CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figures 2-1, 2-2, and 2-3 provide an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene was also conducted; the results of this review are presented in Appendix C.

Animal studies of naphthalene are presented in Table 2-1 and Figure 2-4 for inhalation exposure, Table 2-2 and Figure 2-5 for oral exposure, and Table 2-3 for dermal exposure. Animal studies of 1- and 2-methylnaphthalene are presented in Table 2-4 and Figure 2-6 for inhalation exposure, Table 2-5 and Figure 2-7 for oral exposure, and Table 2-6 for dermal exposure.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies.

Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of naphthalene are indicated in Table 2-1 and Figure 2-4. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1- and 2-methylnaphthalene are indicated in Table 2-5 and Figure 2-7.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The discussion of the available data for health effects in this chapter is organized into chemical-specific subsections provided in the following order: naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene. Studies in humans were located only for naphthalene and are discussed under the corresponding health effect subsections.

Health effects data for naphthalene are shown in Figure 2-1. As indicated in the figure, there were a number of human studies (primarily case reports); the largest numbers of studies examined developmental endpoints and/or reported gastrointestinal effects. The animal studies of naphthalene primarily examined ocular and respiratory effects. Animal studies suggest that respiratory, immunological, and neurological effects are sensitive targets of naphthalene toxicity.

Respiratory endpoints: Respiratory tract toxicity is a presumed health effect in humans based on low level of evidence in humans and high level of evidence in animals. Human studies reported associations between nasal irritation and inflammation and occupational exposure to

naphthalene, and between decreases in lung function and airborne naphthalene concentrations in general population studies. In animals, nasal histopathological lesions were consistently seen in rats and mice after inhalation exposure for acute, intermediate, and chronic durations, and lung pathology was reported in mice after acute- and chronic-duration exposures.

Neurological endpoints: Nervous system toxicity is a suspected health effect in humans based on a moderate level of evidence in animals. Clinical signs of neurotoxicity (lethargy) were observed in rats exposed orally during gestation (NTP 1991) or in a 13-week study (NTP 1980b) and in mice exposed orally for 13 weeks (NTP 1980a).

Immunological endpoints: Immunological toxicity is not classifiable due to low evidence in both human and animal studies. Human studies suggested associations between naphthalene and cytokine levels and/or differential leukocyte counts. Animal studies showed reduced thymus weights in rats exposed by inhalation and mice exposed orally; a low incidence of lymphoid depletion of the thymus in female rats exposed by gavage for 13 weeks; increased serum inflammatory markers in mice given a single oral dose of naphthalene; and reduced mitogenic response to concanavalin A in mice exposed orally for 2 weeks.

Figure 2-2 provides an overview of the health effects data for 1-methylnaphthalene. No human studies of 1-methylnaphthalene were located, and there were very few animal studies. The animal studies indicate that the respiratory tract and liver are sensitive targets of 1-methylnaphthalene toxicity.

Respiratory endpoints: Respiratory tract toxicity is a presumed health effect in humans based on a high level of evidence in animals. Significantly increased incidences of nasal lesions were observed in rats exposed for 13 weeks by inhalation and significantly increased incidences of pulmonary alveolar proteinosis in mice exposed chronically by diet. The hazard identification conclusion is supported by findings of pulmonary alveolar proteinosis in mice exposed to the structurally related compound 2-methylnaphthalene in the diet and in mice exposed by dermal application to a mixture of methylnaphthalenes.

Hepatic endpoints: Hepatic toxicity is a suspected health effect in humans based on a moderate level of evidence in animals. Significantly increased liver weights were observed in a combined repeat-dose and reproductive/developmental toxicity screening study of rats exposed via gavage. No liver effects were reported in the chronic dietary study of 1-methylnaphthalene, but the estimated doses were lower, and there is uncertainty in the dose estimates for the chronic study due to potential for volatilization of the test material from the diet. The hazard identification conclusion is supported by observations of liver effects (liver weight, serum enzyme, and/or histopathology changes) in animals exposed to the structurally related compounds 2-methylnaphthalene and naphthalene.

Data on the health effects of 2-methylnaphthalene are summarized in Figure 2-3. As with 1-methylnaphthalene, human studies of 2-methylnaphthalene were not located, and the database of animal studies is very small. The studies of animals exposed by inhalation and oral routes show that the respiratory tract and liver are sensitive targets of 2-methylnaphthalene.

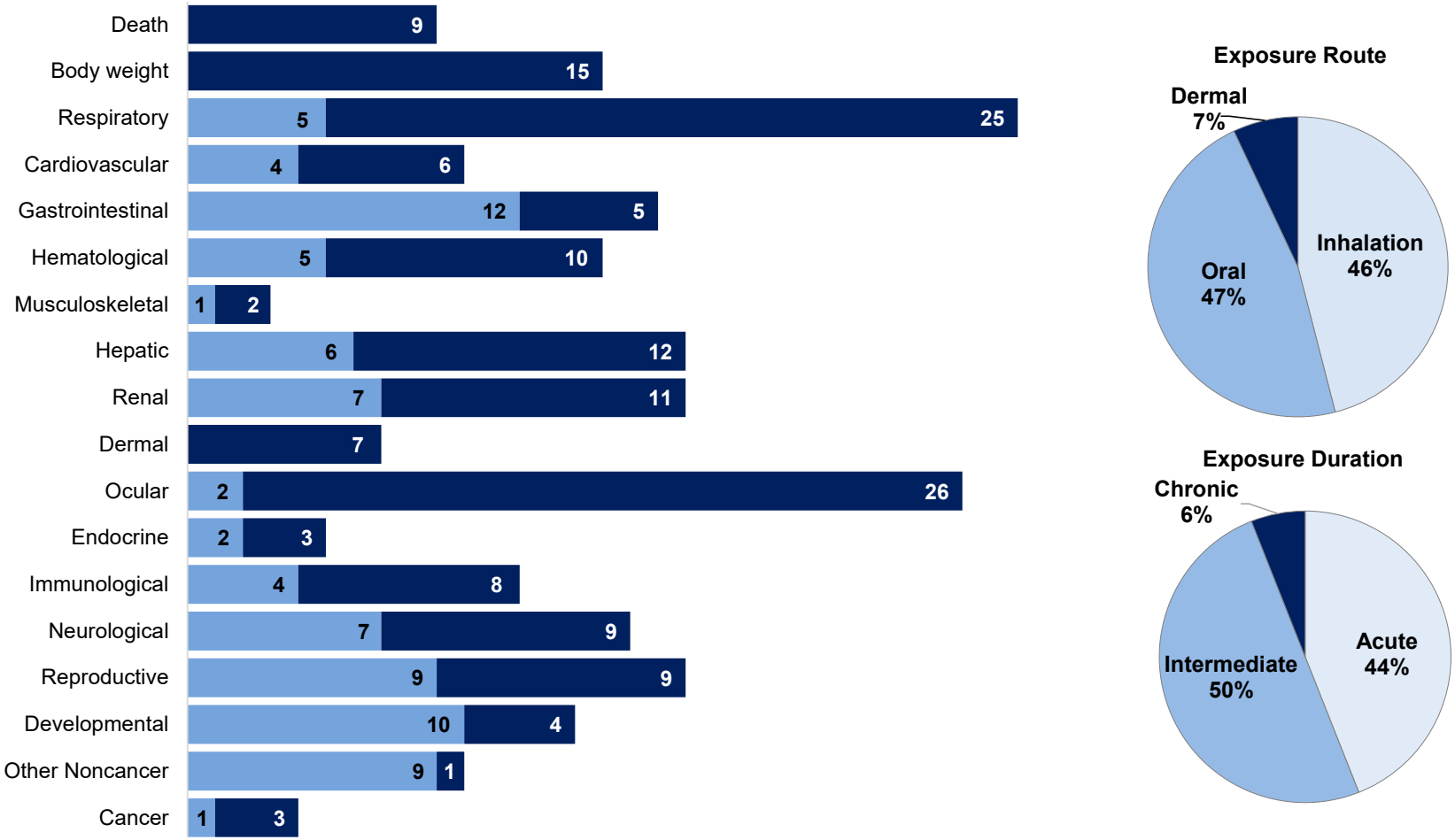
Respiratory endpoints: Respiratory tract toxicity is a presumed health effect in humans based on a high level of evidence in animals. Significantly increased incidences of nasal lesions were observed in rats exposed for 13 weeks by inhalation and significantly increased incidences of pulmonary alveolar proteinosis in mice exposed chronically by diet. The hazard identification conclusion is supported by findings of pulmonary alveolar proteinosis in mice exposed to the structurally related compound 2-methylnaphthalene in the diet and in mice exposed by dermal application to a mixture of methylnaphthalenes.

Hepatic endpoints: Hepatic toxicity is a presumed health effect in humans based on a high level of evidence in animals. Dose-related increases in the incidences of bile duct hyperplasia were observed in rats exposed by inhalation for 4 weeks. The hazard identification conclusion is supported by observations of liver effects (liver weight, serum enzyme, and/or histopathology changes) in animals exposed to the structurally related compounds 1-methylnaphthalene and naphthalene.

Figure 2-1. Overview of the Number of Studies Examining Naphthalene Health Effects*

Most studies examined the potential respiratory and ocular effects of naphthalene

Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)

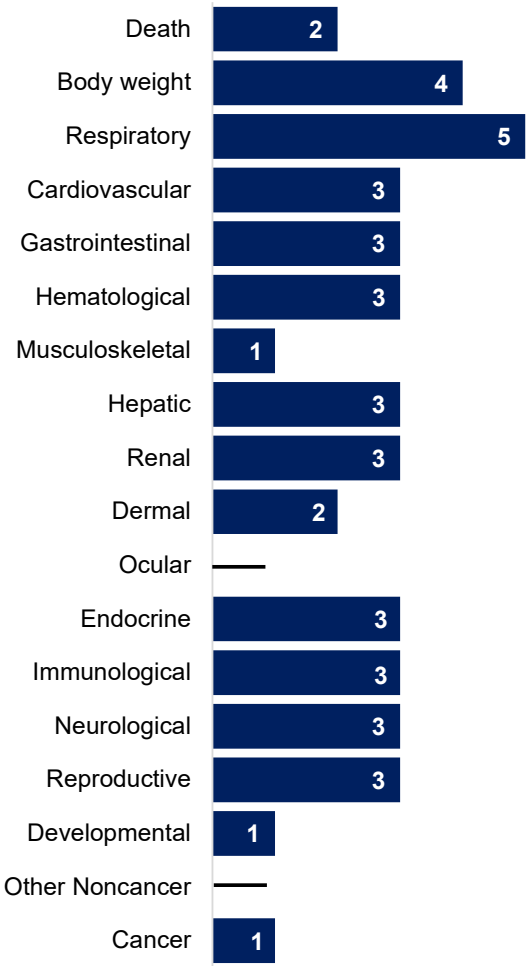


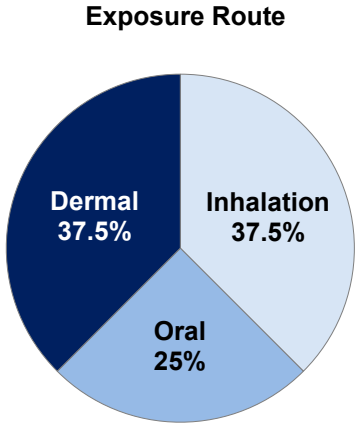
*Includes studies discussed in Chapter 2. A total of 153 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

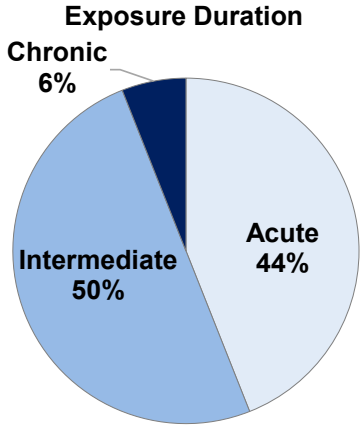
Figure 2-2. Overview of the Number of Studies Examining 1-Methylnaphthalene Health Effects*

Most studies examined the potential respiratory and body weight effects of 1-methylnaphthalene

The majority of the studies examined dermal exposure in animals; no data were identified for humans (counts represent studies examining endpoint)





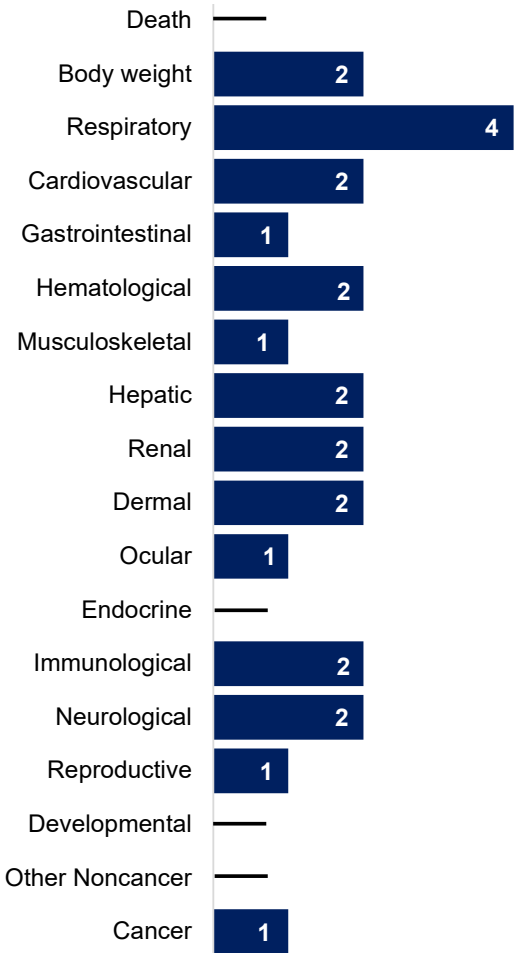


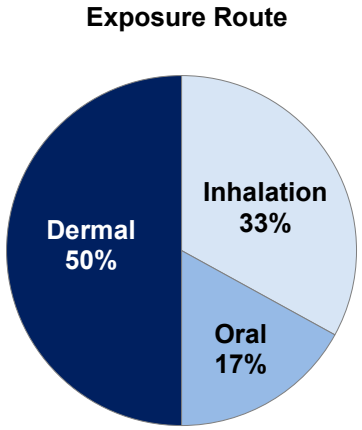
*Includes studies discussed in Chapter 2. A total of 11 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

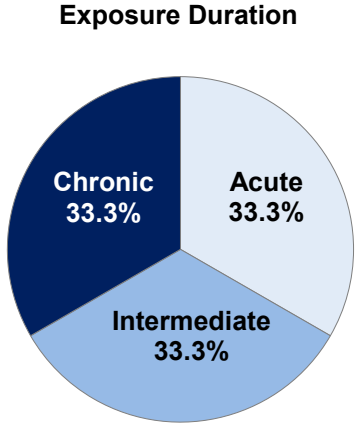
Figure 2-3. Overview of the Number of Studies Examining 2-Methylnaphthalene Health Effects*

Most studies examined the potential respiratory effects of 2-methylnaphthalene

The majority of the studies examined dermal exposure in animals; no data were identified for humans (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 10 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Naphthalene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Cichocki et al. 2014									
1	Rat (Fischer-344) 6 M, 6 F	Once 4 or 6 hours (N)	0, 15, 30	HP	Resp		15		Cytotoxicity of olfactory and respiratory/transitional mucosa
Dodd et al. 2010									
2	Rat (Fischer-344) 5 M, 5 F	Once 6 hours (WB)	0, 0.1, 0.3, 1, 10, 30	LE, CS, BW, GN, HP	Bd wt Resp	30 0.3	 1		 Minimal severity necrosis of the nasal olfactory epithelium
Dodd et al. 2010									
3	Rat (Fischer-344) 5–10 M, 5–10 F	5 days 6 hours/day (WB)	0, 0.1, 1, 10	LE, CS, BW, GN, HP	Bd wt Resp	10 0.1	 1.0		 Minimal severity necrosis of the nasal olfactory epithelium and nasopharyngeal goblet cell hyperplasia
Dodd et al. 2010									
4	Rat (Sprague-Dawley) 5 M, 5 F	Once 6 hours (WB)	0, 0.1, 0.3, 1, 10, 30	LE, CS, BW, GN, HP	Bd wt Resp	30 	 0.1[b]		 Minimal severity necrosis of the nasal olfactory epithelium
Dodd et al. 2010									
5	Rat (Sprague-Dawley) 5–10 M, 5–10 F	5 days 6 hours/day (WB)	0, 0.1, 1, 10	LE, CS, BW, GN, HP	Bd wt Resp	10 0.1 M	 0.1 F 1.0 M		 Minimal severity necrosis of the nasal olfactory epithelium
Lee et al. 2005									
6	Rat (Sprague-Dawley) 6 M	Once 4 hours (WB)	0, 3.4, 23.8	HP	Resp		3.4		Necrosis, vacuolation, and exfoliation of the nasal olfactory epithelium

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
West et al. 2001									
7	Rat (Sprague-Dawley) NS/M	Once 4 hours (WB)	0, 2, 10, 30, 75, 100	HP	Resp	100			
Carratt et al. 2016									
8	Mouse (C57BL/6) 3 M, 3 F	Once 4 hours (WB)	0, 5, 10, 20	GN, HP	Resp		5		Epithelial damage (vacuolization and swelling) in proximal airways
Carratt et al. 2019b									
9	Mouse (B6:129) NS	Once 4 hours (WB)	0, 5, 10	HP	Resp		5		Epithelial damage (vacuolization and swelling) in proximal airways
Kovalchuk et al. 2020									
10	Mouse (C57BL/6) 3–4 M	Once 4 hours (N)	0, 10	HP	Resp			10	Proximal and distal airway epithelial swelling, detachment, decreased thickness, and cell proliferation; increased LDH and total protein in BALF at sacrifice 20 hours post-exposure
Li et al. 2017									
11	Mouse (C57BL/6) 3–6 M	1 day 2 times/day 2 hours (N)	0, 10	HP	Resp			10	Necrosis of epithelial cells in the lung, detachment of club cells in the lung and severe cytotoxicity of the olfactory mucosa, including necrosis, detachment, sloughing, and ulceration
NTP 1992a									
12	Mouse (B6C3F1) 4–10 M, 4–10 F	14 days 5 days/week 6 hours/day (WB)	0, 10, 30	HE	Hemato	30			

Table 2-1. Levels of Significant Exposure to Naphthalene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Phimister et al. 2004									
13	Mouse (Swiss) 4 M	Once 4 hours (WB)	0, 15	HP	Resp			15	Necrotic club cells in proximal and distal airways and lumen; squamous ciliated cell replacement of club cells; nasal olfactory epithelium nearly devoid of cells
Phimister et al. 2004									
14	Mouse (Swiss) 4 M	Once 2 hours (WB)	0, 1.5	HP	Resp		1.5		Mild cell loss in olfactory epithelium
West et al. 2001									
15	Mouse (Swiss-Webster) NS/M	Once 4 hours (WB)	0, 2, 10, 30, 75, 100	HP	Resp	2	10	75	LOAEL: Club cell necrosis and decreased club cell mass in proximal airways SLOAEL: Proximal and terminal epithelium devoid of club cells
INTERMEDIATE EXPOSURE									
Dodd et al. 2012									
16	Rat (Fischer-344) 10 M, 10 F	90 days 5 days/week 6 hour/day (WB)	0, 0.1, 1, 10, 30	LE, CS, BW, FI, WI, GN, OW, HP	Bd wt	30			
					Resp	0.1	1		Increased incidence of transitional/respiratory epithelial hyperplasia
					Immuno	0.1 F 1 M	1 F 10 M		Reduced absolute and relative thymus weights in females; reduced absolute thymus weights in males

Table 2-1. Levels of Significant Exposure to Naphthalene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
NTP 2000 (Abdo et al. 2001)									
17	Rat (Fischer-344) 49 M, 49 F	105 weeks 5 days/week 6 hours/day (WB)	0, 10, 30, 60	LE, CS, BW, NX, GN, HP	Bd wt	60			
					Resp		10		Inflammation of the nose; nasal olfactory epithelium atypical hyperplasia, atrophy, and degeneration; nasal respiratory epithelium hyperplasia, squamous metaplasia, and degeneration; Bowman's glands hyperplasia
					Cardio	60			
					Gastro	60			
					Musc/skel	60			
					Hepatic	60			
					Renal	60			
					Dermal	60			
					Ocular	60			
					Endocr	60			
					Immuno	60			
					Neuro	60			
					Repro	60			
					Cancer			10	CEL: nasal respiratory epithelial adenomas in males and in females at higher concentrations; olfactory epithelial neuroblastomas in both sexes at higher concentrations

Table 2-1. Levels of Significant Exposure to Naphthalene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1992a									
18	Mouse (B6C3F1) 75–150 M, 75–150 F	104 weeks 5 days/week 6 hours/day (WB)	0, 10, 30	LE, CS, BW, GN, HP	Resp		10		Inflammation of the nose and lung, metaplasia of the olfactory epithelium, and hyperplasia of the nasal respiratory epithelium
					Cardio	30			
					Gastro	30			
					Musc/skel	30			
					Hepatic	30			
					Renal	30			
					Dermal	30			
					Endocr	30			
					Immuno	30			
					Neuro	30			
					Repro	30			
					Cancer			30	CEL: pulmonary alveolar adenomas in females

[a]The number corresponds to entries in Figure 2-4.
[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.00006 ppm ($6x10^{-5}$ ppm) for naphthalene based on benchmark dose modeling of nasal olfactory epithelial necrosis incidences in male and female rats. The $BMCL_{10}$ of 0.017 ppm was adjusted for continuous exposure and converted to a $BMCL_{HEC}$ of 0.0017 ppm. The $BMCL_{HEC}$ was divided by an uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after dosimetric adjustment) to derive the MRL; see Appendix A for more detailed information regarding the MRL.

BALF = bronchoalveolar lavage fluid; Bd wt or BW = body weight; $BMCL_{10}$ = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); Cardio = cardiovascular; CEL = Cancer Effect Level; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = males(s); Musc/skel = musculoskeletal; (N) = nose only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OW = organ weight; Repro = reproductive; Resp = respiratory; SLOAEL = serious lowest-observed-adverse-effect level; (WB) = whole body; WI = water intake

Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation
Acute (≤14 days)

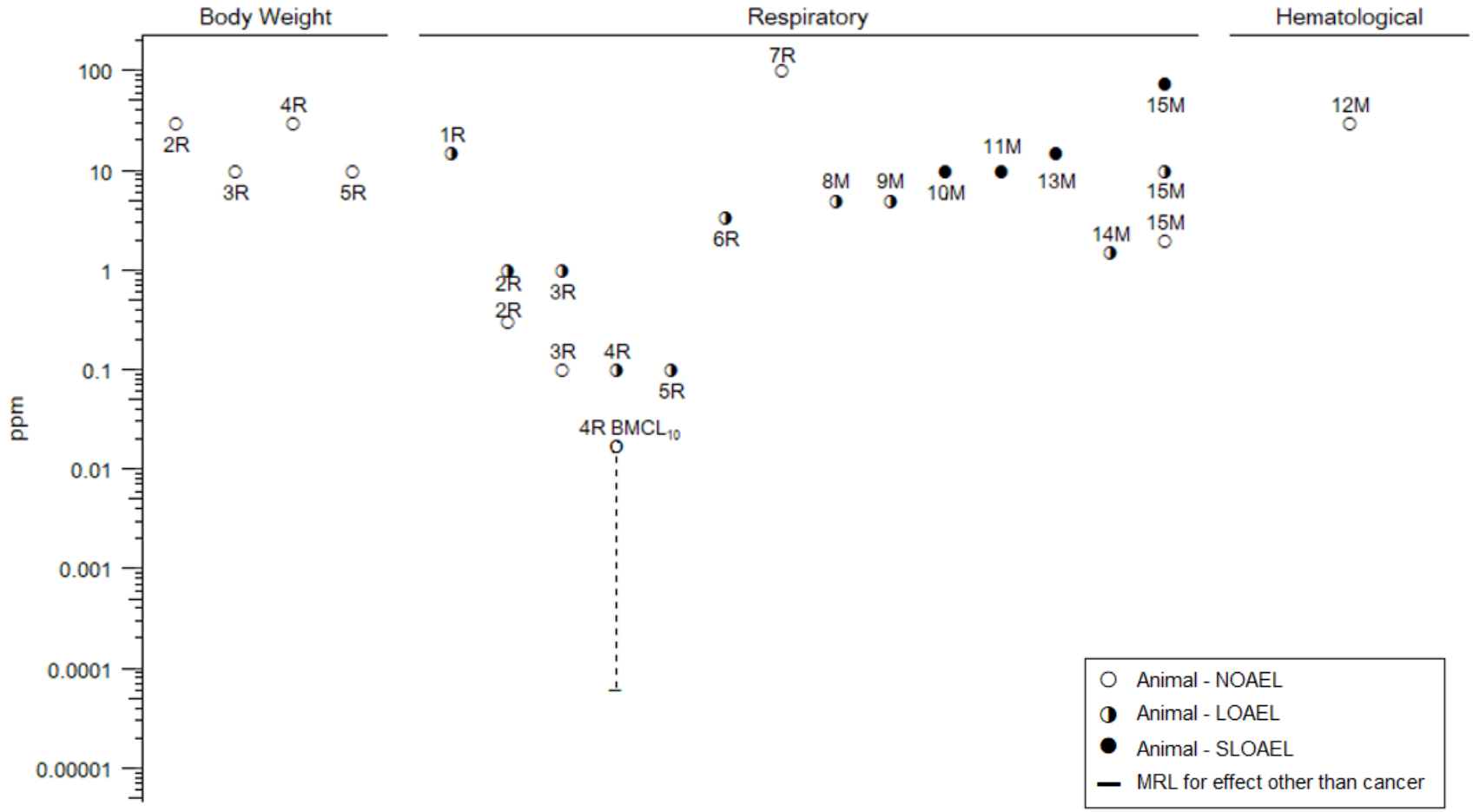

Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation
Intermediate (15–364 days)

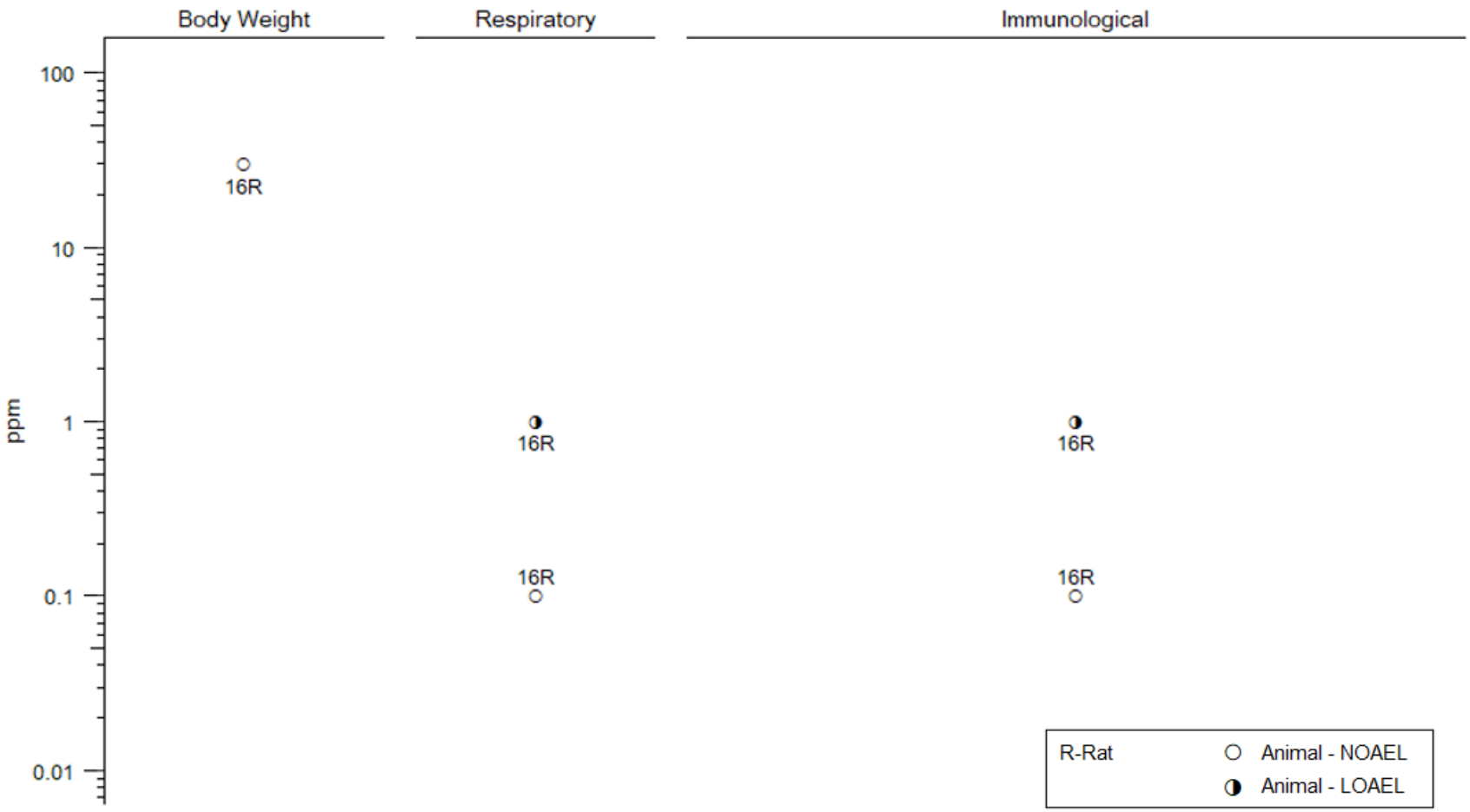

Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation
Chronic (≥365 days)

