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. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Naphthalene
CAS Numbers: 91-20-3
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
Provisional MRL: $6x10^{-5}$ ppm ($3x10^{-4}$ mg/m^3)
Critical Effect: Nasal olfactory epithelial necrosis
References: Dodd et al. 2010
Point of Departure: $BMCL_{HEC}$ of 0.0017 ppm
Uncertainty Factor: 30
LSE Graph Key: 4
Species: Rat

MRL Summary: A provisional acute-duration inhalation MRL of $6x10^{-5}$ ppm was derived for naphthalene based on a $BMCL_{HEC}$ of 0.0017 ppm for increased incidences of nasal olfactory epithelial necrosis in Sprague-Dawley rats exposed to naphthalene by inhalation for 6 hours (Dodd et al. 2010). The $BMCL_{HEC}$ was divided by a total uncertainty factor of 30 (10 for human variability and 3 for extrapolation from animals to humans when a dosimetric adjustment is used).

Selection of the Critical Effect: Most acute-duration inhalation studies of naphthalene focused on effects in the respiratory tract, a well-known target organ for inhaled naphthalene. Effects seen at the lowest exposure concentrations consisted of nasal lesions in rats. Table A-1 shows the lowest effect levels for acute-duration inhalation studies of naphthalene. As Table A-1 shows, the lowest LOAELs were for nasal olfactory lesions in rats.

Table A-1. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Inhalation Exposure to Naphthalene[a]

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$ (ppm)	$LOAEL_{ADJ}$ (ppm)	Effect	Reference
Rat (Sprague-Dawley)	Once, 6 hours	ND	0.1	ND	0.025	Minimal severity necrosis of the nasal olfactory epithelium	Dodd et al. 2010
Rat (F344)	Once, 6 hours	0.3	1.0	0.075	0.25	Minimal severity necrosis of the nasal olfactory epithelium	Dodd et al. 2010
Rat (Sprague-Dawley)	5 days, 6 hours/day		0.1		0.025	Minimal severity necrosis of the nasal olfactory epithelium in females	Dodd et al. 2010
Rat (F344)	5 days, 6 hours/day	0.1	1.0	0.025	0.25	Minimal severity necrosis of the nasal olfactory epithelium and nasopharyngeal goblet cell hyperplasia	Dodd et al. 2010
Mouse (Swiss)	Once, 2 hours	ND	1.5	ND	0.13	Mild cell loss in nasal olfactory epithelium	Phimister et al. 2004

Table A-1. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Inhalation Exposure to Naphthalene[a]

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$ (ppm)	$LOAEL_{ADJ}$ (ppm)	Effect	Reference
Rat (Sprague-Dawley)	Once, 4 hours	ND	3.4	ND	0.57	Necrosis, vacuolation, and exfoliation of the nasal olfactory epithelium	Lee et al. 2005
Mouse (B6:129)	Once, 4 hours	ND	5	ND	0.83	Epithelial damage (vacuolization and swelling) in proximal airways	Carratt et al. 2016
Mouse (C57BL/6)	Once, 4 hours	ND	5	ND	0.83	Epithelial damage (vacuolization and swelling) in proximal airways	Carratt et al. 2019b

[a]Green shading shows principal study for MRL derivation.

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

Selection of the Principal Study: The study by Dodd et al. (2010) identified the lowest LOAEL (0.1 ppm) and was selected as the principal study.

Summary of the Principal Study:

Dodd DE, Gross EA, Miller RA, et al. 2010. Nasal olfactory epithelial lesions in F344 and SD rats following 1- and 5-day inhalation exposure to naphthalene vapor. Int J Toxicol 29(2):175-184.

Sprague-Dawley and Fischer-344 rats (5/sex/strain/group) were exposed whole body to naphthalene vapor at concentrations of 0, 0.1, 0.3, 1, 10, and 30 ppm for 6 hours. During exposure, animals were monitored for mortality, clinical signs of toxicity, and body weight. One day following the exposure, animals were sacrificed for gross necropsy and histopathology of nasal tissues. No mortality or clinical signs occurred, and no effects on body weight or gross necropsy findings were observed. Necrosis of the nasal olfactory epithelium was observed at all concentrations in Sprague-Dawley rats and at concentrations ≥1 ppm in F344 rats; incidences are summarized in Table A-2. Mean severity scores for each exposure level were not reported; however, in a later publication, Dodd et al. (2012) reported that the severity of this effect at 1 ppm in the 1-day experiment was minimal. Necrosis of the nasal respiratory epithelium was observed in all rats of both strains and sexes at 10 and 30 ppm; controls and animals of lower exposure groups did not show this effect. Severity scores for necrosis of the nasal respiratory epithelium were not reported qualitatively or quantitatively.

Table A-2. Incidence of Selected Nasal Lesions in Sprague-Dawley and Fischer-344 Rats Exposed to Naphthalene for 6 Hours (Once) or 5 Days (6 Hours/Day)

		Exposure concentration (ppm)					
Strain	Sex	0	0.1	0.3	1	10	30
Nasal olfactory epithelium necrosis (Level 3), 6-hour exposure							
Sprague-Dawley	M	0/5	2/5	3/5	4/5	5/5	5/5
	F	1/5	1/5	2/5	4/5	5/5	5/5
F344	M	0/5	0/5	0/5	5/5	5/5	5/5
	F	0/5	0/5	0/5	4/5	5/5	5/5
Nasal olfactory epithelium degeneration (Level 3), 5-day exposure							
Sprague-Dawley	M	0/5	0/10		9/10	10/10	
	F	0/5	2/10		10/10	10/10	
F344	M	0/5	0/10		8/10	10/10	
	F	0/5	0/10		10/10	10/10	

Source: Dodd et al. 2010

Selection of the Point of Departure for the MRL: Necrosis of the olfactory epithelium occurred at a lower exposure level in Sprague-Dawley rats than in F344 rats, so the data for Sprague-Dawley rats were selected as the basis for the MRL derivation. BMD modeling was conducted to identify a POD using the data for necrosis of the olfactory epithelium in male and female Sprague-Dawley rats administered naphthalene via inhalation for 6 hours. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.2.0.1) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMC (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen. BMDS recommended the frequentist restricted log-logistic model for the data, and after verifying the model fit by the four criteria listed above, this model was selected as the basis for estimating this MRL. The BMC/BMCL values considered for MRL derivation are presented in Table A-3 and the fit of the selected model is presented in Figure A-1.

Table A-3. Model Predictions for Increased Incidence of Necrosis of the Olfactory Epithelium in Male and Female Sprague-Dawley Rats Exposed to Naphthalene via Inhalation for 6 Hours (Dodd et al. 2010)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	0.062	0.017	0.87	51.00	-0.10	0.27
Gamma[d]	0.064	0.037	0.99	46.85	-0.24	0.31
Log-Logistic[e,f]	**0.062**	**0.017**	**0.96**	**49.00**	**-0.10**	**0.27**
Multistage Degree 5[g]	0.064	0.037	0.97	48.85	-0.24	0.31

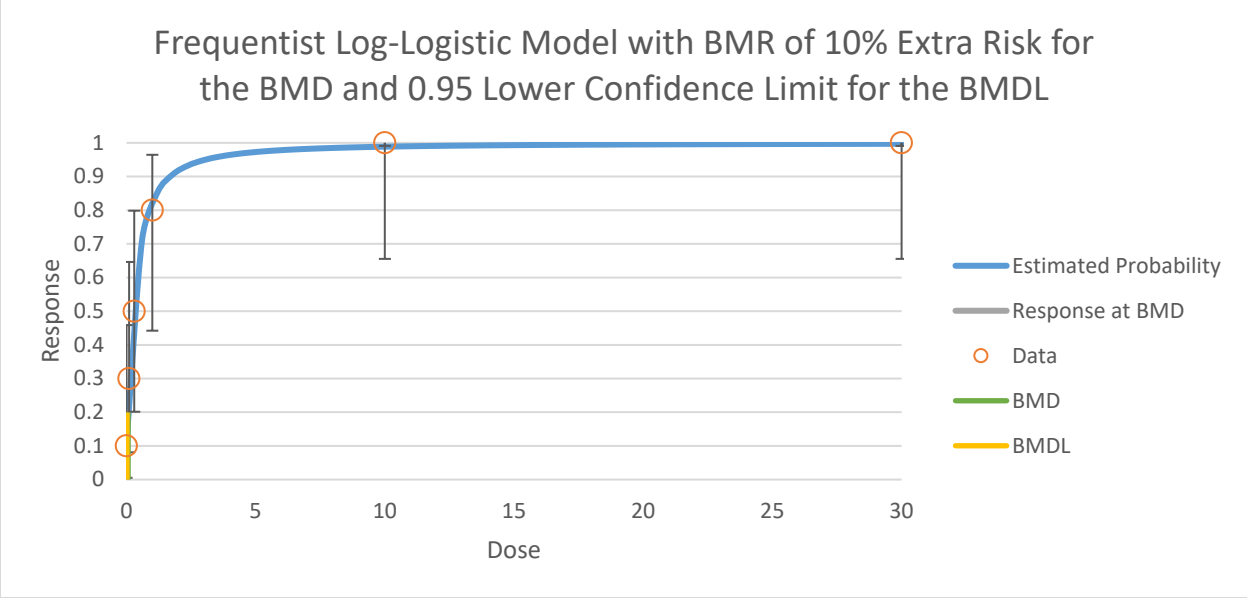
Table A-3. Model Predictions for Increased Incidence of Necrosis of the Olfactory Epithelium in Male and Female Sprague-Dawley Rats Exposed to Naphthalene via Inhalation for 6 Hours (Dodd et al. 2010)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Multistage Degree 4[g]	0.064	0.037	0.97	48.85	-0.24	0.31
Multistage Degree 3[g]	0.064	0.037	0.99	46.85	-0.24	0.31
Multistage Degree 2[g]	0.064	0.037	0.99	46.85	-0.24	0.31
Multistage Degree 1[g]	0.064	0.034	0.99	46.85	-0.24	0.31
Weibull[d]	0.064	0.037	0.99	46.85	-0.24	0.31
Logistic	0.144	0.094	0.85	48.09	0.27	0.70
Log-Probit			0.99	48.78	-0.06	0.20
Probit	0.289	0.221	0.40	50.52	-1.62	-0.43

[a]BMC and BMCLs values for models that do not provide adequate fit or yield BMCLs more than 10-fold lower than the lowest nonzero exposure concentration are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]All models provided an adequate fit to the data. BMCLs were not sufficiently close (differed by >3-fold). Therefore, the model with the lowest BMCL was selected (Log-Logistic).
[g]Betas restricted to ≥0.

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

Figure A-1. Fit of the Log-logistic Model to Data for Naphthalene, Necrosis Olfactory Epithelium in Male and Female Sprague-Dawley Rats (Dodd et al. 2010)



Calculations

Adjustment for Intermittent Exposure: Dodd et al. (2010) exposed rats to naphthalene for 6 hours of 1 day. Therefore, the $BMCL_{10}$ was adjusted for intermittent exposure as follows:

$$BMCL_{ADJ} = BMCL \times \frac{6\ hours}{24\ hours} = 0.017\ ppm \times \frac{6\ hours}{24\ hours} = 0.0043\ ppm$$

Human Equivalent Concentration: The critical effect was nasal olfactory epithelium necrosis in the respiratory system. PBPK modeling was considered for interspecies extrapolation. There are hybrid computational fluid dynamics-PBPK models that predict nasal tissue concentrations of naphthalene metabolites in rats and humans exposed by inhalation, namely Campbell et al. (2014) and Kapraun et al. (2020). However, there has been no direct evaluation of the Campbell et al. (2014) or Kapraun et al. (2020) models for predicting nasal tissue doses in human. The calibration of the Kapraun et al. (2020) model was limited to observations of blood naphthalene levels following dermal exposures to JP-8. While the calibrated model performed well for predicting observed blood naphthalene levels, the predicted blood naphthalene levels were relatively insensitive to nasal cavity parameter values and highly sensitive to dermal and systemic parameters (e.g., blood flow to liver, skin exposure surface area, partition coefficients for skin and systemic tissues). Therefore, the model could perform well for predicting blood naphthalene following dermal exposures but perform poorly at predicting nasal cavity doses following inhalation. For this reason, the models were not used.

The $BMCL_{ADJ}$ was converted to a $BMCL_{HEC}$ using guidance from EPA (1994) on dosimetric adjustments for respiratory effects using the RGDR for extrathoracic effects ($RGDR_{ET}$). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994):

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h} = \frac{0.413}{15} \div \frac{13.8}{200} = 0.40$$

where:
V_{E_a} = ventilation rate for male and female Sprague-Dawley rats = 0.413 L/minute (EPA 2012)
SA_a = surface area of the extrathoracic region in rats = 15 cm^2 (EPA 1994)
V_{E_h} = ventilation rate for humans = 13.8 L/minute (EPA 1994)
SA_h = surface area of the extrathoracic region in humans = 200 cm^2 (EPA 1994)

Applying this equation results in an RGDR of 0.40 for extrathoracic effects in rats, and the HEC is calculated as:

$$BMCL_{10HEC} = BMCL_{10ADJ} \times RGDR = 0.0043\ ppm \times 0.40 = 0.0017\ ppm$$

Uncertainty Factor: The $BMCL_{HEC}$ was divided by a composite uncertainty factor of 30:

- 10 for human variability
- 3 for animal to human extrapolation after dosimetric adjustment.

This results in the following MRL:

$$MRL = \frac{BMCL_{HEC}}{UFs} = \frac{0.0017\ ppm}{30} \approx 0.00006\ ppm\ (6x10^{-5}\ ppm)$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target of naphthalene exposure. In humans exposed occupationally, effects of naphthalene on the respiratory system include inflammation and irritation of the nasal tissue (Sucker et al. 2021). Studies in rats and mice exposed to naphthalene by inhalation consistently demonstrate adverse effects on the olfactory and respiratory epithelium of the nasal cavity. Acute-duration exposures typically result in nasal tissue injury (necrosis, vacuolation, swelling, and exfoliation) (Carratt et al. 2016, 2019a; Cichocki et al. 2014; Dodd et al. 2010; Lee et al. 2005; Li et al. 2017; Phimister et al. 2004). With longer exposure durations, regenerative changes consisting of hyperplasia and metaplasia and lesions deeper in the nasal cavity are seen (Abdo et al. 2001; Dodd et al. 2012; NTP 1992a, 2000). Available data suggest that rats may be more sensitive to the nasal effects of naphthalene than mice, and that Sprague-Dawley rats may be more sensitive than F344 rats. However, the only studies using exposure concentrations <1 ppm were those by Dodd et al. (2010, 2012). These studies tested only rats, and Sprague-Dawley rats were tested only in the acute-duration experiments (Dodd et al. 2010).

The odor threshold for naphthalene in air is 0.44 mg/m^3 or 0.084 ppm (see Section 4.2).

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Naphthalene
CAS Numbers: 91-20-3
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: A provisional intermediate-duration inhalation MRL was not derived for naphthalene. The one available intermediate-duration study (Dodd et al. 2012) identified a NOAEL for nasal lesions in F344 rats at the same concentration (0.1 ppm) as the LOAEL for nasal lesions after acute-duration exposure in Sprague-Dawley rats, precluding use of the intermediate-duration study for deriving an MRL. No intermediate-duration inhalation studies using Sprague-Dawley rats were located. Based on current information, it is possible that the acute-duration inhalation MRL may be protective for intermediate-duration exposure, but this cannot be known with certainty without intermediate-duration studies using Sprague-Dawley rats. Nevertheless, a health-protective option available at present would be to use the acute-duration MRL to assess intermediate-duration exposure. This option is considered to be health-protective because studies conducted in F344 rats have found that the LOAELs for acute-duration and subchronic-duration studies are similar (1 ppm), which suggests that adverse effects on the nasal cavity in rats may be independent of exposure duration.

Rationale for Not Deriving an MRL: There is one intermediate-duration inhalation study of naphthalene in laboratory animals: a 13-week study in rats (Dodd et al. 2012). In this study, groups of F344 rats (10/sex/group) were exposed, whole body, to naphthalene vapor at concentrations of 0 (air control), 0.1, 1, 10 or 30 ppm for 6 hours/day, 5 days/week for 90 days. At the LOAEL of 1 ppm, effects included reduced absolute (but not relative to body weight) thymus weights in females and minimal hyperplasia of the transitional/respiratory epithelium at Level 2 of the nasal cavity (in all exposed males; incidence not reported for females). At higher concentrations, transitional/respiratory epithelium metaplasia was seen at Level 2, and olfactory epithelium degeneration/necrosis and basal cell hyperplasia were observed at Levels 2–5. In males, severity scores for olfactory epithelial degeneration/necrosis were minimal to mild at 10 ppm and mild to moderate at 30 ppm; severity scores for basal cell hyperplasia were minimal at 10 ppm and mild at 30 ppm. Severity in females was not reported. Minimal severity goblet cell hyperplasia of the nasopharyngeal duct was noted at Level 5.

The nasal lesions seen in F344 rats exposed for 90 days are consistent with the effects seen in acute-duration (1- and 5-day) exposures and with those seen in the 2-year study (Abdo et al. 2001; NTP 2000). Acute-duration exposures are associated with necrosis of the olfactory and respiratory epithelia in the anterior portions of the nose. With longer exposure durations, regenerative changes consisting of hyperplasia and metaplasia and lesions deeper in the nasal cavity are seen. Table A-4 provides an overview of the progression of nasal lesions with time and exposure concentration. As the table shows, Sprague-Dawley rats appear to be more sensitive than F344 rats to naphthalene at the 6-hour exposure duration. With a 5-day exposure, the two strains respond differently but do not appear to differ in sensitivity. There are no 90-day or 2-year studies in Sprague-Dawley rats. The table also demonstrates that the NOAEL for F344 rats in the 90-day study is the same concentration as the LOAEL for Sprague-Dawley rats in the 1-day study. Thus, the one available intermediate-duration study is not suitable for use in deriving an MRL.

Table A-4. Treatment-related Nasal Lesions in Male and Female Rats exposed to Naphthalene by Inhalation

Duration	Rat strain	Exposure concentration[a] (ppm)					
		0.1	0.3	1	10	30	60
1 Day, 6 hours	Sprague-Dawley	OE necrosis in 3/10 (L3)	OE necrosis in 5/10 (L3)	**OE necrosis (L3)** RE necrosis in 1/10	**OE necrosis (L3) RE necrosis (tip to L3)**	**OE necrosis (L3) RE necrosis (tip to L3)**	
	F344	None	None	**OE necrosis (L3)**	**OE necrosis (L3) RE necrosis (tip to L3)**	**OE necrosis (L3) RE necrosis (tip to L3)**	
5 Days, 6 hours/day	Sprague-Dawley	OE degeneration in 2/10 (L3)		**OE degeneration (L3)**	**OE degeneration (L3–5);** Goblet cell hyperplasia (L4 and L5)		
	F344	Goblet cell hyperplasia in 2/10 (L5)		**OE degeneration (L3)** Goblet cell hyperplasia in 3/10 (L5)	**OE degeneration (L3–5) Goblet cell hyperplasia (L4 and L5)**		
90 Days, 5 days/week, 6 hours/day	F344	None		**T/RE hyperplasia (L2)**	**T/RE squamous metaplasia (L2) OE necrosis and hyperplasia (L2–L5)**	**T/RE squamous metaplasia (L2) OE necrosis and hyperplasia (L2–L5)** Goblet cell hyperplasia (NPD)	

Table A-4. Treatment-related Nasal Lesions in Male and Female Rats exposed to Naphthalene by Inhalation

Duration	Rat strain	Exposure concentration[a] (ppm)					
		0.1	0.3	1	10	30	60
2 Years, 5 days/week, 6 hours/day	F344				**OE hyperplasia, atrophy, inflammation, hyaline degeneration**; RE hyperplasia, squamous metaplasia, **hyaline degeneration,** goblet cell hyperplasia, **glandular hyperplasia and squamous metaplasia;** nasal tumors	**OE hyperplasia, atrophy, inflammation, hyaline degeneration;** RE hyperplasia, squamous metaplasia, **hyaline degeneration,** goblet cell hyperplasia, **glandular hyperplasia** and squamous metaplasia; nasal tumors	**OE hyperplasia, atrophy, inflammation, hyaline degeneration;** RE hyperplasia, squamous metaplasia, **hyaline degeneration,** goblet cell hyperplasia, **glandular hyperplasia** and squamous metaplasia; nasal tumors

[a]Gray shading shows exposure concentrations that were not tested for the corresponding duration. Bold indicates lesions observed in most animals at this exposure level.

