 90 days were similar to those after 30 days.

Neither of the studies by Roszczenko et al. (1996a, 1996b) evaluated organ weights or liver or other organ histopathology; thus, the severity of the effect levels in the intermediate-duration experiments conducted by these authors is uncertain. In a third study by these investigators (Moniuszko-Jakoniuk et al. 1999), groups of eight male Wistar rats were exposed to NDMA in drinking water (0.03 and 0.045 mg/L) at estimated doses of 0.002 and 0.003 mg/kg/day for 30 or 90 days; iron content of the liver and spleen and histopathology of the liver, bone marrow, and spleen were assessed. After 30 days, liver histopathology changes including degeneration, argyrophilic and collagenic fibers, and inflammatory infiltrations near the portal biliary tract were observed at both doses, and at 0.003 mg/kg/day, there were bone marrow changes including focal necrosis, edema, and degeneration. After 90 days, the liver effects at both doses were more severe, including steatosis and parenchymatosis, and there were histopathology changes at both doses in the spleen and bone marrow. The authors did not report incidences or severity scores for any of the histopathology changes.

The study by Moniuszko-Jakoniuk et al. (1999) demonstrated exposure duration- and dose-related increases in the severity of liver histopathology changes in rats exposed to doses as low as 0.002 mg/kg/day (0.03 mg/L in water) NDMA. Because there are no histopathology data for lower doses/concentrations (0.01 and 0.02 mg/L or 0.0007 and 0.0016–0.002 mg/kg/day) in the 30- and 90-day experiments by Roszczenko et al. (1996a, 1996b), a clear NOAEL cannot be determined, and the LOAELs are of uncertain severity. Therefore, the data for the intermediate duration are insufficient for derivation of a MRL.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-10 summarizes results from candidate chronic-duration oral studies in laboratory animals.

Table A-10. Summary of Chronic-Duration Oral Studies of N-Nitrosodimethylamine in Animals

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Other (death, cancer)					
Rat (Wistar)	3.5 years, 7 days/week (W)	ND	0.022 (serious LOAEL, CEL)	Decreased survival due to liver tumors	Peto et al. 1984, 1991a, 1991b
Mink (NS)	1–2 years, 7 days/week (F)	ND	0.1 (serious LOAEL, CEL)	Decreased survival, liver tumors	Koppang and Rimeslatten 1976
Rat (Wistar)	96 weeks, 7 days/week (F)	ND	0.13 (CEL)	Liver tumors	Arai et al. 1979; Ito et al. 1982
Mouse (A/JNCr)	72 weeks, 7 days/week (W)	ND	0.24 (CEL)	Lung tumors	Anderson et al. 1992a
Rat (Wistar)	54 weeks, 7 days/week (F)	ND	0.5 (CEL)	Testicular tumors	Terao et al. 1978
Mouse (RF)	Lifetime (mean 406 days), 7 days/week (W)	ND	0.43 (serious LOAEL, CEL)	Decreased survival and liver and lung tumors	Clapp and Toya 1970
Hepatic effects					
Dog (Beagle)	56 weeks, 2 days/week at 2 mg/kg (C)	ND	0.6[a] (serious LOAEL)	Fibrosis, cirrhosis, necrosis	Butler-Howe et al. 1993

[a]Adjusted for discontinuous exposure (2 mg/kg x 2/7 days/week).

(C) = capsule; CEL = cancer effect level; (F) = feed; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; (W) = water

Peto et al. (1984, 1991a, 1991b) conducted a large cancer dose-response study of NDMA in rats. Groups of 60 rats/sex were exposed to 1 of 15 concentrations of NDMA in drinking water (between 0.033 and 16.896 ppm) for 3.5 years. The authors noted that the longer duration was intended to enable effects to be

detected at very low doses. These water concentrations yielded estimated doses of 0.001–0.697 mg/kg/day (Peto et al. 1984, 1991b). Controls received untreated water. Groups of six rats/sex/dose were sacrificed after 12 and 18 months, and the remaining animals were observed until natural death, moribund appearance, or appearance of palpable liver abnormalities. Macroscopic necropsies were performed on all animals. Histopathology examinations were performed on grossly observed lesions; apart from these, only the liver and esophagus were routinely examined microscopically. Results for the interim sacrifices were not reported separately. In both male and female rats, NDMA doses ≥0.022 mg/kg/day were associated with decreased survival due to liver tumors. Significant dose-related trends were observed for several liver lesions, including hyperplastic nodules, cytomegaly, cysts, hepatocyte shrinkage (males only), and abnormality of glycogen-containing cells (females only). The incidences of these lesions were not significantly different from controls at doses <0.022 mg/kg/day in pairwise statistical tests (Fisher's exact test). However, these lesions may reflect preneoplastic changes, and the incidences may have been influenced by progression to tumors (liver neoplasms were observed at all doses); thus, neither NOAEL nor LOAEL values can be identified from these data.