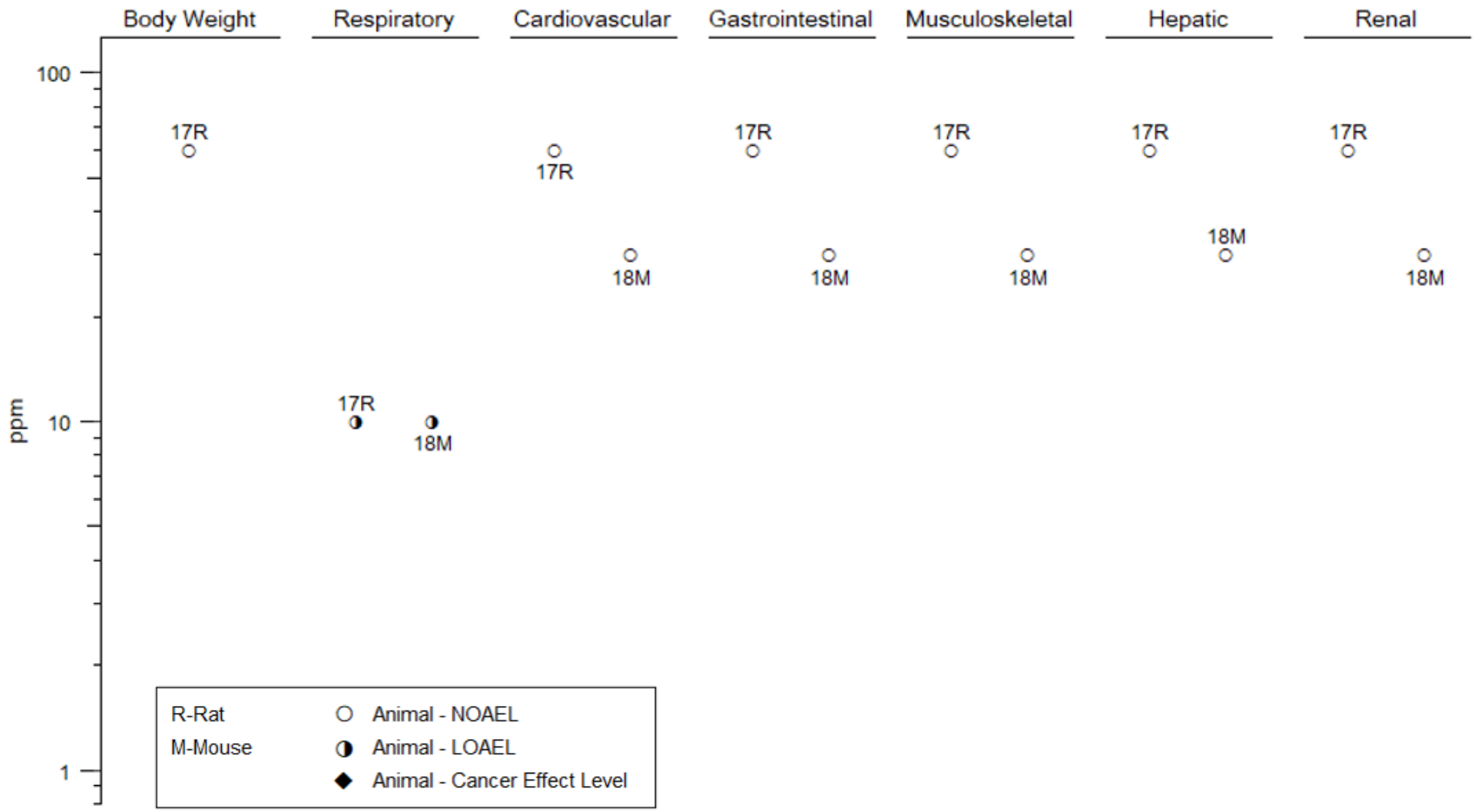

Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation
Chronic (≥365 days)

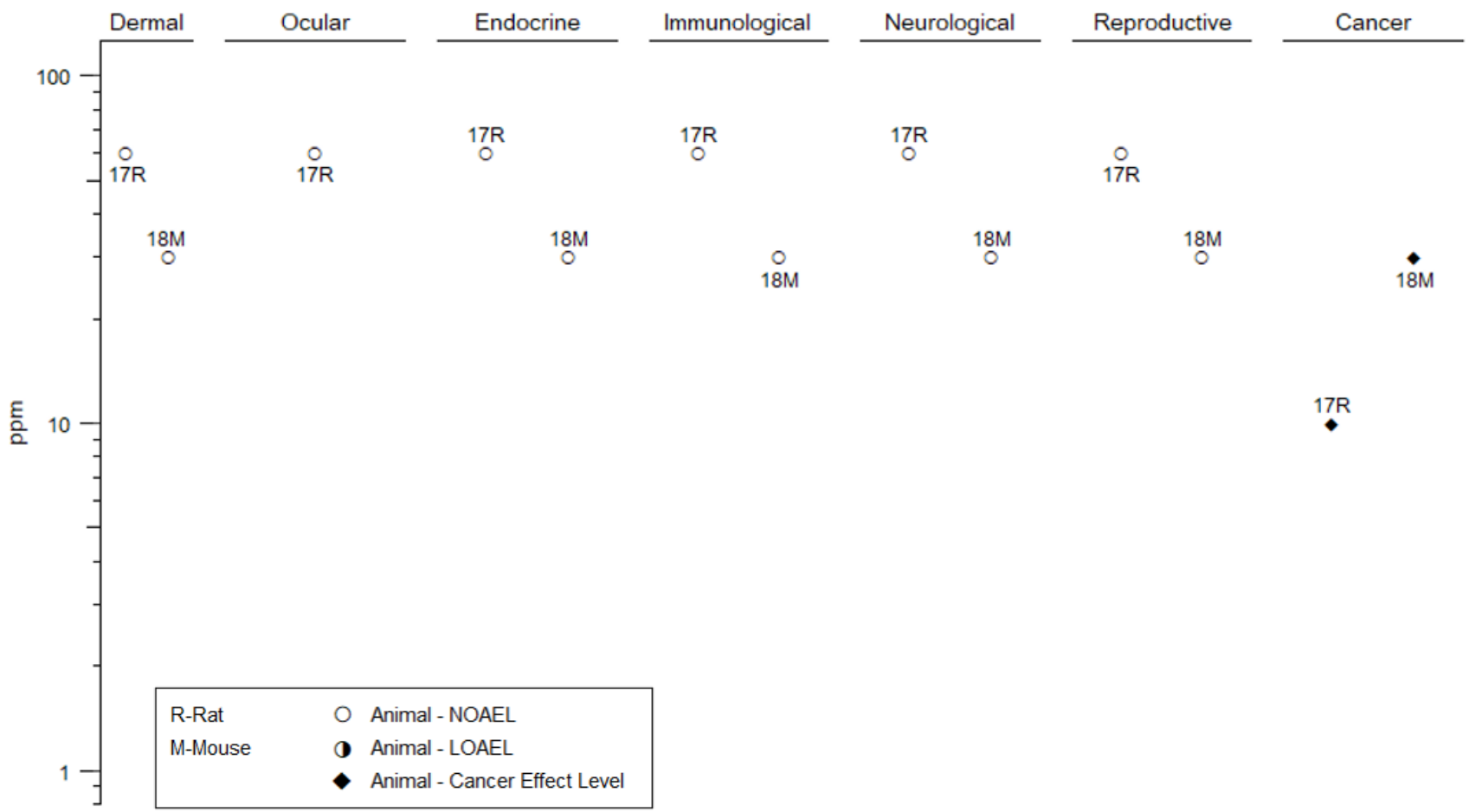

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Gidron and Leurer 1956									
1	Human 1 F	Once	109	CS, BC, HE, UR	Gastro		109		Abdominal pain
					Hemato			109	Hemolytic anemia
					Other noncancer			109	106°F fever
Gaines 1969									
2	Rat (Sherman) 10 M, 10 F	Once (GO)	ND		Death			2,400 F 2,200 M	LD_{50}
NTP 1991									
3	Rat (Sprague-Dawley) 25–26 F	GDs 6–15 (GO)	0, 50, 150, 450	BW, OW, DX	Bd wt	50		150	31% decrease in maternal body weight gain
					Neuro		50[b,c]		Transient clinical signs of toxicity (lethargy) in dams; at higher exposure levels, signs were more persistent
					Develop	450			
Papciak and Mallory 1990									
4	Rat (Sprague-Dawley) 5 M, 5 F	Once (GO)	1,000, 1,600, 2,500, 3,200, 4,000	CS, GN	Death			2,600	LD_{50}
Rao and Pandya 1981									
5	Rat (NS) 6 M	Once (G)	0, 1,000	OW, BI	Hepatic		1,000		Increased liver weight
					Renal	1,000			
					Ocular	1,000			

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kelty et al. 2020									
6	Mouse (B6C3F1) 3–5 M, 3–5 F	Once (GO)	0, 150	HP	Resp		150		Respiratory epithelial cytotoxicity
Plasterer et al. 1985									
7	Mouse (CD-1) 33–45 F	GDs 7–14 (GO)	0, 300	BW, DX, RX	Death			300	5/33 died
					Develop	300			
Plasterer et al. 1985									
8	Mouse CD-1 10 F	8 days (GO)	0, 125, 250, 500, 1,200, 2,000	LE, BW	Death			354	LD_{50}
Shopp et al. 1984									
9	Mouse (CD-1) 116–188 M 116–188 F	14 days (GO)	0, 27, 53, 267	BW, HE, BC, OW	Death			267	10/96 males and 3/60 females died
					Bd wt	53	267		6% (female) or 13% (male) decreased final body weight
					Resp	53 F 267 M	267 F		Increase in lung weight
					Hemato	267			
					Hepatic	267			
					Renal	267			
					Immuno	53	267		Decrease in thymus weight in males; decrease in spleen weight in females
					Neuro	267			
Shopp et al. 1984									
10	Mouse (CD-1) 8 M, 8 F	Once (GO)	200, 400, 600, 800, 1,000	CS, GN	Death			710 F 533 M	LD_{50}

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Zhang et al. 2015									
11	Mouse (Kunming) 10 M, 10 F	Once (G)	0, 100	BC, HP	Resp			100	Lung histopathology including structural degeneration, vasocongestion, edema, inflammatory cell infiltration and destroyed interalveolar septa with large, irregular alveolar space
Zhang et al. 2016									
12	Mouse (Kunming) 10 M, 10 F	Once (NS)	0, 100	BC, BI, HP	Resp			100	Lung structural degeneration, inflammatory cell infiltrate, vasocongestion, edema, alterations of alveoli and alveolar septa
					Hepatic			100	Increased serum levels of AST (>5-fold) and ALT (>13-fold), extensive hepatocellular necrosis, moderate inflammatory cell infiltration, massive fatty degeneration, and structural degeneration
NTP 1992b									
13	Rabbit (New Zealand White) 20–23 F	GDs 6–19 (GO)	0, 20, 80, 120	BW, DX	Develop	120			
Texaco 1985d, 1986									
14	Rabbit (New Zealand White) 18 F	GDs 6–18 (G)	0, 40, 200, 400	BW, FI, CS, DX, RX	Resp			200	Maternal dyspnea and cyanosis
					Neuro		200		Maternal body drop and hypoactivity with no pathological changes
					Develop	400			

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Chen et al. 2010a, 2010b									
15	Rat (Sprague-Dawley) 15 F	9 weeks 7 days/week (GO)	0, 1,000	OP, OW	Ocular			1,000	Cataracts
Chen et al. 2012									
16	Rat (Sprague-Dawley) 7–8 M, 6–8 F	10 weeks 7 days/week (GO)	0, 1,000	OP, OW, HP	Hepatic		1,000		Changes in structural morphology of hepatocytes
					Ocular			1,000	Cataracts
Germansky and Jamall 1988									
17	Rat (Blue Spruce) 8–24 M	9 weeks 7 days/week (GO)	0, 169 (TWA)	BI, CS, BW	Bd wt			169	20% decreased body weight at termination
Holmén et al. 1999									
18	Rat (Brown-Norway) 3–15 F	10 weeks 2 days/week (G)	0, 100, 500, 1,000, 1,500	OP, BW, OW	Bd wt		1,500		17% decreased body weight
					Ocular	100		500	Cataracts
Katsnelson et al. 2014									
19	Rat (NS) 12–15 F	7 weeks 3 days/week (G)	0, 87.5	LE, NX, HE, BC, UR	Bd wt	87.5			
					Hemato	87.5			
					Hepatic		87.5		Increased serum AST and ALT
					Neuro		87.5		Inhibition of withdrawal reflex (increased temporal summation of subthreshold impulses)
Kojima 1992									
20	Rat (Brown-Norway) 3–12 F	4 weeks 3.5 days/week (GO)	0, 1,000	GN, BI, OP	Ocular			1,000	Cataracts

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Murano et al. 1993									
21	Rat (Sprague-Dawley and Brown-Norway) 6 M	6 weeks 3.5 days/week (G)	0, 1,000	CS, OP	Ocular			1,000	Cataracts
NTP 1980b									
22	Rat (Fischer 344) 10 M, 10 F	13 weeks 5 days/week (GO)	0, 25, 50, 100, 200, 400	HE, BC, CS, HP, BW	Bd wt	100	200	400	LOAEL: Decreased terminal body weight (12% in male & 6% in females) SLOAEL: Decreased terminal body weight (28% in males & 23% in females)
					Resp	400			
					Cardio	400			
					Gastro		400		Intermittent diarrhea
					Hemato	400			
					Hepatic	400			
					Renal	400 F			
						200 M	400 M		1/10 had cortical tubular degeneration
					Ocular	400			
					Immuno	200 F 400 M	400 F		Lymphoid depletion of thymus in 2/10 females
					Neuro		400		Hunched posture and lethargy
					Repro	400			
Patel and Patel 2018									
23	Rat (Wistar) 6 M, 6 F	28 days (GO)	0, 1,000	OP	Ocular			1,000	Cataracts

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Rathbun et al. 1990									
24	Rat (Black-hooded) NS	79 days (GO)	0, 5,000	OP, BI	Ocular			5,000	Cataracts
Siddiqui et al. 2002									
25	Rat (albino) 6 F	4 weeks 7 days/week (GW)	0, 1,000	OP	Ocular			1,000	Cataracts
Singh and Bodakhe 2020									
26	Rat (Sprague-Dawley) 6 M	4 weeks 7 days/week (GO)	0, 1,000	OP	Ocular			1,000	Cataracts
Tao et al. 1991									
27	Rat (Brown-Norway) 4–6 F	102 days (GO)	0, 700	OP, HP	Ocular			700	Cataracts
Xu et al. 1992b									
28	Rat (5 Strains) 6–10 M	4–6 weeks 7 days/week (GO)	0, 1,000	OP, BI, GN	Ocular			1,000	Cataracts
Yamauchi et al. 1986									
29	Rat (Wistar) 4–5 M	18 days (G)	0, 1,000	OP, BI, BC	Ocular			1,000	Cataracts
Zhu and Lu 2012									
30	Rat (Sprague-Dawley) 3–6 F	5 weeks 7 days/week (NS)	0, 1,000	OP, HP	Hepatic	1,000			
					Renal	1,000			
					Ocular			1,000	Cataracts

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1980a									
31	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 times/week (GO)	0, 12.5, 25, 50, 100, 200	BC, BW, FI, GN, HP	Bd wt	200			
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Hepatic	200			
					Renal	200			
					Ocular	200			
					Neuro	200			
					Repro	200			
Shopp et al. 1984									
32	Mouse (CD-1) 116–188 M, 116–188 F	90 days 7 days/week 1 time/day (GO)	0, 5.3, 53, 133	HE, BI, BC, OW	Bd wt	133			
					Resp	133			
					Hemato	53 F 133 M	133 F		Decrease in absolute and relative spleen weight in females
					Hepatic	53 F 133 M	133 F		Decreased absolute liver weights in females
					Renal	133			
					Immuno	133			
					Neuro	133			
					Repro	133 M			
Darious et al. 2020									
33	Hamster (Syrian) 8 M	3 weeks 7 days/week (NS)	0, 1,000	HE, HP	Hemato		1,000		Reduced red blood cells, hemoglobin, and hematocrit; severe spleen congestion, hemosiderin deposition, hemolysis in red pulp, and hyperplasia in white pulp

Table 2-2. Levels of Significant Exposure to Naphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Orzalesi et al. 1994									
34	Rabbit (NS) 31 M	5 weeks 3.5 days/week (GO)	0, 1,000	OP	Ocular			1,000	Destruction of retinal photoreceptors and vascularization of the retinal area
Rossa and Pau 1988									
35	Rabbit (Chinchilla Bastard New Zealand White) 4 NS	12 weeks 2 days/week (GO)	0, 1,000	OP, CS	Ocular			1,000	Cataracts
van Heyningen and Pirie 1967									
36	Rabbit (NS) NS	4 weeks 7 days/week (GO)	0, 1,000	OP, CS	Ocular			1,000	Cataracts, retinal damage

[a]The number corresponds to entries in Figure 2-5.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.2 mg/kg/day for naphthalene based on the LOAEL of 50 mg/kg/day. The LOAEL was divided by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a minimal LOAEL) to derive the MRL; see Appendix A for more detailed information regarding the MRL.
[c]The acute-duration oral MRL was adopted as the intermediate-duration oral MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; (GW) = gavage in water; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = medial lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = males(s); ND = no data; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level; TWA = time-weighted average; UR = urinalysis

Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral
Acute (≤14 days)

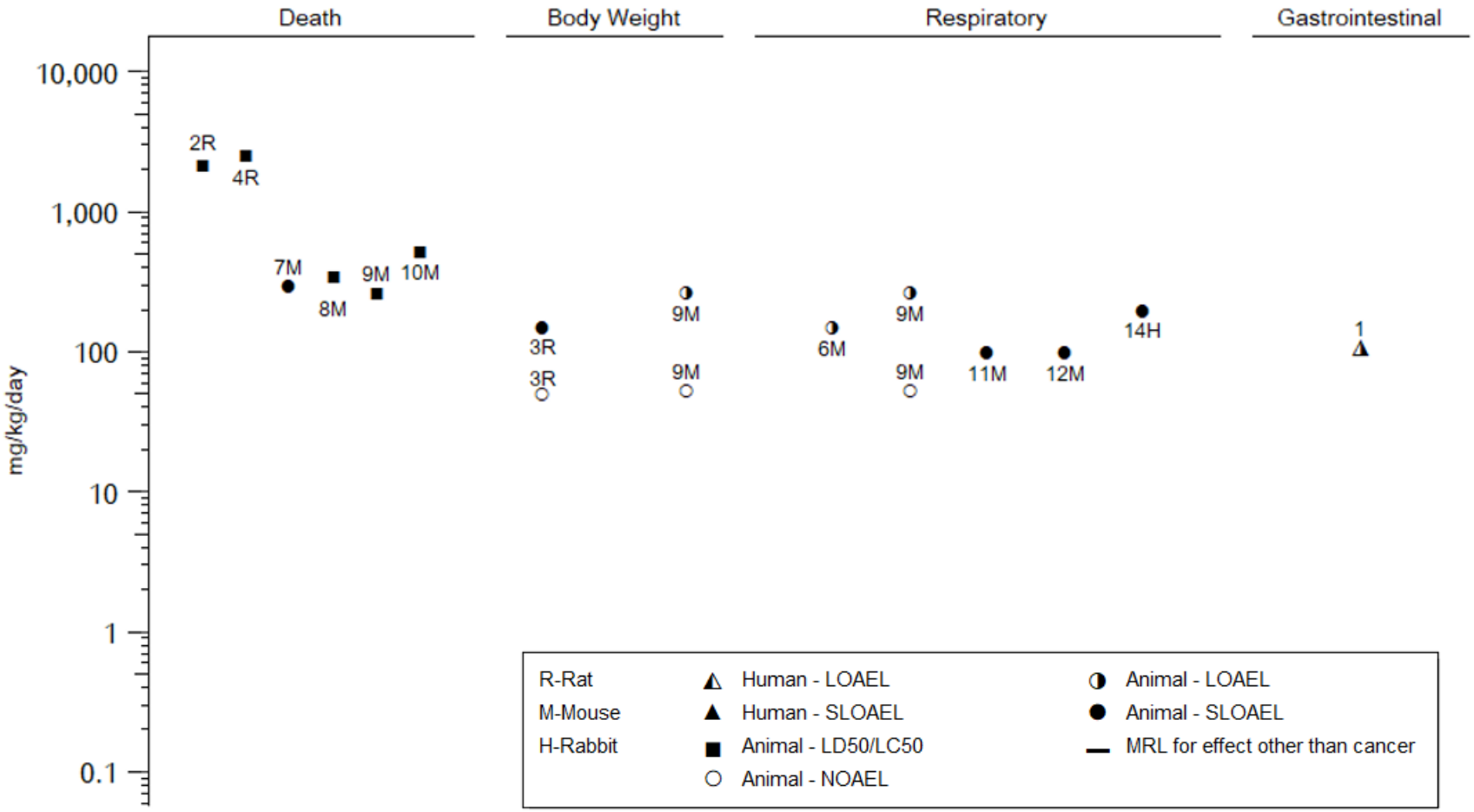

Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral

Acute (≤14 days)

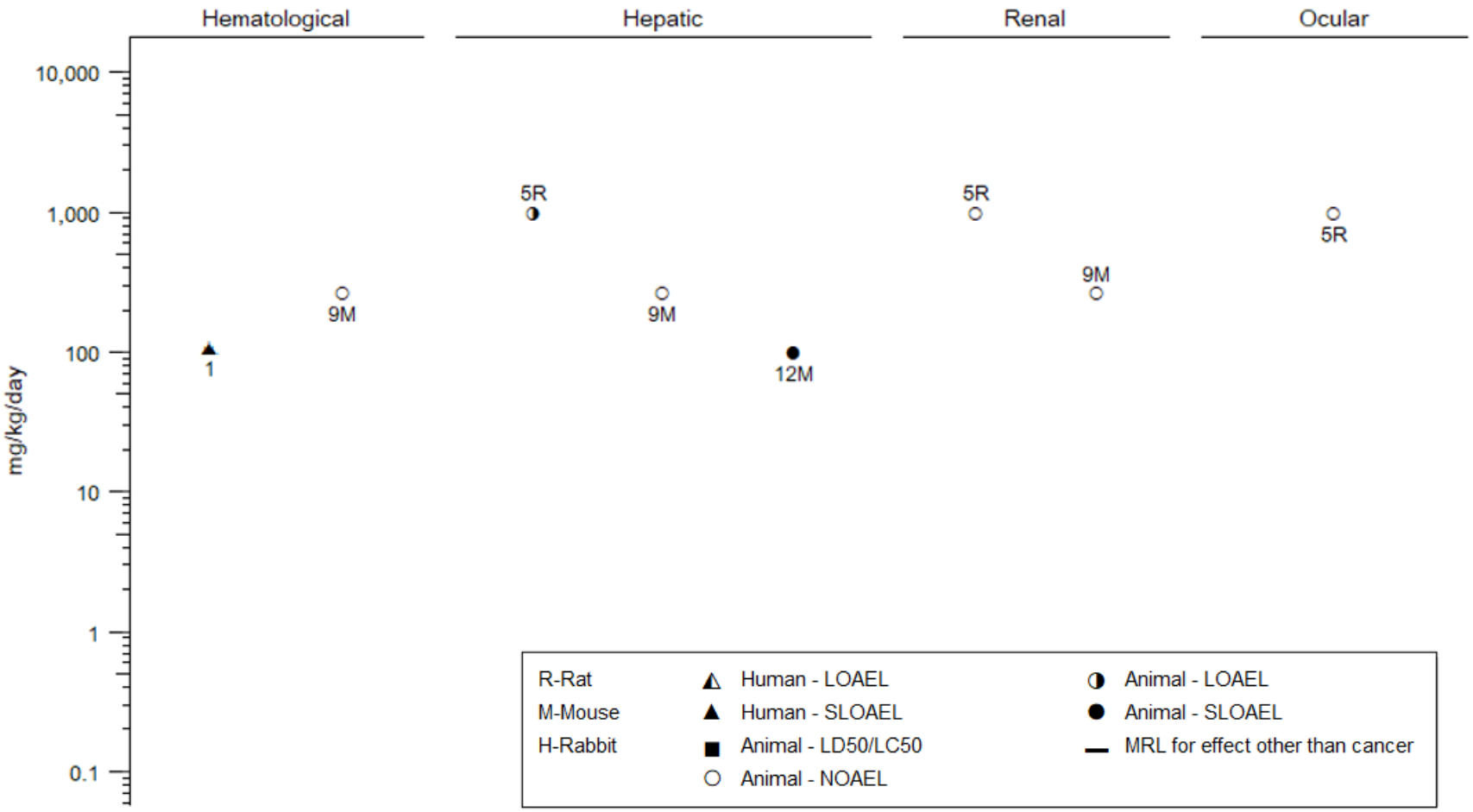

Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral

Acute (≤14 days)

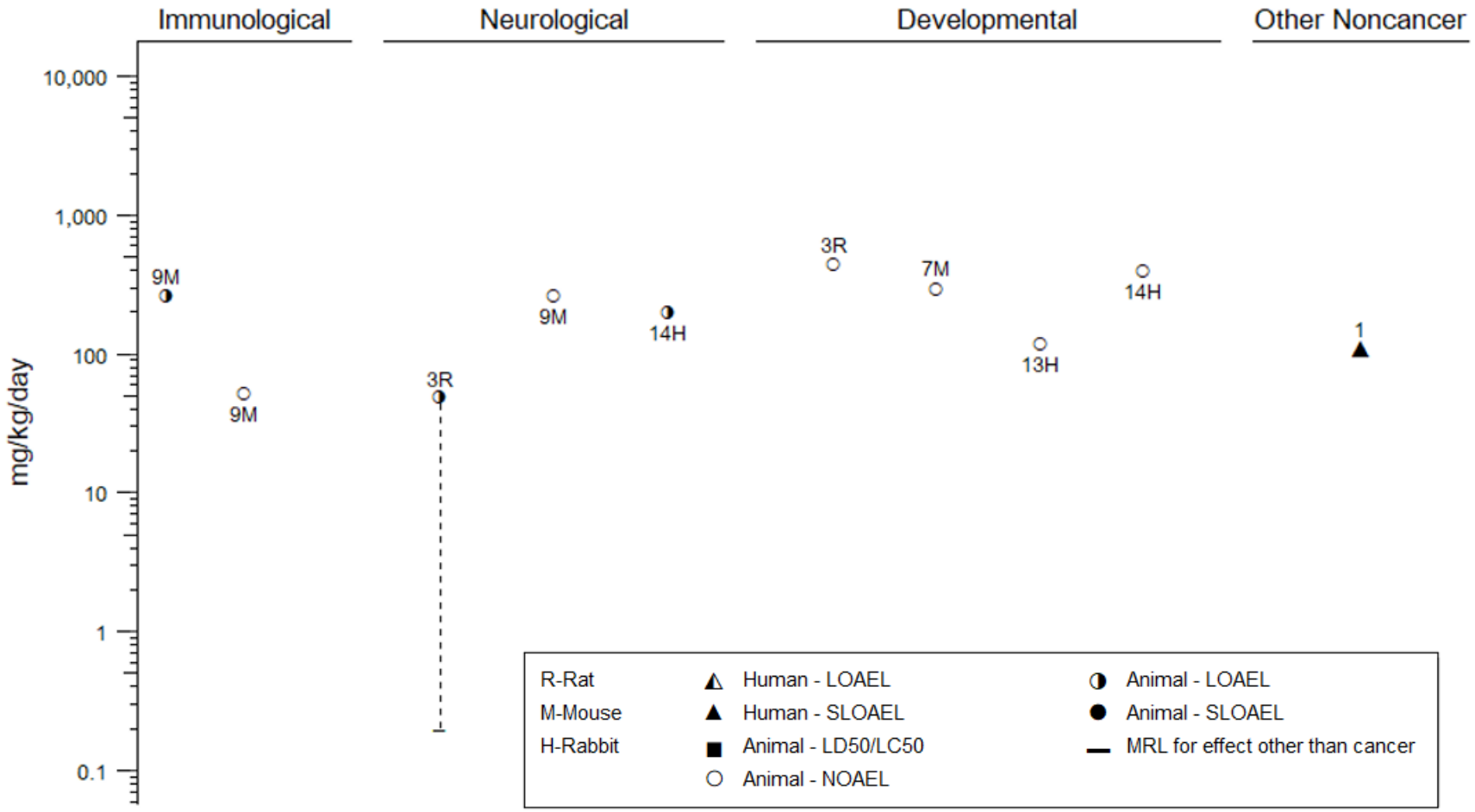

Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral
Intermediate (15–364 days)