L1–L5 Nasal cavity levels 1–5; NPD = nasopharyngeal duct; OE = olfactory epithelium; RE = respiratory epithelium (of the nasal cavity); T/RE = transitional/ respiratory epithelium (of the nasal cavity)

Sources: Abdo et al. 2001; Dodd et al. 2010, 2012; NTP 2000

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Naphthalene
CAS Numbers: 91-20-3
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: A provisional chronic-duration inhalation MRL was not derived for naphthalene. Available chronic-duration studies identified LOAELs without NOAELs at a concentration (10 ppm) 2 orders of magnitude higher than the LOAEL for acute-duration exposure (0.1 ppm), precluding their use in deriving an MRL. Consistent with acute- and intermediate-duration inhalation studies of naphthalene, the available chronic-duration inhalation studies of naphthalene also identified nasal lesions as the critical effect. In the absence of chronic-duration inhalation studies at lower concentrations, a chronic-duration MRL could not be derived. Based on current information, it is possible that the acute-duration inhalation MRL may be protective for chronic-duration exposures, but this cannot be known with certainty without chronic-duration inhalation studies at lower concentrations. Nevertheless, a health-protective option available at present would be to use the acute-duration MRL to assess chronic-duration exposures. This option is considered to be health-protective because a chronic MRL based on the LOAEL from the NTP (2000) chronic study would be higher (less health-protective) than the acute-duration MRL, and because studies conducted in F344 rats have found that the LOAELs for acute- and subchronic-duration studies are similar (1 ppm), which suggests that adverse effects on the nasal cavity in rats may be independent of exposure duration.

Rationale for Not Deriving an MRL: The NTP (Abdo et al. 2001; NTP 1992a, 2000;) conducted 2-year bioassays in B6C3F1 mice and F344/N rats exposed to naphthalene by inhalation at concentrations of 0, 10, or 30 ppm. The lowest exposure level was a LOAEL in both sexes of both species for nonneoplastic lesions in the olfactory and respiratory epithelium of the nasal cavity affecting essentially all of the animals. Mice also exhibited increased incidences of lung inflammation at the LOAEL (NTP 1992a), and an increased incidence of nasal respiratory epithelial adenomas was seen in male rats at the LOAEL (NTP 2000; Abdo et al. 2001); see Table A-3.

The LOAEL of 10 ppm for both mice and rats in the available chronic-duration inhalation studies is 100-fold higher than the LOAEL of 0.1 ppm for nasal lesions in Sprague-Dawley rats in the 1-day exposure study (Dodd et al. 2010) that was used for the acute-duration inhalation MRL. In the absence of chronic-duration studies using lower exposure concentrations, a chronic-duration inhalation MRL could not be derived.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Naphthalene
CAS Numbers: 91-20-3
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute
Provisional MRL: 0.2 mg/kg/day
Critical Effect: Clinical signs of neurotoxicity (slow respiration, lethargy, or prone body posture)
Reference: NTP 1991
Point of Departure: LOAEL of 50 mg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 3
Species: Rat

MRL Summary: A provisional acute-duration oral MRL of 0.2 mg/kg/day was derived for naphthalene based on a LOAEL of 50 mg/kg/day for clinical signs of neurotoxicity (slow respiration, lethargy, and pronation) in rats administered naphthalene via gavage during gestation (NTP 1991). The LOAEL was divided by a total uncertainty factor of 300 (10 for extrapolation from animals to humans, 3 for use of a minimal LOAEL, and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of naphthalene following acute-duration oral exposure; these studies examined a variety of endpoints including developmental (NTP 1991, 1992a, 1992b; Plasterer et al. 1985; Texaco 1985d, 1986), hepatic (Rao and Pandya 1981; Zhang et al. 2016), respiratory (Kelty et al. 2020; Shopp et al. 1984; Zhang et al. 2015, 2016), and neurological (NTP 1991). The lowest LOAELs for these studies range from 50 to 300 mg/kg/day and are shown in Table A-5. The available data indicate that clinical signs of neurotoxicity were the most sensitive endpoint following acute-duration oral exposure. In pregnant female Sprague-Dawley rats exposed to naphthalene via gavage during GDs 6–15, a LOAEL of 50 mg/kg/day was determined based on clinical signs of neurotoxicity including slowed respiration, lethargy, and pronation (NTP 1991). The next highest LOAEL was 100 mg/kg/day, which was a serious LOAEL for respiratory effects (Zhang et al. 2016, 2017).

Table A-5. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Oral Exposure to Naphthalene[a]

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Sprague-Dawley rat	GDs 6–15	ND	50	Transient clinical signs of toxicity (lethargy) in dams; at higher exposure levels, signs were more persistent	NTP 1991
New Zealand rabbit	GDs 6–18	40	200	Maternal body drop and hypoactivity with no pathological changes	Texaco 1985d 1986

Table A-5. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Oral Exposure to Naphthalene[a]

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Respiratory effects					
Kunming mouse	Once	ND	100 (SLOAEL)	Lung histopathology including structural degeneration, vasocongestion, edema, inflammatory cell infiltration and destroyed interalveolar septa with large, irregular alveolar space	Zhang et al. 2015
Kunming mouse	Once	ND	100 (SLOAEL)	Lung structural degeneration, inflammatory cell infiltrate, vasocongestion, edema, alterations of alveoli and alveolar septa	Zhang et al. 2016
B6C3F1 mouse	Once	ND	150	Respiratory epithelial cytotoxicity	Kelty et al. 2020
New Zealand rabbit	GDs 6–18	40	200 (SLOAEL)	Maternal dyspnea, cyanosis	Texaco 1985d 1986
Hepatic effects					
Kunming mouse	Once	ND	100 (SLOAEL)	Increased serum levels of AST (>5-fold) and ALT (>13-fold), extensive hepatocellular necrosis, moderate inflammatory cell infiltration, massive fatty degeneration, and structural degeneration	Zhang et al. 2016
Death					
CD-1 mouse	14 days	NA	267 (SLOAEL)	10/96 male and 3/60 females died	Shopp et al. 1984
CD-1 mouse	GDs 7–4	NA	300 (SLOAEL)	5/33 dams died	Plasterer et al. 1985

[a]Green shading shows principal study for MRL derivation.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Selection of the Principal Study: The lowest LOAEL was 50 mg/kg/day based on clinical signs of toxicity in rats in the developmental study by NTP (1991); the next highest LOAEL was a serious LOAEL of 100 mg/kg/day for respiratory effects in mice (Zhang et al. 2015, 2016). Therefore, the study by NTP (1991) was selected as the principal study.

Summary of the Principal Study:

NTP. 1991. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Research Triangle Park, NC: National

Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. TER91006.

Groups of 25 pregnant female Sprague-Dawley rats were administered naphthalene in corn oil at doses of 0, 50, 150, and 450 mg/kg/day during GDs 6–15. Dams were monitored for death and clinical signs of toxicity daily. Body weights were measured. Dams were sacrificed on GD 20 for necropsy. Uteruses were weighed and uterine contents were examined for number of implantation sites, resorptions, dead and live fetuses, fetal body weights, and external and visceral malformations.

There were no treatment-related mortalities. Rat dams in exposed groups showed one or more of several clinical signs of toxicity (slow respiration, lethargy, or prone body posture) on the first day of dosing (81, 96, and 96% of rats in the 50-, 150-, and 450-mg/kg/day groups, respectively). By the third day of dosing, these signs did not occur in any of the 50-mg/kg/day rats. A similar trend was noted in the 150-mg/kg/day group, but apparent tolerance did not develop until the sixth day of dosing. In the 450-mg/kg/day group, the incidence of rats exhibiting these signs of toxicity also declined during the exposure period but did not fall below 15%. With the development of "tolerance," the slow respiration, lethargy, and prone body posture were replaced with rooting behavior, a common behavior of rodents following gavage administration of chemicals with strong odors or irritant properties. At the end of the exposure period (GD 15), incidence of rats showing rooting behavior was 0% for the control and 50-mg/kg/day groups, compared with 24 and 92% of dams in the 150- and 450-mg/kg/day groups, respectively. Weight gain during exposure (GDs 6–15) was similar between the control and 50-mg/kg/day group but was decreased by 31 and 53% in the 150- and 450-mg/kg/day groups, compared with controls. From these results, 50 mg/kg/day was judged to be a minimal less serious LOAEL for transient clinical signs of maternal toxicity in pregnant rat dams. At higher doses (150 and 450 mg/kg/day), these effects were more persistent and were accompanied by decreased weight gain. No effects were observed on uterus weights, pregnancy rate, number of implantation sites, resorptions, dead and live fetuses, or fetal body weights. At 0, 50, 150, and 450 mg/kg/day, the percentages of malformed fetuses per litter were 4, 4, 7, and 10%, respectively, and the percentages of litters with malformed fetuses were 23, 27, 33, and 50%, respectively. Both effects were statistically significant by trend test, but pairwise comparisons between individual exposure groups and the control were not statistically significant.

Selection of the Point of Departure for the MRL: The lowest LOAEL was 50 mg/kg/day based on transient clinical signs of toxicity in rats exposed during gestation. As the data were not amenable to BMD modeling, a LOAEL approach was used.

Calculations

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The LOAEL of 50 mg/kg/day was divided by a total uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a minimal LOAEL), resulting in an MRL of 0.2 mg/kg/day.

- 10 for extrapolation from animals to humans
- 10 for human variability
- An uncertainty factor of 3 was selected for the use of a minimal LOAEL of 50 mg/kg/day. At this dose level, the only adverse effects observed in the pregnant rat dams were signs of maternal toxicity, which were only observed on the first 2 days of exposure.

MRL = LOAEL ÷ UF
= 50 mg/kg/day ÷ (10 × 10 × 3) = 0.16 mg/kg/day, rounded to 0.2 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Neurologic symptoms have been reported in humans following ingestion of naphthalene at unknown, but presumably high dose levels. These include confusion (Ojwang et al. 1985) and listlessness and lethargy (Bregman 1954; Chusid and Fried 1955; Kurz 1987; MacGregor 1954; Zuelzer and Apt 1949), as well as decreased responses to painful stimuli and coma prior to death (Gupta et al. 1979; Kurz 1987). Persistent neurologic symptoms were not recorded in 13-week studies with rats or mice exposed to doses as high as 200 mg/kg/day (NTP 1980a, 1980b), but the highest exposure level tested in these studies, 400 mg/kg/day, produced lethargy in exposed rats (only rats were exposed to 400 mg/kg/day).

Hemolytic anemia has been identified in many human cases of acute accidental or intentional ingestion of naphthalene (e.g., Gidron and Leurer 1956; MacGregor 1954). Estimations of dose levels involved in these cases, however, are limited to a report (Gidron and Leurer 1956) of hemolytic anemia in a 16-year-old girl who swallowed 6 g of naphthalene (estimated dose=109 mg/kg, assuming body weight of 55 kg). Laboratory animals do not appear to be susceptible to the hemolytic activity of naphthalene. No pronounced changes in red-cell-related hematologic parameters were observed following 13-week oral exposures to doses up to 200 mg/kg/day in mice (NTP 1980a) and 400 mg/kg/day in rats (NTP 1980b), or in mice exposed by inhalation for 14 days to air concentrations as high as 30 ppm (NTP 1992a). Naphthalene-induced hemolytic anemia has been observed in dogs exposed to a single dose of 1,525 mg/kg or 263 mg/kg/day for 7 days (Zuelzer and Apt 1949), but more information on the dose-response relationship for hemolytic anemia in humans or animals acutely exposed to naphthalene is not available.

Development of cataracts is also associated with acute or repeated oral exposure to naphthalene in animals (Kojima 1992; Murano et al. 1993; van Heyningen and Pirie 1967; Xu et al. 1992b). These ocular effects, however, appear to occur at dose levels (in the range of 500–1,000 mg/kg/day) much higher than the lowest dose level (50 mg/kg/day) producing clinical signs of toxicity in pregnant rats.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Naphthalene
CAS Numbers: 91-20-3
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
Provisional MRL: 0.2 mg/kg/day (based on the provisional acute-duration oral MRL)
Critical Effect: Clinical signs of neurotoxicity (slow respiration, lethargy, or prone body posture)
Reference: NTP 1991 (see acute-duration oral MRL)
Point of Departure: LOAEL of 50 mg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 3
Species: Rat

MRL Summary: The provisional acute-duration oral MRL of 0.2 mg/kg/day based on a LOAEL of 50 mg/kg/day for clinical signs of slow respiration, lethargy, and pronation in rats administered naphthalene via gavage during gestation (NTP 1991) was adopted as the provisional intermediate-duration oral MRL. Three intermediate-duration oral toxicity studies in rats and mice that included comprehensive toxicological evaluations provide support for the use of the acute-duration oral MRL for the intermediate duration.

Selection of the Critical Effect: See worksheet for provisional acute-duration oral MRL.

Selection of the Principal Study: See worksheet for provisional acute-duration oral MRL.

Summary of the Principal Study: See worksheet for provisional acute-duration oral MRL.

Selection of the Point of Departure for the MRL: See worksheet for provisional acute-duration oral MRL.

Calculations: See worksheet for provisional acute-duration oral MRL.

Uncertainty Factor: See worksheet for provisional acute-duration oral MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: A number of studies have evaluated the toxicity of naphthalene following intermediate-duration oral exposure. The majority of these studies used naphthalene to induce cataracts and used only high doses known to give this result (Chen et al. 2010a, 2010b, 2012; Holmén et al. 1999; Kojima 1992; Murano et al. 1993; Orzalesi et al. 1994; Patel and Patel 2018; Rathbun et al. 1990; Rossa and Pau 1988; Siddiqui et al. 2002; Singh and Bodakhe 2020; Tao et al. 1991; van Heyningen and Pirie 1967; Xu et al. 1992b; Yamauchi et al. 1986).

Apart from the studies of cataracts, there are three single dose studies of limited endpoints (Darious et al. 2020; Germansky and Jamall 1988; Katsnelson et al. 2014) and three comprehensive intermediate-duration oral toxicity studies in laboratory animals (NTP 1980a, 1980b; Shopp et al. 1984). A 13-week oral toxicity study in Fischer 344 rats found no adverse exposure-related effects other than decreased body weight (NTP 1980b). This study identified a LOAEL of 200 mg/kg/day based on decreased body weights and a NOAEL of 100 mg/kg/day. A 13-week oral toxicity study in B6C3F1 mice found no

adverse effects in mice exposed to doses as high as 200 mg/kg/day (NTP 1980a). A 90-day gavage study in mice that focused on immune toxicity identified 133 mg/kg/day as a LOAEL for weight decreases in several organs (brain, liver, and spleen) and 53 mg/kg/day as a NOAEL but found no biologically significant exposure-related changes in other endpoints evaluated (Shopp et al. 1984). This study, however, did not include histopathological examination of tissues.

In the three comprehensive toxicity studies, the most sensitive effects were decreased spleen and liver weights in mice exposed to 133 mg/kg/day; the NOAEL for these effects was 53 mg/kg/day (Shopp et al. 1984). Considering that the NOAEL for the lowest LOAEL in intermediate-duration studies was greater than the LOAEL (50 mg/kg/day) used as the POD for the acute-duration MRL, the acute-duration oral MRL of 0.2 mg/kg/day is expected to be protective for intermediate-duration exposure scenarios and was adopted as the provisional intermediate-duration oral MRL.

Summaries of the three comprehensive studies of intermediate-duration exposure are provided below as support for the adopting the provisional acute-duration oral MRL for intermediate durations:

1. **NTP. 1980b. Subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.**

Naphthalene (>99% pure) in corn oil was administered by gavage to groups of 10 male and 10 female Fischer 344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg/day, 5 days/week for 13 weeks (NTP 1980b). Endpoints included weekly measurement of food consumption and body weight, twice daily observation for clinical signs of toxicity, measurement of hematological parameters for blood collected at termination (hemoglobin, hematocrit, total and differential white blood cell count, red blood cell count, mean cell volume, mean cell hemoglobin concentration), necropsy of all rats in the study, and complete histopathological examination of 27 organs and tissues (including the eyes, lungs, stomach, liver, reproductive organs, thymus, and kidneys) from all control and 400 mg/kg/day rats. Male kidneys and female thymuses from the 200 mg/kg/day group were also examined histopathologically (according to the histopathology tables; however, the report text states that the 100 mg/kg group was examined). Organ weight data were not reported.

At the highest dose level, two male rats died during the last week of treatment, and rats of both sexes displayed diarrhea, lethargy, hunched posture, and rough coats at intermittent intervals throughout the study. Food consumption was not affected by exposure. Mean terminal body weights were decreased by more than 10% relative to the controls in several groups (28 and 12% decrease in the 400- and 200-mg/kg/day males, respectively and 23% decrease in 400-mg/kg females). The terminal body weights at 13 weeks of exposure were 250.6, 306.7, 333.4, 351.2, 353.4, and 348.9 g for males and 156.7, 190.5, 197.2, 203.5, 197.8, and 203.4 g for females for the 400, 200, 100, 50, 25, and 0 mg/kg/day dose groups, respectively. Differences between mean values of hematological parameters in exposed groups and those in control groups were <10% of control values, except for a 94% increase in numbers of mature neutrophils and a 25.1% decrease in numbers of lymphocytes in male 400 mg/kg rats and a 37.2% increase in mature neutrophils in 400 mg/kg females. Due to a lack of a consistent pattern of change in the hematologic parameters, the observed changes are not considered adverse. Histological examinations revealed low incidences of lesions in exposed male kidneys and exposed female thymuses; no lesions were observed in respective control kidneys or thymuses. Focal cortical lymphocytic infiltration or focal tubular regeneration were observed in kidneys in 2/10 male rats exposed to 200 mg/kg/day naphthalene, and diffuse renal tubular degeneration occurred in 1/10 male rats exposed to 400 mg/kg/day. Lymphoid depletion of the thymus occurred in 2/10 females exposed to 400 mg/kg/day, but not in any other females or in males. No other tissue lesions were detected. In this study, 100 mg/kg/day was a NOAEL,

200 mg/kg/day was a LOAEL, and 400 mg/kg/day was a serious LOAEL for decreased body weight in rats orally exposed to naphthalene for 13 weeks.

2. NTP. 1980a. Subchronic toxicity study: Naphthalene (C52904), B6C3F1 mice. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.

Ten male and 10 female B6C3F1 mice were administered gavage doses of naphthalene in corn oil at levels of 0, 12.5, 25, 50, 100, or 200 mg/kg/day, 5 days/week for 13 weeks (NTP 1980a). Seven mice (three males and two females of the 200 mg/kg/day group, one female of the 25 mg/kg/day group, and one control male) died during the second, third, and fourth weeks from gavage trauma or accident. Transient signs of toxicity (lethargy, rough hair coats, and decreased food consumption) occurred between weeks 3 and 5 in the 200 mg/kg/day groups. Due to their transient nature, these effects are not considered to be adverse. All exposed male mice gained more weight during the study than did control males (weight gains expressed as a percentage of control weight gain were 154.3, 116.0, 125.9, 122.2, and 107.4% for the 12.5–200 mg/kg/day groups, respectively). Exposed female mice displayed decreased weight gain compared with controls (weight gains expressed as a percentage of control weight gain were 97.5, 81.5, 81.5, 77.8, and 76.5% for the 12.5–200 mg/kg/day groups, respectively). The average change in body weight between day 0 and the 13th week was 6.2 g/mouse for the 200 mg/kg/day female mice compared with 8.1 g/mouse for the control females. The study authors believed that a difference in weight gain of 1.9 g over a 13-week period "was not large enough to conclusively indicate a toxic effect." Respective mean terminal body weights for control through the 200 mg/kg/day group were: 33.2, 37.7, 34.7, 34.7, 36.0, and 34.7 g for males, and 26.7, 26.8, 25.4, 26.0, 26.1, and 25.6 g for females. Mean terminal body weight values in exposed females were ≥95% of control values.