As Table A-5 shows, the remaining chronic studies used single exposure levels much higher than the serious LOAEL of 0.022 mg/kg/day from Peto et al. (1984, 1991a, 1991b) and identified serious LOAELs for decreased survival and/or CELs. Therefore, the available data do not provide an adequate basis for derivation of a chronic-duration oral MRL.

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NDMA

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 NDMA.

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

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for NDMA. 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 NDMA 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	("Dimethylnitrosamine"[mh] OR 62-75-9[rn] OR "dimethyl-nitrosamine"[tw] OR "Dimethylamine, N-nitroso-"[tw] OR "Dimethylnitrosamine"[tw] OR "Dimethylnitrosoamine"[tw] OR "Methanamine, N-methyl-N-nitroso-"[tw] OR "N,N-Dimethylnitrosamine"[tw] OR "N,N-dimethylnitrous amide"[tw] OR "N-Dimethyl-nitrosamine"[tw] OR "N-Methyl-N-nitrosomethanamine"[tw] OR "N-Nitroaodimethylamine"[tw] OR "N-Nitroso-N,N-dimethylamine"[tw] OR "n-Nitrosodimethylamine"[tw] OR "Nitrosamine, dimethyl-"[tw] OR "Nitrosodimethylamine"[tw] OR "P082"[tw] OR (("DMNA"[tw] OR "NDMA"[tw]) AND ("Nitrosamines"[mh] OR carcinogen*[tw] OR mutagen*[tw] OR disinfect*[tw] OR drinking[tw])) OR (("DMNA"[tw] OR "NDMA"[tw]) NOT medline[sb])) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp])
NTRL	
06/2022	Date Published 2018 to 2022 "dimethyl-nitrosamine" OR "Dimethylamine, N-nitroso-" OR "Dimethylnitrosamine" OR "Dimethylnitrosoamine" OR "Methanamine, N-methyl-N-nitroso-" OR "N,N-Dimethylnitrosamine" OR "N,N-dimethylnitrous amide" OR "N-Dimethyl-nitrosamine" OR "N-Methyl-N-nitrosomethanamine" OR "N-Nitroaodimethylamine" OR "N-Nitroso-N,N-dimethylamine" OR "n-Nitrosodimethylamine" OR "Nitrosamine, dimethyl-" OR "Nitrosodimethylamine" OR "DMNA" OR "NDMA"
Toxcenter	
6/2022	FILE 'TOXCENTER' ENTERED AT 15:12:07 ON 09 JUN 2022 CHARGED TO COST=EH038.12.05.LB.04 L1 13422 SEA FILE=TOXCENTER 62-75-9 L2 13208 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 13184 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 486 SEA FILE=TOXCENTER L3 AND ED>=20190701 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?)

Table B-2. Database Query Strings

Database search date	Query string
	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?)
	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

Table B-2. Database Query Strings

Database search date	Query string
	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 369 SEA FILE=TOXCENTER L4 AND L37 DIS COST FULL L39 96 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L41 273 SEA FILE=TOXCENTER L38 NOT MEDLINE/FS L42 308 DUP REM L39 L41 (61 DUPLICATES REMOVED) L*** DEL 96 S L38 AND MEDLINE/FS L*** DEL 96 S L38 AND MEDLINE/FS L43 96 SEA FILE=TOXCENTER L42 L*** DEL 273 S L38 NOT MEDLINE/FS L*** DEL 273 S L38 NOT MEDLINE/FS L44 212 SEA FILE=TOXCENTER L42 L45 212 SEA FILE=TOXCENTER (L43 OR L44) NOT MEDLINE/FS D SCAN L45