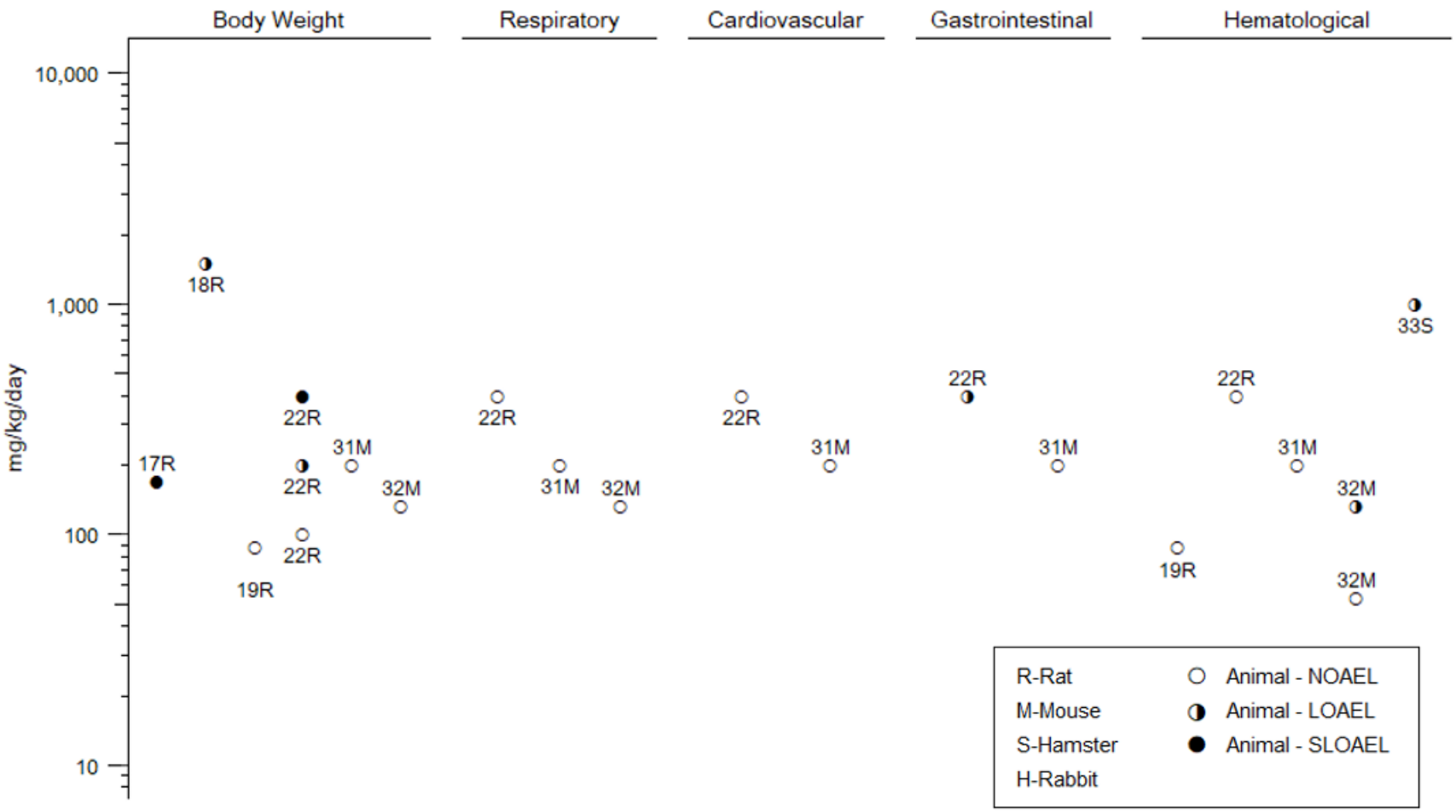

Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral
Intermediate (15–364 days)

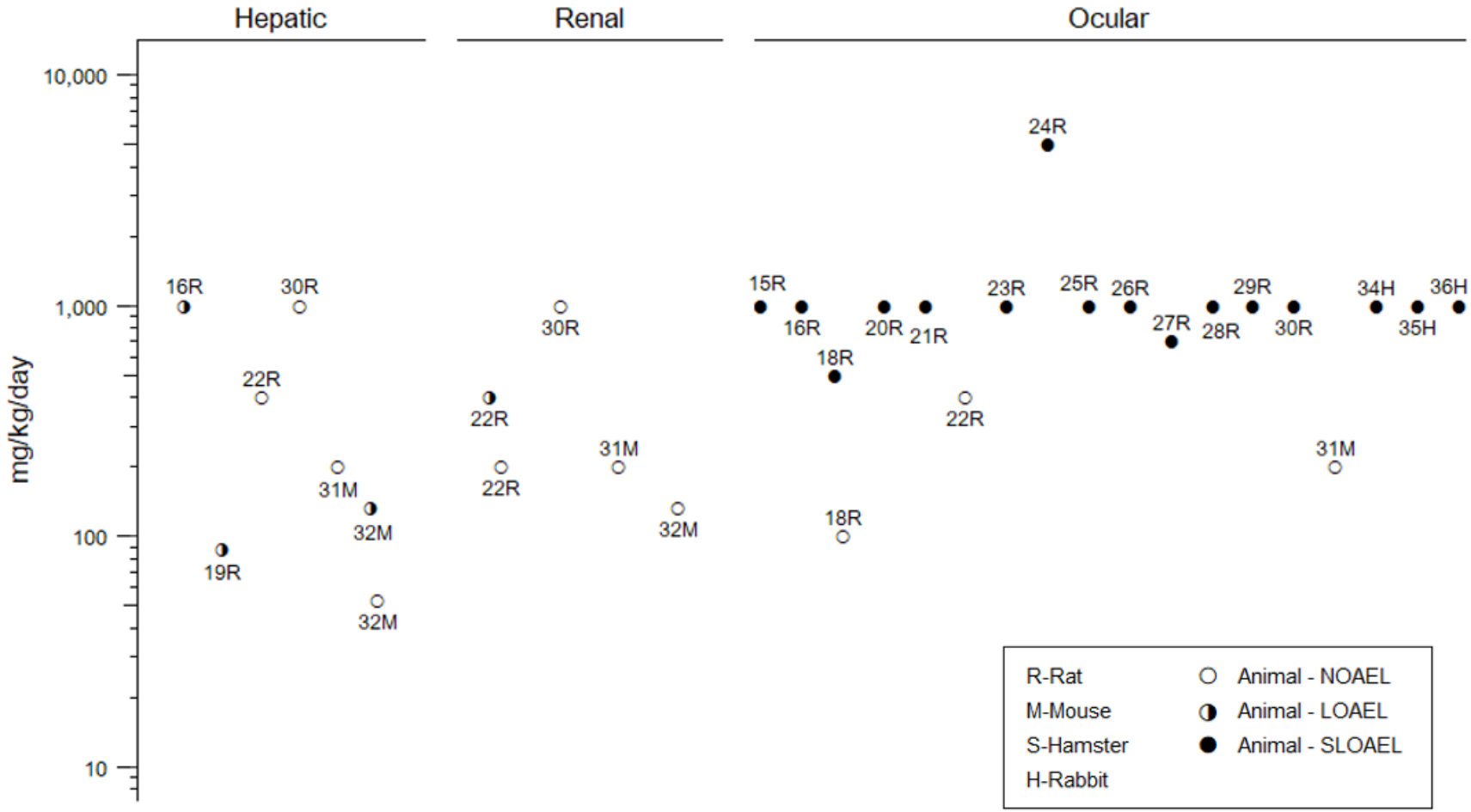

Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral
Intermediate (15–364 days)

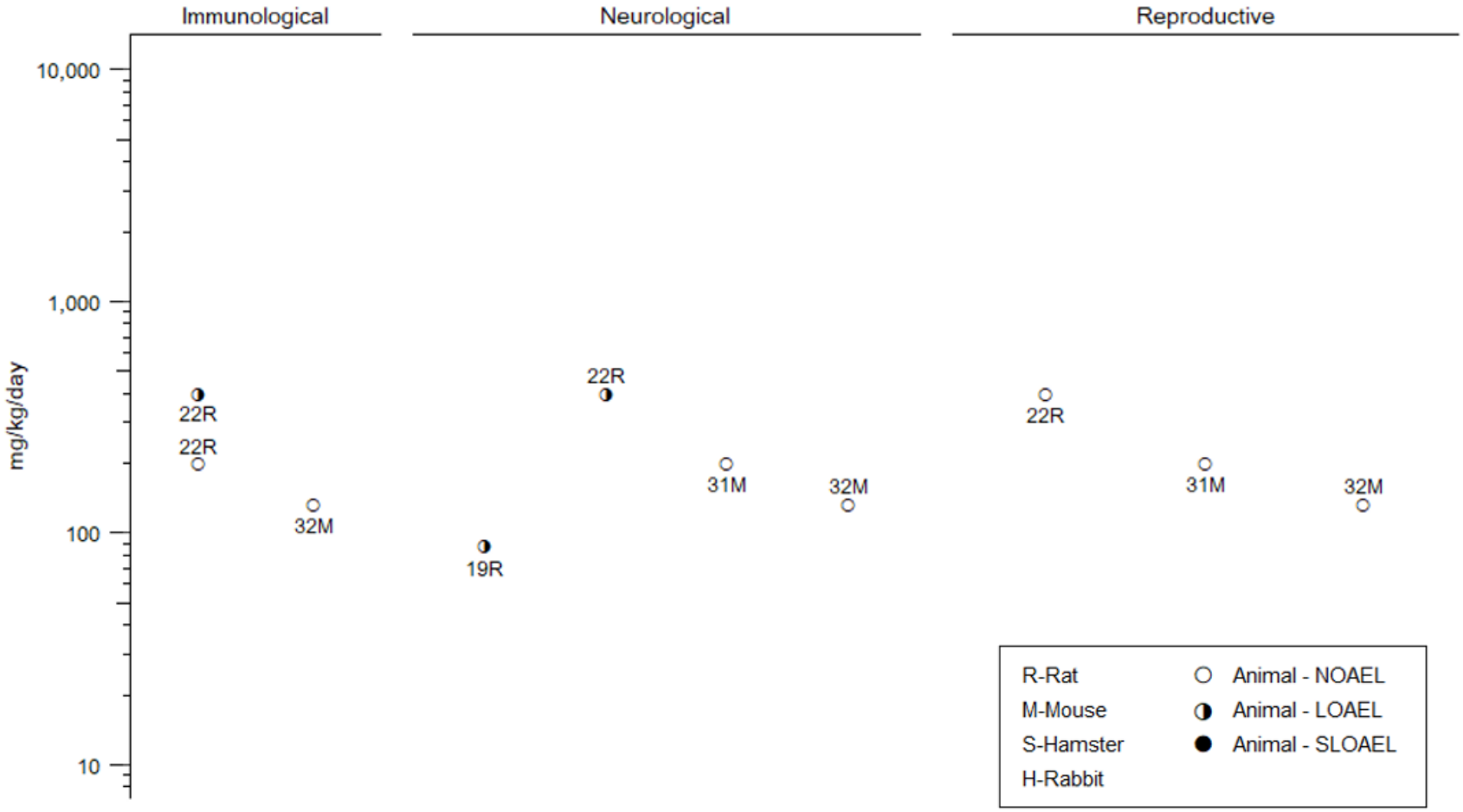

Table 2-3. Levels of Significant Exposure to Naphthalene – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Alalaiwe et al. 2020								
Mouse (NS) NS M	5 days 1 time/day	0, 0.35 mL of 8 mM solution	HP	Dermal	0.35			
Papciak and Mallory 1990; Texaco 1985a								
Rabbit (New Zealand) 3 M, 3 F	4 hours	0, 500 mg	CS	Dermal		500		Reversible erythema
Singh and Singh 2004								
Rabbit (New Zealand) 6 M	24 hours	0, 0.05 mL/3 cm^2	HP	Dermal		0.05		Skin erythema and edema; increased transepidermal water loss, skin temperature, and epidermal thickness; reduced collagen fiber length and thickness
Muhammad et al. 2005								
Pig (NS) 4 NS	1 or 4 days	0, 0.3 mL	HP	Dermal	0.3			
INTERMEDIATE EXPOSURE								
Frantz et al. 1986								
Rat (Sprague-Dawley) 10–20 M, 10–20 F	90 days 5 days/week 6 hours/day	0, 100, 300, 1,000 mg/kg/day	BW, OW, FI, GN, HP, BC, CS, UR	Resp	1,000			
				Cardio	1,000			
				Gastro	1,000			
				Hemato	1,000			
				Hepatic	1,000			
				Renal	1,000			
				Dermal	300	1,000		Increased incidence of excoriated skin and papules

Table 2-3. Levels of Significant Exposure to Naphthalene – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Papciak and Mallory 1990; Texaco 1985c								
Guinea pig (Hartley) 10 M, 10 F	3 weeks 1 time/week	0, 400 mg	IX	Immuno	400			

BC = blood chemistry; BW = body weight; Cardio = cardiovascular; CS = clinical signs; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LOAEL = lowest-observed-adverse-effect level; M = males(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Resp = respiratory; UR = urinalysis

Table 2-4. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Korsak et al. 1998									**1-Methylnaphthalene**
1	Rat (Wistar) 10 M	4 hours	0, 26, 44, 70	NX	Neuro	26	44		Decreased pain sensitivity
Korsak et al. 1998									**2-Methylnaphthalene**
2	Rat (Wistar) 10 M	4 hours	0, 39, 61, 90	NX	Neuro	39	61		Decreased pain sensitivity
Świercz and Stępnik 2020									**1-Methylnaphthalene**
3	Rat (Wistar) 3 M	5 days 6 hour/day (N)	0, 8.6, 34.4	BW, FI, WI, BC	Bd wt	34.4			
INTERMEDIATE EXPOSURE									
Kim et al. 2020									**1-Methylnaphthalene**
4	Rat (Fischer-344) 10 M, 10 F	13 weeks 6 hour/day 5 days/week (WB)	0, 0.52, 4.08, 30.83	CS, BW, HE, BC, GN, OW, HP	Bd wt	30			
					Resp	0.5 F	4 F 0.5[b] M		Hyperplasia of mucous cells in nasopharyngeal tissue
					Cardio	30			
					Gastro	30			
					Hemato	30			
					Musc/skel	30			
					Hepatic	30			
					Renal	30			
					Dermal	30			
					Endocr	30			
					Immuno	30			
					Repro	30			

Table 2-4. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Świercz et al. 2011									**2-Methylnaphthalene**
5	Rat (Wistar) 5 M, 5 F	4 weeks 5 days/week 6 hours/day (WB)	0, 0.34, 1.89, 8.77	BW, FI, HE, BC, GN, OW, HP	Bd wt	8.77			
					Resp		0.34[c]		Increased incidence of bronchial goblet cell metaplasia
					Cardio	8.77			
					Hemato	8.77			
					Hepatic	0.34	1.89		Bile duct hyperplasia
					Renal	8.77			
					Immuno	8.77			
					Repro	8.77			

[a]The number corresponds to entries in Figure 2-6.
[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.00009 ppm ($9x10^{-5}$ ppm) for 1-methylnaphthalene based on benchmark dose modeling of nasal mucous cell hyperplasia incidences in male rats. The $BMCL_{10}$ of 0.06 ppm was adjusted to continuous exposure and converted to a $BMCL_{HEC}$ of 0.0027 ppm. The $BMCL_{HEC}$ was divided by an uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after dosimetric adjustment) to derive the MRL; see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration inhalation MRL of 0.0003 ppm ($3x10^{-4}$ ppm) for 2-methylnaphthalene based on the LOAEL. The LOAEL of 0.34 ppm was adjusted to continuous exposure and converted to a $LOAEL_{HEC}$ of 0.081 ppm. The $LOAEL_{HEC}$ was divided by an uncertainty factor of 300 (10 for human variability, 3 for animal to human extrapolation after dosimetric adjustment, and 10 for use of a LOAEL) to derive the MRL; see Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; Bd wt or BW = body weight; $BMCL_{10}$ = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; HEC = human equivalent dose; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = males(s); Musc/skel = musculoskeletal; (N) = nose only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurological function; OW = organ weight; Repro = reproductive; Resp = respiratory; (WB) = whole body; WI = water intake

Figure 2-6. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Inhalation
Acute (≤14 days)

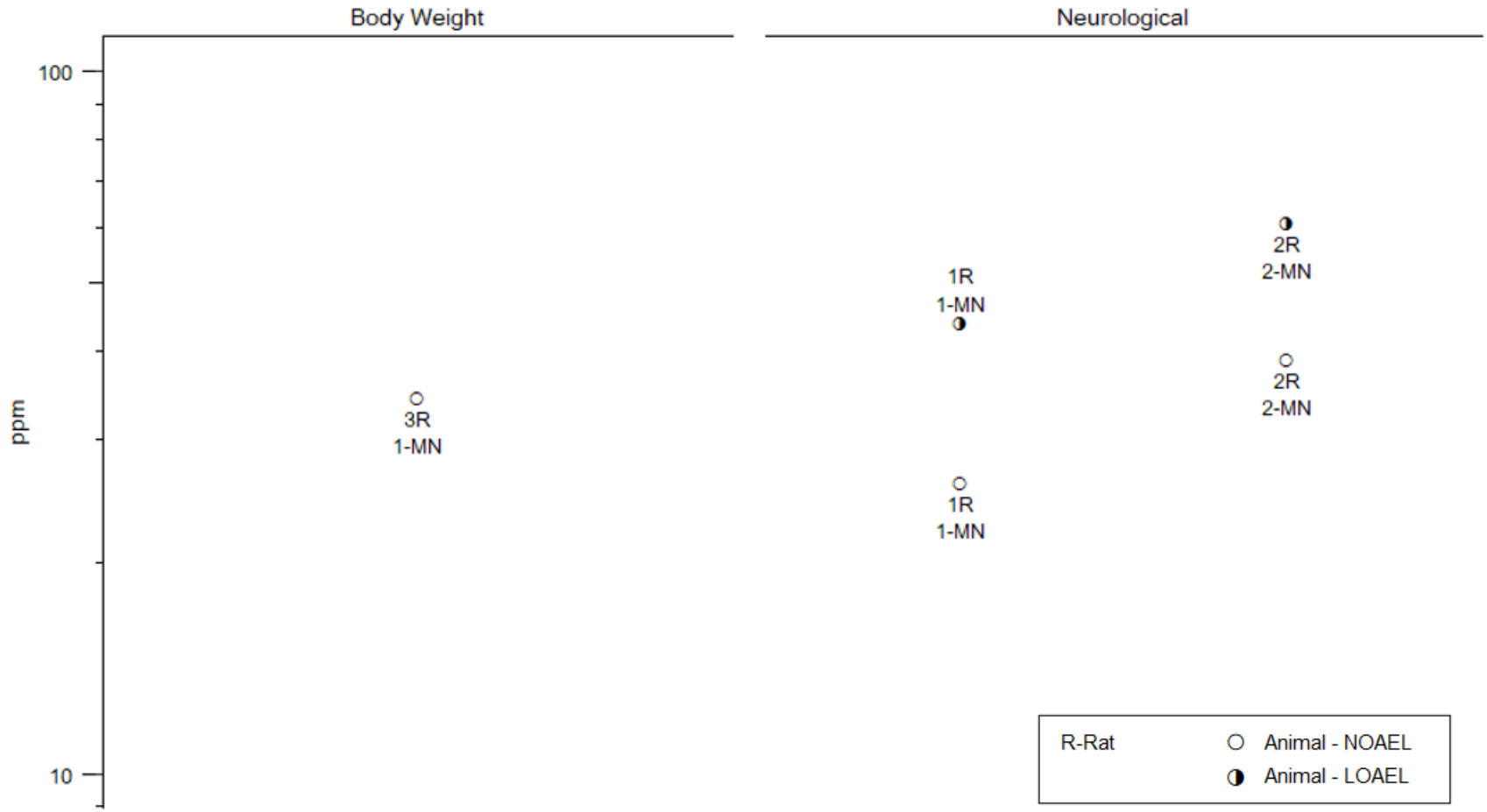

Figure 2-6. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Inhalation
Intermediate (15–364 days)

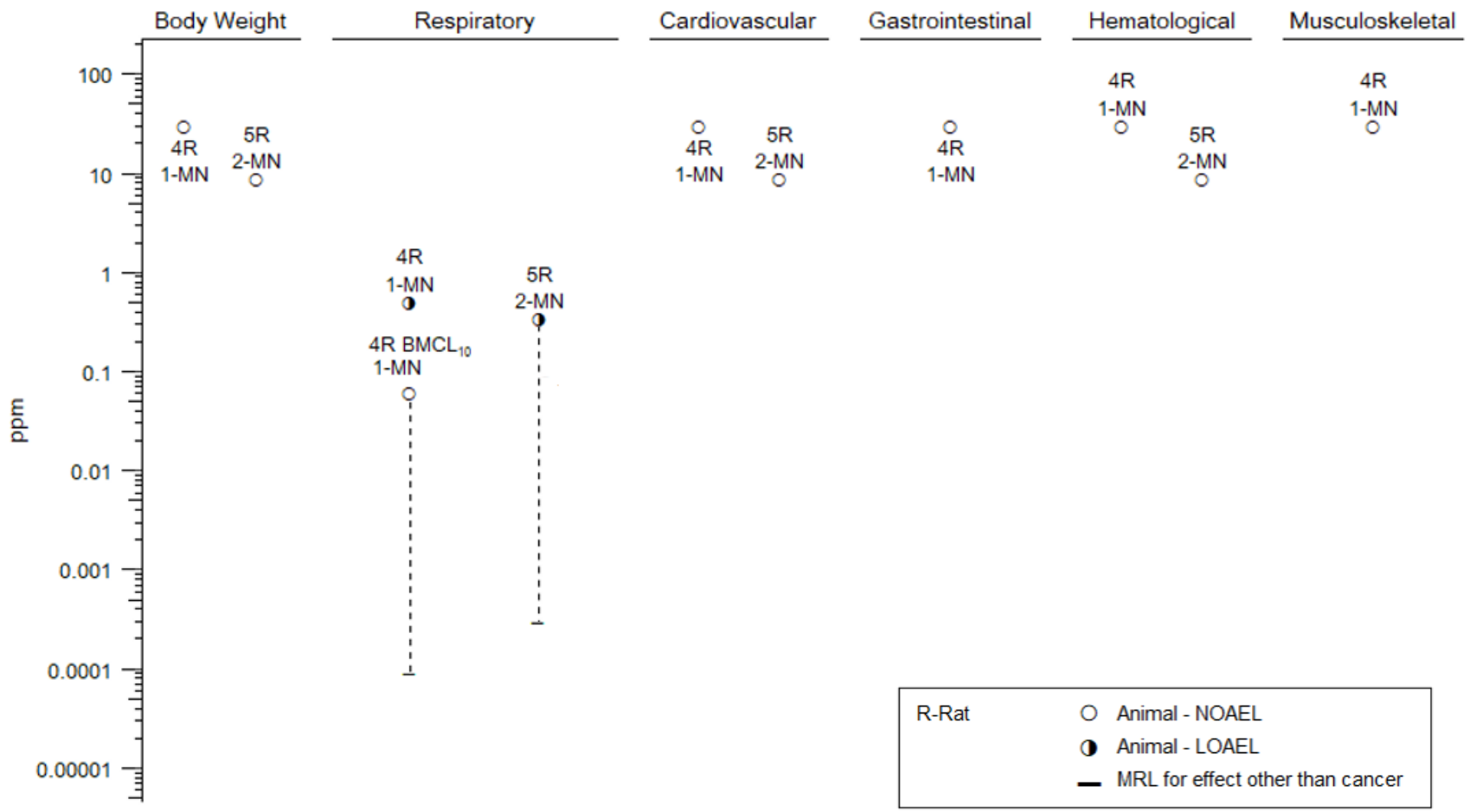

Figure 2-6. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Inhalation
Intermediate (15–364 days)

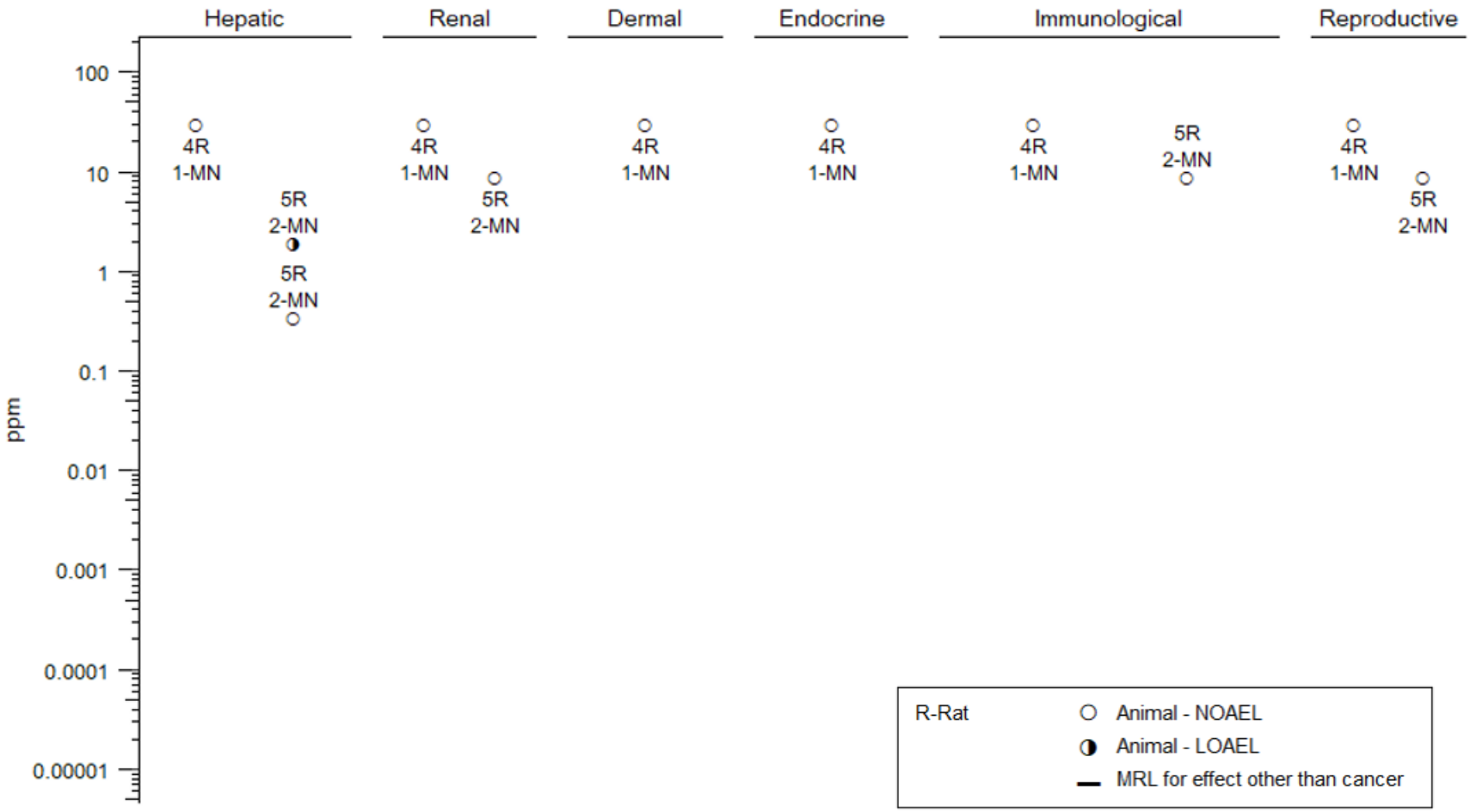

Table 2-5. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
NITE 2009									**1-Methylnaphthalene**
1	Rat (Sprague-Dawley) 12 M, 12 F	~42 days, premating–PND 4 (GO)	0, 10, 50, 250	LE, NX, BW, FI, HE, BC, UR, GN, OW, HP, RX, DX	Bd wt	250			
					Resp	250			
					Cardio	250			
					Gastro	250			
					Hemato	250			
					Hepatic	50[b]	250		Increased relative liver weights; in males and females; increased absolute liver weights in males
					Renal	250			
					Endocr	250			
					Immuno	250			
					Neuro	250			
					Repro	250			
					Develop	250			
CHRONIC EXPOSURE									
Murata et al. 1993									**1-Methylnaphthalene**
2	Mouse B6C3F1 50 M, 50 F	81 weeks (F)	M: 0, 71.6, 143.7 F: 0, 75.1, 140.2	BW, OW, FI, BI, GN, HP, BC, CS	Bd wt	143.7			
					Resp		71.6[c]		Increased incidence of pulmonary alveolar proteinosis in males and females
					Cardio	143.7			
					Gastro	143.7			
					Hemato	143.7			
					Hepatic	143.7			
					Renal	143.7			
					Endocr	143.7			
					Immuno	143.7			