All mice were necropsied, and 27 organs (including the eyes, thymus, reproductive organs, and lungs) from the mice in the control and high-dose groups were examined histologically. No exposure-related lesions were observed in any organs. The highest incidence of lesions observed was for minimal to mild, focal or multifocal, subacute pneumonia in both controls (4/10 males and 2/10 females) and high-dose mice (4/10 males and 5/10 females). Organ weight data were not reported. Hematological analyses were performed on all groups. Exposed groups displayed mean values that were within 10% of the control means for the following parameters: hemoglobin, hematocrit, total white blood cells, and total red blood cells. An increase in lymphocytes (18% increase) and a decrease in segmented neutrophils (38.8% decrease) in high-dose males were not considered biologically significant by the study authors. The highest dose in this study, 200 mg/kg/day, is judged to be a NOAEL for nonneoplastic lesions, hematologic changes, and adverse neurologic symptoms.

3. Shopp GM, White KL JR, Holsapple MP, et al. 1984. Naphthalene toxicity in CD-1 mice: General toxicology and immunotoxicology. Fundam Appl Toxicol 4:406-419.

Groups of male and female albino CD-1 mice (approximately 6 weeks old at the start) were administered gavage doses of 0, 5.3, 53, or 133 mg/kg naphthalene (99.3% pure) in corn oil for 90 consecutive days (Shopp et al. 1984). A naive control group and the 5.3 and 53 mg/kg/day dose groups each contained 76 male mice and 40 female mice. The vehicle control group contained 112 male mice and 76 female mice. The high-dose group contained 96 male mice and 60 female mice. Statistical analysis consisted of a one-way analysis of variance of means and Dunnett's t-test to compare control and treatment means using a significance level of $p<0.05$. Statistically significant chemical-related decreases in terminal body weights or survival were not observed in either sex. Respective mean terminal body weight values were (naïve, vehicle, 5.3, 53, and 133 mg/kg/day groups): 39.3, 37.3, 37.2, 36.2, and 36.8 g for male mice and 29.2, 29.0, 27.9, 27.0, and 27.1 g for female mice. No significant alterations in absolute or relative organ weights occurred in exposed male mice. Significant decreases in absolute weights of brain (9%), liver

(18%), and spleen (28%) and relative weight of spleen (24%) occurred in high-dose females compared with controls. Histopathological examination of organs was not conducted, but the study authors noted that cataracts were not formed in exposed mice (methods used to assess the presence of cataracts were not specified).

Examination of hematological parameters (including numbers of leucocytes, erythrocytes, and platelets and determination of hematocrit and hemoglobin) at termination revealed only slight, but statistically significant, increases in hemoglobin in high-dose females only; however, the hematological data were not shown in the available report. Chemical analysis of serum showed statistically significant decreased BUN in all exposed female groups. Compared with vehicle controls, the percent decreases in BUN were 16, 20, and 34% for the 5.3, 53, and 133 mg/kg/day groups, respectively. Increased serum globulin (about 55%) and protein (about 40%) occurred in the two highest female dose groups compared with vehicle control values. Hepatic microsomal activities of aniline hydroxylase and aminopyrine N-demethylases were not statistically significantly changed in exposed versus control mice, but benzo[a]pyrene hydroxylase activities were statistically significantly decreased in exposed groups compared with control values (0.8, 0.62*, 0.55* and 0.41* nmol/minute/mg protein for males in the control through high-dose group, and 1.40, 1.24, 1.13*, and 0.89* nmol/minute/mg protein for females; statistically significant differences from control noted with *). The toxicological significance of the statistically significant changes in hematological parameters, hepatic enzyme activities, and serum chemical parameters is not clear, and these changes are not considered to be adverse.

No exposure-related responses were found in a battery of immunological assays (humoral immune response, lymphocyte responsiveness, delayed-type hypersensitivity response, popliteal lymph node response, and bone marrow function); immunotoxic responses were observed in positive controls given i.p. injections of 50 mg/kg cyclophosphamide on days 87, 88, 89, and 90. The study identified a LOAEL of 133 mg/kg/day and a NOAEL of 53 mg/kg/day for statistically significant decreases in absolute weight of brain, liver, and spleen and relative weight of spleen in female mice, but not male mice. The effects were only observed in female mice, and histological changes in these organs were not observed in Fischer 344 rats (NTP 1980b) or B6C3F1 mice (NTP 1980a) exposed to naphthalene for 13 weeks.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Naphthalene
CAS Numbers: 91-20-3
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: Chronic-duration toxicity studies of oral exposure to naphthalene were not located, precluding derivation of a provisional chronic-duration oral MRL.

Rationale for Not Deriving an MRL: Chronic-duration toxicity studies of oral exposure to naphthalene were not located.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1-Methylnaphthalene
CAS Numbers: 90-12-0
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: The available data are not sufficient for derivation of a provisional acute-duration inhalation MRL for 1-methylnaphthalene.

Rationale for Not Deriving an MRL: The database of acute-duration inhalation toxicity studies of 1-methylnaphthalene is limited, consisting of only two animal studies (Korsak et al. 1998; Świercz and Stepnik 2020). Korsak et al. (1998) evaluated neurological endpoints of pain sensitivity (hotplate) and rotarod performance in rats following a single 4-hour exposure to 0, 26, 44, or 70 ppm. No other endpoints were assessed. The other study (Świercz and Stepnik 2020) was focused on assessment of serum corticosterone levels. Rats were exposed to concentrations of 0, 9.54, and 38.15 ppm 1-methylnaphthalene on 6 hours/day for 5 days and endpoints were limited to body weights, food and water consumption, and serum corticosterone levels. The limited endpoints evaluated in these studies do not provide enough information on the toxicity of 1-methylnaphthalene after acute-duration inhalation exposure. Thus, a provisional acute-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1-Methylnaphthalene
CAS Numbers: 90-12-0
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
Provisional MRL: $9x10^{-5}$ ppm ($5x10^{-4}$ mg/m^3)
Critical Effect: Nasal mucous cell hyperplasia
Reference: Kim et al. 2020
Point of Departure: BMCL of 0.06 ppm ($BMCL_{HEC}$ of 0.0027 ppm)
Uncertainty Factor: 30
LSE Graph Key: 4
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of $9x10^{-5}$ ppm was derived for 1-methylnaphthalene based on mucous cell hyperplasia in male F344 rats following exposure for 6 hours/day, 5 days/week for 13 weeks (Kim et al. 2020). The MRL is based on a $BMCL_{10}$ of 0.06 ppm, which was adjusted for continuous duration exposure and converted to a $BMCL_{HEC}$ of 0.0027 ppm. The $BMCL_{HEC}$ was divided by a total uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after applying dosimetric adjustment).

Selection of the Critical Effect: The database of intermediate-duration inhalation toxicity studies for 1-methylnaphthalene is limited to a single 13-week study in male and female F344 rats (Kim et al. 2020). The effects observed at the lowest exposure concentrations in male (0.5 ppm) and female (4 ppm) rats include effects on the respiratory tract (nasal lesions).

Selection of the Principal Study: Only one intermediate-duration inhalation study of 1-methylnaphthalene was located (Kim et al. 2020). In this study, male and female F344 rats were exposed by inhalation for 13 weeks and comprehensive toxicological endpoints were evaluated. This study was selected as the primary study for derivation of a provisional intermediate-duration inhalation MRL.

Summary of the Principal Study:

Kim YS, Lee MJ, Seo DS, et al. 2020. Thirteen-week inhalation toxicity study of 1-methylnaphthalene in F344 rats. Toxicol Res 36:13-20.

Kim et al. (2020) evaluated intermediate-duration toxicity of inhaled 1-methylnaphthalene. Groups of F344 rats (10/sex/group) were exposed, whole body, to 1-methylnaphthalene (purity 97.3%) vapor at concentrations of 0, 0.52, 4.08, or 30.83 ppm (analytical) for 6 hours/day, 5 days/week, for 13 weeks. Mortality and clinical signs were recorded daily during the exposure period and body weights were measured twice a week for 4 weeks and weekly thereafter. Food consumption was measured with unknown frequency. After the exposure period, rats were sacrificed, and blood was collected for analysis of hematological parameters (including differential white blood counts and clotting parameters) and serum chemistry. Bronchoalveolar lavage (BAL) fluid was collected from 5/sex/group and examined for differential cell counts and LDH. Rats then underwent necropsy followed by excision of organs for organ weights (adrenal glands, brain, heart, kidneys, liver, spleen, testes, thymus, epididymides, lungs, ovaries,

and uterus) and comprehensive histopathology including gonads, lungs, and nasopharyngeal tissue. Histological analysis was performed on fixed tissues from the control and high-exposure animals only, except for nasopharyngeal tissue, which was examined from animals from all exposure groups.

No mortality occurred, and no clinical signs of toxicity were observed. Body weights were comparable to controls throughout the study. No statistically significant changes were found in differential cell counts or LDH in BAL. At 30.83 ppm, activated partial thromboplastin time (APTT) and prothrombin time (PT) were significantly increased in males by 8 and 10%, respectively, and PT was significantly increased in females by 8%. Serum chemistry changes included significantly increased albumin (4%) and sodium (1%) in males at 30 ppm. No significant changes in organ weights were observed. Histopathological changes in nasopharyngeal tissue of both sexes included mucous cell hyperplasia; males also exhibited transitional epithelial cell hyperplasia. Table A-6 shows the incidences and severities of these changes. No other treatment-related histopathology changes were noted.

Table A-6. Incidence of Nasal Lesions in Rats Exposed to 1-Methylnaphthalene via Inhalation for 13 Weeks

	Exposure concentration (ppm)			
Nasal lesion	0	0.52	4.08	30.83
Males				
Mucous cell hyperplasia, minimal	0/10	4/10	4/10	0/10
Mucous cell hyperplasia, mild	0/10	0/10	6/10	0/10
Mucous cell hyperplasia, moderate	0/10	0/10	0/10	10/10
Mucous cell hyperplasia (total)	**0/10**	**4/10**	**10/10**	**10/10**
Transitional epithelial cell hyperplasia, mild	0/10	0/10	5/10	5/10
Females				
Mucous cell hyperplasia, minimal	0/10	0/10	3/10	2/10
Mucous cell hyperplasia, mild	0/10	0/10	0/10	6/10
Mucous cell hyperplasia, moderate	0/10	0/10	0/10	2/10
Mucous cell hyperplasia (total)	0/10	0/10	3/10	10/10

Bold indicates dataset selected for benchmark dose modeling.

Source: Kim et al. 2020

Selection of the Point of Departure for the MRL: BMD modeling was conducted to identify a POD using the data for mucous cell hyperplasia (all severity levels) in male rats administered 1-methylnaphthalene via inhalation for 6 hours/day, 5 days/week for 13 weeks. The data modeled are shown in bold in Table A-6. Male rat incidence data were selected because the males exhibited effects at the lowest concentration, while females did not. The data were fit to all available dichotomous models in EPA's BMDS (version 3.2) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMC (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. BMDS recommended the frequentist dichotomous Hill model for mucous cell hyperplasia, and after verifying the model fit by the four criteria

listed above, this model was selected as the basis for estimating this MRL. The model predictions are presented in Table A-7 and the fit of the selected model is presented in Figure A-2.

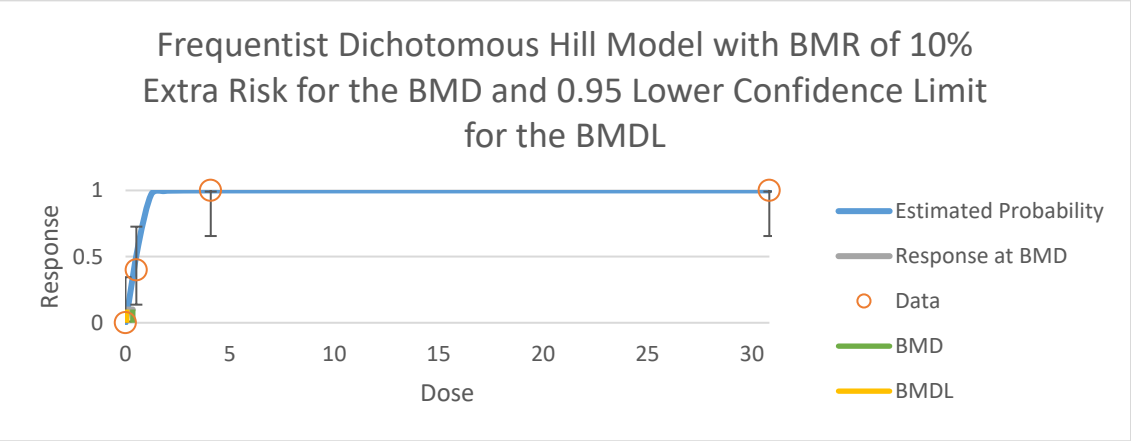
Table A-7. Model Predictions for Increased Incidence of Nasal Mucous Cell Hyperplasia in Male Rats Exposed to 1-Methylnaphthalene via Inhalation (Kim et al. 2020)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Dichotomous Hill[d]	**0.35**	**0.06**	**0.9993**	**17.46**	**-0.0004**	**-0.0005**
Gamma[e]			1.0000	17.46	-0.0007	-0.0007
Log-Logistic[f]	0.35	0.06	0.9993	17.46	-0.0004	-0.0004
Multistage Degree 3[g]			0.9969	19.46	-0.0004	-0.0004
Multistage Degree 2[g]			1.0000	17.46	-0.0004	-0.0004
Multistage Degree 1[g]			0.9825	15.74	-0.0004	-0.0004
Weibull[e]			0.9967	17.47	-0.0004	-0.0004
Logistic	0.27	0.15	0.7612	17.41	-0.9332	0.5430
Log-Probit			1.0000	17.46	-0.0004	-4.5×10^{-10}
Probit	0.46	0.30	0.2916	21.68	-1.5295	0.83

[a]BMC and BMCLs values for models that do not provide adequate fit or yield BMCLs more than 10-fold lower than the lowest nonzero exposure concentration are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]All models provided an adequate fit to the data. BMCLs were not sufficiently close (differed by >3-fold). Therefore, the model with the lowest BMCL was selected (Dichotomous Hill).
[e]Power restricted to ≥1.
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

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

Figure A-2. Fit of the Dichotomous Hill Model to Data for 1-Methylnaphthalene, Mucous Cell Hyperplasia in Male Rats (Kim et al. 2020)



Calculations

Adjustment for Intermittent Exposure: The animals in the study by Kim et al. (2020) were exposed 6 hours/day, 5 days/week. Therefore, the BMCL of 0.06 ppm was adjusted for intermittent exposure as follows:

$$BMCL_{ADJ} = BMCL \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.06\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.011\ ppm$$

Human Equivalent Concentration: The critical effects of 1-methylnaphthalene were nasal lesions, therefore, the $BMCL_{10ADJ}$ was converted to a HEC by multiplying the $BMCL_{10}$ by the rat-specific regional gas dose ratio that corresponds with the extrathoracic region ($RGDR_{ET}$). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994):

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h} = \frac{0.254}{15} \div \frac{13.8}{200} = 0.25$$

where:
V_{E_a} = ventilation rate for male F344 rats = 0.254 L/minute (EPA 2012)
SA_a = surface area of the extrathoracic region in rats = 15 cm^2 (EPA 1994)
V_{E_h} = ventilation rate for humans = 13.8 L/minute (EPA 1994)
SA_h = surface area of the extrathoracic region in humans = 200 cm^2 (EPA 1994)

Applying this equation results in an RGDR of 0.25 for extrathoracic effects in rats, and the HEC is calculated as:

$$BMCL_{10HEC} = BMCL_{10ADJ} \times RGDR = 0.011\ ppm \times 0.25 = 0.0027\ ppm$$

Uncertainty Factor: The $BMCL_{HEC}$ of 0.0027 ppm is divided by a total UF of 30:

- 10 for human variability
- 3 for animal to human extrapolation after dosimetric adjustment

MRL = $BMCL_{HEC}$ ÷ UFs
MRL = 0.0027 ppm ÷ (3x10) = 0.00009 ppm ($9x10^{-5}$ ppm)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Significantly increased incidences of pulmonary alveolar proteinosis were observed in mice exposed chronically by dietary administration (Murata et al. 1993). In addition, the association between 1-methylnaphthalene exposure and respiratory effects is supported by findings of pulmonary alveolar proteinosis in mice exposed to the structurally related compound 2-methylnaphthalene in the diet (Murata et al. 1997) and in mice exposed by dermal application to a mixture of methylnaphthalenes (Emi and Konishi 1985; Murata et al. 1992).

The odor threshold for 1-methylnaphthalene in air is 0.12 mg/m^3 or 0.02 ppm (see Section 4.2).

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1-Methylnaphthalene
CAS Numbers: 90-12-0
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: Chronic-duration toxicity studies of inhaled 1-methylnaphthalene were not located, precluding derivation of a provisional chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: Chronic-duration toxicity studies of inhaled 1-methylnaphthalene were not located.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1-Methylnaphthalene
CAS Numbers: 90-12-0
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: Acute-duration oral toxicity studies of inhaled 1-methylnaphthalene were not located, precluding derivation of a provisional acute-duration oral MRL.

Rationale for Not Deriving an MRL: Acute-duration toxicity studies of orally-administered 1-methylnaphthalene were not located.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1-Methylnaphthalene
CAS Numbers: 90-12-0
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
Provisional MRL 0.6 mg/kg/day
Critical Effect: Increased liver weight
Reference: NITE 2009
Point of Departure: $BMDL_{1SD}$ of 64 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 1
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.6 mg/kg/day was derived for 1-methylnaphthalene based on a $BMDL_{1SD}$ of 64 mg/kg/day for increased relative liver weights in male Sprague-Dawley rats. An uncertainty factor of 100 (10 for human variability and 10 for extrapolation from animals to humans) was applied to the $BMDL_{1SD}$.

Selection of the Critical Effect: There is one study that evaluated intermediate-duration oral exposure to 1-methylnaphthalene (NITE 2009). NITE (2009) was a combined repeat-dose and reproductive/ developmental screening study in rats that followed OECD 422 guidelines. Treatment-related effects observed in the study consisted of increased absolute and relative liver weights and increased relative kidney weights in males, and increased relative liver weights in females, all occurring at the highest dose (250 mg/kg/day). Liver effects were selected as the critical effect because liver weights were affected in both sexes, both absolute and relative liver weights were affected in males, and the magnitude of liver weight change was larger than the magnitude of kidney weight change.

Selection of the Principal Study: NITE 2009 is the only available intermediate-duration oral exposure study. This study evaluated a comprehensive set of endpoints and identified both NOAEL and LOAEL values, so it was selected as the principal study.

Summary of the Principal Study:

NITE. 2009. 1-Methylnapthalene summary: [Combined repeat dose and reproductive/developmental toxicity screening test of 1-methylnaphthalene by oral administration in rats]. Japanese National Institute of Technology and Evaluation. https://www.nite.go.jp/chem/jcheck/tempfile_list.action?tpk=23402&ppk=7239&kinou=100&type=ja. (Japanese)

In a combined repeated dose reproduction/developmental toxicity screening study, groups of Sprague-Dawley rats (12/sex/group) were housed as breeding pairs and administered 1-methylnaphthalene via gavage in olive oil at doses of 0, 10, 50, 250 mg/kg/day for approximately 42 days. Animals were administered the test substance starting during premating (14 days), throughout mating, and gestation until lactation day (LD) 4 in females and from premating through sacrifice (42 days) in males. A group of five per sex in the control and high dose groups were included in a 14-day untreated recovery period. An additional satellite group of five unmated females were treated with the control and high dose groups.

During treatment, rats were observed for mortality and clinical signs of toxicity twice daily. Neurobehavioral observations were evaluated weekly including open field test (rises, clonic and tonic involuntary movements, pace, mobility, wakefulness, behavior, defecations, and urinations) and FOB tests were performed on 5/sex/group during the last week of treatment. Body weights and food consumption were evaluated throughout the study (unknown intervals). At sacrifice, endpoints evaluated included hematology, clinical chemistry (including globulin differentiation), urinalysis (control and high dose only), gross necropsy, organ weights, and histopathology. Reproductive (fertility index, estrous length, days to copulation, conception rate, numbers pregnant, corpora lutea, implantation index, gestation period, pre- and post-implantation loss, delivery and birth indices, and nursing status) and developmental endpoints (pup survival rate at birth, sex ratio, pup body weight, and number of live/dead pups on postnatal days [PNDs] 0 and 4, and examination of pups at sacrifice on PND 4 for external abnormalities) were evaluated.