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via Chemview	
06/2022	Compounds searched: 62-75-9
NTP	
06/2022	Years: 2020-2022, 2010-2019 "62-75-9" "Dimethylnitrosamine" "Dimethylnitrosoamine" "Nitrosodimethylamine" Obtained duplicates of above: "dimethyl-nitrosamine" "N-Methyl-N-nitrosomethanamine" "DMNA" "NDMA" "Dimethylamine, N-nitroso-" "Methanamine, N-methyl-N-nitroso" "N,N-dimethylnitrous amide" "N-Dimethyl-nitrosamine" "N-Nitroaodimethylamine" "N-Nitroso-N,N-dimethylamine" "Nitrosamine, dimethyl-" Redundant, search results not considered: "N,N-Dimethylnitrosamine" "n-Nitrosodimethylamine"
Regulations.gov	
06/2022	Limited to: postedDateFrom=2018-01-01&postedDateTo=2022-06-10; dockets and EPA notices. "62-75-9" "Dimethylnitrosamine" "Dimethylnitrosoamine"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Nitrosodimethylamine" "dimethyl-nitrosamine" "N-Methyl-N-nitrosomethanamine" "DMNA" "NDMA
NIH RePORTER	
08/2022	Text Search: "dimethyl-nitrosamine" OR "Dimethylamine, N-nitroso-" OR "Dimethylnitrosamine" OR "Dimethylnitrosoamine" OR "Methanamine, N-methyl-N-nitroso-" OR "N,N-Dimethylnitrosamine" OR "N,N-dimethylnitrous amide" OR "N-Dimethyl-nitrosamine" OR "N-Methyl-N-nitrosomethanamine" OR "N-Nitroaodimethylamine" OR "N-Nitroso-N,N-dimethylamine" OR "n-Nitrosodimethylamine" OR "Nitrosamine, dimethyl-" OR "Nitrosodimethylamine" Fiscal Year: Active Projects (and) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed and TOXCENTER (after duplicate removal): 482
- Number of records identified from other strategies: 78
- Total number of records to undergo literature screening: 560

B.1.2 Literature Screening

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

- 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.

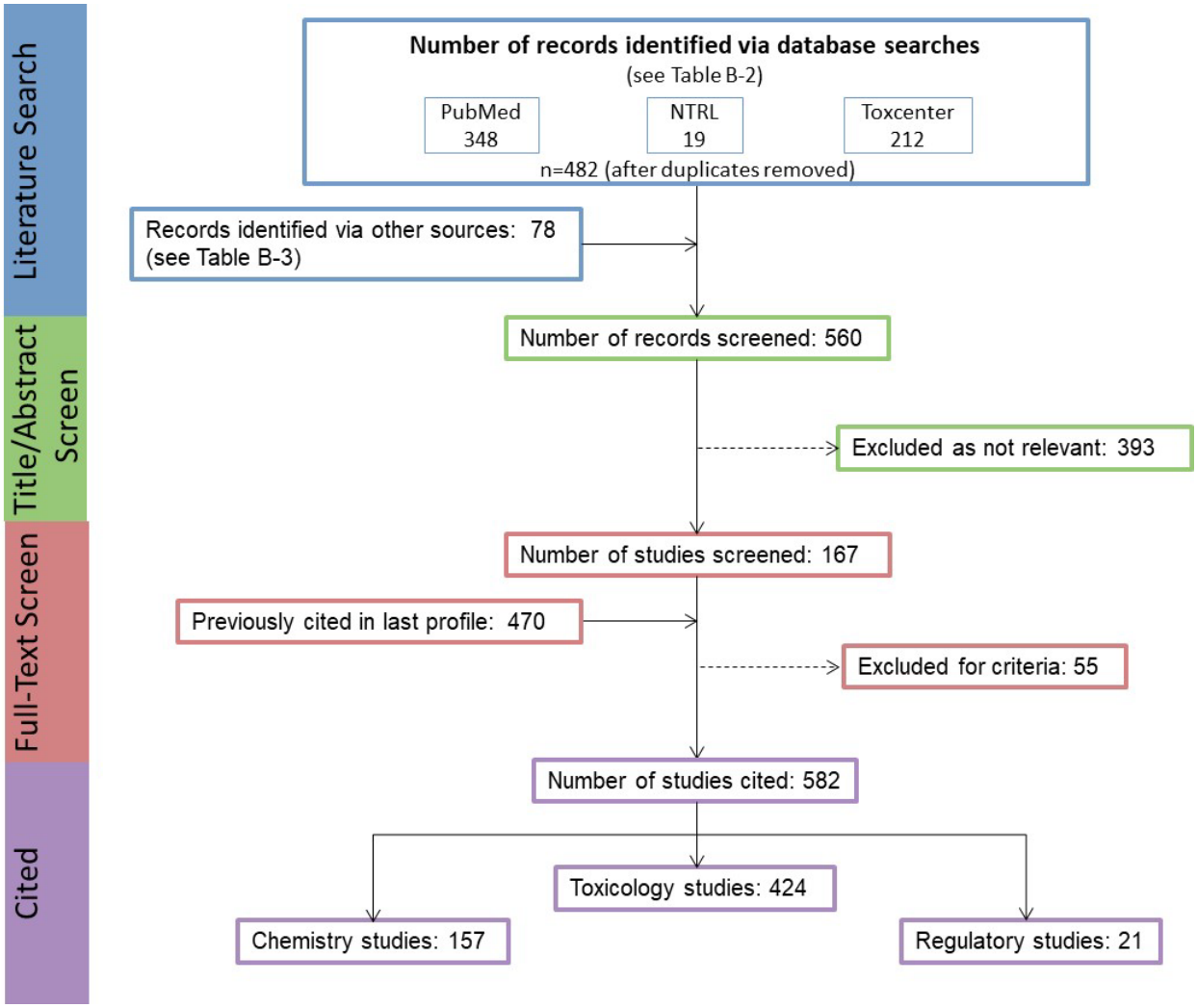
- Number of titles and abstracts screened: 560
- Number of studies considered relevant and moved to the next step: 167