Table 2-5. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	143.7			
					Repro	143.7			
					Cancer			71.6 M	CEL: increased incidence of lung adenomas in males
Murata et al. 1997									**2-Methylnaphthalene**
3	Mouse (B6C3F1) 50 M, 50 F	81 weeks (F)	0, 54.3, 113.8 M; 0, 50.3, 107.6 F	LE, BW, FI, HE, OW, HP	Bd wt	113.8			
					Resp		50.3[d]		Increased incidence of pulmonary alveolar proteinosis in males and females
					Cardio	113.8			
					Gastro	113.8			
					Hemato	113.8			
					Musc/skel	113.8			
					Hepatic	113.8			
					Renal	113.8			
					Dermal	113.8			
					Ocular	113.8			
					Immuno	113.8			
					Neuro	113.8			
					Repro	113.8			

Table 2-5. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cancer			54.3 M	CEL: increased incidence of lung adenomas in males

[a]The number corresponds to entries in Figure 2-7.
[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.6 mg/kg/day for 1-methylnaphthalene based on BMD modeling data for relative liver weight in males. The $BMDL_{1SD}$ of 64 mg/kg/day was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive the MRL; see Appendix A for more detailed information regarding the MRL.
[c]Used to derive a chronic-duration oral MRL of 0.07 mg/kg/day for 1-methylnaphthalene. The LOAEL of 71.6 was divided by an uncertainty factor of 1,000 (10 for animal to human extrapolation, 10 for human variability, and 10 for use of a LOAEL) to derive the MRL; see Appendix A for more detailed information regarding the MRL.
[d]Used to derive a chronic-duration oral MRL of 0.06 mg/kg/day for 2-methylnaphthalene based on BMD modeling of data on pulmonary alveolar proteinosis incidences in males. The $BMDL_{05}$ of 6.4 mg/kg/day was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive the MRL; see Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMD = benchmark dose; BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., 05 = dose associated with 5% extra risk); Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; (F) = feed; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = males(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurological function; OW = organ weight; PND = postnatal day; Repro = reproductive; RX = reproductive function; SD = standard deviation; UR = urinalysis

Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral

Intermediate (15–364 days)

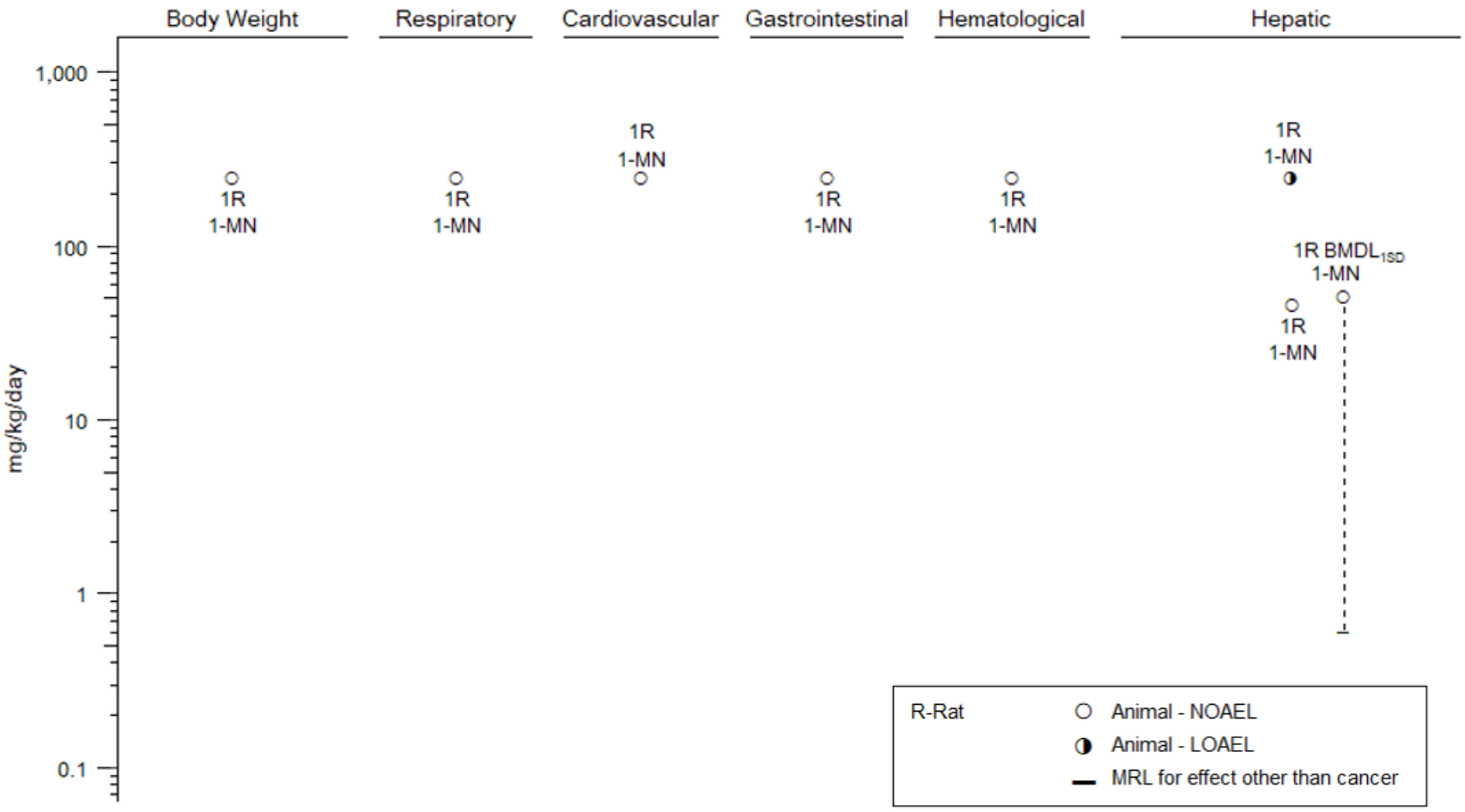

Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral

Intermediate (15–364 days)

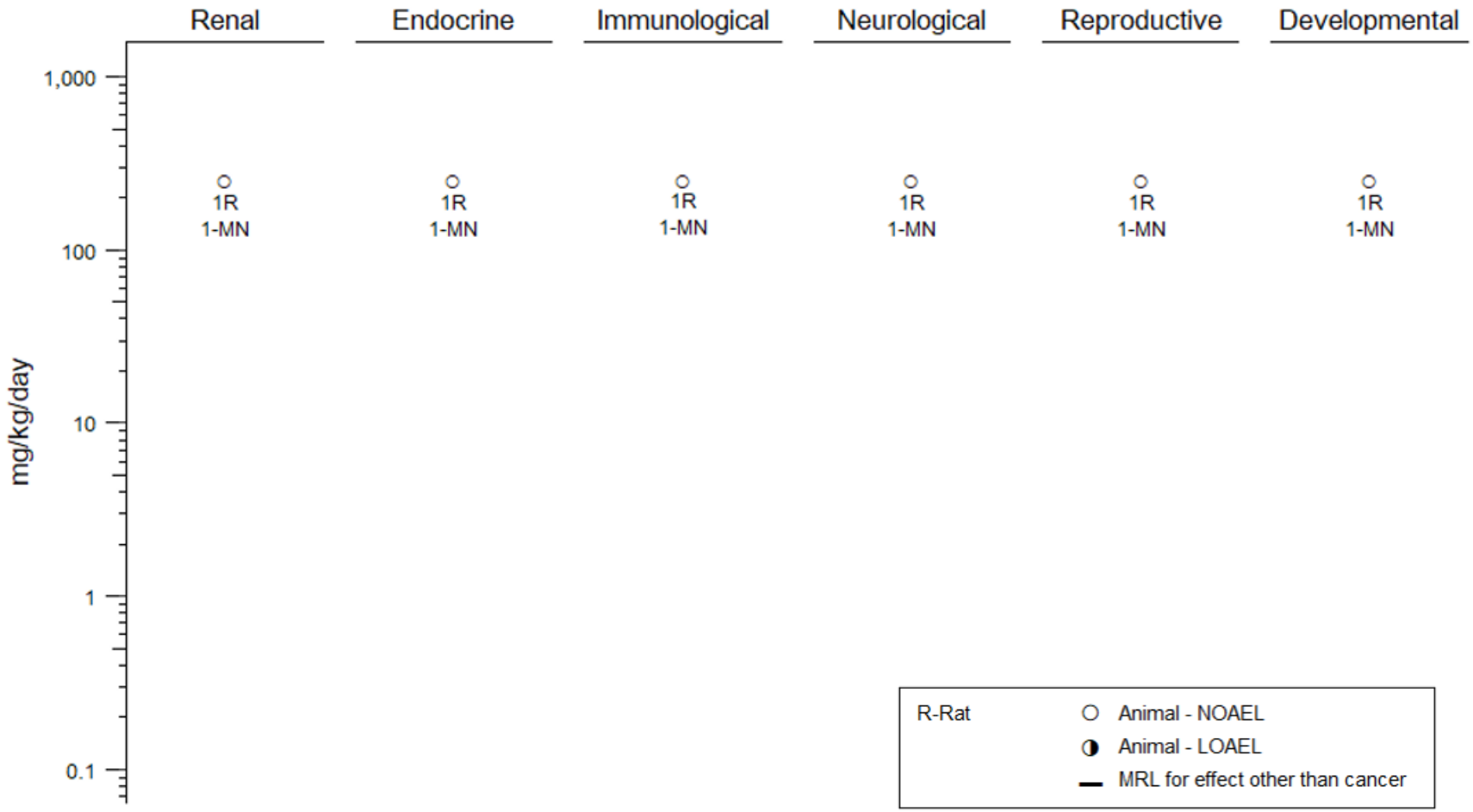

Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral

Chronic (≥365 days)

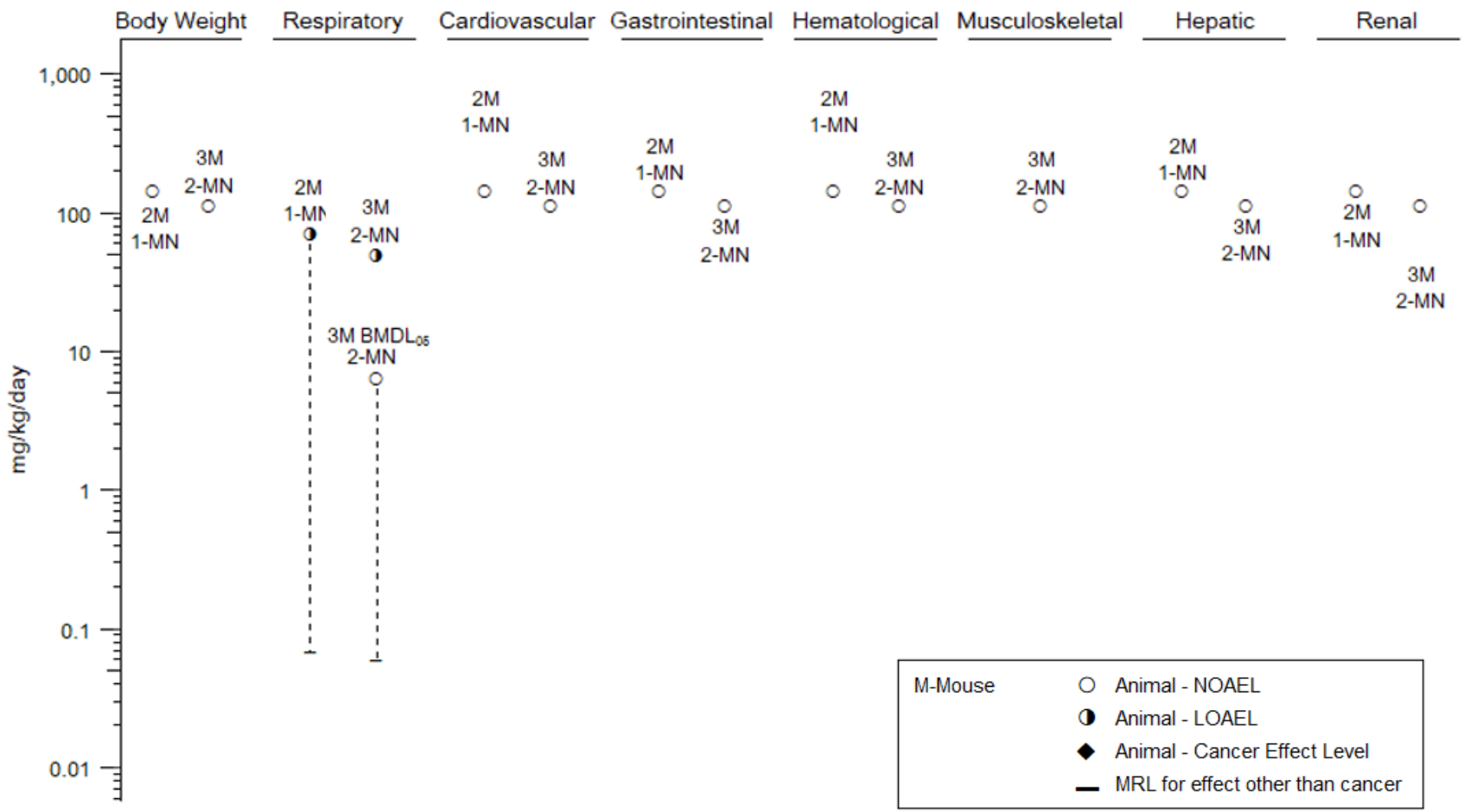

Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral

Chronic (≥365 days)

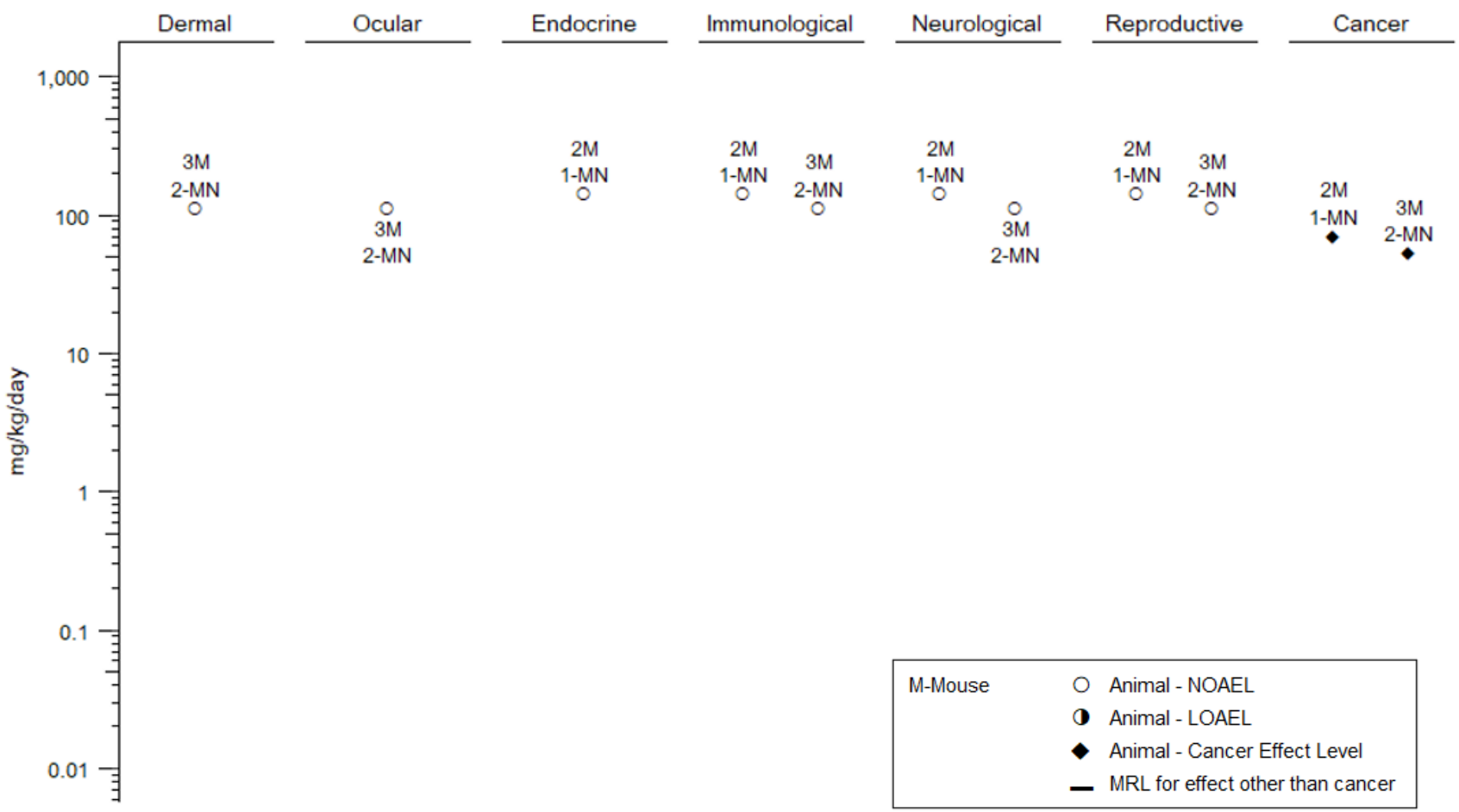

Table 2-6. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE								
Murata et al. 1992								**Mixture of 1- and 2-methylnaphthalene**
Mouse (B6C3F1) 15 F	30 weeks 2 times/week	0, 119 mg/kg	HP	Resp		119		100% incidence of mice with pulmonary alveolar proteinosis

F = female(s); HP = histopathology; LOAEL = lowest-observed-adverse-effect level; M = males(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory

2.2 DEATH

Naphthalene. Mortalities have been reported in human infants exposed by inhalation of naphthalene vapors in household products. Two infants (3–7 days old) from Athens, Greece died as a consequence of acute hemolysis that resulted from exposure to naphthalene-treated materials (clothing, diapers, blankets, rugs, etc.) at unknown exposure levels (Valaes et al. 1963). Both infants exhibited a severe form of jaundice (kernicterus), which often causes brain damage in infancy. The infants were tested for genetic glucose 6-phosphate dehydrogenase (G6PD) deficiency; one infant had the deficiency, and the other was heterozygous for the deficiency. Individuals with a G6PD genetic defect are prone to hemolysis after exposure to a variety of chemical oxidizing agents including nitrates, nitrites, aniline, phenols (Dean et al. 1992), and naphthalene.

Two cases of hemolytic anemia were observed in infants exposed to naphthalene-treated diapers resulting in one mortality (Schafer 1951; Valaes et al. 1963). Jaundice, methemoglobinemia, hemolysis, and cyanosis were noted. In the fatal case, the symptoms persisted, even after the naphthalene-containing diapers were no longer used (Schafer 1951). The study author suggested that use of baby oil on the infant's skin might have facilitated the naphthalene absorption.

In animals exposed by inhalation, lethal concentrations have not been identified. Exposure to 78 ppm naphthalene for 4 hours did not cause any deaths in rats (Fait and Nachreiner 1985). No conclusions regarding survival could be drawn in male mice exposed to 10 or 30 ppm naphthalene for 6 hours/day, 5 days/week for 2 years because the mortality rate in control animals was high; however, no effects on mortality were observed in female animals (NTP 1992a). Similarly, exposure of male and female rats to 10, 30, or 60 ppm naphthalene (6 hours/day, 5 days/week) for 2 years did not affect survival, compared to controls (Abdo et al. 2001; NTP 2000).

Death has been documented in humans who intentionally ingested naphthalene. The death of a 17-year-old boy was reported 5 days following intentional ingestion of an unknown dose of naphthalene in the form of naphthalene balls (Gupta et al. 1979). Symptoms include severe vomiting, gastrointestinal tract bleeding, jaundice, red urine, and altered sensorium at the time of admission. These symptoms were followed quickly by coma and anuria, with findings of neuroedema, hemolysis, and renal tubular necrosis in the postmortem. A 30-year-old female died following similar sequelae 5 days after reportedly swallowing 40 mothballs (25 were recovered intact from the stomach upon autopsy) (Kurz 1987).

Several animal studies have been conducted to estimate lethal doses of naphthalene. LD_{50} values in mice exposed once by gavage were 533 mg/kg in males and 710 mg/kg in females (Shopp et al. 1984). In a study where naphthalene was administered to female mice via gavage daily for 8 days during gestation, the estimated LD_{50} was 354 mg/kg (Plasterer et al. 1985). The dose response curve appeared to be very steep because no deaths (0/10) occurred at 250 mg/kg/day, about 15% died at 300 mg/kg/day, and all animals (10/10) died with a dose of 500 mg/kg/day (Plasterer et al. 1985). In a 14-day gavage study in mice, 10/96 (10%) males and 3/60 (5%) females died at 267 mg/kg/day (Shopp et al. 1984).

The oral LD_{50} values in rats were 2,200 mg/kg in males and 2,400 mg/kg in females (Gaines 1969), and 2,600 mg/kg in a second study that did not stratify by sex (Papciak and Mallory 1990). No deaths occurred in rats administered up to 1,000 mg/kg/day naphthalene for 10 days (Rao and Pandya 1981) or 18 days (Yamauchi et al. 1986). Germansky and Jamall (1988) administered increasing doses of naphthalene beginning with 100 mg/kg/day and raised weekly to a dose of 750 mg/kg/day at 6 weeks, and found no mortalities over the course of the 9-week study. No increase in mortality was observed in rats administered naphthalene at 41 mg/kg/day in a 2-year feeding study (Schmahl 1955).

Although few data are available, rabbits appear to tolerate naphthalene in doses similar to those administered to rats. Two different rabbit strains were administered 1,000 mg/kg twice per week for 12 weeks without lethality (Rossa and Pau 1988).

No treatment-related deaths occurred within the 14-day observation period when naphthalene was applied once at 2,500 mg/kg to the skin of male and female rats or when doses of up to 1,000 mg/kg/day were applied to the skin for 6 hours/day, 5 days/week for 13 weeks (Frantz et al. 1986; Gaines 1969). There were also no deaths in New Zealand White rabbits after application of 2,000 mg/kg naphthalene to intact and abraded shaved areas of skin in an LD_{50} study (Papciak and Mallory 1990).

1-Methylnaphthalene. No studies were located that documented lethal effects in humans after inhalation, oral, or dermal exposure to 1-methylnaphthalene, or in animals exposed via dermal application to 1-methylnaphthalene.

No mortality occurred in rats that were exposed to 1-methylnaphthalene by inhalation to concentrations up to 70 ppm for 4 hours (Korsak et al. 1998), up to 34.4 ppm for 5 days (Świercz and Stępnik 2020), or up to 30 ppm for 13 weeks (Kim et al. 2020). There were no deaths in Sprague-Dawley rats administered up to 250 mg/kg/day 1-methylnaphthalene by gavage for at least 42 days (NITE 2009). Survival in male

and female mice (B6C3F1) was unchanged when 1-methylnaphthalene doses of 71.6–143.7 mg/kg/day were administered in the diet for 81 weeks (Murata et al. 1993).

2-Methylnaphthalene. No studies were located that documented lethal effects in humans after exposure by any route, or in animals exposed by dermal contact to 2-methylnaphthalene. No deaths were reported when rats were exposed by inhalation to concentrations up to 90 ppm for 4 hours (Korsak et al. 1998) or up to 8.6 ppm for 4 weeks (Świercz et al. 2011). Likewise, chronic dietary administration of 2-methylnaphthalene at doses up to 113.8 mg/kg/day did not alter survival rates of mice (Murata et al. 1997).

2.3 BODY WEIGHT

Naphthalene. No studies were located that documented effects on body weight in humans after inhalation, oral, or dermal exposure to naphthalene. In human epidemiology studies, the associations between naphthalene and obesity-related parameters (body fat percentage, regional fat distribution, waist circumference, and body mass index [BMI]) were examined (see Table 2-7). In a cross-sectional study of adult National Health and Nutrition Examination Survey (NHANES) participants, associations were observed between urinary hydroxy-naphthalene metabolites and several measures of obesity; however, no concentration-response relationship was seen when exposures were stratified into tertiles (Zhang et al. 2022). Another cross-sectional study of adult NHANES participants reported that the metabolite, 2-naphthol, was correlated with increased fat mass percentage, BMI, and waist circumference, whereas 1-naphthol was inversely correlated with these parameters (Wang et al. 2022a). A study of 20 bariatric patients (Mlyczyńska et al. 2023) found a positive association between naphthalene concentration in adipose tissue (mesenteric, omental, and subcutaneous) and BMI in French, but not Polish, patients. Plasma naphthalene levels were not associated with BMI in either group (Mlyczyńska et al. 2023). In a meta-analysis of five cross-sectional studies, an association between naphthalene metabolites (1- and 2-naphthol) and obesity was observed (pooled odds ratio [OR] 1.43; 95% confidence interval [CI] 1.07–1.90) (Liu et al. 2023).