No treatment-related adverse effects were observed on mortality, clinical signs of toxicity, body weights, food consumption, hematology, urinalysis, reproduction, or development. There were no significant differences between treated and control groups in the behavioral observations in the open field or FOB. Organ weight changes were observed at the highest dose, as shown in Table A-8. Males in the 250 mg/kg/day group had increases in absolute and relative liver weights and relative kidney weights at the end of exposure. Females of the 250 mg/kg/day group had increased relative liver weights, but no change in absolute liver weights. Histopathology evaluations did not show any treatment-related changes.

Table A-8. Significant Organ Weight Changes in Rats Exposed to 1-Methylnaphthalene via Gavage for 42 Days

	Dose (mg/kg/day)			
Nasal lesion	0	10	50	250
Males				
Relative liver weight (g%)	**2.628±0.233**	**2.678±0.223 (+2%)**	**2.685±0.17 (+2%)**	**3.309±0.416 (+26%)[a]**
Absolute liver weight (g)	12.94±1.905	12.895±1.604 (−0%)	13.043±1.272 (+1%)	15.159±1.934 (+17%)[a]
Relative kidney weight (g%)	0.593±0.057	0.626±0.053 (+6%)	0.62±0.053 (+5%)	0.683±0.06 (+15%)[a]
Mated females				
Relative liver weight (g%)	**3.193±0.227**	**3.148±0.275 (−1%)**	**3.188±0.169 (−0%)**	**3.521±0.373 (+10%)[a]**
Unmated females				
Relative liver weight (g%)	2.368±0.138	Not tested	Not tested	2.663±0.106 (+12%)[a]

[a]Significantly different from control at p<0.05 by Student's t-test or Dunnett's test performed by the study authors.

Bold indicates datasets selected for benchmark dose modeling.

Source: NITE 2009

Selection of the Point of Departure for the MRL: BMD modeling was conducted to identify a POD using the data for relative liver weight in male and female rats given 1-methylnaphthalene by gavage in a repeated dose toxicity and reproduction/developmental study. BMD modeling of continuous data (relative liver weight) was conducted with the EPA's BMDS (version 3.2.0.1). For these data, the

Exponential, Hill, Linear, Polynomial, and Power continuous models available within the software were fit employing a BMR of 1 SD. An adequate fit was judged based on the $\chi 2$ goodness-of-fit p-value ($p>0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2; p-value >0.1), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (p-value <0.1), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3; p-value <0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied >3-fold; otherwise, the BMDL from the model with the lowest AIC was selected.

For both the male and female rat relative liver weight data, the constant variance model did not provide an adequate fit to the data (Test 2; p-value < 0.1); however, the nonconstant variance model did provide an adequate fit. With the nonconstant variance model applied, all models except for the Exponential 5 and Hill models provided adequate fit to the means for both datasets. For both datasets, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected: this was the Polynomial 3-degree model for both datasets. Predicted BMD_{1SD} and $BMDL_{1SD}$ values for male rat relative liver weight data were 166 and 64 mg/kg/day, respectively. Predicted BMD_{1SD} and $BMDL_{1SD}$ values for female rat relative liver weight data were 212 and 109 mg/kg/day, respectively. The BMD/BMDL values considered for MRL derivation are presented in Tables A-9 and A-10 (males and females, respectively) and the fits of the selected models are presented in Figures A-3 and A-4 (males and females, respectively). The $BMDL_{1SD}$ of 64 mg/kg/day from modeling of the male rat data was lower than the $BMDL_{1SD}$ for females and was selected as the POD for MRL derivation.

Table A-9. Results from Benchmark Dose (BMD) Analysis (Nonconstant Variance) of Increased Relative Liver Weight in Male Rats Following Oral Exposure to 1-Methylnaphthalene (NITE 2009)

					Scaled residuals[c]	
Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Dose below BMD	Dose above BMD
Exponential (model 2)[d]	80.41	56.62	0.35	3.69	-0.8605	0.2692
Exponential (model 3)[d]	188.61	65.54	0.62	3.85	0.2628	-0.0030
Exponential (model 4)[d]	75.67	75.31	0.29	4.05	-0.9530	0.3611
Exponential (model 5)[d]			NA	5.85	0.2542	-0.0012
Hill[d]			NA	5.85	0.2520	-0.0013
Polynomial (3-degree)[d,e]	**165.80**	**63.73**	**0.89**	**1.85**	**0.1818**	**-0.0194**
Polynomial (2-degree)[d]	137.23	62.66	0.84	1.94	0.0009	0.0012
Power[d]	178.39	63.63	0.62	3.85	0.2494	-0.0036

Table A-9. Results from Benchmark Dose (BMD) Analysis (Nonconstant Variance) of Increased Relative Liver Weight in Male Rats Following Oral Exposure to 1-Methylnaphthalene (NITE 2009)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Linear	75.67	51.57	0.29	4.05	-0.9530	0.3615

[a]BMD and BMDL values for models that do not provide adequate fit or yield BMDLs more than 10-fold lower than the lowest nonzero dose are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model (lowest AIC). The constant variance model did not provide an adequate fit to the data (Test 2; p-value < 0.1); however, the nonconstant variance model did provide an adequate fit. With the nonconstant variance model applied, all models except for the Exponential 5 and Hill models, provided adequate fit to the means. Of these models, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Polynomial 3-degree model).

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

Figure A-3. Fit of the 3-Degree Polynomial Model (Nonconstant Variance) to Data for 1-Methylnaphthalene, Relative Liver Weight in Male Rats (NITE 2009)

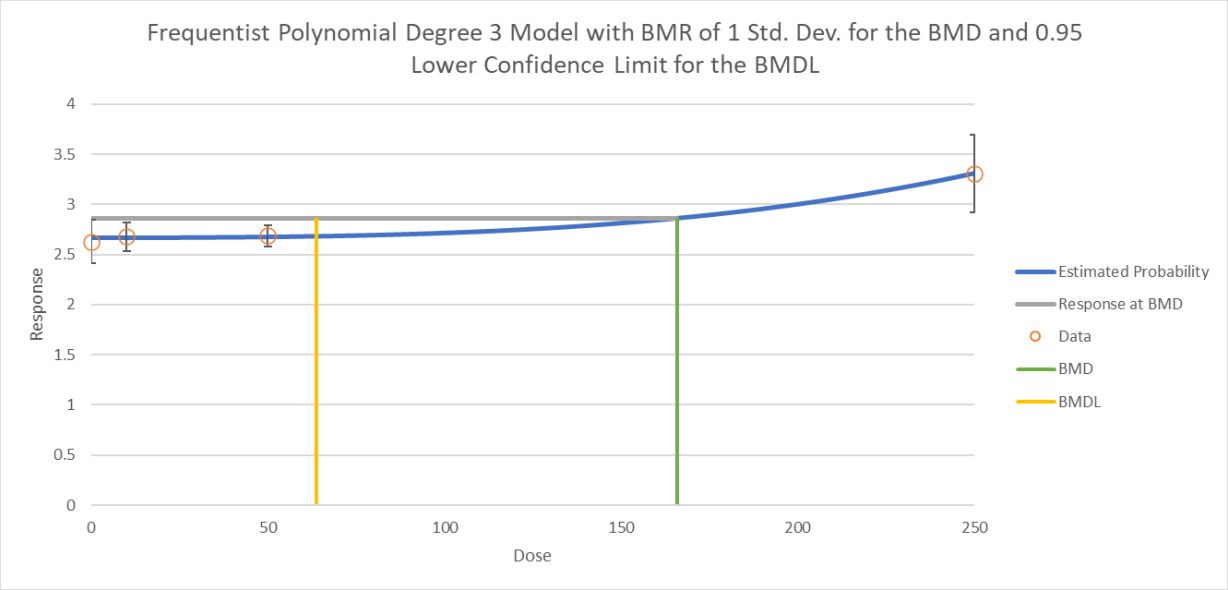


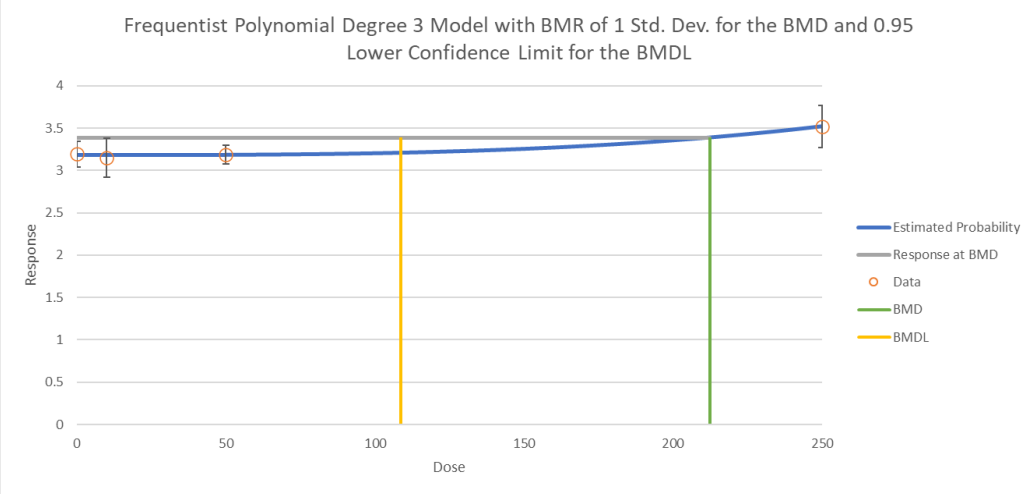
Table A-10. Results from Benchmark Dose (BMD) Analysis (Nonconstant Variance) of Increased Relative Liver Weight in Female Rats Following Oral Exposure to 1-Methylnaphthalene (NITE 2009)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential (model 2)[d]	152.66	124.78	0.45	9.18	-0.51	0.16
Exponential (model 3)[d]	235.64	109.65	0.68	9.74	0.14	-2.6×10^{-5}
Exponential (model 4)[d]	150.40	92.52	0.19	11.28	-0.54	0.19
Exponential (model 5)[d]			NA	11.74	0.14	0.0008
Hill[d]			NA	11.74	0.14	-0.001
Polynomial (3-degree)[d,e]	**212.35**	**108.64**	**0.98**	**5.78**	**0.11**	**-0.001**
Polynomial (2-degree)[d]	194.57	105.04	0.84	7.93	0.00	0.007
Power[d]	245.04	107.35	0.68	9.74	0.14	-0.002
Linear	150.34	92.29	0.43	9.27	-0.54	0.18

[a]BMD and BMDL values for models that do not provide adequate fit or yield BMDLs more than 10-fold lower than the lowest nonzero dose are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model (lowest AIC). The constant variance model did not provide an adequate fit to the data (Test 2; p-value < 0.1); however, the nonconstant variance model did provide an adequate fit. With the nonconstant variance model applied, all models except for the Exponential 5 and Hill models, provided adequate fit to the means. Of these models, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Polynomial 3-degree model).

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

Figure A-4. Fit of the 3-Degree Polynomial Model (Nonconstant Variance) to Data for 1-Methylnaphthalene, Relative Liver Weight in Female Rats (NITE 2009)



Calculations

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{1SD}$ of 64 mg/kg/day was divided by a composite UF of 100:

- 10 for human variability
- 10 for animal to human extrapolation

This results in the following MRL:

$$MRL = \frac{BMDL}{UF} = \frac{64}{100} \approx 0.6 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No liver effects were reported in the chronic-duration dietary study of 1-methylnaphthalene (Murata et al. 1993), but the estimated doses were lower, and there is uncertainty in the dose estimates for Murata et al. (1993) due to potential for volatilization of the test material from the diet. The association between 1-methyl-naphthalene exposure and adverse liver effects is supported by observations of liver changes (increased liver weights and serum enzyme levels, and/or histopathology changes) in animals exposed to the structurally related compounds, 2-methylnaphthalene (Świercz et al. 2011) and naphthalene (Chen et al. 2012; Katsnelson et al. 2014; Zhang et al. 2016).

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1-Methylnaphthalene
CAS Numbers: 90-12-0
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
Provisional MRL: 0.07 mg/kg/day
Critical Effect: Increased pulmonary alveolar proteinosis
Reference: Murata et al. 1993
Point of Departure: LOAEL of 71.6
Uncertainty Factor: 1,000
LSE Graph Key: 2
Species: Mice

MRL Summary: A provisional chronic-duration oral MRL of 0.07 mg/kg/day was derived for 1-methylnaphthalene based on a LOAEL of 71.6 mg/kg/day for increased incidences of pulmonary alveolar proteinosis in male and female mice administered 1-methylnaphthalene in the diet for 81 weeks. The LOAEL was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: There is one chronic-duration study that evaluated the effects of 1-methylnaphthalene (Murata et al. 1993). The only noncancer effect observed was pulmonary alveolar proteinosis at both doses and in both sexes.

Selection of the Principal Study: The only study of chronic-duration oral exposure to 1-methylnaphthalene was the 81-week dietary study by Murata et al. (1993). This study evaluated a comprehensive list of endpoints and was selected as the principal study.

Summary of the Principal Study:

Murata Y, Denda A, Maruyama H, et al. 1993. Chronic toxicity and carcinogenicity studies of 1-methyl-naphthalene in B6C3F1 mice. Fundam Appl Toxicol 21:44-51.

Groups of B6C3F1 mice (50/sex/group) were fed a diet of 0, 0.075, or 0.15% 1-methylnaphthalene (>97% purity) for 81 weeks. Doses consumed were estimated to be 0, 71.6, and 140.2 mg/kg/day in males and 0, 75.1 and 143.7 mg/kg/day in females. Mortality and clinical observations were performed daily. Body weights were measured weekly for 16 weeks and biweekly, thereafter. Food consumption was monitored at unknown intervals. After the treatment period, animals were sacrificed, and blood was collected for hematology and serum chemistry. Animals underwent gross necropsy and selected organs were weighed (brain, salivary glands, heart, thymus, lungs, liver, pancreas, spleen, kidneys, and testes) and evaluated histologically (brain, salivary glands, heart, thymus, lungs, liver, pancreas, spleen, kidneys, testes, adrenals, trachea, stomach, small intestine, large intestine, seminal vesicles, ovaries, uterus, vagina, mammary glands, skeletal muscle, eyes, Harderian glands, spinal cord, bone (sternal, rib, vertebral), skin, and gross lesions).

There were no treatment-related mortalities. No effects were observed on clinical signs, body weights, body weight gain, or food consumption. Increased monocytes were noted in treated groups of both sexes; no other treatment-related changes in hematology were observed. No treatment-related changes were

noted in serum chemistry or organ weights. Increased incidences of lung lesions characterized as pulmonary alveolar proteinosis were observed at both doses and in both sexes. This lesion was characterized by an accumulation of phospholipids in the alveolar lumens that appeared grossly as white protuberant nodules approximately 1–5 mm in diameter. The incidences of pulmonary alveolar proteinosis in controls, low-dose, and high-dose groups were 4/49, 23/50, and 19/50 in males and 5/50, 23/50, and 17/49 in females, respectively (see Table A-11). In addition to the nonneoplastic lesions, increased incidences of lung tumors were observed in males (but not females) at both doses. No other treatment-related increased incidences of tumors were observed.

Table A-11. Incidences[a] of Pulmonary Alveolar Proteinosis in Mice Exposed to 1-Methylnaphthalene in the Diet for 81 Weeks

	Dose in mg/kg/day		
	0	71.6	140.2
Males	4/49 (8.2%)	23/50 (46%)	19/50 (38%)
Females	5/50 (10%)	23/50 (46%)	17/39 (34.7%)

[a]Number affected/number examined (percent).

Source: Murata et al. 1993

Selection of the Point of Departure for the MRL: The lowest exposure level (71.6 mg/kg/day) was a LOAEL for increased incidence of pulmonary alveolar proteinosis in male and female mice. The incidences of this lesion in male and female mice (see Table A-11) were subjected to BMD modeling to determine a POD for the provisional chronic-duration oral MRL. The data were fit to all available dichotomous models in EPA's BMDS (version 3.2.0.1) using BMRs of 10% and 5% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMD (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. None of the models provided adequate fit for either the male or female data. Therefore, the LOAEL of 71.6 mg/kg/day was selected as the POD for the derivation of the provisional chronic-duration oral MRL.

Calculations: Not applicable

Uncertainty Factor: The LOAEL of 71.6 mg/kg/day was divided by a total uncertainty factor of 1,000:

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

This results in the following MRL:

$$MRL = \frac{LOAEL}{UF} = \frac{71.6}{1{,}000} \approx 0.07 \frac{mg}{kg}/day$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Increased incidences of pulmonary alveolar proteinosis have also been reported in B6C3F1 mice exposed to the related compound 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1997), and in mice

dermally exposed to a mixture of 1- and 2-methylnaphthalene for 30–61 weeks (Emi and Konishi 1985; Murata et al. 1992).

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Methylnaphthalene
CAS Numbers: 91-57-6
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: Data are insufficient for derivation of a provisional acute-duration inhalation MRL for 2-methylnaphthalene.

Rationale for Not Deriving an MRL: The only study that evaluated acute-duration toxicity for 2-methylnaphthalene was Korsak et al. (1998). In this study, male mice and rats were exposed to 2-methylnaphthalene for 4 hours for evaluation of neurological endpoints (pain sensitivity using hot plate test and rotarod performance). The limited endpoints evaluated in this study do not provide enough information on the toxicity of 2-methylnaphthalene after acute-duration inhalation exposure. Thus, a provisional acute-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Methylnaphthalene
CAS Numbers: 91-57-6
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
Provisional MRL: $3x10^{-4}$ ppm (0.002 mg/m^3)
Critical Effect: Bronchial goblet cell metaplasia
Reference: Świercz et al. (2011)
Point of Departure: $LOAEL_{HEC}$ of 0.081 ppm
Uncertainty Factor: 300
LSE Graph Key: 5
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of $3x10^{-4}$ ppm was derived for 2-methylnaphthalene based on the $LOAEL_{HEC}$ of 0.081 ppm for increased incidences of respiratory bronchial goblet cell metaplasia in male and female rats exposed to 2-methylnaphthalene 6 hours/day, 5 days/week, for 4 weeks. The $LOAEL_{HEC}$ of 0.081 ppm was divided by a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans after dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: There was only one intermediate-duration inhalation study of 2-methylnaphthalene (Świercz et al. 2011) but this study evaluated a comprehensive list of endpoints. Groups of Wistar rats were exposed to 2-methylnaphthalene for 6 hours/day, 5 days/week, for 4 weeks. The most sensitive effect was metaplasia of goblet cells in the primary and lobar bronchi. A LOAEL of 0.34 ppm was identified at the lowest exposure level and no NOAEL was identified.

Selection of the Principal Study: One study was available for intermediate-duration inhalation exposure to 2-methylnaphthalene (Świercz et al. 2011). This study evaluated a comprehensive list of endpoints and identified a LOAEL for respiratory effects (no NOAEL was identified). Therefore, Świercz et al. (2011) was selected as the study for derivation of the intermediate-duration inhalation MRL.

Summary of the Principal Study:

Świercz R, Wąsowicz W, Stetkiewicz J, et al. 2011. 4-Week inhalation toxicity of 2-methylnaphthalene in experimental animals. Int J Occup Med and Environ Health 24(4):399-408.

Groups of Wistar rats (5/sex/group) were exposed whole body in dynamic chambers to 2-methylnaphthalene (97% purity) vapor at measured concentrations of 0, 2.0, 11.0, or 51.0 mg/m^3 (corresponding 0, 0.34, 1.89, and 8.77 ppm) for 6 hours/day, 5 days/week for 4 weeks. Body weights and food consumption were measured weekly. Blood was collected for hematology (including clotting parameters) and clinical chemistry after the end of exposure. Animals were sacrificed and selected organs (lungs with larynx and trachea, liver, kidneys, heart, spleen, adrenals, testes, and ovaries) were collected, weighed, and prepared for histology.

Body weights and food consumption were comparable to controls in all exposure groups. Hematology findings in male rats suggested a trend toward increased reticulocyte counts, but no group was significantly different from the control. Female rats had significantly increased reticulocyte counts at 1.89 and 8.77 ppm. There were no other treatment-related effects on hematology in exposed males or

females. In male rats, serum alkaline phosphatase was increased in a concentration-related manner in all exposure groups and serum γ-glutamyl transferase (GGT) was increased at 8.77 ppm. In male rats, serum levels of albumin were decreased at 1.89 and 8.77 ppm. In female rats, serum levels of urea were increased at 8.77 ppm. Absolute and relative liver weights were reduced in male rats at all exposure concentrations. In female rats, reduced liver weights were observed at 8.77 ppm. In female rats, heart weights were reduced in a concentration-related manner and kidney weights were decreased at 1.89 and 8.77 ppm.