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: 167
- Number of studies cited in the pre-public draft of the toxicological profile: 470
- Total number of studies cited in the profile: 582

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 NDMA



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									

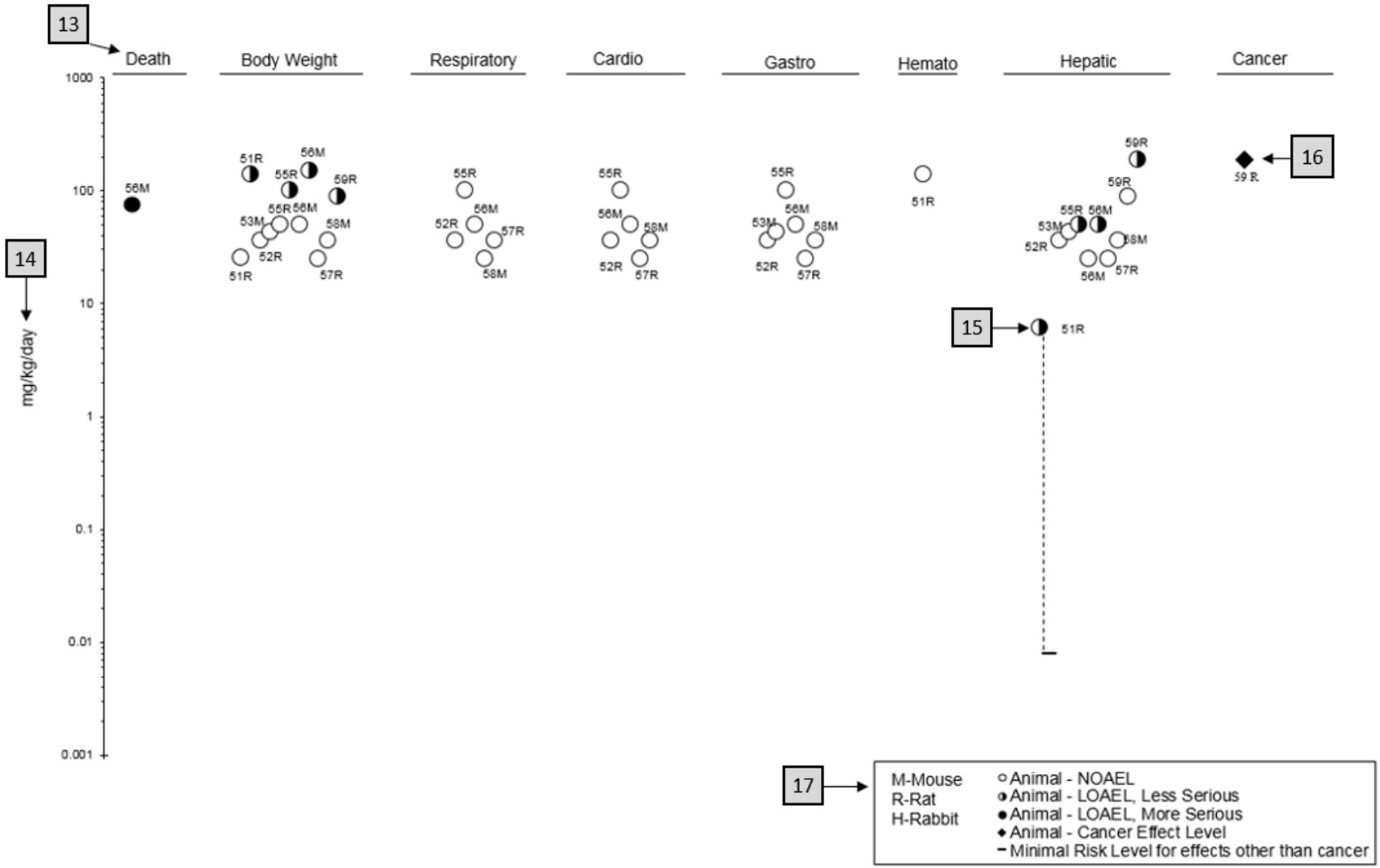
[a]The number corresponds to entries in Figure 2-x.

(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	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

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

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

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