Table 2-7. Summary of Epidemiological Studies of Naphthalene Exposure and Obesity-Related Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Liu et al. 2023 Systematic review and meta-analysis of five cross-sectional studies	Blood or urine naphthalene metabolites	NA	Obesity	↑
Mlyczyńska et al. 2023, Cross-sectional, 20 bariatric patients: 10 in France (mean age 45 years) and 10 in Poland (mean age 37 years)	Naphthalene concentrations in adipose tissues and plasma	France: 14.76, 15.1, and 15.6 ng/g (mean in mesenteric, omental, and subcutaneous fat, respectively); 0.52 ng/mL in plasma	BMI	↑
		Poland: 44.19, 31.56, and 50.02 ng/g (mesenteric, omental, and subcutaneous fat, respectively); 1.07 ng/mL in plasma	BMI	↔
Wang et al. 2022a Cross-sectional, 2,691 nonsmoking adult (≥20 years old) NHANES participants (2001–2016), median age 37.9 years, United States	Urinary 1-naphthol	1,254.7 ng/L (geometric mean)	Total FM%	↓
			Trunk fat	↓
			Leg fat	↔
			Trunk:leg ratio	↔
			Total lean mass	↔
			BMI	↓
			Waist circumference	↓
	Urinary 2-naphthol	2,848.4 ng/L (geometric mean)	Total FM%	↔
			Trunk fat	↑
			Leg fat	↔
			Trunk:leg ratio	↑
			Total lean mass	↔
			BMI	↑
			Waist circumference	↑
Zhang et al. 2022 Cross-sectional, 4,813 adult (≥20 years old) NHANES participants (2005–2012), United States	Sum of urinary naphthalene metabolites	55.95 nM/L (geometric mean)	General obesity	↑
			BMI	↑
			Abdominal obesity	↑
			Waist circumference	↑

↑ = association with increase; ↓ = association with decrease; ↔ = no association; BMI = body mass index; FM% = fat mass percent; NA = not applicable; NHANES = National Human and Nutrition Examination Survey

No change in body weight was observed in rats (Sprague-Dawley and Fisher 344) exposed to concentrations up to 30 ppm naphthalene for 6 hours or concentrations up to 10 ppm for 6 hours/day, for 5 days (Dodd et al. 2010). In an intermediate-duration study, no change in body weight occurred in F344

rats exposed to concentrations up to 30 ppm for 6 hours/day, 5 days/week for 13 weeks (Dodd et al. 2012). No effect was observed on body weights in rats (NTP 2000) and mice (NTP 1992a) exposed by inhalation to concentrations up to 60 and 30 ppm (respectively) for 105 weeks.

In pregnant Sprague-Dawley rats exposed by gavage on gestation days (GDs) 6–15, maternal body weight gains were depressed by 31 and 53% at 150 and 450 mg/kg/day, respectively, but were unaffected at 50 mg/kg/day (NTP 1991). The decreased body weight gains were accompanied by persistent clinical signs of toxicity. Mice exposed orally to 267 mg/kg/day naphthalene for 14 days showed decreased body weight gain; terminal body weights were decreased by 6% in females and 13% in males compared with control values (Shopp et al. 1984).

After 13 weeks of oral exposure to naphthalene, mean terminal body weights in F344/N rats exposed to gavage doses ≥200 mg/kg/day were decreased by more than 10% relative to control values (NTP 1980b). Body weights were decreased by 12 and 28% in 200- and 400-mg/kg/day male rats (respectively), and by 23% in 400-mg/kg/day female rats. Food consumption was not affected by exposure (NTP 1980b). Blue Spruce rats receiving escalating doses (from 100 to 750 mg/kg/day) over 9 weeks that resulted in a time-weighted average (TWA) dose of 169 mg/kg/day showed a 20% reduction in body weight at the end of exposure (Germansky and Jamall 1988). In another study, female Norway rats administered 1,500 mg/kg/day naphthalene twice a week for 10 weeks exhibited a body weight decrease of 17% (Holmén et al. 1999). No effects on body weights were found in female Sprague-Dawley rats administered 500 mg/kg/day naphthalene for 3 days followed by 1,000 mg/kg/day for the remaining 5 weeks or in female white rats administered 87.5 mg/kg/day, 3 times/week for 7 weeks (Katsnelson et al. 2014; Zhu and Lu 2012). In B6C3F1 mice exposed to naphthalene doses up to 200 mg/kg/day for 13 weeks, exposed males gained more weight than controls during exposure, whereas exposed females gained less weight than controls (NTP 1980a). However, terminal body weights in exposed female mice were within 95% of control values (NTP 1980a). In male and female CD-1 mice exposed to doses as high as 133 mg/kg/day for 90 days, average terminal body weight in exposed groups were within 10% difference from control values (Shopp et al. 1984).

1-Methylnaphthalene. No studies were located regarding effects on body weights in humans after inhalation, oral, or dermal exposure to 1-methylnaphthalene or in animals after dermal exposure to 1-methylnaphthalene.

There was no significant difference in mean body weights in rats exposed to 0, 9.54, or 38.15 ppm 1-methylnaphthalene for 6 hours/day for 5 days, despite a transient increase on day 1 in the 38.15 ppm group (Świercz and Stępnik 2020). In F344 rats exposed to up to 30.83 ppm 1-methylnaphthalene for 6 hours/day, 5 days/week for 13 weeks, no effects on body weight were observed (Kim et al. 2020).

In a combined repeat-dose and reproductive/developmental toxicity screening study, no effects on body weight were observed in Sprague-Dawley rats administered up to 250 mg/kg/day for at least 42 days (NITE 2009). There was no significant difference between body weights of mice that were given up to 143.7 mg/kg/day 1-methylnaphthalene in their diets and those of the control animals throughout an 81-week exposure period (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding effects on body weights in humans after inhalation, oral, or dermal exposure to 2-methylnaphthalene or in animals after dermal exposure to 2-methylnaphthalene.

Wistar rats exposed to up to 8.77 ppm 2-methylnaphthalene vapor for 4 weeks did not have any changes in body weights (Świercz et al. 2011). A range-finding 13-week study reported with few details that 2-methylnaphthalene doses ≥276 mg/kg/day in the diet of mice resulted in growth retardation, but the study authors attributed this effect to food refusal (Murata et al. 1997). In the subsequent chronic study, mice were exposed to 2-methylnaphthalene in the diet at doses as high as 113.8 mg/kg/day for up to 81 weeks, and mean body weights remained within 10% of control values throughout the study (Murata et al. 1997).

2.4 RESPIRATORY

Naphthalene. Epidemiological studies in humans exposed to naphthalene include five studies summarized in Table 2-8. A positive association between air concentrations of naphthalene and self-reported eye and nasal irritation and inflammation of nasal tissue (measured by endoscopic examination) was reported in a study of 40 workers in the abrasives industry in Europe (Sucker et al. 2021). This industry was selected because naphthalene was widely used, and there were only low exposures to other chemicals. The same study examined urinary levels of combined 1- and 2-naphthol and found an inverse association with serum club cell secretory protein 16, a sensitive marker of lung injury that is increased after acute exposure but often decreased after chronic exposure to lung toxicants (Sucker et al. 2021). In a cross-sectional study in Canada, there was an inverse association between indoor air concentrations of

naphthalene and measures of lung function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and FEV_1/FVC) in female participants, but not male participants (Cakmak et al. 2014). A cohort study of adults in China provided support for an inverse association between FVC and particle-bound (particulate matter ≤2.5 μm in diameter [$PM_{2.5}$]) naphthalene concentrations in personal air samples (Mu et al. 2019). In a cohort of 50 asthmatic children, urinary levels of 1- and 2-naphthol were associated with increased asthma symptom scores but no association was observed with measures of lung function (FEV_1, FVC, and FEV_1/FVC or mean forced expiratory flow between 25 and 75% of the FVC [$FEF_{25–75}$]) (Cilluffo et al. 2022). Urinary 1- and 2-naphthol levels were not corelated with measures of lung function in 36 students in China (Zhang et al. 2023).

Table 2-8. Summary of Epidemiological Studies of Naphthalene Exposure and Respiratory Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Cakmak et al. 2014 Cross-sectional, 3,039 persons aged 3–79 years, mean age 39 years, Canada	Indoor air concentration of naphthalene	0.89 (0.79, 1) μg/m^3 (mean, [95% CI])	FEV_1, FVC, and FEV_1/FVC (all)	↓
			FEV_1, FVC, and FEV_1/FVC (females)	↓
			FEV_1, FVC, and FEV1/FVC (males)	↔
Cilluffo et al. 2022, Cohort, 50 children with asthma, aged 6–11 years, Italy	Urinary 1-naphthol	2.57–4.72 μg/g creatinine (range of means over four visits)	Asthma symptom score	↑
			FEV_1, FVC, FEV_1/FVC, and $FEF_{25–75}$	↔
	Urinary 2-naphthol	4.84–7.97 μg/g creatinine (range of means over four visits)	Asthma symptom score	↑
			FEV_1, FVC, FEV_1/FVC, and $FEF_{25–75}$	↔
Mu et al. 2019 Cohort, 224 adult participants in community-based prospective study, mean age 57 years, China	$PM_{2.5}$ particle-bound naphthalene in personal air	3.50 ng/m^3 (mean, all samples)	FVC	↓
			FEV_1	↔
Zhang et al. 2023 Cohort, 36 students (17 male, 19 female), China	Urinary 1-naphthol	2.58–6.99 μg/g creatinine (range of medians in urban and suburban exposure periods)	FEV_1, FVC	↔
	Urinary 2-naphthol	1.52–3.41 μg/g creatinine	FEV_1, FVC	↔

Table 2-8. Summary of Epidemiological Studies of Naphthalene Exposure and Respiratory Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Sucker et al. 2021 Occupational, 40 workers in abrasives industry exposed to naphthalene and 23 unexposed referents, Germany and Austria	Air concentrations of naphthalene	0.15±0.10 mg/m^3 (mean±SD) (referents) 0.66±0.27 (moderately exposed) 6.97±3.10 (highly exposed)	Eye and nasal irritation symptoms; nasal endoscopy score indicative of inflammation	↑
			Serum club cell secretory protein 16 (CC16)	↓
	Sum of urinary 1- and 2-naphthol concentrations	18±11 µg/g creatinine (mean±SD) (referents) 108±49 (moderately exposed) 1,489±999 (highly exposed)	Cellular and humoral parameters of nasal lavage fluid and induced sputum	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; CI = confidence interval; $FEF_{25–75}$ = mean forced expiratory flow between 25 and 75% of the FVC; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; $PM_{2.5}$ = particulate matter ≤2.5 µm in diameter; SD = standard deviation

No reports have been located to indicate that there are direct effects of oral exposure to naphthalene on the respiratory system in humans. In situations where respiratory effects such as hypoxia or pulmonary edema were noted, the respiratory effects appear to be secondary to hemolysis and the events leading to general multiple organ failure (Gupta et al. 1979; Kurz 1987). One male infant admitted to the hospital experienced labored breathing after chewing on a diaper pail deodorant block containing naphthalene (Haggerty 1956); however, it is possible that this was related to a hemolysis-induced decrease in oxygen-carrying capacity.

No studies were located that documented respiratory effects in humans after dermal exposure to naphthalene.

The nose is the most sensitive target of naphthalene in rats and mice following inhalation exposure. In rats, acute exposure to naphthalene concentrations ranging from 3.4 to 15 ppm for 4–6 hours resulted in increased tissue injury in the nasal passages, observed as cytotoxicity (vacuolation, swelling, and exfoliation) to the olfactory mucosa and respiratory transitional mucosa (Carratt et al. 2016, 2019a; Cichocki et al. 2014; Lee et al. 2005,). In another acute study, rats (F344 and Sprague-Dawley) were exposed to naphthalene for 6 hours/day for either 1 or 5 days (Dodd et al. 2010). In Sprague-Dawley rats, exposure to naphthalene at ≥0.1 ppm resulted in concentration-related increases in the incidences of nasal olfactory epithelial degeneration; in F344 rats, the same lesion was observed at ≥1 ppm. After 5 days of

exposure, nearly all rats of both strains exhibited this effect at 1 and 10 ppm, and 2/10 female Sprague-Dawley rats showed this lesion at 0.1 ppm (Dodd et al. 2010). In the 5-day exposure study, both F344 and Sprague-Dawley rats exhibited nasopharyngeal goblet cell hyperplasia/hypertrophy at 10 ppm (Dodd et al. 2010). F344 rats appeared to be more sensitive to this effect, as the severity scores were higher in F344 rats than in Sprague-Dawley rats, a few incidences of the lesions were observed at lower exposure levels in F344 (but not Sprague-Dawley) rats, and the lesions persisted after a 14-day recovery period in F344 (but not Sprague-Dawley) rats exposed to 10 ppm (Dodd et al. 2010). The study authors concluded that there were minimal rat strain differences with 6-hour or 5-day exposures to naphthalene. In a single exposure study in rats that did not include a control group, 78 ppm naphthalene exposure for 4 hours induced a change to mouth breathing but no other effects on respiration were noted (Fait and Nachreiner 1985).

Acute (4-hour) inhalation exposure to naphthalene induced necrosis of club cells in the epithelium of the proximal airways of the lungs of mice at exposure levels as low as 10 ppm but did not affect lung tissue in rats at concentrations as high as 100 ppm (West et al. 2001), suggesting that mice are more susceptible to lung injury than rats from inhaled naphthalene. Mice that were exposed to 10 ppm naphthalene for 4 hours exhibited airway epithelial injury characterized by swelling, cell detachment, cell proliferation, and increased total protein and lactate dehydrogenase (LDH) levels in the bronchoalveolar lavage fluid (BALF) (Kovalchuk et al. 2020). Mice exposed nose only to naphthalene concentrations of 10 ppm during two sessions of 2 hours each for a total of 4 hours on 1 day, exhibited cytotoxicity of the olfactory epithelium characterized by necrosis of the olfactory mucosa epithelium including detachment, sloughing, and ulceration, and necrosis of the lung epithelium, and detachment of club cells in the lung (Li et al. 2017). In another study, mice exposed to 15 ppm for 2 or 4 hours exhibited club cell swelling and vacuolation in the airway epithelium for up to 24 hours post-exposure and focal absence of club cells in the epithelium (sloughing of necrotic club cells observed in the lumen) that were replaced by squamated ciliated cells (Phimister et al. 2004).

Intermediate-duration inhalation exposure in rats to naphthalene concentrations of 0.1, 1, 10, or 30 ppm for 6 hours/day, 5 days/week for 13 weeks resulted in increased incidence and severity of degeneration and necrosis of the olfactory epithelium (Dodd et al. 2012). At 1 ppm, minimal hyperplasia of the transitional/respiratory epithelium in the nasal cavity was seen in all exposed males (incidence was not reported for females). At higher concentrations, minimal to moderate transitional/respiratory epithelium metaplasia and olfactory epithelium degeneration/necrosis and basal cell hyperplasia were observed. Minimal severity goblet cell hyperplasia of the nasopharyngeal duct was noted at the highest exposure

concentration. After a 4-week untreated recovery, the lesions in the olfactory epithelium remained, but the severity was reduced (Dodd et al. 2012).

Chronic-duration inhalation exposure to naphthalene resulted in increased incidences of nonneoplastic and neoplastic lesions in the nose of rats (Abdo et al. 2001; Long et al. 2003; NTP 2000), nonneoplastic lesions in the nose of mice (NTP 1992a), and neoplastic and nonneoplastic lesions in the lungs of mice (NTP 1992a). No exposure-related lesions were found in other tissues or organs in these studies, which included comprehensive histopathological examinations of major tissues and organs. In rats, concentrations of 10, 30, or 60 ppm naphthalene for 2 years induced neoplastic and nonneoplastic lesions of the nasal cavity (Abdo et al. 2001; NTP 2000). Nearly all rats (>95%) in each exposure group exhibited nonneoplastic nasal lesions, including (1) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of olfactory epithelium, and (2) hyperplasia, metaplasia, or degeneration of the nasal respiratory epithelium or glands of the nasal cavity. Neoplastic lesions observed in rats exposed to naphthalene include olfactory epithelial neuroblastoma (a rare malignant tumor) and respiratory adenoma of the nasal cavity. (Abdo et al. 2001; NTP 2000). Nearly all mice exposed to 10 or 30 ppm naphthalene vapors for 2 years exhibited chronic inflammation and metaplasia of the olfactory epithelium and hyperplasia of the nasal respiratory epithelium (NTP 1992a). Chronic lung inflammation was also observed in exposed mice, but at lower incidences than incidences for nasal lesions. Incidences for chronic lung inflammation were 0/70, 21/69, and 56/135 for male mice and 3/69, 13/65, and 52/135 for female mice exposed to 0, 10, or 30 ppm, respectively.

In an acute-duration oral lethality study, animals that died after being administered a single dose of 1,000–4,000 mg/kg naphthalene exhibited lesions of the lung that were not observed in animals that survived (Papciak and Mallory 1990). Mice administered a single dose of 150 mg/kg naphthalene had cytotoxicity of the respiratory epithelia characterized by increased swollen or vacuolated cell volume in the intrapulmonary airways, terminal bronchioles, and airway bifurcations (Kelty et al. 2020). Similarly, after mice received a single oral dose of 100 mg/kg naphthalene, effects in the lung included structural degeneration, vasocongestion, edema, inflammatory cell infiltration, and destruction of interalveolar septa with large, irregular alveolar space (Zhang et al. 2015, 2016). In a study that did not include histopathology examination, female mice exposed to 267 mg/kg/day naphthalene for 14 days had increased lung weights, but these effects were not observed in males or when mice were administered 133 mg/kg/day for 90 days (Shopp et al. 1984).

In intermediate-duration (13-week) studies of oral exposure, no gross or histopathological lesions of the lungs were noted in mice at doses up to 200 mg/kg/day (NTP 1980a) or in rats at doses of 400 mg/kg/day (NTP 1980b).

No histological changes of the lungs were noted in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Mechanisms. The mechanisms underlying the effects of naphthalene on the respiratory tracts of rats and mice have been extensively studied. As discussed further below, a key first step in the effects of naphthalene on both the upper and lower respiratory tracts is metabolism to electrophilic intermediates, especially the 1,2-epoxide (see Section 3.1.3). The electrophilic metabolites may bind to cellular proteins, altering their structure and/or function. Furthermore, these intermediates are conjugated to glutathione for elimination from the body; at higher exposure levels, this may deplete the supply of reduced glutathione and increase oxidative stress. These changes are believed to result in injury to the respiratory tract tissues manifested as necrosis, degeneration, and exfoliation of epithelial cells. With repeated and prolonged injury, the respiratory tract responds with stimulation of cell proliferation and differentiation and recruitment of cells to fill in the exfoliated areas; these changes are seen histologically as hyperplasia and metaplasia.

In rat nasal microsomes incubated with naphthalene, the primary metabolite was the glutathione conjugate of the 1,2-epoxide (Buckpitt et al. 2013; Lee et al. 2005), although smaller quantities of other electrophilic metabolites (1,2- and 1,4-naphthoquinones) have also been reported in this system (Kedderis et al. 2014). *In vitro* studies have also demonstrated that naphthalene may covalently bind to actin, tubulin, molecular chaperone proteins, and proteins involved in cellular redox homeostasis and ATP synthesis in rat nasal tissues (DeStefano-Shields et al. 2010; Pham et al. 2012). Further, Cichocki et al. (2014) observed depletion of reduced glutathione (without increases in oxidized glutathione) in the nasal tissues of rats exposed to naphthalene by inhalation. Evidence for the role of oxidative stress comes from studies showing changes in the expression of genes in oxidative stress pathways. Cichocki et al. (2014) and Clewell et al. (2014) reported alterations in genes controlled by the antioxidant response element in the nasal tissues in rats exposed by inhalation to naphthalene.

In mice, but not rats, naphthalene exposure by inhalation or intraperitoneal (i.p.) injection triggers similar changes in the lungs. Metabolism by CYP2F2 to the 1,2-epoxide intermediate appears to be a critical step in the mouse lung toxicity of naphthalene. In CYP2F2-null mice exposed to naphthalene by i.p. injection,

only one of five animals showed any lung toxicity, and it was mild (Li et al. 2011). In contrast, wild-type mice treated with the same dose exhibited necrosis and detachment of club cells in the airway epithelium (Li et al. 2011). Experiments using epoxide-hydrolase-null mice did not show any reduction in susceptibility (Carratt et al. 2016; Hu et al. 2014), indicating that the epoxide-hydrolase pathway is not as important in the mechanism of mouse lung toxicity. Studies of protein binding in the lungs of mice exposed to naphthalene, in isolated mouse airway explants, and/or in club cells *in vitro* have shown covalent binding to some of the same proteins affected in rat nasal tissue (cytoskeletal proteins, molecular chaperone proteins, proteins involved in ATP synthesis) as well as the antioxidant peroxiredoxin 6 (Buchholz et al. 2010; Cho et al. 1994a, 1994b; Kanekal et al. 1990; Lakritz et al. 1996; Lin et al. 2005; O'Brien et al. 1985; Phimister et al. 2004; Tsuruda et al. 1995; Williams et al. 2003; Zheng et al. 1997). Binding of naphthalene metabolites to proteins involved in ATP synthesis is supported by evidence for ATP depletion in mouse terminal bronchial explants and mouse lungs cells treated with naphthalene (Kedderis et al. 2014; Phimister et al. 2006).

Increases in oxidative stress (measured as malondialdehyde and nitric oxide) have been observed in the lungs of mice after i.p. injection (Aktay et al. 2000; Omurtag et al. 2005; Sehirli et al. 2008) or oral exposure (Zhang et al. 2015, 2016). The increases in measures of oxidative stress were associated with corresponding decreases in reduced glutathione in these studies (Aktay et al. 2000; Omurtag et al. 2005; Sehirli et al. 2008; Zhang et al. 2015, 2016). Finally, there is some evidence that, in addition to necrosis, naphthalene also induces apoptosis in the epithelium of the lungs of mice. Royce et al. (2014a, 2014b) observed increased staining with Annexin V (used to detect apoptotic cells) in the airways when mice were exposed by i.p. injection.

Repair of injury to the mouse lung epithelium is initiated by a variety of cell signaling pathways. For example, upregulation of several growth factors (epidermal growth factor; trefoil factors 1 and 2; transforming growth factor beta; connective tissue growth factor; fibroblast growth factor 10; nerve growth factor; and keratinocyte growth factor) has been shown to occur in the distal airways of mice exposed to naphthalene by i.p. injection (Aoshiba et al. 2014; Atkinson et al. 2007; Greeley et al. 2010; Royce et al. 2014a, 2014b; Snyder et al. 2009; Sonar et al. 2010; Van Winkle et al. 1997; Volckaert et al. 2011). In response to these signals, epithelial cell proliferation occurs. Naphthalene administration by i.p. injection has been shown to increase the proliferation of bronchiolar epithelial cells in mice, measured as increased bromodeoxyuridine incorporation, ^{3}H-thymidine labeling, and/or using immunohisto-chemistry (Aoshiba et al. 2014; Atkinson et al. 2007; Oliver et al. 2009, 2011; Rawlins et al. 2007; Toba et al. 2015; Van Winkle et al. 2004).

1-Methylnaphthalene. No studies were located regarding respiratory effects in humans after inhalation, oral, or dermal exposure to 1-methylnaphthalene. Rats exposed by inhalation (whole body) to 1-methylnaphthalene at concentrations of 4 ppm for 6 hours/day, 5 days/week for 13 weeks had increased incidences of mucous cell hyperplasia (Kim et al. 2020).

No respiratory effects were observed in Sprague-Dawley rats administered up to 250 mg/kg/day by gavage for at least 42 days in a combined repeated-dose and reproduction/development toxicity study (NITE 2009). There were significantly increased incidences of pulmonary alveolar proteinosis in male and female B6C3F1 mice fed diets containing 1-methylnaphthalene for 81 weeks (Murata et al. 1993). Average administered doses were 0, 71.6, or 140.2 mg/kg/day for males and 0, 75.1, or 143.7 mg/kg/day for females and respective incidences for pulmonary alveolar proteinosis were 4/49, 23/50, and 19/49 for males and 5/50, 23/50, and 17/49 for females. The lesions contained acidophilic amorphous material, foam cells, and cholesterol crystals but there was no apparent inflammation, edema, or fibrosis of the tissues. Pulmonary alveolar proteinosis is characterized by the accumulation of surfactant material in the alveolar lumen and has been hypothesized to be caused by either excessive secretion of surfactant by type II pneumocytes, or disruption of surfactant clearance by macrophages (Lee et al. 1997; Mazzone et al. 2001; Wang et al. 1997).

2-Methylnaphthalene. No studies were located regarding respiratory effects in humans after inhalation, oral, or dermal exposure to 2-methylnaphthalene, or in animals after dermal exposure to 2-methyl-naphthalene.

In Wistar rats exposed to 2-methylnaphthalene at doses of 0, 0.34, 1.89, and 8.77 ppm for 6 hours/day, 5 days/week for 4 weeks, there were increased incidences of goblet cell metaplasia in the bronchi at ≥0.34 ppm, increased incidences of bronchiolar and alveolar mononuclear cell infiltration associated with proteinosis at ≥1.89 ppm, and an increased incidence of peribronchial lymphatic tissue hyperplasia at ≥1.89 ppm in females and at the highest concentration in males (Świercz et al. 2011).

Pulmonary alveolar proteinosis was the only exposure-related lesion found in B6C3F1 mice of both sexes exposed to 2-methylnaphthalene at doses as low as 50.3 mg/kg/day in the diet for 81 weeks (Murata et al. 1997). Average administered doses were 0, 54.3, or 113.8 mg/kg/day for males and 0, 50.3, or 107.6 mg/kg/day for females with respective incidences for pulmonary alveolar proteinosis of 4/49,

21/49, and 23/49 for males and 5/50, 27/49, and 22/49 for females. No other oral studies in animals were identified.

Mixed 1- and 2-Methylnaphthalene. Mice exposed dermally to a mixture of 1- and 2-methylnaphthalene 2 times/week for 61 weeks exhibited alveolar spaces of the lungs filled with numerous myelinoid structures resembling lamellar bodies of type II pneumocytes by electron microscope (Murata et al. 1992). Pulmonary alveolar proteinosis was noted in 31/32 female B6C3F1 mice given dermal applications of a mixture of 1- and 2-methylnaphthalene at a dose level of 119 mg/kg twice a week for 30 weeks (Murata et al. 1992) and in 15/15 female B6C3F1 mice similarly exposed for 61 weeks (Emi and Konishi 1985). In the same study, a dose of 30 mg/kg twice a week for 61 weeks had pulmonary alveolar proteinosis incidence of 3/11 in female mice. No occurrences of pulmonary alveolar proteinosis were found in control mice of either study. In Emi and Konishi (1985), dermal exposure to 119 mg/kg methylnaphthalene twice a week for 61 weeks also resulted in early deaths; the number of mice that died was not specified.

Mechanisms. The mechanisms by which 1- or 2-methylnaphthalene may cause pulmonary alveolar proteinosis are poorly understood, but light and electron microscopic observations of lung tissues from mice repeatedly exposed to dermal doses of methylnaphthalene indicate that type II pneumocytes are a specific cellular target (Murata et al. 1992). It has been hypothesized that, in response to 1- or 2-methylnaphthalene, type II pneumocytes produce increased amounts of lamellar bodies due to hyperplasia and hypertrophy, and eventually transform into balloon cells (Murata et al. 1992). The rupture of balloon cells is hypothesized to lead to the accumulation of proteinaceous materials rich in lipids in the alveolar lumen. It is unknown whether the methylnaphthalenes themselves or their metabolites are responsible for the development of pulmonary alveolar proteinosis. A study in transgenic *gpt* delta B6C3F1 mice (used primarily to assess genotoxicity) exposed to 1-methylnaphthalene in the diet at concentrations up to 0.15% for 13 weeks showed no effect of treatment on cell proliferation rates or histology in the lungs (Jin et al. 2012).

2.5 CARDIOVASCULAR

Naphthalene. Limited epidemiological studies of associations between cardiovascular effects in humans and biomarkers of exposure to naphthalene have been conducted and are summarized in Table 2-9. A cross-sectional study in adults in the United States (NHANES) found no association between urinary levels of 1- or 2-naphthol and serum levels of fibrinogen, homocysteine, or white blood cell count (Clark

et al. 2012). In another cross-sectional study in adults in the United States, the urinary metabolite, 1-naphthol, was positively associated with dyslipidemia and type 2 diabetes, while 2-naphthol was positively associated with obesity, hypertension, dyslipidemia, type 2 diabetes, and metabolic syndrome (Ranjbar et al. 2015). An association between urinary 1-naphthol concentration (but not 2-naphthol concentration) and coronary heart disease was found in a case-control study in China (Zhang et al. 2024). In a cross-sectional study, an association was found between hypertension and urinary 1-naphthol concentration (Wang et al. 2022b). In contrast, hypertension was not associated with modeled air concentrations of naphthalene in a cohort study of women in the United States (Xu et al. 2022) or with urinary naphthalene metabolite concentrations in a cohort of petrochemical workers (Sun et al. 2023). No studies were located that demonstrate any direct effects of naphthalene ingestion on the cardiovascular system. In those reports where cardiovascular effects, such as increased heart rate and decreased blood pressure, were noted in humans, the cardiovascular effects appeared to be secondary to the hemolytic effects and the events leading to general multiple organ failure (Gupta et al. 1979; Kurz 1987). No studies were located that documented cardiovascular effects in humans after dermal exposure to naphthalene.