Histopathology changes related to treatment were observed in the respiratory tract and liver. Incidences of the effects are shown in Table A-12. Respiratory tract lesions included goblet cell metaplasia, hyperplasia of the peribronchial lymphatic tissue, and proteinosis with mononuclear cell infiltration. Increased incidences of goblet cells in the bronchi were observed in both sexes at all exposure levels. The study authors implied that all animals had goblet cells in the bronchi at 8.77 ppm but did not report actual incidences. Hyperplasia of the peribronchial lymphatic tissue was noted at all exposure levels in males and at ≥1.89 ppm in females. Mononuclear cell infiltration and proteinosis were reported in both sexes at ≥1.89 ppm. In the liver, bile duct hyperplasia was observed ≥1.89 ppm in both males and females (see Table A-12).

Table A-12. Incidence of Histopathology Changes in Rats Exposed to 2-Methylnaphthalene via Inhalation for 4 Weeks

	Exposure concentration (ppm)			
Target tissue and lesion	0	0.34	1.89	8.77
Males				
Bronchi-goblet cell metaplasia	0/5	2/5	4/5	Not reported
Bronchi-hyperplasia of peribronchial lymphatic tissue	0/5	1/5	1/5	2/5
Bronchi-proteinosis	0/5	0/5	3/5	3/5
Liver-bile duct hyperplasia	0/5	0/5	2/5	5/5
Females				
Bronchi-goblet cell metaplasia	0/5	3/5	3/5	Not reported
Bronchi-hyperplasia of peribronchial lymphatic tissue	0/5	0/5	4/5	3/5
Bronchi-proteinosis	0/5	0/5	4/5	3/5
Liver-bile duct hyperplasia	0/5	0/5	3/5	5/5

Source: Świercz et al. 2011

Selection of the Point of Departure for the MRL: As shown in Table A-12, the lowest exposure level (0.34 ppm) was a LOAEL for increased incidences of goblet cell metaplasia in the primary and lobar bronchi in male and female rats. Because the publication did not report the incidences of this effect at the highest exposure level, BMD modeling was not possible for these data. Therefore, the LOAEL was selected as the POD for derivation of the provisional intermediate-duration inhalation MRL.

Adjustment for Intermittent Exposure: The animals in the study by Świercz et al. (2011) were exposed at a frequency of 6 hours/day, 5 days/week. Therefore, the LOAEL of 0.34 ppm was adjusted for intermittent exposure as follows:

$$LOAEL_{ADJ} = LOAEL \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.061\ ppm$$

Human Equivalent Concentration: The critical effect at the LOAEL (bronchus goblet cell metaplasia) was in the tracheobronchial portion of the respiratory tract. Therefore, the $LOAEL_{ADJ}$ was converted to a $LOAEL_{HEC}$ using guidance from EPA (1994) on dosimetric adjustments for tracheobronchial effects. The $LOAEL_{ADJ}$ was converted to a $LOAEL_{HEC}$ using the RGDR for tracheobronchial effects (EPA 1994) calculated as follows:

$$RGDR_{TB} = \frac{(Dose_{TB})_a}{(Dose_{TB})_h} = \frac{(\frac{V_E}{SA_{tb}})_a}{(\frac{V_E}{SA_{tb}})_h} \frac{(e^{\frac{-SA_{et}}{V_E}})_a}{(e^{\frac{-SA_{et}}{V_E}})_h}$$

where:

$[V_E]_a$= minute volume for rats = 0.141 L/min
$SA_{TB\ a}$ = TB surface area for rats = 22.5 cm^2
$e^{-(SAet/Ve)_a}$ = Fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in rats = 0.899
$[V_E]_h$= minute volume for humans = 13.8 L/min
$SA_{TB\ h}$ = TB surface area for humans = 3200 cm^2
$e^{-(SAet/Ve)_a}$ = Fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in humans = 0.986

Applying this equation results in an RGDR of 1.33 for tracheobronchial effects in rats, and the HEC is calculated as:

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR = 0.061\ ppm \times 1.33 = 0.081\ ppm$$

Uncertainty Factor: The $LOAEL_{HEC}$ is divided by a total uncertainty factor of 300:

- 10 for human variability
- 10 for use of a LOAEL
- 3 for animal to human extrapolation after dosimetric adjustment

MRL = $LOAEL_{HEC}$ ÷ uncertainty factors
= 0.081 ppm ÷ (3x10x10) ≈ 0.0003 ppm ($3x10^{-4}$ ppm)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a clear target for 2-methylnaphthalene and the related compound, 1-methylnaphthalene, after oral exposure. Chronic-duration studies of these compounds in mice exposed via the diet have resulted in increased incidences of pulmonary alveolar proteinosis (Murata et al. 1993, 1997). Exposure to the related compound, naphthalene, via inhalation is also associated with effects on the respiratory tract in both mice and rats (Abdo et al. 2001; Carratt et al. 2016, 2019a; Cichocki et al. 2014; Dodd et al. 2010, 2012; NTP 1992a, 2000).

The odor threshold for 2-methylnaphthalene in air is in the range of 0.0581–0.2905 mg/m^3 or 0.0099–0.04939 ppm (see Section 4.2).

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Methylnaphthalene
CAS Numbers: 91-57-6
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: Chronic-duration toxicity studies of inhaled 2-methylnaphthalene were not located, precluding derivation of a provisional chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: Chronic-duration toxicity studies of inhaled 2-methylnaphthalene were not located.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Methylnaphthalene
CAS Numbers: 91-57-6
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: Acute-duration oral toxicity studies of 2-methylnaphthalene were not located, precluding derivation of a provisional acute-duration oral MRL.

Rationale for Not Deriving an MRL: Acute-duration oral toxicity studies of 2-methylnaphthalene were not located.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Methylnaphthalene
CAS Numbers: 91-57-6
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: Intermediate-duration oral toxicity studies of 2-methylnaphthalene were not adequate for derivation of a provisional intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: In a range-finding study, groups of B6C3F1 mice (10/sex/group) were fed diets containing 2-methylnaphthalene for 13 weeks delivering approximate average daily doses of 0, 31, 92, 276, 827, or 2,500 mg/kg/day (Murata et al. 1997). No histopathologic lesions were found in tissues and organs of male or female mice exposed to 827 or 2,500 mg/kg/day; tissues from mice in lower dose groups were not examined histologically. Decreased body weights, compared with control values, were seen at the three highest dose levels in both males and females, and were attributed to food refusal (Murata et al. 1997). The limited reporting of experimental details and results from this intermediate-duration study precludes its use as the basis of a provisional intermediate-duration oral MRL for 2-methylnaphthalene.

Agency Contacts (Chemical Managers): Gaston Casillas, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Methylnaphthalene
CAS Numbers: 91-57-6
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
Provisional MRL: 0.06 mg/kg/day
Critical Effect: Pulmonary alveolar proteinosis
Reference: Murata et al. 1997
Point of Departure: $BMDL_{05}$ of 6.4 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Mouse

MRL Summary: A provisional chronic-duration oral MRL of 0.06 mg/kg/day was derived for 2-methylnaphthalene based on increased incidences of pulmonary alveolar proteinosis in male mice fed 2-methylnaphthalene via diet (Murata et al. 1997). BMD modeling of the incidences yielded a $BMDL_{05}$ of 6.4 mg/kg/day; application of an uncertainty factor of 100 (10 for human variability and 10 for interspecies extrapolation) resulted in the MRL of 0.06 mg/kg/day.

Selection of the Critical Effect: Only one study evaluated the effects of chronic-duration oral exposure to 2-methylnaphthalene. Murata et al. (1997) evaluated a comprehensive list of toxicological endpoints in mice following dietary administration of 2-methylnaphthalene for 81 weeks. The only noncancer effect identified was an increased incidence of pulmonary alveolar proteinosis in both male and female mice. Thus, pulmonary alveolar proteinosis was selected as the critical effect.

Selection of the Principal Study: Murata et al. (1997) conducted the only chronic-duration oral study of 2-methylnaphthalene. This study evaluated comprehensive toxicological endpoints and was selected as the principal study.

Summary of the Principal Study:

Murata Y, Denda A, Maruyama H, et al. 1997. Chronic toxicity and carcinogenicity studies of 2-methyl-naphthalene in B6C3F1 mice. Fundam Appl Toxicol 36(1):90-93.

Groups of B6C3F1 mice (50/sex/group) were fed a diet of 0, 0.075, or 0.15% 2-methylnaphthalene (97% purity) for 81 weeks. Doses consumed were estimated by the study authors to be 0, 54.3, and 113.8 mg/kg/day in males and 0, 50.3 and 107.6 mg/kg/day in females. Observations for mortality and clinical signs were performed daily. Body weights were measured weekly for 16 weeks and biweekly thereafter. Food consumption was monitored at regular intervals. After the treatment period, animals were sacrificed, and blood was collected for hematology and serum chemistry. Animals underwent gross necropsy and selected organs were weighed (brain, salivary glands, heart, thymus, lungs, liver, pancreas, spleen, kidneys, and testes) and evaluated for histopathology (brain, salivary glands, heart, thymus, lungs, liver, pancreas, spleen, kidneys, testes, adrenals, trachea, stomach, small intestine, large intestine, seminal vesicles, ovaries, uterus, vagina, mammary glands, skeletal muscle, eyes, Harderian glands, spinal cord, bone, skin, and gross lesions).

There were no treatment-related mortalities. No effects were observed on clinical signs, body weights, body weight gain, or food consumption. Increased monocytes were noted in treated groups of both sexes.

No other treatment-related changes in hematology, and no effects on serum chemistry or organ weights were observed. Histopathology changes were seen only in the lungs of treated mice and were identified as pulmonary alveolar proteinosis, characterized by an accumulation of phospholipids in the alveolar lumens. The incidences of pulmonary alveolar proteinosis in controls, low-dose, and high-dose groups were 4/49, 21/49, and 23/49 in males and 5/50, 27/49, and 22/48 in females, respectively.

The study authors noted the rarity of pulmonary alveolar proteinosis among historical controls (not found in >5,000 controls) and considered the high incidence found in control animals to be related to potential inhalation of volatilized methylnaphthalene from the diet through improper ventilation in the exposure room.

Selection of the Point of Departure for the MRL: Pulmonary alveolar proteinosis was observed in both sexes at both doses. The incidences of this lesion are summarized in Table A-13.

Table A-13. Incidences[a] of Pulmonary Alveolar Proteinosis in B6C3F1 Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks

	Dose (mg/kg/day)		
	0	54.3 (males); 50.3 (females)	113.8 (males); 107.6 (females)
Males	4/49	21/49[b]	23/49[b]
Females	5/50	27/49[b]	22/48[b]

[a]Incidence reported as number affected/number examined.
[b]Statistically significantly different from control at p<0.05 as reported by study authors.

Source: Murata et al. 1997

BMD modeling was conducted to identify a POD using pulmonary alveolar proteinosis incidence data from male and female mice in the study by Murata et al. (1997). The data were fit to all available dichotomous models in EPA's BMDS (version 3.2.0.1) using a BMR of 5% extra risk. A BMR of 5% extra risk was selected over the default value of 10% extra risk due to the potentially severe complications that may result in humans with pulmonary alveolar proteinosis. These complications include opportunistic pulmonary infections including tuberculosis as well as death from respiratory failure (Bush and Pabary 2020). The use of a BMR of 5% is also supported by reports that children with pulmonary alveolar proteinosis (albeit of unknown etiology) experience more severe symptoms of respiratory dysfunction than adults (EPA 2003; Mazzone et al. 2001). For example, in newborns with congenital pulmonary alveolar proteinosis, respiratory distress requiring intubation and mechanical ventilation develops rapidly (Bush and Pabary 2020).

Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMD (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 the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen.

None of the models provided adequate fit to the data in female mice. For male mice, the BMD software recommended the frequentist multi-stage degree 1 model for pulmonary alveolar proteinosis, and after verifying the model fit by the four criteria listed above, this model was selected as the basis for estimating

this MRL. The BMD05/BMDL05 values considered for MRL derivation are presented in Table A-14 and the fit of the selected model is presented in Figure A-5.

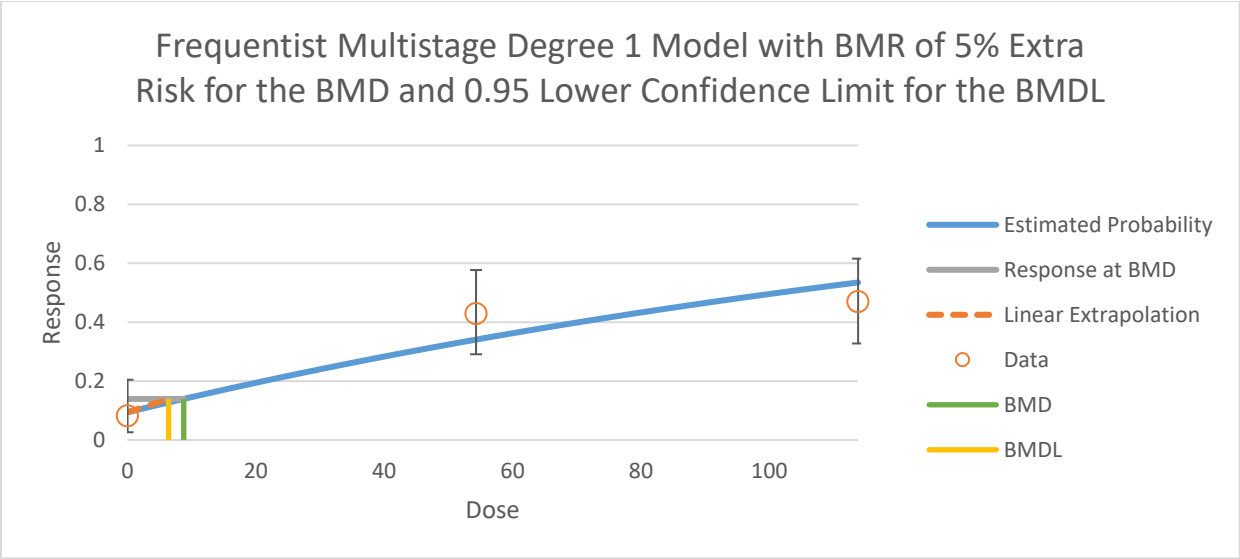
Table A-14. Model Predictions for Increased Incidence of Pulmonary Alveolar Proteinosis in Male Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1997)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill			NA	168.38	-5.9×10^{-5}	0.00
Gamma[d]	8.76	6.40	0.11	168.93	-0.30	1.29
Log-Logistic[e]			0.23	167.81	-0.13	0.90
Multistage Degree 2[f]	8.76	6.40	0.11	168.93	-0.30	1.29
Multistage Degree 1[f,g]	**8.76**	**6.40**	**0.11**	**168.93**	**-0.30**	**1.29**
Weibull[d]	8.76	6.40	0.11	168.93	-0.30	1.29
Logistic			0.01	172.84	-1.33	1.98
Log-Probit			NA	168.38	8.95×10^{-7}	1.69×10^{-6}
Probit			0.01	172.40	-1.20	1.95

[a]BMD and BMDLs values for models that do not provide adequate fit or yield BMDLs more than 10-fold lower than the lowest nonzero dose are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]The Gamma, Log-Logistic, Multistage 1- and 2-degree, and Weibull models provided adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold). The log-logistic model had the lowest AIC; however, at a BMR of 5%, the BMDL for this model was 10 times lower than the lowest non-zero dose. The Gamma, Weibull, and Multistage 2- and 1-degree models converged on the same model; the 1-degree Multistage model was selected as the most parsimonious choice.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 05 = dose associated with 5% extra risk); BMR = benchmark response

Figure A-5. Fit of the Multistage Degree 1 Model to Data for Increased Incidence of Pulmonary Alveolar Proteinosis in Male Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1997)



Calculations

Adjustment for Intermittent Exposure: Not applicable

Uncertainty Factor: The BMDL of 6.4 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability, 10 for extrapolation from animals to humans), resulting in an MRL of 0.06 mg/kg/day.

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

MRL = $BMDL_{05}$ ÷ UF
= 6.4 mg/kg/day ÷ (100) ≈ 0.06 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Increased incidences of pulmonary alveolar proteinosis has also been reported in B6C3F1 mice exposed to 1-methylnaphthalene in the diet for 81 weeks (Murata et al. 1993), and in mice dermally exposed to mixed methylnaphthalenes (a mixture of 1- and 2-methylnaphthalene) for 30–61 weeks (Emi and Konishi 1985; Murata et al. 1992). In a range-finding study, groups of B6C3F1 mice (10/sex/group) were fed diets containing 2-methyl naphthalene for 13 weeks delivering approximate average daily doses of 0, 31, 92, 276, 827, or 2,500 mg/kg/day (Murata et al. 1997). No histopathologic lesions were found in tissues and organs of male or female mice exposed to 827 or 2,500 mg/kg/day; tissues from mice in lower dose groups were not examined histologically (Murata et al. 1997). The absence of pulmonary alveolar proteinosis in the subchronically exposed mice, which were exposed to much higher doses than those experienced by mice with this lesion in the chronic-duration study, suggests that the development of pulmonary alveolar proteinosis from oral exposure to 2-methyl naphthalene requires chronic-duration exposure.

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE

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 naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene.