Table 2-9. Summary of Epidemiological Studies of Naphthalene Exposure and Cardiovascular Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Clark et al. 2012 Cross-sectional, 3,219 adults ≥20 years old, participants in NHANES 2001–2004, United States	Urinary 1- and 2-naphthol	NR	Serum fibrinogen and homocysteine; white blood cell count	↔
Ranjbar et al. 2015 Cross-sectional, 4,765 adults ≥20 years old, participants in NHANES 2001–2008, United States	Urinary 1- and 2-naphthol	1-naphthol: 2,823 ng/L(mean) (not obese) 2,675 ng/L (obese)	Obesity	↔
			Hypertension	↔
			Dyslipidemia	↑
			Type 2 diabetes	↑
			Metabolic syndrome	↔
		2-naphthol: 3,270 ng/L (mean) (not obese) 3,805 ng/L (obese)	Obesity	↑
			Hypertension	↑
			Dyslipidemia	↑
			Type 2 diabetes	↑
			Metabolic syndrome	↑
Sun et al. 2023 Occupational, 746 petrochemical plant workers, China	Urinary 1- and 2-naphthol	1-naphthol: 10.1 ng/mL (median)	Hypertension	↔
		2-naphthol: 21.7 ng/mL	Hypertension	↔

Table 2-9. Summary of Epidemiological Studies of Naphthalene Exposure and Cardiovascular Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Wang et al. 2022b Cross-sectional, 6,332 adults ≥18 years old, participants in NHANES 2009–2016, United States	Urinary 1- and 2-naphthol	1-naphthol: 2,136 ng/g creatinine (geometric mean)	Hypertension	↑
		2-naphthol: 5,051 ng/g creatinine (geometric mean)	Hypertension	↔
Xu et al. 2022 Cohort, 47,467 adult women in the "Sister Study" cohort, United States	Modeled naphthalene air concentration at enrollment address	0.0412 µg/m^3 (median census tract concentration)	Hypertension	↔
Zhang et al. 2024 Case-control, 116 adult cases of CHD and 175 healthy controls, mean age 52.4 years, China	Urinary 1- and 2-naphthol	1-naphthol (median): 5.23 ng/mL (cases) 3.05 ng/mL (controls)	CHD	↑
		2-naphthol (median): 6.84 ng/mL (cases) 7.88 ng/mL (controls)	CHD	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; CHD = coronary heart disease; NHANES = National Health and Nutrition Examination Survey; NR = not reported

Studies in animals have not shown clear evidence of cardiovascular effects of naphthalene. Male rats exposed by inhalation to 30 ppm naphthalene for 6 hours/day, 5 days/week for 13 weeks had no changes in absolute or relative heart weights (Dodd et al. 2012). Female rats in this study showed decreases in absolute (but not relative) heart weights but the changes did not show a clear dose relationship. No histological changes were seen in the hearts of mice (30 ppm) or rats (60 ppm) that inhaled naphthalene for 2 years (Abdo et al. 2001; NTP 1992a, 2000).

No gross or histopathological lesions of the heart were noted in mice at doses up to 200 mg/kg/day (NTP 1980a) or in rats at doses of 400 mg/kg/day (NTP 1980b) after 13 weeks of oral exposure. No differences in organ weight or histological changes of the heart were noted in rats dermally treated with 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

1-Methylnaphthalene. No studies were located regarding cardiovascular effects in humans after inhalation, oral, or dermal exposure to 1-methylnaphthalene, or in animals exposed to 1-methylnaphthalene via inhalation or dermal contact. No effects were observed on heart weights or pathology in Sprague-Dawley rats administered 250 mg/kg/day by gavage for at least 42 days (NITE

2009). Heart weights were significantly decreased (6–7%) in male and female mice that were fed 1-methylnaphthalene for 81 weeks in their diet; however, the changes in heart weight were not dose-related and there were no accompanying tissue abnormalities (Murata et al. 1993). Histopathological examination revealed no lesions in the hearts at doses as high as 143.7 mg/kg/day (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding cardiovascular effects in humans after inhalation, oral, or dermal exposure or in animals after dermal exposure to 2-methylnaphthalene. No changes in heart weights were observed in Wistar rats exposed to up to 8.77 ppm of 2-methylnaphthalene for 6 hours/day, 5 days/week for 4 weeks (Świercz et al. 2011). No microscopic lesions were observed in the hearts when mice were fed 2-methylnaphthalene at doses up to 113.8 mg/kg/day in the diet for 81 weeks (Murata et al. 1997).

2.6 GASTROINTESTINAL

Naphthalene. Eight adults and one child exposed to naphthalene vapors from large quantities of mothballs (300–500) had nausea, vomiting, and abdominal pain, which subsided after discontinued use (Linick 1983). Air samples collected in one home contained naphthalene at 20 ppb; concentrations could have been higher when the mothballs were fresh.

Gastrointestinal disorders are common following naphthalene ingestion by humans. These effects have been attributed to the irritant properties of naphthalene (Kurz 1987). Nausea, vomiting, abdominal pain, and diarrhea (occasionally containing blood) have been reported (Bregman 1954; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). While the presence of blood in the stool is indicative of intestinal bleeding, only a few areas of mucosal hemorrhage were noted in the intestines during a postmortem examination of a 30-year-old female who died 5 days after ingesting at least 40 mothballs (Kurz 1987). These areas were restricted to the small bowel and colon. No frank erosions or perforations were noted anywhere in the gastrointestinal tract.

A single cross-sectional epidemiology study in adults in rural Kenya found a positive association between urinary levels of creatinine-corrected 2-naphthol (but not 1-naphthol) and a precancerous lesion (esophageal squamous dysplasia), after correction for covariates including tobacco and alcohol use (Mwachiro et al. 2021).

There were no histopathological changes in the gastrointestinal tract (stomach or intestines) of mice exposed by inhalation to naphthalene concentrations up to 30 ppm or rats exposed to concentrations up to 60 ppm for 2 years (Abdo et al. 2001; NTP 1992a, 2000). A single oral dose of 1,000–4,000 mg/kg was associated with stomach lesions and discoloration of the intestines in rats that died during an LD_{50} study; the survivors were not affected (Papciak and Mallory 1990). No gross or histopathological lesions of the stomach, small intestine, or colon were noted in mice given oral doses up to 200 mg/kg/day (NTP 1980a) or in rats given doses up to 400 mg/kg/day for 13 weeks (NTP 1980b). There was some intermittent diarrhea in the rats given the highest dose. No histological changes of the esophagus, stomach, or intestines were noted in rats dermally treated with 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

1-Methylnaphthalene. No studies were located regarding gastrointestinal effects in humans following inhalation, oral, or dermal exposure to 1-methylnaphthalene.

There were no studies found that assessed gastrointestinal effects after acute- or chronic-duration inhalation exposures in animals. No histopathological lesions were seen in the stomach or intestines of rats exposed to up to 30 ppm 1-methylnaphthalene for 6 hours/day, 5 days/week for 13 weeks (Kim et al. 2020) or by gavage at doses up to 250 mg/kg/day for 42 days (NITE 2009), or in mice fed 71.6–143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding gastrointestinal effects following inhalation, oral, or dermal exposure in humans or in animals following dermal exposure to 2-methylnaphthalene. In rats exposed by inhalation for 4 weeks to concentrations up to 8.77 ppm and in mice fed 50.3–113.8 mg/kg/day 2-methylnaphthalene for 81 weeks, there were no histopathological lesions in the stomach or intestines (Murata et al. 1997; Świercz et al. 2011).

2.7 HEMATOLOGICAL

Naphthalene. Hemolytic anemia is the most frequently reported manifestation of naphthalene exposure in humans. Twenty-one infants (3–90 days old) had acute hemolytic anemia after exposure to naphthalene via mothball-treated fabrics (blankets, clothes, or other materials) (Valaes et al. 1963). Ten of the infants had G6PD genetic deficiency that increased their susceptibility to hemolysis. Clinical observations in the infants included high serum bilirubin levels, methemoglobin, Heinz bodes, and

fragmented red blood cells. The relevant route of exposure appeared to be inhalation as the naphthalene material was not worn near the skin with one exception (the infant who wore a treated diaper).

Anemia was also reported in eight adults and one child exposed to naphthalene vapor via a large (300–500) number of mothballs throughout the home (Linick 1983). The nature of the anemia and specific levels of naphthalene exposure were not identified. In one home, the naphthalene concentration was determined to be 20 ppb at the time of testing but could have been higher when the mothballs were first distributed.

One woman who was exposed to a combination of reportedly high (but not measured) concentrations of naphthalene and paradichlorobenzene for several weeks in a hot, poorly ventilated work area developed aplastic anemia (Harden and Baetjer 1978). The contribution from naphthalene was difficult to determine in the presence of other chemicals.

The most commonly reported hematologic effect in humans following the ingestion of naphthalene is hemolytic anemia (Ahmad et al. 2019; Anand et al. 2023; Dawson et al. 1958; Dela Cruz et al. 2019; Ekambaram et al. 2017; Eskandarani and Alghamdi 2020; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kuwada et al. 2022; Kurz 1987; MacGregor 1954; Mackell et al. 1951; Mathur and Garg 2023; Mehdi et al. 2023; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Shannon and Buchanan 1982; Tannor and Hutton-Mensah 2019; Thangatorai 2022; Uthuman et al. 2019). Changes observed in hematology and blood chemistry in these cases are consistent with hemolysis: decreased hemoglobin and hematocrit values, and increased reticulocyte counts, serum bilirubin levels, and Heinz bodies. Most of the reported case studies provided no information on dose. However, in one case report, a 16-year-old girl swallowed 6 g of naphthalene before exhibiting hemolytic anemia (Gidron and Leurer 1956). This corresponds to a dose of 109 mg/kg assuming a 55-kg body weight. Two publications reported cases of hemolytic anemia in newborn infants after their mothers consumed naphthalene-containing mothballs during pregnancy (Sahni et al. 2019; Shafer et al. 2020).

There is a strong association between G6PD deficiency and the hemolytic effects of naphthalene (Dawson et al. 1958; Melzer-Lange and Walsh-Kelly 1989; Shannon and Buchanan 1982). Individuals with a genetic defect for this enzyme show an increased susceptibility to hemolysis from naphthalene exposure. Hemolytic anemia was reported in infants dermally exposed to diapers or other clothing treated with naphthalene mothballs (Dawson et al. 1958; Schafer 1951; Valaes et al. 1963). Jaundice, fragmentation of erythrocytes, Heinz bodies, methemoglobinemia, and reticulocytosis were observed. Several of the

infants had G6PD deficiencies. Individuals with this genetic disorder are particularly susceptible to hemolysis from chemical agents. The application of oil to the skin may have aided absorption of naphthalene, as shown by the increasing severity of symptoms (jaundice and cyanosis) even after the use of the naphthalene-containing diapers ceased (Schafer 1951).

The few epidemiological studies of hematology changes in humans exposed to naphthalene are summarized in Table 2-10. In a cross-sectional study in U.S. adults without anemia, increases in hemoglobin and hematocrit were positively associated with 1-naphthol (but not 2-naphthol) levels in urine (Sudakin et al. 2011). In contrast, urinary levels of 1- and 2-naphthol were inversely associated with hemoglobin concentration, erythrocyte count, and mean corpuscular volume in a cohort of male brick workers (Kamal et al. 2014). A positive association between 1-naphthol concentration and leukocyte count was observed in the same study. A cohort of male workers in a coke oven plant reported a positive association between air concentrations of naphthalene in the workplace and hemoglobin concentration, and inverse associations with eosinophil and leukocyte counts (Wang et al. 2019).

Table 2-10. Summary of Epidemiological Studies of Naphthalene Exposure and Hematological Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Kamal et al. 2014 Cohort, 46 male brick kiln workers (mean age 42 years), 34 male controls without occupational exposure (mean age 40 years), Pakistan	Naphthalene metabolite levels in urine	1-naphthol: µmol/mol-creatinine (mean±SD) 3.29±0.5 (exposed) 0.62±0.18 (unexposed) 2-naphthol: 1.55±0.95 (exposed) 0.61±0.16 (unexposed)	Hemoglobin concentration	↓
			Erythrocyte count	↓
			Mean corpuscular volume	↓
			Leukocyte count	↑
			Platelet count	↔
Sudakin et al. 2011 Cross-sectional, 2,450 adults (18+ years old) without treated anemia from 2003–2004 NHANES, United States	Naphthalene metabolite levels in urine	1-naphthol: (ng/mL) (weighted mean±SE) 8.1±0.5 (males) 8.1±0.9 (females)	Hemoglobin concentration	↑
			Hematocrit	↑
		2-naphthol (ng/mL) (weighted mean±SE) 7.2±0.5 (males) 6.3±0.5 (females)	Hemoglobin concentration	↔
			Hematocrit	↔

Table 2-10. Summary of Epidemiological Studies of Naphthalene Exposure and Hematological Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Wang et al. 2019 Cohort, 473 male workers in coke-oven plant and 166 unexposed workers from other facilities, China	Naphthalene in workplace air	21.54 ng/m^3 (median, high-PAH coke oven workers) 17.70 (low-PAH coke oven workers) 4.72 (unexposed workers)	Eosinophil count	↓
			Lymphocyte count	↓
			Hemoglobin concentration	↑
			White blood cell, neutrophil, monocyte, red blood cell, and platelet counts	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; NHANES = National Health and Nutrition Examination Survey; PAH = polycyclic aromatic hydrocarbon; SD = standard deviation; SE = standard error

No biologically significant exposure-related hematological effects (hematocrit, hemoglobin concentration, erythrocyte counts, mean cell volume, reticulocytes, and leukocytes) were observed in mice exposed by inhalation to 10–30 ppm naphthalene for 14 days (NTP 1992a).

Dogs and hamsters exposed orally to naphthalene exhibited changes consistent with hemolysis, but the data are limited. Hemolytic anemia was reported by Zuelzer and Apt (1949) in a dog receiving a single 1,525 mg/kg dose of naphthalene in food and in another dog receiving approximately 263 mg/kg/day for 7 days in food. Hamsters exposed to 1,000 mg/kg/day for 3 weeks had reduced hemoglobin, hematocrit, and erythrocyte counts (Darious et al. 2020). Histopathology of the spleen showed hemolysis in the red pulp and congestion of the white pulp, as well as hemosiderin deposition (Darious et al. 2020).

Rats and mice do not appear to be as sensitive as humans or other species to the hemolytic effects of naphthalene. In CD-1 mice, naphthalene at doses up to 267 mg/kg/day for 14 days did not result in hemolytic anemia, however, there was an increase in eosinophils in males and a decrease in prothrombin time in females (Shopp et al. 1984). In an intermediate-duration (90 day) study by Shopp et al. (1984), CD-1 mice exposed by gavage to naphthalene at doses up to 133 mg/kg/day did not show signs of hemolytic anemia but did have an increase in eosinophils. Females in this study exhibited reductions in absolute and relative spleen weights at the highest dose (133 mg/kg/day) (Shopp et al. 1984). When rats were administered 87.5 mg/kg naphthalene 3 times/week for 7 weeks, the percent of segmented neutrophils was significantly reduced by 24%; however, no other hematological changes occurred (Katsnelson et al. 2014). There were no pronounced changes in red cell-related hematological parameters following 13-week exposures to doses of up to 200 mg/kg/day in mice (NTP 1980a) and up to

400 mg/kg/day in rats (NTP 1980b). In male mice exposed to 200 mg/kg/day for 13 weeks, there was a decrease in segmented neutrophils and an increase in lymphocytes, but in male rats given 400 mg/kg/day, there were increased neutrophils and decreased lymphocytes. These effects are not considered to be biologically significant or adverse.

There were no changes in hemoglobin, hematocrit, red blood cell count, leukocyte count, or platelet count at 4 and 13 weeks in rats treated with doses of up to 1,000 mg/kg/day applied to the skin (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Mechanisms. While the specific molecular mechanisms of naphthalene-induced hemolytic anemia have not been fully elucidated, this health effect is believed to result from exposure of erythrocytes to oxidative stress induced by naphthalene metabolites, leading to erythrocyte lysis and oxidation of heme iron. Conjugation of naphthalene metabolites with glutathione may deplete glutathione levels that normally protect erythrocytes from oxidation. Further, individuals with G6PD deficiency are more susceptible to naphthalene-induced hemolytic anemia because they are unable to rapidly replenish reduced glutathione. G6PD deficiency results in reduced capacity to produce NADPH, a cofactor required by glutathione reductase to reduce glutathione. Studies identifying the key metabolite(s) and/or evidence in relevant cell types were not located.

1-Methylnaphthalene. No studies were located regarding hematological effects in humans following inhalation, oral, or dermal exposure to 1-methylnaphthalene.

Groups of dogs (intact or splenectomized) were exposed to 1-methylnaphthalene (pure or practical grade) in kerosene (via a fogger) for 4 consecutive days (Lorber 1972). Quantitative exposure concentrations were not reported and there was not sufficient information reported to determine them. In animals exposed to 1-methylnaphthalene, reticulocytes were increased in splenectomized, but not intact, dogs for 10 days after exposure. Leukocyte counts were elevated in all dogs and neutrophils were elevated in intact (but not splenectomized) dogs exposed to practical-grade 1-methylnaphthalene, but not pure 1-methylnaphthalene. 1-Methylnaphthalene had no effect on hematocrit values, suggesting that this compound does not cause hemolysis under the conditions of the study. Since the increased reticulocyte counts were seen only in splenectomized dogs, it is difficult to interpret whether the change reflected increased hematopoiesis in response to 1-methylnaphthalene exposure (Lorber 1972). In an intermediate-duration study of rats, Kim et al. (2020) found that exposure to 1-methylnaphthalene concentrations up to 30 ppm for 6 hours/day, 5 days/week for 13 weeks did not result in any hematological changes.

Rats administered up to 250 mg/kg/day for approximately 42 days exhibited no hematological effects (NITE 2009). In female mice, administration of 75.1 or 143.7 mg/kg/day 1-methylnaphthalene in the diet for 81 weeks was associated with slight but statistically significant increases in hemoglobin concentration, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (Murata et al. 1993). Corresponding changes were not observed in male mice given comparable doses of 1-methylnaphthalene.

2-Methylnaphthalene. No studies were located regarding hematological effects in humans following inhalation, oral, or dermal exposure or in animals following dermal exposure to 2-methylnaphthalene.

In female rats exposed to concentrations ≥1.89 ppm 2-methylnaphthalene for 6 hours/day, 5 days/week, for 4 weeks, reticulocyte counts were increased (Świercz et al. 2011). While male rats showed a trend of increased reticulocyte counts, no group was significantly different from controls. In the dog study by Lorber (1972) described above, 2-methylnaphthalene (pure and practical grade) had no effect on any of the parameters monitored. Similarly, there were no hematology changes in male or female mice exposed to 2-methylnaphthalene doses as high as 113.8 mg/kg/day in the diet for 81 weeks (Murata et al. 1997).

2.8 MUSCULOSKELETAL

Naphthalene. No studies were located that documented musculoskeletal effects in humans after inhalation exposure to naphthalene. A single epidemiological study in U.S. women (NHANES 2005–2010) suggested an association between urinary levels of 1-naphthol and reduced bone mass density and increased likelihood of osteoporosis (Guo et al. 2018). No naphthalene-related effects on bone (femur) histology were noted in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed by inhalation for 2 years to concentrations as high as 30 or 60 ppm, respectively.

1-Methylnaphthalene. No studies of musculoskeletal effects in humans exposed to 1-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed by oral or dermal routes were located. No treatment-related effects were noted upon histological examination of the femur in rats exposed to up to 30 ppm 1-methylnaphthalene for 13 weeks (Kim et al. 2020).

2-Methylnaphthalene. No studies of musculoskeletal effects in humans or animals exposed to 2-methylnaphthalene by inhalation, oral, or dermal routes were located.

2.9 HEPATIC

Naphthalene. Jaundice has been reported in infants and adults after exposure to naphthalene (Linick 1983; Valaes et al. 1963); however, jaundice is a consequence of hemolysis rather than a direct effect of naphthalene on the liver. In these cases, infant exposures lasted 1–7 days (Valaes et al. 1963); adult exposure durations were not provided (Linick 1983). Dose was not determined in either instance, although an air concentration of 20 ppb was measured in the home of one affected individual (Linick 1983).

Hepatotoxicity following oral exposure to naphthalene has been reported in humans, based on elevated plasma levels of hepatic enzymes (such as aspartate aminotransferase [AST] and LDH) (Kurz 1987; Ojwang et al. 1985) and liver enlargement (Gupta et al. 1979; MacGregor 1954). The liver was also enlarged in two infants who experienced acute hemolysis after dermal exposure to naphthalene (Dawson et al. 1958; Schafer 1951).

No treatment-related changes in relative liver weights were observed in rats exposed to up to 30 ppm naphthalene for 13 weeks (Dodd et al. 2012). Female rats exhibited reductions in absolute liver weight at ≥10 ppm, but the toxicological significance of this change is uncertain. No treatment-related gross or histopathological lesions of the liver were reported in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively.

There is some limited evidence of hepatic effects in laboratory animals exposed orally. Mice administered a single dose of 100 mg/kg had increased serum levels of AST and alanine aminotransferase (ALT) and histopathology changes including focal necrosis, inflammatory infiltrate, fatty degeneration, cellular necrosis, loss of cell boundaries, and structural chords (Zhang et al. 2016). A 39% increase in liver weight, a modest elevation in activity of aniline hydroxylase, and evidence of lipid peroxidation were observed in male rats treated with naphthalene at 1,000 mg/kg/day for 10 days (Rao and Pandya 1981). No effects on liver weight were observed in male or female mice receiving naphthalene at doses up to 267 mg/kg/day for 14 days (Shopp et al. 1984).

Rats administered 1,000 mg/kg/day for 10 weeks (after 3 days of dosing at 500 mg/kg/day) exhibited changes in hepatocyte morphology including ballooning and reduced hepatocyte number (Chen et al. 2012); however, no hepatic histopathological changes were observed when the same strain of rat was exposed at this dose for 5 weeks (Zhu and Lu 2012). Changes in clinical chemistry consisting of

significantly increased ALT and AST were observed in female rats administered 87.5 mg/kg/day, 3 times/week for 7 weeks (Katsnelson et al. 2014); however, liver weights, gross pathology, and histopathology were not evaluated.

No effects on liver weight were observed in male mice receiving naphthalene at doses up to 133 mg/kg/day for 90 days (Shopp et al. 1984). Absolute liver weight was statistically significantly decreased (by about 18% compared with the control value), in female mice receiving 133 mg/kg/day naphthalene for 90 days, but the biological significance of this change is unclear. Relative liver weight in exposed females was not changed to a statistically significant degree, and several serum biochemical endpoints indicative of liver damage (e.g., LDH, ALT, AST, and alkaline phosphatase [ALP]) were unaffected in female or male mice (Shopp et al. 1984). No other consistent biologically relevant exposure-related changes in serum chemistry endpoints were found. Activities of two hepatic microsomal mixed function oxidases (aniline hydroxylase, aminopyrine N-demethylase) were unchanged in exposed mice, although hepatic activities of benzo[a]pyrene hydroxylase were statistically significantly decreased in exposed mice (Shopp et al. 1984). The biological significance of this change is unclear. No gross or histopathological lesions of the liver were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b).

There were no differences in liver weights or histological damage to the liver in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986). In addition, the levels of AST, ALT, urea nitrogen, and bilirubin were not elevated in the exposed rats as compared to the controls.

Mechanisms. Hepatic changes were accompanied with increased markers of oxidative stress in hepatic tissue. Mice administered a single oral dose of 100 mg/kg showed increased markers of oxidative stress (increased lipid peroxidation and decreased antioxidant enzymes) in the liver (Zhang et al. 2016). Elevation of hepatic lipid peroxides was observed in male rats after oral naphthalene doses of 1,000 mg/kg/day for 18 days (Yamauchi et al. 1986). In rats administered increasing doses of naphthalene up to 750 mg/kg/day (TWA of 169 mg/kg/day), hepatic lipid peroxides were doubled at the end of 9 weeks of treatment (Germansky and Jamall 1988). Evidence for glutathione depletion in the livers of mice exposed to naphthalene supports a role for oxidative stress in hepatic effects. After exposure to naphthalene by i.p. injection (300 mg/kg) or inhalation (10 ppm for 4 hours), mice exhibited reduced capacity for glutathione conjugation of naphthalene metabolites (Li et al. 2011; Kovalchuk et al. 2017).

1-Methylnaphthalene. No studies were located regarding hepatic effects in humans exposed to 1-methylnaphthalene by any exposure route or in animals exposed by dermal contact.

In a toxicokinetic study, Świercz et al. (2022) observed a 40% increase in serum ALT in rats exposed to 200 mg/m^3 1-methylnaphthalene by inhalation 6 hours/day for 5 consecutive days. Serum AST was not affected by exposure (Świercz et al. 2022). Rats exposed to 30 ppm 1-methylnaphthalene vapor for 13 weeks showed no changes in serum chemistry or liver weight, and no gross or histopathological changes in the liver (Kim et al. 2020). In a combined repeat-dose and reproductive/developmental screening study, rats administered 250 mg/kg/day had increased liver weights (NITE 2009). No corresponding histopathological effects or changes in serum chemistry were observed. There were no changes in liver weight or histopathology in male or female mice that consumed 71.6–143.7 mg/kg/day 1-methylnaphthalene in the diet for 81 weeks (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding hepatic effects in humans exposed to 2-methylnaphthalene by any exposure route or in animals exposed by dermal contact.

In mice given a single oral dose of 0, 100, 200, or 300 mg/kg 2-methylnaphthelene as part of a toxicokinetic study, dose-related increases in serum ALT were observed; the increase relative to controls was >2-fold at 200 mg/kg (Li et al. 2022). Serum AST was increased by ~3-fold at the highest dose of 300 mg/kg (Li et al. 2022). Rats exposed by inhalation to 0.34–8.77 ppm concentrations of 2-methylnaphthalene for 4 weeks exhibited decreased liver weights at all concentrations in males and at 8.77 ppm in females (Świercz et al. 2011). The toxicological significance of the reduced liver weights is uncertain. However, increased incidences of bile duct hyperplasia were reported in both sexes at 1.89 and 8.77 ppm. Incidences of this lesion at 0, 0.34, 1.89 and 8.77 ppm were 0/5, 0/5, 2/5, and 5/5, respectively, in males and 0/5, 0/5, 3/5, and 5/5, respectively in females (Świercz et al. 2011).

Mice exposed to 50.3–113.8 mg/kg/day 2-methylnaphthalene in the diet for 81 weeks exhibited no alterations in liver weights or histopathology (Murata et al. 1997).

2.10 RENAL

Naphthalene. Human studies of the kidney effects of naphthalene include numerous case reports of renal effects secondary to hemolysis and a single epidemiology study of renal function. Renal disease was

reported in nine individuals (details not specified) exposed to large numbers of mothballs in their homes, but symptoms were not described, and dose could not be determined (Linick 1983). Renal toxicity has been reported in case studies of humans who ingested naphthalene. Frequent findings included the elevation of creatinine and blood urea nitrogen (BUN) and the presence of proteinuria and hemoglobinuria (Ahmad et al. 2019; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Mehdi et al. 2023; Ojwang et al. 1985; Paiva et al. 2022; Zuelzer and Apt 1949). The presence of blood in the urine and increased concentrations of urobilinogen are a consequence of acute hemolysis and do not reflect any direct action of naphthalene on the kidney. Oliguria (Kurz 1987) and anuria (Gupta et al. 1979; Mathur and Garg 2023) were noted in three case reports, although urine output was normal in a fourth (Ojwang et al. 1985). Painful urination with swelling of the urethral orifice was also associated with medicinal naphthalene ingestion (Lezenius 1902). A 14-month-old toddler who chewed on a mothball developed acute renal failure and rhabdomyolysis 3–4 days after exposure (Kuwada et al. 2022). In another case, a newborn infant exposed to naphthalene *in utero* (via maternal ingestion of mothballs prior to delivery) developed renal failure (Sahni et al. 2019). Proximal tubule damage and general tubular necrosis were found in postmortem examinations of two individuals who died following naphthalene ingestion (Gupta et al. 1979; Kurz 1987). In the single epidemiological study located, there was no association between measured $PM_{2.5}$-bound naphthalene concentration and renal function indicators (serum creatinine, BUN, urea acid, estimated glomerular filtration rate, and endogenous creatinine clearance rate) in a repeated measures study of 35 college students in China (Peng et al. 2022).