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 naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene 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 naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene 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

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

Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the 2005 toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene; thus, the literature search was restricted to studies published between January 2003 and April 2022 The following main databases were searched in April 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 naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. 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 naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene 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	
04/2022	((((91-20-3[rn] OR 90-12-0[rn] OR 91-57-6[rn]) OR ("1-METHYL-NAPHTHALENE"[tw] OR "1-Methylnaphtalene"[tw] OR "1-Methylnaphthalene"[tw] OR "1-Methylnaphthalin"[tw] OR "alpha-Methylnaphthalene"[tw] OR "Mechinafu H"[tw] OR "METHYL NAPHTHALENE"[tw] OR "Methylnaphthalene"[tw] OR "Methylnaphthalene, 1-"[tw] OR "Methynaph H"[tw] OR "Naphthalene, 1-methyl-"[tw] OR "Naphthalene, alpha-methyl-"[tw] OR "α-Methylnaphthalene"[tw] OR "2-Methylnaphtalene"[tw] OR "2-Methylnaphthalene"[tw] OR "2-Methylnaphthalin"[tw] OR "2-Methylnapthalene"[tw] OR "beta-Methylnaphthalene"[tw] OR "Methylnaphthalene, 2-"[tw] OR "Naphthalene, 2-methyl-"[tw] OR "Naphthalene, beta-methyl-"[tw] OR "β-Methylnaphthalene"[tw])) OR ((("Albocarbon"[tiab] OR "Camphor tar"[tiab] OR "Dezodorator"[tiab] OR "Mighty 150"[tiab] OR "Mighty RD1"[tiab] OR "Moth balls"[tiab] OR "Moth flakes"[tiab] OR "Mothballs"[tiab] OR "Naphtalene"[tiab] OR "Naphtalinum"[tiab] OR "Naphthalene"[tiab] OR "Naphthalin"[tiab] OR "Naphthaline"[tiab] OR "Naphthalinum"[tiab] OR "Naphthene"[tiab] OR "Napthalene"[tiab] OR "Tar camphor"[tiab] OR "White tar"[tiab])) AND ((("Naphthalenes/toxicity"[mh] OR "Naphthalenes/adverse effects"[mh] OR "Naphthalenes/poisoning"[mh] OR "Naphthalenes/pharmacokinetics"[mh]) OR ("Naphthalenes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Naphthalenes"[mh] AND toxicokinetics[mh:noexp]) OR ("Naphthalenes/blood"[mh] OR "Naphthalenes/cerebrospinal fluid"[mh] OR "Naphthalenes/urine"[mh]) OR ("Naphthalenes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Naphthalenes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Naphthalenes/antagonists and inhibitors"[mh]) OR ("Naphthalenes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Naphthalenes/pharmacology"[majr])) OR (("Polycyclic Aromatic Hydrocarbons/toxicity"[mh] OR "Polycyclic Aromatic Hydrocarbons/adverse effects"[mh] OR "Polycyclic Aromatic Hydrocarbons/poisoning"[mh] OR "Polycyclic Aromatic Hydrocarbons/pharmacokinetics"[mh]) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND toxicokinetics[mh:noexp]) OR ("Polycyclic Aromatic Hydrocarbons/blood"[mh] OR "Polycyclic Aromatic Hydrocarbons/cerebrospinal fluid"[mh] OR "Polycyclic Aromatic Hydrocarbons/urine"[mh]) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Polycyclic Aromatic Hydrocarbons/antagonists and inhibitors"[mh]) OR ("Polycyclic Aromatic Hydrocarbons/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Polycyclic Aromatic Hydrocarbons/pharmacology"[majr])))))) AND 2003:3000[dp]) (((("Albocarbon"[tw] OR "Camphor tar"[tw] OR "Dezodorator"[tw] OR "Mighty 150"[tw] OR "Mighty RD1"[tw] OR "Moth balls"[tw] OR "Moth flakes"[tw] OR "Mothballs"[tw] OR "Naphtalene"[tw] OR "Naphtalinum"[tw] OR "Naphthalene"[tw] OR "Naphthalin"[tw] OR "Naphthaline"[tw] OR "Naphthalinum"[tw] OR "Naphthene"[tw] OR "Napthalene"[tw] OR "Tar camphor"[tw] OR "White tar"[tw] OR "1-METHYL-NAPHTHALENE"[tw] OR "1-Methylnaphtalene"[tw] OR "1-Methylnaphthalene"[tw] OR "1-Methylnaphthalin"[tw] OR "alpha-Methylnaphthalene"[tw] OR "Mechinafu H"[tw] OR "METHYL NAPHTHALENE"[tw] OR "Methylnaphthalene"[tw] OR "Methylnaphthalene, 1-"[tw] OR "Methynaph H"[tw] OR "Naphthalene, 1-methyl-"[tw] OR "Naphthalene, alpha-methyl-"[tw] OR "α-Methylnaphthalene"[tw] OR "2-Methylnaphtalene"[tw] OR "2-Methylnaphthalene"[tw] OR "2-Methylnaphthalin"[tw] OR "2-Methylnapthalene"[tw] OR "beta-Methylnaphthalene"[tw] OR "Methylnaphthalene, 2-"[tw] OR "Naphthalene, 2-methyl-"[tw] OR "Naphthalene, beta-methyl-"[tw] OR "β-Methylnaphthalene"[tw]) NOT medline[sb]) AND 2003:3000[dp]) NOT ((((91-20-3[rn] OR 90-12-0[rn] OR 91-57-6[rn]) OR ("1-METHYL-NAPHTHALENE"[tw] OR "1-Methylnaphtalene"[tw] OR "1-Methylnaphthalene"[tw] OR "1-Methylnaphthalin"[tw] OR "alpha-Methylnaphthalene"[tw] OR "Mechinafu H"[tw] OR "METHYL NAPHTHALENE"[tw] OR "Methylnaphthalene"[tw] OR "Methylnaphthalene, 1-"[tw] OR "Methynaph H"[tw] OR "Naphthalene, 1-methyl-"[tw] OR "Naphthalene, alpha-methyl-"[tw] OR "α-

Table B-2. Database Query Strings

Database search date	Query string
	Methylnaphthalene"[tw] OR "2-Methylnaphtalene"[tw] OR "2-Methylnaphthalene"[tw] OR "2-Methylnaphthalin"[tw] OR "2-Methylnapthalene"[tw] OR "beta-Methylnaphthalene"[tw] OR "Methylnaphthalene, 2-"[tw] OR "Naphthalene, 2-methyl-"[tw] OR "Naphthalene, beta-methyl-"[tw] OR "β-Methylnaphthalene"[tw])) OR ((("Albocarbon"[tiab] OR "Camphor tar"[tiab] OR "Dezodorator"[tiab] OR "Mighty 150"[tiab] OR "Mighty RD1"[tiab] OR "Moth balls"[tiab] OR "Moth flakes"[tiab] OR "Mothballs"[tiab] OR "Naphtalene"[tiab] OR "Naphtalinum"[tiab] OR "Naphthalene"[tiab] OR "Naphthalin"[tiab] OR "Naphthaline"[tiab] OR "Naphthalinum"[tiab] OR "Naphthene"[tiab] OR "Napthalene"[tiab] OR "Tar camphor"[tiab] OR "White tar"[tiab])) AND ((("Naphthalenes/toxicity"[mh] OR "Naphthalenes/adverse effects"[mh] OR "Naphthalenes/poisoning"[mh] OR "Naphthalenes/pharmacokinetics"[mh]) OR ("Naphthalenes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Naphthalenes"[mh] AND toxicokinetics[mh:noexp]) OR ("Naphthalenes/blood"[mh] OR "Naphthalenes/cerebrospinal fluid"[mh] OR "Naphthalenes/urine"[mh]) OR ("Naphthalenes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Naphthalenes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Naphthalenes/antagonists and inhibitors"[mh]) OR ("Naphthalenes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Naphthalenes/pharmacology"[majr])) OR (("Polycyclic Aromatic Hydrocarbons/toxicity"[mh] OR "Polycyclic Aromatic Hydrocarbons/adverse effects"[mh] OR "Polycyclic Aromatic Hydrocarbons/poisoning"[mh] OR "Polycyclic Aromatic Hydrocarbons/pharmacokinetics"[mh]) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND toxicokinetics[mh:noexp]) OR ("Polycyclic Aromatic Hydrocarbons/blood"[mh] OR "Polycyclic Aromatic Hydrocarbons/cerebrospinal fluid"[mh] OR "Polycyclic Aromatic Hydrocarbons/urine"[mh]) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Polycyclic Aromatic Hydrocarbons/antagonists and inhibitors"[mh]) OR ("Polycyclic Aromatic Hydrocarbons/metabolism"[mh] AND

Table B-2. Database Query Strings

Database search date	Query string
	("humans"[mh] OR "animals"[mh])) OR ("Polycyclic Aromatic Hydrocarbons/pharmacology"[majr])))))) AND 2003:3000[dp]) ((((1321-94-4[rn] OR "C1-Naphthalenes"[tiab] OR "Dycar MN"[tiab] OR "Methylated naphthalenes"[tiab] OR "Methylnaphtalene"[tiab] OR "Methylnaphthalenes"[tiab] OR "Methylnaphthalin"[tiab] OR "Methylnapthalene"[tiab] OR "Monomethylnaphthalene"[tiab] OR "Naphthalene, methyl-"[tiab] OR "PETROL CARBON HYDROXIDE"[tiab] OR "Sure-Sol 187"[tiab] OR "Tetrosin MNLF"[tiab]) AND ((("Naphthalenes/toxicity"[mh] OR "Naphthalenes/adverse effects"[mh] OR "Naphthalenes/poisoning"[mh] OR "Naphthalenes/pharmacokinetics"[mh]) OR ("Naphthalenes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Naphthalenes"[mh] AND toxicokinetics[mh:noexp]) OR ("Naphthalenes/blood"[mh] OR "Naphthalenes/cerebrospinal fluid"[mh] OR "Naphthalenes/urine"[mh]) OR ("Naphthalenes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Naphthalenes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Naphthalenes/antagonists and inhibitors"[mh]) OR ("Naphthalenes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Naphthalenes/pharmacology"[majr])) OR (("Polycyclic Aromatic Hydrocarbons/toxicity"[mh] OR "Polycyclic Aromatic Hydrocarbons/adverse effects"[mh] OR "Polycyclic Aromatic Hydrocarbons/poisoning"[mh] OR "Polycyclic Aromatic Hydrocarbons/pharmacokinetics"[mh]) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND toxicokinetics[mh:noexp]) OR ("Polycyclic Aromatic Hydrocarbons/blood"[mh] OR "Polycyclic Aromatic Hydrocarbons/cerebrospinal fluid"[mh] OR "Polycyclic Aromatic Hydrocarbons/urine"[mh]) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Polycyclic Aromatic Hydrocarbons"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Polycyclic Aromatic Hydrocarbons/antagonists and inhibitors"[mh]) OR ("Polycyclic Aromatic Hydrocarbons/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Polycyclic Aromatic Hydrocarbons/pharmacology"[majr]))))) OR (("C1-Naphthalenes"[tw] OR "Dycar MN"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Methylated naphthalenes"[tw] OR "Methylnaphtalene"[tw] OR "Methylnaphthalenes"[tw] OR "Methylnaphthalin"[tw] OR "Methylnapthalene"[tw] OR "Monomethylnaphthalene"[tw] OR "Naphthalene, methyl-"[tw] OR "PETROL CARBON HYDROXIDE"[tw] OR "Sure-Sol 187"[tw] OR "Tetrosin MNLF"[tw]) NOT medline[sb])) AND (2003:3000[dp]))
NTRL	
04/2022	"Albocarbon" OR "Camphor tar" OR "Dezodorator" OR "Mighty 150" OR "Mighty RD1" OR "Moth balls" OR "Moth flakes" OR "Mothballs" OR "Naphtalene" OR "Naphtalinum" OR "Naphthalene" OR "Naphthalin" OR "Naphthaline" OR "Naphthalinum" OR "Naphthene" OR "Napthalene" OR "Tar camphor" OR "White tar" OR "1-METHYL-NAPHTHALENE" OR "1-Methylnaphtalene" OR "1-Methylnaphthalene" OR "1-Methylnaphthalin" OR "alpha-Methylnaphthalene" OR "Mechinafu H" OR "METHYL NAPHTHALENE" OR "Methylnaphthalene" OR "Methylnaphthalene, 1-" OR "Methynaph H" OR "Naphthalene, 1-methyl-" OR "Naphthalene, alpha-methyl-" OR "α-Methylnaphthalene" OR "2-Methylnaphtalene" OR "2-Methylnaphthalene" OR "2-Methylnaphthalin" OR "2-Methylnapthalene" OR "beta-Methylnaphthalene" OR "Methylnaphthalene, 2-" OR "Naphthalene, 2-methyl-" OR "Naphthalene, beta-methyl-" OR "β-Methylnaphthalene" "C1-Naphthalenes" OR "Dycar MN" OR "Methylated naphthalenes" OR "Methylnaphtalene" OR "Methylnaphthalenes" OR "Methylnaphthalin" OR "Methylnapthalene" OR "Monomethylnaphthalene" OR "Naphthalene, methyl-" OR "PETROL CARBON HYDROXIDE" OR "Sure-Sol 187" OR "Tetrosin MNLF" "Albocarbon" OR "Camphor tar" OR "Dezodorator" OR "Mighty 150" OR "Mighty RD1" OR "Moth balls" OR "Moth flakes" OR "Mothballs" OR "Naphtalene" OR "Naphtalinum" OR "Naphthalene" OR "Naphthalin" OR "Naphthaline" OR "Naphthalinum" OR "Naphthene" OR "Napthalene" OR "Tar camphor" OR "White tar" OR "1-METHYL-NAPHTHALENE" OR "1-Methylnaphtalene" OR "1-Methylnaphthalene" OR "1-Methylnaphthalin" OR "alpha-Methylnaphthalene" OR "Mechinafu H" OR "METHYL NAPHTHALENE" OR "Methylnaphthalene" OR "Methylnaphthalene, 1-" OR "Methynaph H" OR "Naphthalene, 1-methyl-" OR "Naphthalene, alpha-methyl-" OR "α-Methylnaphthalene" OR "2-Methylnaphtalene" OR "2-Methylnaphthalene" OR "2-Methylnaphthalin" OR "2-Methylnapthalene" OR "beta-Methylnaphthalene" OR "Methylnaphthalene, 2-" OR "Naphthalene, 2-methyl-" OR "Naphthalene, beta-methyl-" OR "β-Methylnaphthalene" OR "C1-Naphthalenes" OR "Dycar MN" OR "Methylated naphthalenes" OR "Methylnaphtalene" OR "Methylnaphthalenes" OR "Methylnaphthalin" OR "Methylnapthalene" OR "Monomethylnaphthalene" OR "Naphthalene, methyl-" OR "PETROL CARBON HYDROXIDE" OR "Sure-Sol 187" OR "Tetrosin MNLF"
Toxcenter	
04/2022	FILE 'TOXCENTER' ENTERED AT 16:10:03 ON 06 APR 2022 CHARGED TO COST=EH038.15.05.LB.04 L1 33022 SEA 91-20-3 OR 90-12-0 OR 91-57-6 L2 32785 SEA L1 NOT TSCATS/FS L3 30517 SEA L2 NOT PATENT/DT L4 20636 SEA L3 AND PY>=2002 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	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

Table B-2. Database Query Strings

Database search date	Query string
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 9198 SEA L4 AND L37
	L39 614 SEA L38 AND MEDLINE/FS
	L40 8584 SEA L38 NOT MEDLINE/FS
	L41 8313 DUP REM L39 L40 (885 DUPLICATES REMOVED)
	FILE 'TOXCENTER' ENTERED AT 11:22:56 ON 04 MAY 2022
	CHARGED TO COST=EH038.15.05.LB.04
	L1 1062 SEA FILE=TOXCENTER 1321-94-4
	L2 1044 SEA FILE=TOXCENTER L1 NOT TSCATS/FS
	L3 894 SEA FILE=TOXCENTER L2 NOT PATENT/DT
	L4 444 SEA FILE=TOXCENTER L3 AND PY>2002
	ACTIVATE TOXQUERY/Q

	L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,
	IT)
	L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR
	DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR
	OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

Table B-2. Database Query Strings

Database search date	Query string
	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
	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 158 SEA FILE=TOXCENTER L4 AND L37
	L39 0 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
	L40 154 DUP REM L38 (4 DUPLICATES REMOVED)

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
04/2022	91-20-3 90-12-0 91-57-6 1321-94-4
NTP	
04/2022	Limited: 2000- present 91-20-3 90-12-0 91-57-6 1321-94-4 "Naphthalene" "Methylnaphthalene"
Regulations.gov	
04/2022	Limited: posted 2003-present; dockets or EPA notices 91-20-3 90-12-0 91-57-6 1321-94-4 Naphthalene Methylnaphthalene "Methyl naphthalene"
NPIRS	
04/2022	91-20-3 90-12-0 91-57-6
NIH RePORTER	
01/2023	Search Criteria-- Fiscal Year: Active Projects, Text Search: "Albocarbon" OR "Camphor tar" OR "Dezodorator" OR "Mighty 150" OR "Mighty RD1" OR "Moth balls" OR "Moth flakes" OR "Mothballs" OR "Naphtalene" OR "Naphtalinum" OR "Naphthalene" OR "Naphthalin" OR "Naphthaline" OR "Naphthalinum" OR "Naphthene" OR "Napthalene" OR "Tar camphor" OR "White tar" OR "1-METHYL-NAPHTHALENE" OR "1-Methylnaphtalene" OR "1-Methylnaphthalene" OR "1-Methylnaphthalin" OR "alpha-Methylnaphthalene" OR "Mechinafu H" OR "METHYL NAPHTHALENE" OR "Methylnaphthalene" OR "Methylnaphthalene, 1-" OR "Methynaph H" OR "Naphthalene, 1-methyl-" OR "Naphthalene, alpha-methyl-" OR "α-Methylnaphthalene" OR "2-Methylnaphtalene" OR "2-Methylnaphthalene" OR "2-Methylnaphthalin" OR "2-Methylnapthalene" OR "beta-Methylnaphthalene" OR "Methylnaphthalene, 2-" OR "Naphthalene, 2-methyl-" OR "Naphthalene, beta-methyl-" OR "β-Methylnaphthalene" OR "C1-Naphthalenes" OR "Dycar MN" OR "Methylated naphthalenes" OR "Methylnaphtalene" OR "Methylnaphthalenes" OR "Methylnaphthalin" OR "Methylnapthalene" OR "Monomethylnaphthalene" OR "Naphthalene, methyl-" OR "PETROL CARBON HYDROXIDE" OR "Sure-Sol 187" OR "Tetrosin MNLF" (advanced), Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 14,258
- Number of records identified from other strategies: 210
- Total number of records to undergo literature screening: 14,468

B.1.2 Literature Screening

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

- 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.

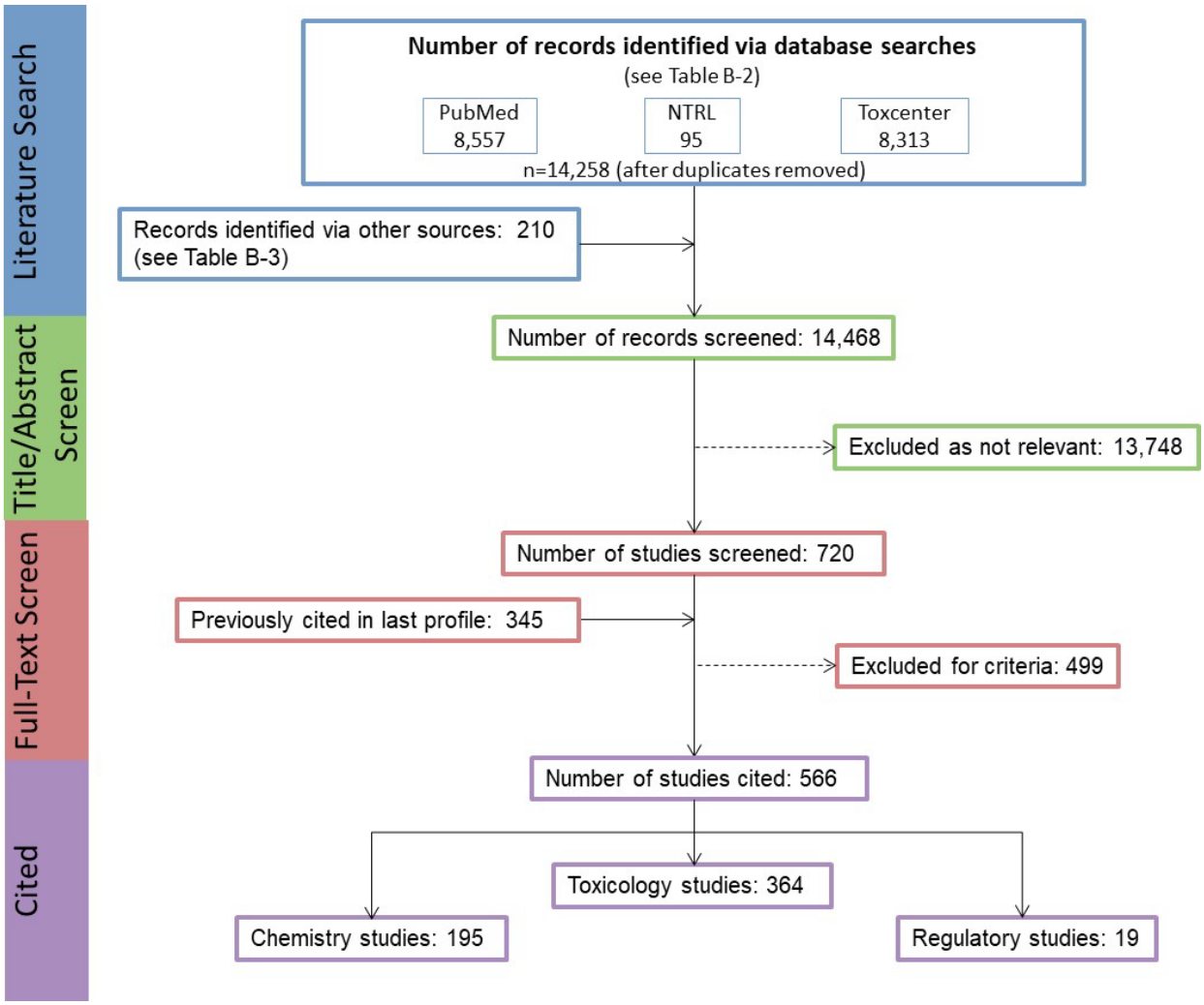
- Number of titles and abstracts screened: 14,468
- Number of studies considered relevant and moved to the next step: 720

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: 720
- Number of studies cited in the previous toxicological profile: 345
- Total number of studies cited in the profile: 566

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

Figure B-1. April 2022 Literature Search Results and Screen for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene



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

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

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

The systematic review for this profile is divided into four sections:

1. Steps 1, 2, and 3 for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene (Sections C.1, C.2, and C.3)
2. Steps 4, 5, 6, 7, and 8 for naphthalene (Sections C.4, C.5, C.6, C.7, and C.8)
3. Steps 4, 5, 6, 7, and 8 for 1-methylnaphthalene (Sections C.9, C.10, C.11, C.12, and C.13)
4. Steps 4, 5, 6, 7, and 8 for 2-methylnaphthalene (Sections C.14, C.15, C.16, C.17, and C.18)

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. The inclusion criteria used to identify relevant studies examining the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are presented in Table C-1.