There is little indication that the kidney is a target of naphthalene toxicity in animals. In rats exposed to air concentrations up to 30 ppm for 13 weeks (Dodd et al. 2012), kidney weights were not affected by exposure. No treatment-related gross or histopathological lesions of the kidneys were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively.

Following 10 days of exposure of rats to naphthalene at 1,000 mg/kg/day, no changes were noted in kidney weight (Rao and Pandya 1981). No changes were observed in the kidney weights of mice administered naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). Female rats administered 87.5 mg/kg/day naphthalene by gavage 3 times/week for 7 weeks had no treatment-related changes in serum chemistry markers of kidney toxicity or urinalysis compared with controls; kidney weights and histopathology were not evaluated (Katsnelson et al. 2014). No renal histopathological changes were observed in rats given gavage doses up to 1,000 mg/kg/day for 5 weeks (Zhu and Lu 2012). No gross or histopathological lesions of the kidney were noted in mice at doses of up

to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 200 mg/kg/day after 13 weeks of exposure (NTP 1980b). In the male rats exposed to 400 mg/kg/day, 10% showed cortical tubular degeneration that may have been related to exposure (NTP 1980b).

There were no differences in kidney weights or histological damage to the kidney in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986). In addition, the results of urinalysis conducted at 4 and 13 weeks were not different from the control results, indicating that there was no exposure-related impairment of kidney function.

Naphthalene doses of 400 and 600 mg/kg administered by i.p. injection resulted in damage to the renal proximal tubules of mice consisting of vacuolar and hydropic degeneration of cells (O'Brien et al. 1985). In contrast, rats in the same study receiving doses up to 1,600 mg/kg exhibited no renal changes (O'Brien et al. 1985).

1-Methylnaphthalene. No studies were located regarding renal effects in humans exposed to 1-methylnaphthalene by any route or in animals exposed by dermal contact.

Rats exposed to 30 ppm 1-methylnaphthalene vapor for 13 weeks showed no changes in serum chemistry markers of renal toxicity or kidney weight, and there were no gross or histopathological lesions in the kidneys (Kim et al. 2020). Relative kidney weights were increased in male Sprague-Dawley rats treated with 250 mg/kg/day for 42 days, but absolute kidney weights did not differ from controls, and no corresponding changes were observed in histopathology or serum chemistry (NITE 2009). Absolute and relative kidney weights were decreased slightly in male mice fed diets containing 140.2 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The females were not affected, and there were no histopathological lesions in the males or females.

2-Methylnaphthalene. No studies were located regarding renal effects in humans exposed to 2-methylnaphthalene by any route or in animals exposed by dermal contact.

Serum chemistry markers of renal toxicity, kidney weights, and renal histopathology were not affected by exposure in rats exposed for 4 weeks by inhalation to 2-methylnaphthalene concentrations up to 8.77 ppm (Świercz et al. 2011). Likewise, there were no changes in kidney weights or histopathology in mice consuming 50.3–113.8 mg/kg/day 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1997).

2.11 DERMAL

Naphthalene. No studies were located that documented dermal effects in humans after inhalation, oral, or dermal exposure to naphthalene.

No treatment-related gross or histopathological lesions of the skin were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively.

When 0.35 mL of an 8 mM solution of naphthalene was applied to mouse skin once a day for 5 days, there were no changes in gross skin appearance or skin histology compared with controls (Alalaiwe et al. 2020). Prostaglandin (PGE2) production in the mouse skin was increased 3-fold, when compared to control. A study in rabbits showed that naphthalene is a mild dermal irritant, causing erythema and fissuring, when directly applied to the shaved, abraded, or non-abraded skin under a dressing for 4 hours; healing occurred within 6–7 days (Papciak and Mallory 1990; Texaco 1985a). In another study, rabbits that were exposed dermally to naphthalene (50 µL) under occlusion for 24 hours showed initial increases in skin temperature, erythema, and edema (moderate to severe), trans-epidermal water loss, and epidermal thickness, as well as reduced collagen fiber length and thickness (Singh and Singh 2004). In pigs, 0.3 mL of 98% pure naphthalene (dissolved in ethanol) applied to the skin did not induce erythema or changes in epidermal thickness or lipids after 1 or 4 days of exposure (Muhammad et al. 2005). In rats that were dermally treated for 6 hours/day, 5 days/week for 13 weeks with 1,000 mg/kg/day naphthalene, there was an increased incidence of excoriated skin lesions and papules (Frantz et al. 1986). However, similar lesions were seen in the controls and lower dose group animals. At the high dose, naphthalene appeared to exacerbate the severity of the lesions.

1-Methylnaphthalene. No studies of dermal effects in humans exposed to 1-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed by inhalation were located.

Dietary administration of 1-methylnaphthalene doses up to140.2 mg/kg/day for 81 weeks did not induce any histopathology changes in the skin of mice (Murata et al. 1993). In a dermal exposure study, rabbits were exposed to 1-methylnaphthalene (50 µL, concentration and vehicle not specified) in an occlusive chamber for 24 hours resulting in skin erythema, trans-epidermal water loss, increased skin temperature, and increased epidermal thickness with reduced collagen fiber length and thickness (Singh and Singh 2004).

2-Methylnaphthalene. No studies of dermal effects in humans exposed to 2-methylnaphthalene by any route or in animals exposed by inhalation were located. There were no histopathological effects observed in the skin from mice fed doses of 2-methylnaphthalene up to 113.8 mg/kg/day in the diet for 81 weeks (Murata et al. 1997). Dermal application of 2-methylnaphthalene (50 µL, concentration and vehicle not specified) to the occluded skin of rabbits resulted in erythema, trans-epidermal water loss, increased epidermal thickness, and reduced collagen fiber length and thickness (Singh and Singh 2004).

2.12 OCULAR

Naphthalene. Twenty-one workers exposed to naphthalene for up to 5 years in a plant that manufactured dye intermediates were examined for eye problems (Ghetti and Mariani 1956). During the period of exposure, plant conditions were primitive, involving heating of naphthalene in open vats and considerable worker contact with the naphthalene. Eight of the 21 workers developed multiple pinpoint lens opacities that had no correlation with the age of the workers. These effects were not overtly noticeable and apparently had no effect on vision. They were judged to be a consequence of naphthalene exposure on the basis of their location in the crystalline lens and the fact that occurrence did not correlate with age. Exposure involved long-term inhalation of vapors and direct contact of vapors with the eyes and skin.

In an early report of naphthalene toxicity, a 36-year-old pharmacist became nearly blind 8 or 9 hours after ingesting 5.0 g (units were not reported, assumed grams based on resulting in cataract development and human body weight) of unpurified naphthalene in a castor oil emulsion over a 13-hour period (with hourly ingestion of inconsistent volume) as treatment of an intestinal infection (Lezenius 1902). A medical examination the following month revealed constricted visual fields associated with optic atrophy and bilateral zonular cataracts.

In animals, no treatment-related gross or histopathological lesions of the eyes were observed in rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 60 ppm. However, during a 4-hour exposure of rats to a concentration of 78 ppm, irritation to the eyes was evidenced as lacrimation (Fait and Nachreiner 1985).

Several animal studies have demonstrated ocular changes following oral naphthalene exposure. Cataracts began to develop by the first day after a single 1,000 mg/kg naphthalene dose in three Chinchilla Bastard rabbits (Rossa and Pau 1988). Eight rabbits (strain not identified) developed cataracts during oral

administration of naphthalene at 2,000 mg/kg/day for 5 days (Srivastava and Nath 1969). In the solitary New Zealand White rabbit tested, cataracts began to develop after administration of four 1,000 mg/kg doses (dosing 2 times/week) and maximized after 12 weeks (Rossa and Pau 1988). Within 1 week following exposure to naphthalene (500 or 1,000 mg/kg/day), lens densities were increased in rats and cataracts developed within 4 weeks (Kojima 1992; Murano et al. 1993; Yamauchi et al. 1986). When naphthalene was administered orally at 1,000 mg/kg/day for up to 28 days, cataracts developed in 10 of 16 Dutch (pigmented) rabbits and in 11 of 12 albino rabbits (van Heyningen and Pirie 1967). Lens changes were seen as early as day 2 of exposure. The study authors noted that albino strains were more likely to develop cataracts over a 4-week course of treatment at 1,000 mg/kg/day than pigmented strains such as the Dutch rabbit.

When rats were administered 1,000–1,500 mg/kg/day naphthalene for 5–10 weeks, cataracts developed in all animals (Chen et al. 2010a, 2010b, 2012; Haque and Gilani 2005; Holmén et al. 1999; Siddiqui et al. 2002; Zhu and Lu 2012). Lens opacities were observed as early as 2 weeks and presented as spoke-like water clefts (Holmén et al. 1999; Siddiqui et al. 2002). Holmén et al. (1999) found cataracts in Brown-Norway rats at doses as low as 500 mg/kg twice a week for 10 weeks and emphasized a linear relationship between cataract formation and time. Administration of a TWA 500 mg/kg/day dose of naphthalene in corn oil by gavage for 6 weeks resulted in more rapid development of cataracts in pigmented Brown-Norway rats than in nonpigmented Sprague-Dawley rats (Murano et al. 1993). Cataracts developed in three distinct phases. In the first phase, water clefts formed in the anterior subcapsular region of the eye. The second stage was the development of a semicircular opaque area in the lens, and the last stage was the appearance of a wedge-shaped opacity that could be seen with retroillumination and a wide, zonular-ring opacity that was seen with slit imaging. Each stage occurred about 1 week earlier in the Brown-Norway rats than in the Sprague-Dawley rats, presumably because they more effectively metabolized naphthalene to the toxic compound, naphthoquinone (Murano et al. 1993). The first stage began 1 week after treatment was initiated in the Brown-Norway rats, and stage three cataracts were seen in all animals by the end of the 6 weeks. In another study, oral administration of naphthalene in rats resulted in cataract formation beginning at the posterior outer cortex, suggesting that this region is the most sensitive part of the lens (Kojima 1992). Progressive development of lens opacities was also reported in rats that were exposed to 700 or 5,000 mg/kg/day naphthalene by gavage for 79–102 days (Rathbun et al. 1990; Tao et al. 1991).

Damage to the eyes with continued exposure to naphthalene is not limited to lens opacification (Orzalesi et al. 1994). Retinal damage was noted in pigmented rabbits given TWA doses of 500 mg/kg/day

naphthalene in corn oil by gavage for 5 weeks. The first changes to the retina occurred at about 3 weeks with degeneration of the photoreceptors. There was a subsequent increase in the retinal pigment epithelium as these cells phagocytized the debris from the photoreceptors. By the end of 6 weeks, the photoreceptor layer had almost entirely disappeared and was replaced with fibroglial tissue. As damage progressed, there was dense subretinal neovascularization of the area.

A number of biochemical changes were seen in the eyes after acute- and intermediate-duration oral exposures to naphthalene in oil. Following oral exposure to 1,000 mg/kg/day, rat lenses had increased oxidative damage, as evidenced by increased lipid peroxidation (malondialdehyde) and reactive oxygen species (hydroxyl radicals) and decreased antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase, and reduced glutathione) (Chen et al. 2012; Singh and Bodakhe 2020; Zhu and Lu 2012) as well as decreased soluble protein and water levels and increased insoluble protein (Haque and Gilani 2005; Singh and Bodakhe 2020). After 1 week of treatment with 1,000 mg/kg/day by gavage, glutathione levels in the lens were decreased in rats (Xu et al. 1992b; Yamauchi et al. 1986). After 30 days of treatment with oral doses of 5,000 mg/kg/day, total glutathione levels were reduced by 20% (Rathbun et al. 1990), and there was a 22% reduction at 60 days with a dose of 700 mg/kg/day (Tao et al. 1991). At 60 days, glutathione peroxidase activity in the lens was decreased by up to 45% and there was a 20–30% decrease in glutathione reductase activity (Rathbun et al. 1990). Comparable decreases in the activities of both enzymes were seen at 102 days with lower naphthalene doses (Tao et al. 1991). No changes were observed in the activity of glutathione synthetase or gamma-glutamyl cysteine synthetase (Rathbun et al. 1990). After 4 weeks of oral treatment (500 mg/kg/day), the activities of aldose reductase (also known as aldehyde reductase), sorbitol dehydrogenase, LDH, and glutathione reductase were lower than in controls (Kojima 1992). No changes in ocular lipid peroxides were reported when male Blue Spruce pigmented rats were administered incremental oral doses of naphthalene that peaked at 750 mg/kg/day for 9 weeks (Germansky and Jamall 1988). Lens and capsule LDH activities were greatly reduced in rabbits while *o*-diphenyl oxidase activity was elevated with an oral dose of 2,000 mg/kg/day for 5 days (Srivastava and Nath 1969). In rats administered 1,000 mg/kg/day by gavage, lens opacities were evaluated for post-translational modifications of proteins and showed reduced phosphorylation and methylation of alpha crystallin protein (Chen et al. 2010a).

In 13-week studies, histopathologic examination revealed no ocular lesions in F344/N rats or B6C3F1 mice exposed to doses as high as 400 or 200 mg/kg/day, respectively (NTP 1980a, 1980b). In a 2-year rat feeding study, no eye damage was seen at a naphthalene dosage of 41 mg/kg/day (Schmahl 1955). The details of the eye examination were not provided.

Ocular irritation has also been associated with naphthalene exposure in humans and animals. Two case studies were reported in which humans experienced eye irritation and conjunctivitis as a result of naphthalene exposure (van der Hoeve 1906). In one case, a worker accidentally got naphthalene powder in his left eye. The exact amount was unknown but was described by the worker as "large." Despite immediate cleansing of the eye, the subject experienced conjunctivitis and pain shortly after exposure. Symptoms of irritation subsided, but then reappeared 6 weeks later. At that time, the subject noticed decreased vision in his left eye. When examined by a doctor, the eye had retinal lesions (one fresh and others seemingly older); the entire retina appeared clouded. The subject's vision in the left eye was poorer than in the right. Five years earlier, vision was the same in both eyes.

In the second case study, an adult male who worked in a storage area where naphthalene was used as a pesticide complained of ocular pain, conjunctivitis, and impaired vision (van der Hoeve 1906). Neither the duration nor the mode of exposure was described. The subject most likely was exposed to naphthalene vapors. When examined by a doctor, the subject was found to have retinal bleeding in the left eye and the beginnings of a cataract in both eyes.

Dermal and ocular contact with naphthalene vapors accompanied by inhalation may have contributed to the development of multiple lens opacities in 8 of 21 workers involved with a dye manufacturing process that used naphthalene as a raw material (Ghetti and Mariani 1956). Workers, who were employed at the plant for up to 5 years, melted naphthalene in open vats, resulting in high atmospheric vapor concentrations.

Mild ocular irritation was observed in the nonrinsed eyes of rabbits after instillation of naphthalene at 0.1 mg/eye (Papciak and Mallory 1990; Texaco 1985b). Observed effects were reversible within 7 days after exposure. When the eyes were rinsed with water immediately after exposure, there were no signs of irritation (Papciak and Mallory 1990).

1-Methylnaphthalene. No studies were located regarding effects to the eye in humans exposed to 1-methylnaphthalene by any route or in animals exposed to 1-methylnaphthalene by inhalation or dermal routes. There were no changes in eye tissue histopathology in male or female mice that consumed 71.6–143.7 mg/kg/day 1-methylnaphthalene in the diet for 81 weeks (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding effects to the eye in humans exposed to 2-methylnaphthalene by any route or in animals exposed to 2-methylnaphthalene by inhalation or dermal routes. Ocular tissue histopathology was not affected in mice exposed to 50.3–113.8 mg/kg/day 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1997).

2.13 ENDOCRINE

Naphthalene No studies of endocrine effects in humans exposed to naphthalene, by inhalation, oral, or dermal routes were located.

No association was observed between serum thyroid hormones and urinary levels of 1-naphthol in male partners of subfertile couples attending a fertility clinic at Massachusetts general hospital between 2000 and 2003 (Meeker et al. 2006), creatinine-adjusted urinary levels of 1- or 2-naphthol in a cohort of Chinese men (Zhu et al. 2009), or serum levels of naphthalene in a cross-sectional study of 961 elderly people in China (Han et al. 2024).

No studies of endocrine effects in animals exposed to naphthalene by oral or dermal routes were located. No effects on adrenal gland weights were reported in F344 rats exposed to naphthalene vapor up to 30 ppm for 90 days (Dodd et al. 2012). There were no changes in histopathology of adrenal glands, pancreas, parathyroid glands, pituitary gland, thyroid glands, or preputial glands in mice or rats exposed to 30 or 60 ppm (respectively) for up to 105 weeks (NTP 1992a, NTP 2000).

1-Methylnaphthalene. No studies of endocrine effects in humans exposed to 1-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed by dermal contact were located.

No effects on adrenal gland weights were reported in F344 rats exposed to 1-methylnaphthalene vapor up to 30 ppm for 13 weeks (Kim et al. 2020) or in Sprague-Dawley rats treated with up to 250 mg/kg/day 1-methylnaphthalene by gavage for at least 42 days in a combined repeated-dose and reproduction/ developmental toxicity study (NITE 2009).

2-Methylnaphthalene. No studies of endocrine effects in humans exposed to 2-methylnaphthalene by inhalation, oral, or dermal routes were located. No studies of endocrine effects in animals exposed to 2-methylnaphthalene by inhalation or dermal routes were located.

Histopathological examination of the adrenal glands showed no treatment-related changes in mice fed 2-methylnaphthalene at doses up to 113.8 mg/kg/day for 81 weeks (Murata et al. 1997).

2.14 IMMUNOLOGICAL

Naphthalene. Epidemiological studies regarding the immunological effects of naphthalene are summarized in Table 2-11. Lehmann et al. (2001) found an inverse association between air concentrations of naphthalene in children's bedrooms and interferon-γ producing CD8+ T cells but no association with sensitization to allergens or interleukin (IL)-4 producing T cells in a cohort of children in Germany. In a German cohort of newborn infants, there was a positive association between bedroom air concentrations of naphthalene and levels of IL- 4 in cord blood, but not with levels of IL-2, interferon-γ, or tumor necrosis factor α in cord blood (Lehmann et al. 2002). There was no association between urinary concentrations of 1- and 2-naphthol and serum level of IL-8 in a panel study of 36 healthy Chinese students (Zhang et al. 2023). In a cross-sectional study on U.S. Air Force personnel, air concentrations of naphthalene in the workplace were associated with increased leukocyte, neutrophil, and monocyte counts in peripheral blood (Rhodes et al. 2003). There was no observed association with workplace air naphthalene concentrations and lymphocyte counts (including total lymphocyte, T-cell, T-helper cell, T-suppressor cell, natural killer cell, and B-cells counts) in peripheral blood (Rhodes et al. 2003). A cross-sectional study in Taiwanese children found a positive association between urinary levels of 2-naphthol and asthma but no association with IgE levels or allergic rhinitis or atopic dermatitis (Lin et al. 2018). Two case-control studies examining asthma demonstrated positive associations between naphthalene levels in serum (Aslam et al. 2023) or breath (Shahrokny et al. 2023) and asthma and biomarkers of asthma (serum IgE). In a case-control study of 316 patients with systemic lupus erythematosus (SLE) and 816 controls, there was no association between serum naphthalene and SLE (Jin et al. 2024). In all of the case-control studies, exposure was measured after outcome, limiting their usefulness for hazard identification.

Table 2-11. Summary of Epidemiological Studies of Naphthalene Exposure and Immunological Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Aslam et al. 2023 Case-control, 100 adult asthma cases and 100 controls, mean ages 43 and 42 years (respectively), Pakistan	Serum naphthalene	4.48 ng/mL (mean, cases) 3.07 ng/mL (mean, controls)	Serum IgE	↑
			Resistin	↔
			Superoxide dismutase	↔

Table 2-11. Summary of Epidemiological Studies of Naphthalene Exposure and Immunological Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Jin et al. 2024 Case-control, 316 cases of SLE and 851 healthy controls, median ages 34 and 37 years (respectively), China	Serum naphthalene	1.5 and 1.8 ppb (median, active, and inactive cases, respectively) 1.5 ppb (median, controls)	SLE	↔
Lehmann et al. 2001 Cohort, 200 children 3 years of age at study initiation, Germany	Naphthalene in child's bedroom air	0.73 μg/m^3 (median)	Sensitization to egg white and/or milk allergens	↔
			IFN-γ- producing CD8+ T-cells	↓
			IL-4-producing T-cells	↔
Lehmann et al. 2002 Cohort, 85 newborn infants (42 female and 43 male), Germany	Naphthalene in infant's bedroom air during first month after birth	0.7 μg/m^3 (median)	IL-4 in cord blood	↑
			IL-2, IFN-γ, and TNF-α in cord blood	↔
Lin et al. 2018 Cross-sectional, 453 children 3 years of age, Taiwan	Urinary 2-naphthol	11.84 (3.35) μg/g creatinine (GM [GSD])	Asthma	↑
			Allergic rhinitis, atopic dermatitis	↔
			IgE	↔
Rhodes et al. 2003 Cross-sectional, 123 U.S. Air Force personnel, mean ages 24 years (high exposure) and 27 years (no/low exposure)	Naphthalene in workplace air (breathing zone)	"no/low" exposure: 2.47±1.73 μg/m^3 (mean±SD) "high" exposure: 583.23±268.89	Leukocyte, neutrophil, and monocyte counts in peripheral blood	↑
			Total lymphocyte, T-cell, T-helper cell, T-suppressor cell, natural killer cell, and B-cells counts in peripheral blood	↔
Zhang et al. 2023 Cohort, 36 students (17 male, 19 female), China	Urinary 1-naphthol	2.58–6.99 μg/g creatinine (range of medians in urban and suburban exposure periods)	IL-8 in serum	↔
	Urinary 2-naphthol	1.52–3.41 μg/g creatinine		

↑ = association with increase; ↓ = association with decrease; ↔ = no association; GM = geometric mean; GSD = geometric standard deviation; IFN = Interferon; IgE = Immunoglobulin E; IL = Interleukin; SD = standard deviation; SLE = systemic lupus erythematosus; TNF-α = tumor necrosis factor α

An enlarged spleen is a frequent consequence of naphthalene-induced hemolysis. Spleen enlargement was noted in the postmortem examination of one human subject who died after ingesting a large quantity of naphthalene (Kurz 1987) and in two human subjects dermally exposed to unspecified doses of naphthalene (Dawson et al. 1958; Schafer 1951). The spleen enlargement results from hemolysis rather than a direct effect of naphthalene on the spleen.

In animals, absolute thymus weights were reduced by ≥17% in male rats exposed to ≥10 ppm and by ≥15% in female rats exposed to ≥1 ppm for 13 weeks (Dodd et al. 2012). Relative thymus weights were not different from control at any exposure level in either sex. No exposure-related change in spleen weights was recorded in either sex up to 30 ppm (Dodd et al. 2012). In addition, there were no changes in histopathology of spleen or thymus in mice or rats exposed to 30 or 60 ppm, respectively, for up to 105 weeks (NTP 1992a, 2000).

Some studies in animals exposed orally have suggested immune system effects of naphthalene; only one of these studies (Shopp et al. 1984) examined measures of immune function. Mice given a single dose of 100 mg/kg had increased serum levels of inflammatory markers (tumor necrosis factor-α [TNF-α] and interleukin-8 [IL-8]) (Zhang et al. 2016). Mice treated with naphthalene at oral doses as high as 267 mg/kg/day for 14 days showed no effects on humoral immune responses, delayed hypersensitivity responses, bone marrow stem cell number, or bone marrow deoxyribonucleic acid (DNA) synthesis (Shopp et al. 1984). Mitogenic responses to concanavalin A (but not to lipopolysaccharide) were reduced in high dose females only. None of these effects were noted at doses of 27 or 53 mg/kg/day. At naphthalene doses of 133 mg/kg/day for 13 weeks, naphthalene had no effect on immune function in mice (Shopp et al. 1984). After 14 days, thymus weights were reduced approximately 30% in male mice exposed to 267 mg/kg/day, but no differences were seen with a dose of 133 mg/kg/day at 13 weeks (Shopp et al. 1984). Spleen weights were reduced approximately 20% in female mice exposed to 267 mg/kg/day naphthalene for 14 days and 25% in females exposed to 133 mg/kg/day for 13 weeks (Shopp et al. 1984). There was lymphoid depletion of the thymus in 2 of 10 female rats exposed to 400 mg/kg/day naphthalene for 13 weeks (NTP 1980b).

In animals, dermal application of pure naphthalene (1,000 mg/kg) 1 time/week for 3 weeks did not result in delayed hypersensitivity reactions in guinea pigs (Papciak and Mallory 1990; Texaco 1985c).

1-Methylnaphthalene. No studies were identified regarding effects on the immune system in humans exposed to 1-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed dermally.

No changes in thymus or spleen weights or histopathology were observed when rats were exposed to up to 30 ppm 1-methylnaphthalene for 13 weeks (Kim et al. 2020). There were no changes in white blood cell counts, thymus or spleen weights, or histopathology in rats administered 250 mg/kg/day 1-methylnaphthalene for at least 42 days (NITE 2009). Monocyte concentrations were significantly elevated in male and female mice exposed to 71.6–143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The increase in monocyte counts appeared to be dose-related. The study authors hypothesized that these changes may have been a physiological response to the pulmonary alveolar proteinosis seen in the exposed animals. There were no changes in spleen or thymus weights, and the histopathology of these tissues was normal.

2-Methylnaphthalene. No studies were identified regarding effects on the immune system in humans exposed to 2-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed dermally.

Wistar rats exposed to up to 8.77 ppm 2-methylnaphthalene for 6 hours/day, 5 days/week for 4 weeks had no changes in white blood cell parameters (Świercz et al. 2011). In B6C3F1 mice administered 2-methyl-naphthalene at doses up to 113.8 mg/kg/day for 81 weeks, neutrophils were decreased, and lymphocytes were increased compared with control values, but neither the doses at which these changes occurred, nor the magnitude of these changes, was specified in the study report (Murata et al. 1997). Histologic examination revealed no exposure-related lesions in the spleen or thymus.

2.15 NEUROLOGICAL

Naphthalene. Infants are prone to permanent neurological damage (kernicterus) as a consequence of the jaundice that results from naphthalene-induced hemolysis. Bilirubin is absorbed by vulnerable brain cells, and this leads to convulsions and sometimes death. Survivors often suffer from motor disturbances and mental retardation (McMurray 1977). Kernicterus was diagnosed in 8 of 21 Greek infants that experienced hemolysis as a result of naphthalene exposure (Valaes et al. 1963). Two of the eight died. One of the infants that died had no G6PD enzyme activity and the other had intermediate activity. Two of the infants were normal with regard to the G6PD trait. Of the remaining infants, three had no G6PD activity and the fourth had intermediate activity. Brain damage seldom occurs in adults as a consequence of jaundice (McMurray 1977).

Nausea, headache, malaise, and confusion were reported in several individuals (children and adults) exposed to large numbers of mothballs in their homes (Linick 1983). Actual levels and duration of exposure were unknown, although a concentration of 20 ppb was measured in one of the affected residences.

In an epidemiology study in U.S. Air Force personnel exposed occupationally to naphthalene, no association was observed between urinary levels of 1- or 2-naphthol and neurocognitive performance (Heaton et al. 2017). No association was observed between $PM_{2.5}$-bound-naphthalene concentration and schizophrenia symptom scores in a repeated-measures study of 266 schizophrenic patients in China (Liu et al. 2024).

In animals, clinical signs of neurotoxicity have been reported after oral exposure, but not after inhalation exposure. No sensitive tests of neurotoxicity have been conducted on naphthalene in animals. No changes in brain weights were recorded in rats exposed to up to 30 ppm naphthalene for 13 weeks (Dodd et al. 2012). No treatment-related gross or histopathological lesions of the brain were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively. Clinical observations (made twice daily in these studies) revealed no gross behavioral changes except that exposed mice tended to huddle together in cage corners during exposure periods.