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

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

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 2005 toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene; thus, the literature search was restricted to studies published between January 2003 and April 2022. See Appendix B for the databases searched and the search strategy.

A total of 14,468 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

Title and Abstract Screen. In the Title and Abstract Screen step, 14,468 records were reviewed; 56 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 123 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 123 documents (139 studies), 35 documents (41 studies) were included in the qualitative review.

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are PAHs, and the epidemiological database for PAHs is extensive. Only studies presenting effect estimates specific to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene were included in the Toxicological Profile.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study

Table C-2. Data Extracted From Individual Studies

Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Documents for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene isomers and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 through 2-6).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—NAPHTHALENE

Overviews of the potential health effect outcomes for naphthalene identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The human epidemiological studies examined a variety of endpoints; the largest number of studies evaluated reproductive and developmental endpoints. A number of case reports documented gastrointestinal symptoms. Many of the human studies used measures of naphthalene in blood or metabolites in urine to assess exposure, so the route is unknown; for the purpose of enumerations, these studies are considered to reflect inhalation exposure. Most of the animal studies used oral administration of naphthalene; there were very few dermal animal studies. The available animal studies primarily examined respiratory and ocular effects. The most sensitive effects in animal studies were respiratory, neurological, and immunological. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 41 studies (published in 35 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Naphthalene Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort		3 3			2 2					2 2	1 0	2 2	1 1	3 3	1 0	2 2	
Case control														1 1			1 1
Population		1 1	3 2			1 1					1 0	2 2		5 5	6 5	1 1	
Case series			1 1														
Oral studies																	
Cohort																	
Case control																	
Population				1 1													
Case series		1 1		11 11	3 3		4 4	7 7					6 6		3 3	6 6	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series							2 2										

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

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	4 0	14 13			1 0					1 1							
Intermediate-duration	1 0	1 1	1 1				1 0	1 0			1 0	1 1	1 0	1 0			
Chronic-duration	2 0	2 2	2 0	2 0		2 0	2 0	2 0	2 0	1 0	2 0	2 0	2 0	2 0		1 0	2 2
Oral studies																	
Acute-duration	2 2	4 4			3 2		3 2	2 0		2 1		1 1	2 1	3 1	4 2		
Intermediate-duration	6 3	3 0	2 0	2 1	5 2		5 2	5 2		21 18		2 1	4 2	2 0			
Chronic-duration										1							1 0
Dermal studies																	
Acute-duration									4 2			1 0					
Intermediate-duration		1 0	1 0	1 0	1 0		1 0	1 0	1 1			1 0		1 1			
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—NAPHTHALENE

C.5.1 Risk of Bias Assessment—Naphthalene

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

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

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

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

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

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

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

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

Selective reporting bias
Were all measured outcomes reported?

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

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

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

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

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

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

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

The results of the risk of bias assessment for the naphthalene health effects studies (human observational epidemiology studies and experimental animal studies of respiratory, neurological, and immune system effects) are presented in Tables C-8 and C-9. There were no human controlled experimental studies of naphthalene.

Table C-8. Summary of Risk of Bias Assessment for Naphthalene—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory effects							
Cohort							
Cilluffo et al. 2022	–	– –	++	++	–	+	Second
Mu et al. 2019	–	– –	++	+	+	+	Second
Sucker et al. 2021	++	+	++	+	++	+	First
Cross-sectional							
Cakmak et al. 2014	–	– –	+	+	+	–	Second
Outcome: Immunological effects							
Cohort							
Lehmann et al. 2001	–	– –	–	– –	+	++	Third
Lehmann et al. 2002	–	– –	–	– –	+	+	Third
Cross-sectional							
Lin et al. 2018	+	++	++	++	+	+	First
Rhodes et al. 2003	–	– –	–	+	+	+	Second
Outcome: Neurological effects							
Cohort							
Heaton et al. 2017	+	+	++	++	+	+	First

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

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Naphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects										
Oral acute exposure										
Kelty et al. 2020 (mouse, once)	–	–	+	–	+	+	+	++	NA	First
Shopp et al. 1984 (mouse, 14 days)	+	–	+	–	+	++	+	++	NA	First
Zhang et al. 2015 (mouse, once)	–	–	+	–	–	–	++	+	NA	Second
Zhang et al. 2016 (mouse, once)	–	–	–	–	–	–	++	+	NA	Second
Oral intermediate exposure										
Germansky and Jamall 1988 (rat, 9 weeks)	–	–	++	–	–	–	+	++	NA	Second
NTP 1980b (rat, 13 weeks)	++	–	++	–	+	+	++	++	NA	First
NTP 1980a (mouse, 13 weeks)	++	–	++	–	+	+	++	++	NA	First
Shopp et al. 1984 (mouse, 90 days)	+	–	+	–	+	++	+	+	NA	First
Inhalation acute exposure										
Cichocki et al. 2014 (rat, 4 or 6 hours)	–	–	++	–	–	+	+	+	NA	Second
Dodd et al. 2010 (rat, 6 hours)	+	–	++	–	++	+	+	++	NA	First

Table C-9. Summary of Risk of Bias Assessment for Naphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	
Dodd et al. 2010 (rat, 5 days)	+	–	++	–	++	+	+	++	NA	First
Lee et al. 2005 (rat, 4 hours)	–	–	++	–	–	+	+	+	NA	Second
West et al. 2001 (mouse, 4 hours)	–	–	++	–	–	–	+	+	NA	Second
West et al. 2001 (rat, 4 hours)	–	–	++	–	–	–	+	+	NA	Second
Carratt et al. 2016 (mouse, 4 hours)	–	–	++	–	–	–	++	+	NA	Second
Carratt et al. 2019b (mouse, 4 hours)	–	–	–	–	–	–	+	+	NA	Second
Kovalchuk et al. 2020 (mouse, 4 hours)	–	–	++	–	+	+	++	+	NA	First
Li et al. 2017 (mouse, 4 hours)	–	–	++	–	+	+	+	+	NA	First
Phimister et al. 2004 (mouse, 2 or 4 hours)	–	–	++	–	+	+	+	+	NA	First
Inhalation intermediate exposure										
Dodd et al. 2012 (rat, 90 days)	++	–	++	–	+	+	+	++	NA	First
Inhalation chronic exposure										
NTP 2000 (Abdo et al. 2001) (rat, 105 weeks)	–	–	++	–	++	++	++	++	NA	First
NTP 1992a (mouse, 104 weeks)	–	–	++	–	+	++	++	++	NA	First

Table C-9. Summary of Risk of Bias Assessment for Naphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	
Outcome: Neurological effects										
Oral acute exposure										
NTP 1991 (rat, 9-day gestational exposure)	+	–	++	–	++	++	+	++	NA	First
Shopp et al. 1984 (mouse, 14 days)	+	–	+	–	+	+	+	++	NA	First
Oral intermediate exposure										
Katsnelson et al. 2014 (rat, 20 times over 40 days)	–	–	–	–	–	–	–	++	NA	Third
NTP 1980b (rat, 13 weeks)	++	–	++	–	+	++	–	++	NA	Second
NTP 1980a (mouse, 13 weeks)	++	–	++	–	–	+	–	++	NA	Second
Shopp et al. 1984 (mouse, 90 days)	+	–	+	–	+	++	–	+	NA	Second
Inhalation chronic exposure										
NTP 2000 (Abdo et al. 2001) (rat, 105 weeks)	–	–	++	–	++	++	–	++	NA	Second
NTP 1992a (mouse, 104 weeks)	–	–	++	–	–	+	–	++	NA	Third

Table C-9. Summary of Risk of Bias Assessment for Naphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Immune effects										
Oral acute exposure										
Shopp et al. 1984 (mouse, 14 days)	+	–	+	–	+	++	+	++	NA	First
Oral intermediate exposure										
NTP 1980b (rat, 13 weeks)	++	–	++	–	+	++	++	++	NA	First
Shopp et al. 1984 (mouse, 90 days)	+	–	+	–	+	++	+	+	NA	First
Inhalation intermediate exposure										
Dodd et al. 2012 (rat, 90 days)	++	–	++	–	+	+	+	++	NA	First

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

*Key question used to assign risk of bias tier

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

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

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

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

C.6.1 Initial Confidence Rating—Naphthalene

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to naphthalene and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

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

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

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

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

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

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

Table C-11. Key Features of Study Design for Human Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

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

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, neurological, and immune system effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Naphthalene—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Respiratory effects:					
Cohort					
Cilluffo et al. 2022	No	Yes	Yes	Yes	Moderate
Mu et al. 2019	No	Yes	Yes	Yes	Moderate
Sucker et al. 2021	No	Yes	Yes	Yes	Moderate

Table C-13. Presence of Key Features of Study Design for Naphthalene—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Cross-sectional					
Cakmak et al. 2014	No	Yes	Yes	Yes	Moderate
Neurological effects:					
Cohort					
Heaton et al. 2017	No	Yes	Yes	yes	Moderate
Immune system effects:					
Cohort					
Lehmann et al. 2001	No	Yes	Yes	yes	Moderate
Lehmann et al. 2002	No	Yes	Yes	yes	Moderate
Cross-sectional					
Lin et al. 2018	No	Yes	Yes	yes	Moderate
Rhodes et al. 2003	No	Yes	Yes	yes	Moderate

Table C-14. Presence of Key Features of Study Design for Naphthalene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Oral acute exposure					
Kelty et al. 2020 (mouse, once)	Yes	No	Yes	Yes	Moderate
Shopp et al. 1984 (mouse, 14 days)	Yes	Yes	No	Yes	Moderate
Zhang et al. 2015 (mouse, once)	Yes	Yes	Yes	Yes	High
Zhang et al. 2016 (mouse, once)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Naphthalene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral intermediate exposure					
Germansky and Jamall 1988 (rat, 9 weeks)	Yes	No	No	No	Very Low
NTP 1980b (rat, 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1980a (mouse, 13 weeks)	Yes	Yes	Yes	Yes	High
Shopp et al. 1984 (mouse, 90 days)	Yes	Yes	No	Yes	Moderate
Inhalation acute exposure					
Cichocki et al. 2014 (rat; 4 or 6 hours)	Yes	Yes	No	Yes	Moderate
Dodd et al. 2010 (rat, 6 hours)	Yes	Yes	Yes	Yes	High
Dodd et al. 2010 (rat, 5 days)	Yes	Yes	Yes	Yes	High
Lee et al. 2005 (rat, 4 hours)	Yes	No	Yes	Yes	Moderate
West et al. 2001 (rat, 4 hours)	Yes	No	Yes	Yes	Moderate
Carratt et al. 2016 (mouse, 4 hours)	Yes	No	Yes	Yes	Moderate
Carratt et al. 2019b (mouse, 4 hours)	Yes	No	Yes	Yes	Moderate
Kovalchuk et al. 2020 (mouse, 4 hours)	Yes	No	Yes	Yes	Moderate
Li et al. 2017 (mouse, 4 hours)	Yes	No	Yes	Yes	Moderate
Phimister et al. 2004 (mouse, 2 or 4 hours)	Yes	No	Yes	Yes	Moderate
West et al. 2001 (mouse, 4 hours)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Dodd et al. 2012 (rat, 90 days)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 2000 (Abdo et al. 2001) (rat, 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 1992a (mouse, 104 weeks)	Yes	Yes	Yes	Yes	High
Outcome: Immune effects					
Oral acute exposure					
Shopp et al. 1984 (mouse; 14 days)	Yes	Yes	Yes	Yes	Moderate
Oral intermediate exposure					
NTP 1980b (rat, 13 weeks)	Yes	Yes	No	Yes	High
Shopp et al. 1984 (mouse, 90 days)	Yes	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Naphthalene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Dodd et al. 2012 (rat, 90 days)	Yes	Yes	No	Yes	High
Outcome: Neurological effects					
Oral acute exposure					
NTP 1991 (rat, 9-day gestational exposure)	Yes	Yes	No	Yes	Moderate
Shopp et al. 1984 (mouse, 14 days)	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Katsnelson et al. 2014 (rat, 20 times over 40 days)	Yes	Yes	No	Yes	Moderate
NTP 1980b (rat, 13 weeks)	Yes	Yes	No	No	Low
NTP 1980a (mouse, 13 weeks)	Yes	Yes	No	No	Low
Shopp et al. 1984 (mouse, 90 days)	Yes	Yes	No	Yes	Moderate
Inhalation chronic exposure					
NTP 2000 (Abdo et al. 2001) (rat, 105 weeks)	Yes	Yes	No	Yes	Moderate
NTP 1992a (mouse, 104 weeks)	Yes	Yes	No	Yes	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Naphthalene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Oral acute exposure		
Animal studies		
Kelty et al. 2020 (mouse, once)	Moderate	High
Shopp et al. 1984 (mouse, 14 days)	Moderate	
Zhang et al. 2015 (mouse, once)	High	

Table C-15. Initial Confidence Rating for Naphthalene Health Effects Studies

	Initial study confidence	Initial confidence rating
Zhang et al. 2016 (mouse, once)	High	
Oral intermediate exposure		
Animal studies		
Germansky and Jamall 1988 (rat, 9 weeks)	Very Low	High
NTP 1980b (rat, 13 weeks)	High	
NTP 1980a (mouse, 13 weeks)	High	
Shopp et al. 1984 (mouse, 90 days)	Moderate	
Inhalation acute exposure		
Animal studies		
Cichocki et al. 2014 (rat, 4 or 6 hours)	Moderate	High
Dodd et al. 2010 (rat, 6 hours)	High	
Dodd et al. 2010 (rat, 5 days)	High	
Lee et al. 2005 (rat, 4 hours)	Moderate	
West et al. 2001 (rat, 4 hours)	Moderate	
Carratt et al. 2016 (mouse, 4 hours)	Moderate	
Carratt et al. 2019b (mouse, 4 hours)	Moderate	
Kovalchuk et al. 2020 (mouse, 4 hours)	Moderate	
Li et al. 2017 (mouse, 4 hours)	Moderate	
Phimister et al. 2004 (mouse, 2 or 4 hours)	Moderate	
West et al. 2001 (mouse, 4 hours)	Moderate	
Inhalation intermediate exposure		
Human studies		
Cakmak et al. 2014	Moderate	Moderate
Cilluffo et al. 2022	Moderate	
Mu et al. 2019	Moderate	
Animal studies		
Dodd et al. 2012 (rat, 90 days)	High	High
Inhalation chronic exposure		
Human studies		
Sucker et al. 2021	Moderate	Moderate
Animal studies		
NTP 2000 (Abdo et al. 2001) (rat, 105 weeks)	High	High
NTP 1992a (mouse, 104 weeks)	High	
Outcome: Immune effects		
Oral acute exposure		
Animal studies		
Shopp et al. 1984 (mouse, 14 days)	High	High
Oral intermediate exposure		
Animal studies		
NTP 1980b (rat, 13 weeks)	Moderate	High
Shopp et al. 1984 (mouse, 90 days)	High	

Table C-15. Initial Confidence Rating for Naphthalene Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Human studies		
Lehmann et al. 2001	Moderate	Moderate
Lehmann et al. 2002	Moderate	
Lin et al. 2018	Moderate	
Rhodes et al. 2003	Moderate	
Animal studies		
Dodd et al. 2012 (rat, 90 days)	Moderate	Moderate
Outcome: Neurological effects		
Oral acute exposure		
Animal studies		
NTP 1991 (rat, 9-day gestational exposure)	Moderate	Moderate
Shopp et al. 1984 (mouse, 14 days)	Moderate	
Oral intermediate exposure		
Animal studies		
Katsnelson et al. 2014 (rat, 20 times over 40 days)	Moderate	Moderate
NTP 1980b (rat, 13 weeks)	Low	
NTP 1980a (mouse, 13 weeks)	Low	
Shopp et al. 1984 (mouse, 90 days)	Moderate	
Inhalation chronic exposure		
Human studies		
Heaton et al. 2017	Moderate	Moderate
Animal studies		
NTP 2000 (Abdo et al. 2001) (rat, 105 weeks)	Moderate	Moderate
NTP 1992a (mouse, 104 weeks)	Moderate	

C.6.2 Adjustment of the Confidence Rating—Naphthalene

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for hepatic effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with naphthalene exposure is presented in Table C-17.

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:

  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direction of the effect

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

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

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

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

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

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

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

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

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

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Respiratory effects:			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	+1 consistency, +1 magnitude, +1 dose-response	High
Immune effects:			
Human studies	Moderate	-2 risk of bias, -1 inconsistency	Very low
Animal studies	High	-1 indirectness, -1 inconsistency	Low

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Neurological effects:			
Human studies	Moderate	None	Moderate
Animal studies	Moderate	+1 consistency, -1 indirectness	Moderate

Table C-17. Confidence in the Body of Evidence for Naphthalene

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory	Low	High
Immune	Very low	Low
Neurological	Moderate	Moderate

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

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

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

A summary of the level of evidence of health effects for naphthalene is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Naphthalene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory	Low	Health Effect	Low
Neurological	Moderate	No health effect	Inadequate
Immune	Very low	Health Effect	Inadequate
Animal studies			
Respiratory	High	Health Effect	High
Neurological	Moderate	Health effect	Moderate
Immune	Low	Health Effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—NAPHTHALENE

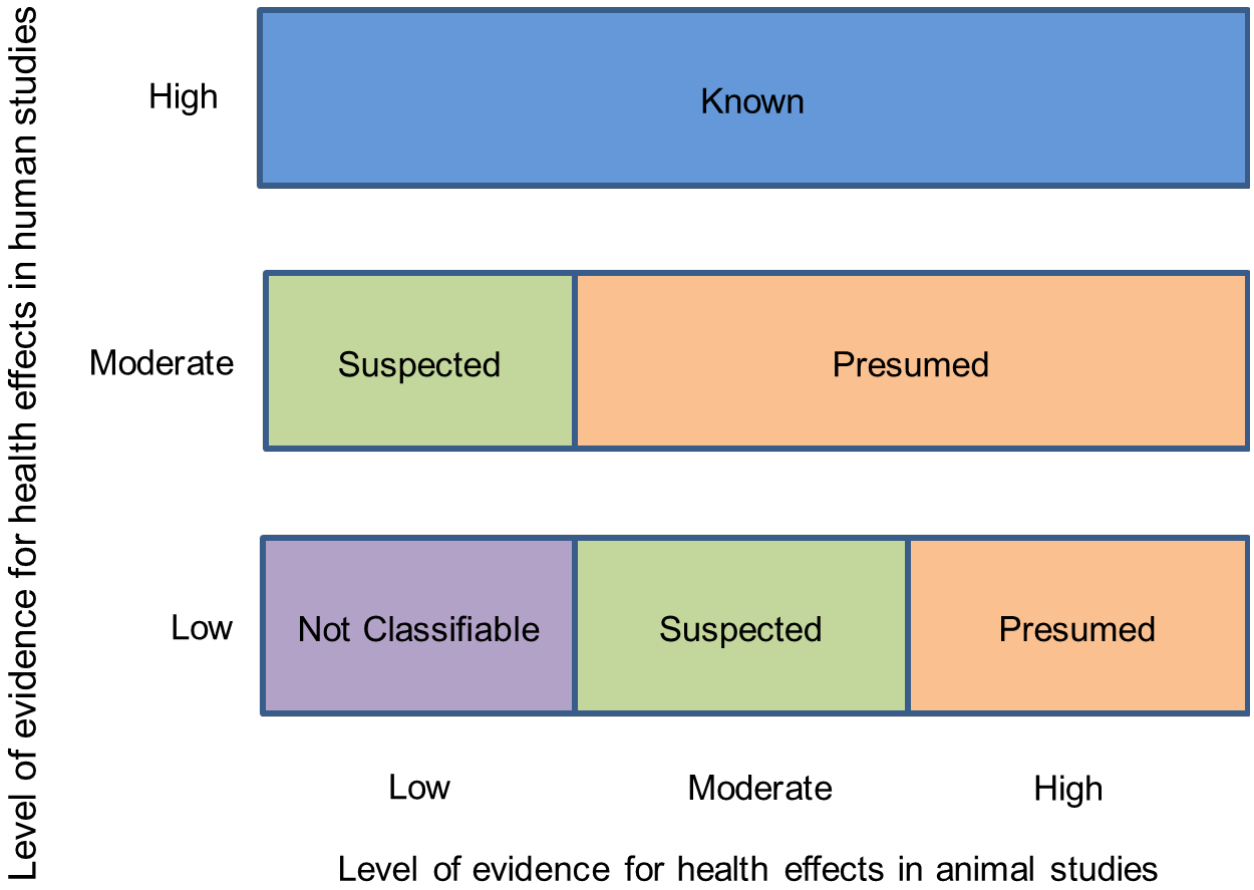
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

The hazard identification conclusions for naphthalene are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory
  - Low level of evidence in humans based on associations between nasal irritation and inflammation and occupational exposure to naphthalene (Sucker et al. 2021) and associations between decreases in lung function and airborne naphthalene in general population studies (Cakmak et al. 2014; Mu et al. 2019).
  - High evidence level in animals including nasal histopathological lesions in rats and mice after inhalation exposure for acute, intermediate, and chronic durations (Abdo et al. 2001; Carratt et al. 2016, 2019a; Cichocki et al. 2014; Dodd et al. 2010, 2012; Lee et al. 2005; Li et al. 2017; NTP 1992a, 2000) and lung pathology in mice after acute- and chronic-duration exposures (Kovalchuk et al. 2020; Li et al. 2017; NTP 1992a; Phimister et al. 2004; West et al. 2001).
  - Plausible mechanism based on metabolism to electrophilic intermediates that bind to proteins, deplete reduced glutathione levels, and increase oxidative stress (see Section 2.4).

Suspected Health Effects

- Neurological
  - Inadequate evidence in humans based on lack of association between neurocognitive endpoints and occupational exposure to JP-8 (Heaton et al. 2017).
  - Moderate level of evidence for effects in animals exposed orally based on clinical signs of neurotoxicity (lethargy) in Sprague-Dawley rats during gestation (NTP 1991) and in F344 rats and B6C3F1 mice exposed for 13 weeks (NTP 1980a, 1980b).

Not Classifiable

- Immune
  - Inadequate evidence for immune effects in humans based on associations between altered cytokine levels and/or differential leukocyte counts and naphthalene concentrations in air (Lehmann et al. 2001, 2002; Rhodes et al. 2003) and between asthma and urinary 2-naphthol levels (Lin et al. 2018).
  - Low level of evidence in animals based on decreases in thymus weights in rats exposed by inhalation for 13 weeks (Dodd et al. 2012) and mice exposed orally for 13 weeks (Shopp et al. 1984); a low incidence of lymphoid depletion of the thymus in female rats exposed by gavage for 13 weeks (NTP 1980b); increased serum inflammatory markers in mice given a single oral dose of naphthalene (Zhang et al. 2016); and reduced mitogenic response to concanavalin A in mice exposed orally for 2 weeks (Shopp et al. 1984).

Table C-19. Hazard Identification Conclusions for Naphthalene

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Neurological effects	Suspected health effect
Immune system effects	Not classifiable

C.9 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—1-METHYLNAPHTHALENE

Overviews of the potential health effect outcomes for 1-methylnaphthalene identified in animal studies are presented in Table C-20. No human studies of 1-methylnaphthalene were located. There were few animal studies, but they examined a number of endpoints. The animal data show that the respiratory tract

and liver are sensitive effects of exposure to 1-methylnaphthalene; studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were three studies examining these potential outcomes carried through to Steps 4–8 of the systematic review.

Table C-20. Overview of the Health Outcomes for 1-Methylnaphthalene Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	1												1				
	0												1				
Intermediate-duration	1	1	1	1	1	1	1	1	1		1	1		1			
	0	1	0	0	0	0	0	0	0		0	0		0			
Chronic-duration																	
Oral studies																	
Acute-duration																	
Intermediate-duration	1	1	1	1	1		1	1			1	1	1	1	1		
	0	0	0	0	0		1	1			0	0	0	0	0		
Chronic-duration	1	1	1	1	1		1	1			1	1	1	1			1
	0	1	0	0	0		0	0			0	0	0	0			1
Dermal studies																	
Acute-duration									1								
									1								
Intermediate-duration		1															
		1															
Chronic-duration		1															
		1															

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

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

C.10 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—1-METHYLNAPHTHALENE

C.10.1 Risk of Bias Assessment—1-Methylnaphthalene

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies were presented above in Tables C-5, C-6, and C-7, respectively. As described in Section C.5.1, each risk of bias question was answered on a four-point scale and studies were assigned to one of three risk of bias tiers.

The results of the risk of bias assessment for the different types of 1-methylnaphthalene health effects studies (animal experimental studies) are presented in Table C-21. No human studies of 1-methylnaphthalene were located.

Table C-21. Summary of Risk of Bias Assessment for 1-Methylnaphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	
Outcome: Respiratory effects										
Oral intermediate exposure										
NITE 2009 (Rat, 42 days)	+	–	++	–	++	++	+	++	NA	First
Oral chronic exposure										
Murata et al. 1993 (mouse, 81 weeks)	–	–	+	–	+	– –	+	++	– –	Second
Inhalation intermediate exposure										
Kim et al. 2020 (rat; 13 weeks)	–	–	++	–	+	+	++	++	NA	First
Outcome: Hepatic effects										
Oral intermediate exposure										
NITE 2009 (Rat, 42 days)	+	–	++	–	++	++	+	++	NA	First
Oral chronic exposure										
Murata et al. 1993 (mouse, 81 weeks)	–	–	+	–	+	– –	+	++	– –	Second

Table C-21. Summary of Risk of Bias Assessment for 1-Methylnaphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	
Inhalation intermediate exposure										
Kim et al. 2020 (Rat 90 days)	–	–	++	–	+	+	+	++	NA	First

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

*Key question used to assign risk of bias tier

C.11 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—1-METHYLNAPHTHALENE

As discussed in greater detail in Section C.6, confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.11.1 Initial Confidence Rating—1-Methylnaphthalene

As discussed in greater detail in Section C.6.1, the body of evidence for an association (or no association) between exposure to 1-methylnaphthalene and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. Refer to Tables C-9, C-10, and C-11, respectively, for the key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies.

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and hepatic effects observed in the animal experimental studies are presented in Table C-22.

Table C-22. Presence of Key Features of Study Design for 1-Methylnaphthalene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Oral Intermediate exposure					
NITE 2009	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Murata et al. 1993 (mouse; 81 weeks)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Kim et al. 2020 (rat; 13 weeks)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Oral intermediate exposure					
NITE 2009	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Murata et al. 1993	Yes	Yes	Yes	Yes	High

Table C-22. Presence of Key Features of Study Design for 1-Methylnaphthalene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Kim et al. 2020 (rat; 13 weeks)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-23. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-23.

Table C-23. Initial Confidence Rating for 1-Methylnaphthalene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Animal studies		
Oral Intermediate exposure		
NITE 2009 (rat; 6 weeks)	High	High
Oral chronic exposure		
Murata et al. 1993 (mouse; 81 weeks)	High	High
Inhalation intermediate exposure		
Kim et al. 2020 (rat; 13 weeks)	High	High
Outcome: Hepatic effects		
Animal studies		
Oral intermediate exposure		
NITE 2009 (rat; 6 weeks)	High	High
Oral chronic exposure		
Murata et al. 1993 (mouse; 81 weeks)	High	High
Inhalation intermediate exposure		
Kim et al. 2020 (rat; 13 weeks)	High	High

C.11.2 Adjustment of the Confidence Rating—1-Methylnaphthalene

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The five properties of the body of evidence that were considered to determine whether the confidence rating should be downgraded and the four properties of the body of evidence that were considered to determine whether the confidence rating should be upgraded are described above in Section C.6.2. The summaries of the assessment of the confidence in the body of evidence for respiratory and hepatic effects are presented in Table C-24. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with 1-methylnaphthalene exposure is presented in Table C-25.

Table C-24. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Respiratory effects			
Human studies	Not applicable		
Animal studies	High	None	High
Hepatic effects			
Human studies	Not applicable		
Animal studies	High	-1 Indirectness	Moderate

Table C-25. Confidence in the Body of Evidence for 1-Methylnaphthalene

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory	Not applicable	High
Hepatic	Not applicable	Moderate

C.12 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—1-METHYLNAPHTHALENE

As described in Section C.7, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted.

A summary of the level of evidence of health effects for 1-methylnaphthalene is presented in Table C-26.

Table C-26. Level of Evidence of Health Effects for 1-Methylnaphthalene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory	NA		
Hepatic	NA		
Animal studies			
Respiratory	High	Health effect	High
Hepatic	Moderate	Health effect	Moderate

C.13 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS–1-METHYLNAPHTHALENE

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. Refer to Section C.8 for the four hazard identification conclusion categories for health effects, the hazard characterization scheme (see Figure C-1), and the hazard identification conclusion categories.

The hazard identification conclusions for 1-methylnaphthalene are listed below and summarized in Table C-27.

Presumed Health Effects

- Respiratory
  - No data in humans.
  - High level of evidence in animals based on significantly increased incidences of nasal lesions in rats exposed for 13 weeks by inhalation (Kim et al. 2020) and significantly increased incidences of pulmonary alveolar proteinosis in mice exposed chronically by dietary administration (Murata et al. 1993).
  - Supported by finding of pulmonary alveolar proteinosis in mice exposed to the structurally related compound 2-methylnaphthalene in the diet (Murata et al. 1997) and in mice exposed by dermal application to a mixture of methylnaphthalenes (Emi and Konishi 1985; Murata et al. 1992).

Suspected Health Effects

- Hepatic
  - No data in humans.
  - Moderate level of evidence in animals based on significantly increased liver weights in combined repeat-dose and reproduction/developmental toxicity screening study of rats exposed via gavage (NITE 2009). No liver effects were reported in the chronic dietary study of 1-methylnaphthalene (Murata et al. 1993), but the estimated doses were lower, and there is uncertainty in the dose estimates for Murata et al. (1993) due to potential for volatilization of the test material from the diet.
  - Supported by observations of liver effects (liver weight, serum enzyme, and/or histopathology changes) in animals exposed to the structurally related compounds, 2-methylnaphthalene (Świercz et al. 2011) and naphthalene (Chen et al. 2012; Katsnelson et al. 2014; Zhang et al. 2016).

Table C-27. Hazard Identification Conclusions for 1-Methylnaphthalene

Outcome	Hazard identification
Respiratory	Presumed health effect
Hepatic	Suspected health effect

C.14 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—2-METHYLNAPHTHALENE

An overview of the potential health effect outcomes for 2-methylnaphthalene identified in animal studies is presented in Table C-28. Human studies of 2-methylnaphthalene were not located. There were few animal studies, but they examined a number of endpoints. The animal data show that the respiratory tract and liver are sensitive effects of exposure to 2-methylnaphthalene; studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were two studies examining these potential outcomes carried through to Steps 4–8 of the systematic review.

Table C-28. Overview of the Health Outcomes for 2-Methylnaphthalene Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration													1 1				
Intermediate-duration	1 0	1 1	1 0		1 0		1 1	1 0				1 0					
Chronic-duration																	
Oral studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration	1 0	1 1	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0		1 0	1 0	1 0			1 1
Dermal studies																	
Acute-duration									1 1								
Intermediate-duration		1 1															
Chronic-duration		1 1															

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

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

C.15 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—2-METHYLNAPHTHALENE

C.15.1 Risk of Bias Assessment—2-Methylnaphthalene

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies were presented above in Tables C-5, C-6, and C-7, respectively. As described in Section C.5.1, each risk of bias question was answered on a four-point scale and studies were assigned to one of three risk of bias tiers.

The results of the risk of bias assessment for the 2-methylnaphthalene health effects studies (animal experimental studies) are presented in Table C-29.

Table C-29. Summary of Risk of Bias Assessment for 2-Methylnaphthalene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects										
Oral chronic exposure										
Murata et al. 1997 (mouse; 81 weeks)	–	–	+	–	+	– –	+	+	– –	Second
Inhalation intermediate exposure										
Świercz et al. 2011	–	–	++	–	+	+	+	+	NA	First
Outcome: Hepatic effects										
Inhalation intermediate exposure										
Świercz et al. 2011	–	–	++	–	+	+	+	+	NA	First

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

*Key question used to assign risk of bias tier

C.16 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—2-METHYLNAPHTHALENE

As discussed in greater detail in Section C.6, confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.16.1 Initial Confidence Rating—2-Methylnaphthalene

As discussed in greater detail in Section C.6.1, the body of evidence for an association (or no association) between exposure to 2-methylnaphthalene and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. Refer to Tables C-9, C-10, and C-11, respectively, for the key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies.

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and hepatic system effects in the animal experimental studies are presented in Table C-30.

Table C-30. Presence of Key Features of Study Design for 2-Methylnaphthalene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Oral chronic exposure					
Murata et al. 1997 (mouse; 81 weeks)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Świercz et al. 2011	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation intermediate exposure					
Świercz et al. 2011 (rat; 28 days)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-31. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-31.

Table C-31. Initial Confidence Rating for 2-Methylnaphthalene Health Effects Studies (Animal Studies)

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Oral chronic exposure		
Murata et al. 1997 (mouse; 81 weeks)	High	High
Inhalation intermediate exposure		
Świercz et al. 2011	High	High
Outcome: Hepatic effects		
Inhalation intermediate exposure		
Świercz et al. 2011	High	High

C.16.2 Adjustment of the Confidence Rating—2-Methylnaphthalene

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The five properties of the body of evidence that were considered to determine whether the confidence rating should be downgraded and the four properties of the body of evidence that were considered to determine whether the confidence rating should be upgraded are described above in Section C.6.2. The summaries of the assessment of the confidence in the body of evidence for respiratory and hepatic effects are presented in Table C-32. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with 2-methylnaphthalene exposure is presented in Table C-33.

Table C-32. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Respiratory effects			
Human studies	NA		
Animal studies	High	None	High
Hepatic effects			
Human studies	NA		
Animal studies	High	None	High

Table C-33. Confidence in the Body of Evidence for 2-Methylnaphthalene

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory	NA	High
Hepatic	NA	High

C.17 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—2-METHYLNAPHTHALENE

As described in Section C.7, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted.

A summary of the level of evidence of health effects for 2-methylnaphthalene is presented in Table C-34.

Table C-34. Level of Evidence of Health Effects for 2-Methylnaphthalene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory	NA		
Hepatic	NA		
Animal studies			
Respiratory	High	Health effect	High
Hepatic	High	Health effect	High

C.18 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—2-METHYLNAPHTHALENE

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. Refer to Section C.8 for the four hazard identification conclusion categories for health effects, the hazard characterization scheme (see Figure C-1), and the hazard identification conclusion categories.

The hazard identification conclusions for 2-methylnaphthalene are listed below and summarized in Table C-35.

Presumed Health Effects

- Respiratory
  - No data in humans.
  - High level of evidence in animals based on significantly increased incidences of bronchial lesions in rats exposed for 4 weeks by inhalation (Świercz et al. 2011) and significantly increased incidences of pulmonary alveolar proteinosis in mice exposed chronically by dietary administration (Murata et al. 1997).
  - Supported by finding of pulmonary alveolar proteinosis in mice exposed to the structurally related compound 1-methylnaphthalene in the diet (Murata et al. 1993) and in mice exposed by dermal application to a mixture of methylnaphthalenes (Emi and Konishi 1985; Murata et al. 1992).
- Hepatic
  - No data in humans.
  - High level of evidence in animals based on dose-related increased incidences of bile duct hyperplasia in rats exposed by inhalation for 4 weeks (Świercz et al. 2011).

- Supported by observations of liver effects (liver weight, serum enzyme, and/or histopathology changes) in animals exposed to the structurally related compounds, 1-methylnaphthalene (NITE 2009) and naphthalene (Chen et al. 2012; Katsnelson et al. 2014; Zhang et al. 2016).

Table C-35. Hazard Identification Conclusions for 2-Methylnaphthalene

Outcome	Hazard identification
Respiratory	Presumed health effect
Hepatic	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

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

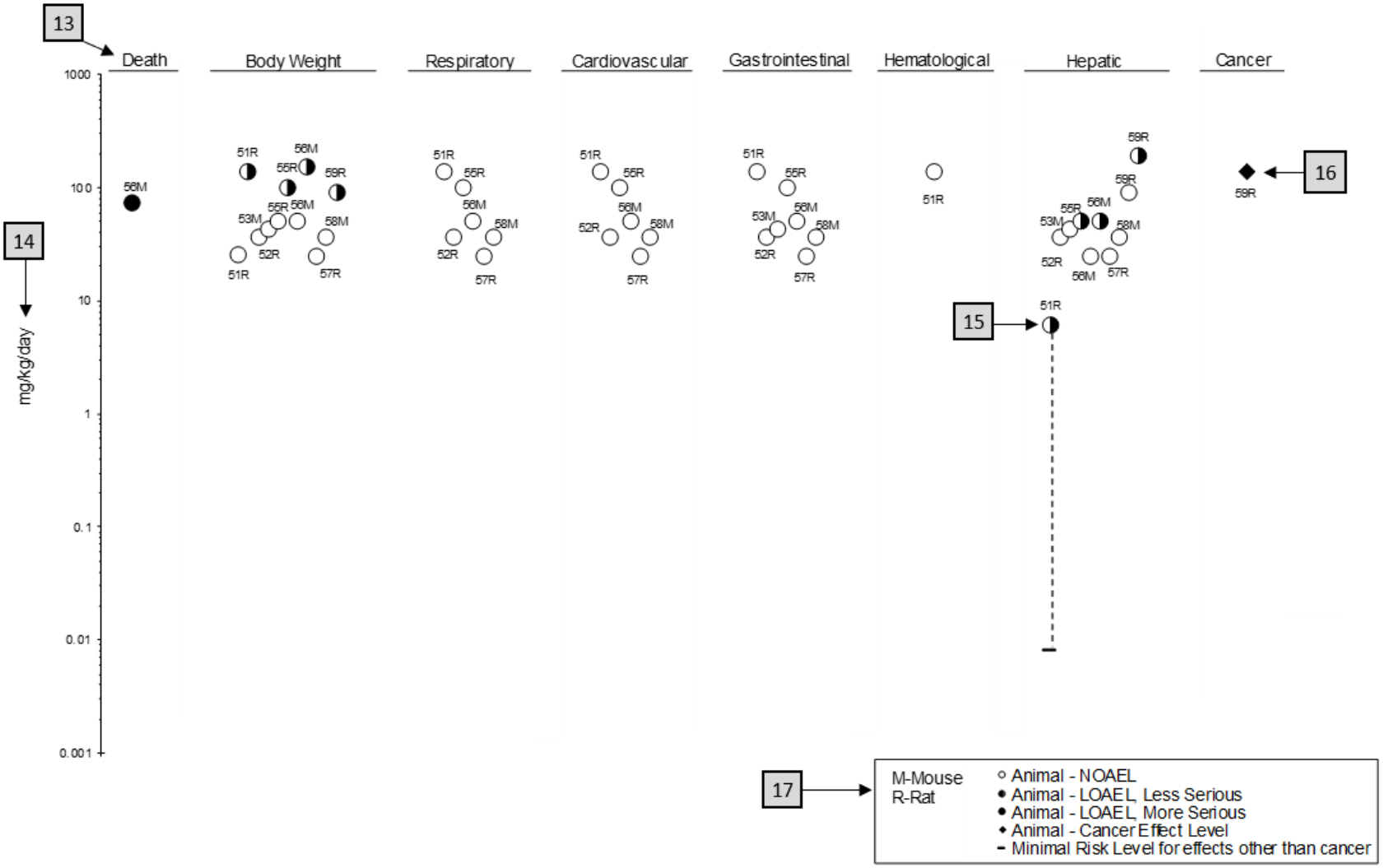
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
(2) **CHRONIC EXPOSURE**									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)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

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

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

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

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

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

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

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

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

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, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant 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 LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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) exposure limit. The REL may be a time-weighted average (TWA) concentration for up to an 8 or 10-hour workday during a 40-hour workweek. The REL may also be a short-term exposure limit (denoted ST), typically a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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