The neurologic symptoms of naphthalene ingestion reported in human case studies include confusion (Ojwang et al. 1985), altered sensorium (Gupta et al. 1979), listlessness and lethargy (Bregman 1954; Chusid and Fried 1955; Kurz 1987; MacGregor 1954; Zuelzer and Apt 1949), and vertigo (Gidron and Leurer 1956). Muscle twitching, convulsions (Kurz 1987; Zuelzer and Apt 1949), decreased responses to painful stimuli, and coma occurred prior to death in individuals who ingested naphthalene (Gupta et al. 1979; Kurz 1987). At autopsy, the brain has in some cases appeared edematous (Gupta et al. 1979; Kurz 1987), with separation of neural fibers and swelling of myelin sheaths being noted histologically (Gupta et al. 1979). The neurologic symptomatology could have resulted from the cerebral edema, which was probably secondary to acute hemolysis.

Dose-related clinical signs of toxicity were apparent in pregnant Sprague-Dawley rats exposed to doses of 50, 150, or 450 mg/kg/day naphthalene for 10 days during organogenesis. Slow respiration and lethargy were observed in a large percentage of the exposed animals. Some rats were dazed, had periods of apnea, or were unable to move after exposure. In the lowest dose group, 73% of the animals were affected on

the first day of dosing. In the two higher dose groups, over 90% of the rats were affected (NTP 1991). The animals in the 50 mg/kg/day group acclimatized quickly. Symptoms were only apparent during the first 2 days of dosing. Clinical signs of toxicity persisted for longer periods in the higher dose groups and were accompanied by decreased body weight gains (31 and 53% decreased at 150 and 450 mg/kg/day, respectively compared with control). It is not known if the observed clinical signs were due to treatment-related effects on the nervous system or were the indirect consequence of severe systemic toxicity, as indicated by the dramatic decreases in body weight gain. Transient clinical signs of neurotoxicity (hunched posture and lethargy) were observed in F344 rats following daily gavage administration of 400 mg/kg/day, but not 200 mg/kg/day (NTP 1980b). In mice, lethargy was observed transiently between weeks 3 and 5 in the highest dose group, 200 mg/kg/day (NTP 1980a). The lack of clinical signs at lower doses in the subchronic study of F344 rats suggests that pregnant animals may be more susceptible to the effects of naphthalene than nonpregnant animals. Alternatively, the difference may stem from greater sensitivity of Sprague-Dawley rats relative to F344 rats.

In rats exposed to 87.5 mg/kg/day, 3 days/week for 7 weeks, neurological tests showed inhibition of the withdrawal reflex (measured as significantly increased temporal summation of subthreshold impulses) (Katsnelson et al. 2014). Structural changes (observed via transmission electron microscopy) were observed in the brains of male Sprague-Dawley rats given naphthalene doses as low as 200 mg/kg/day for 28 days (Angu Bala Ganesh et al. 2024). These changes included dark cytoplasmic inclusions, reduced number of and/or damage to the presynaptic vesicles, and degradation and/or abnormal synapses; however, the changes were reported qualitatively without incidence or severity, precluding identification of effect levels. There were no changes in the brain weights in mice exposed to naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the brain were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b).

1-Methylnaphthalene. No studies were located regarding neurological effects in humans exposed to 1-methylnaphthalene by any route or in animals exposed by dermal application.

In male Wistar rats, decreased sensitivity to pain occurred after 4-hour inhalation exposures to 253 or 407 mg/m^3 1-methylnaphthalene (44 or 70 ppm), but not after exposure to 152 mg/m^3 (26 ppm) 1-methyl-naphthalene (Korsak et al. 1998). Decreased sensitivity to pain was measured as a decreased time to begin licking of the paws after being placed on a hot plate at 54.5°C. The ability of exposed rats to balance on a rotating rod (rotarod performance), however, was not affected by any of these exposure

conditions (Korsak et al. 1998). No neurological effects were observed in a functional observational battery (FOB) examination in rats administered 1-methylnaphthalene by gavage at doses up to 250 mg/kg/day for at least 42 days (NITE 2009). There were no biologically significant changes in brain weights in mice fed up to 143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding neurological effects in humans exposed to 2-methylnaphthalene by any route or in animals exposed by dermal application.

As with 1-methylnaphthalene, decreased sensitivity to pain was observed in male Wistar rats after 4-hour inhalation exposures to 352 or 525 mg/m^3 2-methylnaphthalene (61 or 90 ppm), but not 229 mg/m^3 (39 ppm) (Korsak et al. 1998). Rotarod performance was not affected at any exposure concentration (Korsak et al. 1998). There were no changes to brain weight or histopathology in mice fed 54.3 or 113.8 mg/kg/day 2-methylnaphthalene for 81 weeks (Murata et al. 1997).

2.16 REPRODUCTIVE

Naphthalene. Epidemiology studies of reproductive endpoints in humans exposed to naphthalene are summarized in Table 2-12. In a cohort of male college students in China, there was a positive association between concentrations of naphthalene bound to airborne particulate matter ($PM_{2.5}$) and sperm motility and serum levels of estradiol (Chen et al. 2021). Normal sperm morphology was inversely associated with particle-bound naphthalene. In the cohort, no association was observed with semen volume, sperm concentration, sperm count, DNA stainability, DNA fragmentation index, or serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, progesterone, or testosterone (Chen et al. 2021). There was an inverse association between sperm concentration and urinary levels of 1-naphthol and the sum of 1- and 2-naphthol, as well as an inverse association between sperm count and urinary 1-naphthol in a cohort of adult male partners of subfertile couples in China (Yang et al. 2017). There was no association between urinary 2-naphthol levels and sperm count, concentration, morphology, motility, or semen volume (Yang et al. 2017). Positive associations between urinary levels of 1-naphthol and odds of decreased sperm concentration (< 20 million/mL), motility (<50% motile), and normal morphology (<4% normal) was found in males of adult subfertile couples from two cross-sectional studies (Meeker et al. 2004a, 2004b). Urinary 1-naphthol levels were also associated with increased DNA damage in sperm (Meeker et al. 2004a, 2004b). Two other cross-sectional studies of U.S. adult males conducted by these investigators showed that urinary levels of 1-naphthol were inversely associated with serum levels of testosterone and estradiol (Meeker et al. 2006, 2008). No associations were observed with serum FSH,

LH, inhibin B, sex hormone binding globulin (SHBG), free androgen binding index, prolactin, or estradiol (Meeker et al. 2006, 2008). In a cross-sectional study of Chinese men, Xia et al. (2009) found no associations between creatinine-adjusted urinary levels of 1- or 2-naphthol and semen volume, sperm concentrations, sperm number per ejaculum, or sperm motility. In a case control study of Indian men, higher seminal plasma naphthalene levels were observed in patients with idiopathic male infertility compared with fertile semen donors; the study authors did not conduct more rigorous analysis or consideration of potential confounders (Nayak et al. 2023). An inverse association between umbilical cord serum naphthalene and umbilical cord blood serum anti-mullerian hormone was observed in a Chinese cohort of mother-child pairs, but there was no association between umbilical cord serum naphthalene and umbilical cord blood serum FSH, LH, testosterone, or estradiol (Yin et al. 2017). A case-control study of women in China with premature ovarian failure suggested a positive association between lipid-adjusted serum levels of naphthalene and serum levels of FSH, LH (Ye et al. 2020). An association between premature ovarian failure and odds of higher naphthalene concentrations was also reported in this study; however, as blood levels were measured after outcome, the temporal relationship between exposure and outcome is uncertain.

Table 2-12. Summary of Epidemiological Studies of Naphthalene Exposure and Reproductive Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Chen et al. 2021 Cohort, 656 male college students (median age 20 years), China	$PM_{2.5}$ particle-bound naphthalene	0.653 ng/m^3 (mean in 2013; not detected in 2014 samples)	Sperm motility	↑
			Normal sperm morphology	↓
			Sperm concentration, count, DNA stainability, and DNA fragmentation index	↔
			Semen volume	↔
			Serum estradiol	↑
			Serum FSH, LH, prolactin, progesterone, and testosterone	↔
Meeker et al. 2004a Cross-sectional, 272 adult male partners in subfertile couples, United States	Urinary 1-naphthol	3.19 µg/L (median, adjusted for specific gravity)	Odds of sperm concentration <20 million/mL, <50% motile, and <4% normal	↑
Meeker et al. 2004b Cross-sectional, 260 adult male partners in subfertile couples (mean age 36.1 years), United States	Urinary 1-naphthol	2.75 µg/L (median, adjusted for specific gravity)	DNA damage in sperm	↑

Table 2-12. Summary of Epidemiological Studies of Naphthalene Exposure and Reproductive Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Meeker et al. 2006 Cross-sectional, 322 adult males (mean age 36.1 years), United States	Urinary 1-naphthol	3.01 µg/L (geometric mean, adjusted for specific gravity)	Serum testosterone	↓
			Serum FSH, LH, inhibin B, SHBG, and free androgen index	↔
Meeker et al. 2008 Cross-sectional, 322 adult males, United States	Urinary 1-naphthol	3.23 µg/L (geometric mean, adjusted for specific gravity)	Serum estradiol	↓
			Serum prolactin	↔
Xia et al. 2009 Cross-sectional, 542 infertile men and 176 control men, China	Creatinine-adjusted urinary 1-naphthol	2.13 (1.96, 2.32) (µg/g): (geometric mean [95% CI])	Semen volume, sperm concentration, sperm number per ejaculum, and sperm motility	↔
	2-naphthol:	4.26 (3.94, 4.62) (µg/g)		↔
Yang et al. 2017 Cohort, 933 male partners in subfertile couples, China	Urinary 1-naphthol	4.43± 6.16 µg/L (mean±SD)	Sperm count and sperm concentration	↓
	Urinary 2-naphthol	9.70±8.93 µg/L	Sperm count, sperm concentration, sperm morphology, sperm motility, and semen volume	↔
	Sum urinary naphthols	14.13± 12.81 µg/L	Sperm concentration	↓
Ye et al. 2020 Case-control, 157 women with premature ovarian failure (mean age 34 years) and 217 healthy women (mean age 33 years), China	Lipid-adjusted serum naphthalene	16.04±20.91 µg/g lipid (mean±SD) (cases) 16.04±20.91 µg/g (controls)	Premature ovarian failure	↑
			Serum FSH	↑
			Serum LH	↑
			Serum anti-mullerian hormone	↓
Yin et al. 2017 Cohort, 109 mother-child pairs, China	Umbilical cord serum naphthalene	30.5 (22.1–40.6) ng/g lipid (median [IQR])	Umbilical cord blood serum anti-mullerian hormone	↓
			Umbilical cord blood serum testosterone, estradiol, FSH, and LH	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; CI = confidence interval; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; IQR = interquartile range; LH = luteinizing hormone; $PM_{2.5}$ = particulate matter ≤2.5 µm in diameter; SD = standard deviation; SHBG = sex hormone-binding globulin

Animal studies have not suggested that reproductive organs are a sensitive target of naphthalene exposure. In rats exposed to ≥10 ppm for 13 weeks, absolute testes weights were decreased, but no difference was observed in testes weights adjusted for body weights (Dodd et al. 2012). No differences from control were seen in the weights of female reproductive organs (Dodd et al. 2012). Histological

examination did not reveal damage to male or female reproductive organs in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to 30 or 60 ppm, respectively.

No treatment-related effects were reported on testicular weights of mice administered naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the testes were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b).

1-Methylnaphthalene. No studies were located regarding reproductive effects in humans exposed to 1-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed dermally.

No changes to the weights of male and female reproductive organs and no gross or histopathological lesions of the epididymides, testes, seminal vesicles, ovaries, or uterus were observed in mice exposed to up to 30 ppm 1-methylnaphthalene (Kim et al. 2020). There were no effects on reproduction in rats administered up to 250 mg/kg/day 1-methylnaphthalene throughout mating, gestation, and lactation in a combined repeat-dose and reproduction/developmental toxicity study (NITE 2009). No gross or histopathological lesions of the testes, seminal vesicles, ovaries, uterus, or vagina were observed in mice exposed to 1-methylnaphthalene doses as high as 143.7 mg/kg/day in the diet for 81 weeks (Murata et al. 1993).

2-Methylnaphthalene. No studies were located regarding reproductive effects in humans exposed to 2-methylnaphthalene by inhalation, oral, or dermal routes or in animals exposed dermally.

There were no changes in testes or ovary weights in rats exposed to up to 8.77 ppm 2-methylnaphthalene for 6 hours/day, 5 days/week for 4 weeks (Świercz et al. 2011). Chronic exposure of mice to 2-methyl-naphthalene doses as high as 113.8 mg/kg/day via diet did not result in gross or histopathological lesions of the testes, seminal vesicles, ovaries, uterus, or vagina (Murata et al. 1997).

2.17 DEVELOPMENTAL

Naphthalene. In humans, transplacental exposure of the fetus to naphthalene that had been ingested by the mother resulted in neonatal (and presumably fetal) hemolytic anemia (Anziulewicz et al. 1959; Sahni et al. 2019; Shafer et al. 2020; Zinkham and Childs 1957, 1958). No estimates of dose or duration were

available, although in one case, naphthalene consumption was described as being most pronounced during the last trimester (Zinkham and Childs 1958).

Developmental effects of naphthalene have been evaluated in human populations and in animals. Epidemiological studies of developmental endpoints in humans exposed to naphthalene are summarized in Table 2-13. These studies of developmental effects were conducted in the general population generally using measurements of naphthalene and metabolites in physiological fluids or tissues of mothers and children. In the general population, the route of exposure is unknown. No association was found between birth weights and naphthalene in placental tissue, cord serum, or maternal serum in multiple cross-sectional and cohort studies in pregnant women from Canada, India, and Iran (Agarwal et al. 2022; Bushnik et al. 2020; Dehghani et al. 2022; Khalili Doroodzani et al. 2021). There were no associations between serum naphthalene and birth length, head circumference, or Apgar score in a cohort of Iranian pregnant women (Dehghani et al. 2022). Naphthalene metabolites in urine were associated with body mass index (BMI), waist circumference, waist to height ratio, and central obesity in a cross-sectional study of children in Canada (Bushnik et al. 2020). In a cross-sectional study of Iranian pregnant women, naphthalene in cord serum was inversely associated with birth length (Khalili Doroodzani et al. 2021). A cross-sectional study in Chinese pregnant women found a positive association between urinary 2-naphthol and cephalization index but an inverse association with birth weight (Nie et al. 2018). No association was observed with birth length, head circumference, or ponderal incidence. In a cross-sectional study in children in the United States, there was a positive association between naphthalene metabolites in urine and BMI z score, waist circumference, and obesity, but no association with the overweight category (Scinicariello and Buser 2014). No reason was given to explain why there was no significant association with the overweight category despite the significant association with the obesity category, but it may be due to lower statistical power: there were fewer children in the overweight category compared with the obese category in this study.

Table 2-13. Summary of Epidemiological Studies of Naphthalene Exposure and Developmental Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Agarwal et al. 2022 Cross-sectional, 110 pregnant women aged 18–40 years, India	Naphthalene in placental tissue	0.54±1.62 µg/L (mean±SD)	Birth weight	↔

Table 2-13. Summary of Epidemiological Studies of Naphthalene Exposure and Developmental Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Bushnik et al. 2020 Cross-sectional, 3667 children 3 to 18 years old in Canadian Health Measures Survey, Canada	Naphthalene metabolites in urine	5.21 µg/L (mean)	BMI	↑
			Waste circumference	↑
			Waist-to height ratio	↑
			Central obesity	↑
Dehghani et al. 2022 Birth cohort, 126 pregnant women aged 18–44 years, Iran	Naphthalene in maternal serum	327.91 ng/g lipid (mean)	Birth weight, length, head circumference, and Apgar score	↔
Huang et al. 2023 Case control, 413 cases with unexplained recurrent spontaneous abortions and 434 parous controls, China	Maternal urinary 1-naphthol	2.83 µg/g creatinine (mean, cases) 4.61 µg/g creatinine (mean, controls)	Spontaneous abortion	↔
	Maternal urinary 2-naphthol	7.00 µg/g creatinine (mean, cases) 11.8 µg/g creatinine (mean, controls)		↓
John et al. 2022a Cohort, 358 girls aged 6–16 years followed for at least 7 years, California	Urinary 1-naphthol	678–954 ng/L (range of means across developmental stages, excluding girls with carbaryl exposure)	Earlier breast development	↔
			Pubic hair development	↔
			Age at menarche	↔
			Pubertal tempo[a]	↔
	Urinary 2-naphthol	2,830–3,840 ng/L (range of means across developmental stages)	Earlier breast development	↔
			Pubic hair development	↔
			Age at menarche	↔
			Pubertal tempo[a]	↔
Khalili Doroodzani et al. 2021 Cross-sectional, 199 pregnant women, average age 39 years, Iran	Naphthalene in cord serum	66.17 µg/L (mean, petrochemical area) 61.97 µg/L (mean, urban area)	Birth length	↓
			Birth weight and head circumference	↔
	Naphthalene in maternal serum	96.18 µg/L (mean, petrochemical area)	Birth weight, length, and head circumference	↔
Nie et al. 2018 Cross-sectional 263 pregnant women, mean age 27.3 years, China	2-naphthol in maternal urine	6.34 µg/g creatinine (median)	Birth weight	↓
			Birth length	↔
			Birth head circumference	↔
			Cephalization index	↑
			Ponderal index	↔
Scinicariello and Buser 2014 Cross-sectional, 3,189 children 6–19 years old, participants in NHANES 2001–2006, United States	Naphthalene metabolites in urine	1-naphthol: 1,604.55 ng/L (geometric mean) 2-naphthol: 2,530.30 ng/L	BMI z-score	↑
			Waist circumference	↑
			Overweight	↔
			Obesity	↑

Table 2-13. Summary of Epidemiological Studies of Naphthalene Exposure and Developmental Effects

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Sherris et al. 2024 Cohort, 1,081 parent-child pairs followed for at least 8 years after birth, United States	Maternal urinary 1-naphthol during pregnancy	0.67 ng/mL (median, specific gravity-adjusted)	Child asthma at ages 8–9 years	↓
			Child wheezing ages 4–9 years	↔
	Maternal urinary 2-naphthol during pregnancy	3.85 ng/mL (median, specific gravity-adjusted)	Child asthma at ages 8–9 years	↔
			Child wheezing ages 4–9 years	↔
Wang et al. 2014 Cross-sectional, 203 children aged 4–5 years, China	Naphthalene in dust	0.2 µg/g (median)	Child Behavior Checklist, Gesell Development Inventory, Internalizing Problems score	↑
			Somatic, Anxious, Withdrawn, Social, Thought, Attention, Compulsive, Aggressive, Externalizing, and Total Problems scores	↔
Wanying et al. 2023 Cross-sectional, 450 mother child pairs, Iran	Modeled concentration of pm-bound naphthalene at residence	NR	Umbilical cord serum ALP	↑
			Umbilical cord serum AST, ALT, and GGT	↔

[a]Pubertal tempo was defined as the time between onset of breast development and age at menarche.

↑ = association with increase; ↓ = association with decrease; ↔ = no association; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; GGT = γ glutamyl transferase; NHANES = National Health and Nutrition Examination Survey; NR = not reported; SD = standard deviation

A cross-sectional study in children in China investigating postnatal exposure to naphthalene in house dust and behavior and neurodevelopment found a positive association between naphthalene in dust and "internalizing problems" score using the Child Behavior Checklist (CBCL) and Gesell Development Inventory for developmental quotients and behavioral problems scoring. There was no association with somatic, anxious, withdrawn, social, thought, attention, compulsive, aggressive, externalizing, or total problems scores (Wang et al. 2014). In a birth cohort, no association between prenatal naphthalene exposure (measured as maternal urinary metabolites) and child asthma or wheezing up to age 9 years was observed (Sherris et al. 2024). Urinary naphthalene metabolites were not associated with increased risk of unexplained recurrent spontaneous abortion in a case-control study in China (Huang et al. 2023). In a

California prospective cohort study, there was no association between urinary naphthalene metabolite levels and female pubertal developmental milestones (John et al. 2022a). Finally, a cross-sectional study evaluating the relationship between umbilical cord serum liver enzymes and maternal exposure to particulate-bound naphthalene identified an association with umbilical cord serum ALP, but no association with other enzymes (AST, ALT, or γ-glutamyl transferase [GGT]) (Wanying et al. 2023).

Oral exposures of pregnant rabbits to naphthalene at dosages up to 400 mg/kg/day in methylcellulose during GDs 6–18, resulted in no apparent adverse developmental effects (Texaco 1986); however, naphthalene administered to pregnant mice at a dosage of 300 mg/kg/day in corn oil during GDs 7–14 resulted in a decrease in the number of live pups per litter (Plasterer et al. 1985). It is not clear whether the observed differences in response are attributable to species differences or differences in absorption of naphthalene when it is administered in corn oil compared with as a suspension in methyl cellulose. No congenital abnormalities were observed in offspring of pregnant animals after oral administration of naphthalene in either study (Plasterer et al. 1985; Texaco 1986). Similarly, naphthalene was not teratogenic in rats at doses up to 450 mg/kg/day during GDs 6–15 (NTP 1991). However, there was a slight, but dose-related, increase in fused sternebrae in female pups of rabbits administered doses of 20–120 mg/kg/day on GDs 6–19 (NTP 1992b). These effects were seen in 2 of 21 litters at 80 mg/kg/day and 3 of 20 litters at 120 mg/kg/day. No other developmental effects were noted in this study.

1-Methylnaphthalene. No studies were located that evaluated developmental endpoints in humans after inhalation, oral, or dermal exposure to 1-methylnaphthalene or in animals after inhalation or dermal exposure.

There were no developmental effects in the offspring of rats administered up to 250 mg/kg/day 1-methylnaphthalene throughout mating, gestation, and lactation in a combined repeat-dose and reproduction/development screening study (NITE 2009).

2-Methylnaphthalene. No studies were located that evaluated developmental endpoints in humans or animals after inhalation, oral, or dermal exposure to 2-methylnaphthalene.

2.18 OTHER NONCANCER

Naphthalene. Several humans who consumed naphthalene experienced elevated body temperatures, which may have been related to their hemolytic crisis (Chusid and Fried 1955; Gidron and Leurer 1956;

Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). However, in some situations, bacterial infections rather than hemolysis may have been the cause of the fever (Kurz 1987; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Zuelzer and Apt 1949).

Two meta-analyses and two cohort studies have examined an assortment of other noncancer endpoints in humans exposed to naphthalene. In a meta-analysis with inclusion of six cross-sectional studies with a total of 24,406 participants, there was a positive association between urinary 2-naphthol levels and odds of diabetes; no significant association was observed for 1-naphthol levels (Khosravipour and Khosravipour 2020). Another meta-analysis including seven-cross sectional studies found an association between urinary naphthalene metabolites (1- and 2-naphthol) and type 2 diabetes (pooled OR 1.52; 95% CI 1.19–1.94) (Wang et al. 2022c). Associations between urinary 1- and 2-naphthol and parameters of metabolic syndrome including increased diastolic and systolic blood pressure, increased levels of triglycerides, and increased waist circumference were reported in a cohort study of Iranian adults (Shahsavani et al. 2022). In a cohort of elderly adults, urinary levels of 2-naphthol and total number of disabilities were positively associated when adjusted for covariates (Chen et al. 2019).

No studies were located that evaluated other noncancer endpoints in animals after inhalation, oral, or dermal exposure to naphthalene.

1- and 2-Methylnaphthalene. No studies were located that evaluated other noncancer endpoints in humans or animals after inhalation, oral, or dermal exposure to 1- or 2-methylnaphthalene.

2.19 CANCER

Naphthalene. A case-control study in Spain reported a positive association between colorectal cancer and residential proximity to naphthalene-emitting industries (García-Pérez et al. 2020). A cohort study that followed 48,665 women in California for 10 years found an association (hazard ratio [HR] 1.11; 95% CI 1.02–2.22) between modeled air concentrations of naphthalene and breast cancer (Heck et al. 2024). Exposures in this study were estimated at the census tract level, raising the potential for exposure misclassification. In addition, several other hazardous air pollutants were also associated with increased breast cancer risk, and the analysis did not account for co-exposure to these other chemicals.

In animals, inhalation exposure to naphthalene (6 hours/day) has been associated with: (1) increased incidences of nasal tumors in F344/N rats of both sexes following 2 years of exposure (Abdo et al. 2001;

NTP 2000); (2) increased incidences of female B6C3F1 mice, but not male mice, with lung tumors following 2 years of exposure (NTP 1992a); and (3) increased number of lung tumors per tumor-bearing A/J strain mice following 6 months of exposure (Adkins et al. 1986).

In F344/N rats, incidences of nasal respiratory epithelial adenomas were statistically significantly elevated, compared with controls, in males exposed to 0, 10, 30, or 60 ppm naphthalene (0/49, 6/49, 8/48, and 15/48, respectively), but not in females (0/49, 0/49, 4/49, and 2/49, respectively) (Abdo et al. 2001; NTP 2000). Respective incidences for olfactory epithelial neuroblastoma were 0/49, 0/49, 4/48, and 3/48 in male rats, and 0/49, 2/49, 4/48, and 12/49 in female rats. Both tumor types are rare in NTP control F344/N rats (NTP 2000). For example, neither tumor type was observed in 299 control male rats given NTP-2000 feed or 1,048 control male rats given NIH-07 feed. NTP (2000) concluded that there was clear evidence of carcinogenic activity of naphthalene in male and female F344/N rats based on increased incidences of nasal respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose. Nearly all rats in all exposure groups showed nonneoplastic nasal lesions in both olfactory and respiratory epithelia, including atypical hyperplasia in olfactory epithelium, hyaline degeneration in olfactory and respiratory epithelia, and Bowman's gland hyperplasia.

In B6C3F1 mice, a statistically significant increased incidence of alveolar/bronchiolar adenomas and carcinoma was found in 30-ppm females, but not in 10-ppm females or in males (females: 5/69, 2/65, and 29/135; males: 7/70, 17/69, and 31/135 at 0, 10, and 30 ppm, respectively) (NTP 1992a). Although Fisher Exact tests indicated that incidences in both exposed male groups and the high-dose female group were significantly increased compared with control groups, logistic regression analysis, which modeled tumor incidence as a function of dose and exposure time, indicated that only the incidence in the 30-ppm female group was elevated compared with controls. The response was predominantly benign; only one female mouse in the 30-ppm group developed a carcinoma. Exposed mice of both sexes also showed increased incidences of chronic lung inflammation (males: 0/70, 21/69, and 56/135; females: 3/69, 13/65, and 52/135 at 0, 10, and 30 ppm, respectively). Nonneoplastic nasal lesions were found in nearly all exposed mice, but no nasal tumors developed. On the basis of this analysis, NTP (1992a) determined that there was some evidence of naphthalene carcinogenicity in female mice, but no evidence of carcinogenicity in male mice in this study.

In a 6-month study, there was a statistically significant increase in the number of tumors per tumor-bearing mouse, but not in the number of mice with pulmonary adenomas after exposure to 10 or 30 ppm naphthalene vapors (Adkins et al. 1986). However, the incidence of adenomas in the control group for

this experiment was significantly lower than the pooled incidence observed in the control groups of eight concurrently conducted 6-month studies, and the difference in tumor incidence was not significantly greater than that of the historic controls.

In a 2-year feeding study of rats receiving naphthalene at about 41 mg/kg/day, no tumors were reported (Schmahl 1955). Specific details pertaining to the tissues examined were not provided.

Mechanisms. The mechanisms by which naphthalene causes neoplastic lesions in the respiratory tracts of rodents are incompletely understood, but are thought to involve reactive metabolites of naphthalene, including 1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and possibly 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene. However, it is unknown whether the naphthalene-induced neoplastic lesions found in mice and rats are produced via a genotoxic mode of action or a nongenotoxic mode requiring tissue damage and regenerative responses as precursor events. The general sites of neoplastic lesions, the nose in rats (nasal respiratory epithelial adenomas and olfactory epithelial neuroblastomas) and the lungs in mice (adenomas), show some correspondence (but not complete) with the general sites of nonneoplastic lesions, and may share some of the mechanistic steps outlined for nonneoplastic respiratory tract effects (see Section 2.4). Results from genotoxicity tests for naphthalene suggest that while naphthalene itself is not genotoxic, its metabolites have yielded positive results in studies of gene mutation, sister chromatid exchanges, and DNA damage (see Section 2.20). In addition, exposure of mouse and primate lung explants to naphthalene has resulted in DNA adducts (Buchholz et al. 2019; Carratt et al. 2019a). As the adducts were not further characterized and were identified in explants rather than whole animals, their mechanistic relevance to cancer has not been determined.

1-Methylnaphthalene. Long-term exposure (81 weeks) of mice to 71.6 or 140.2 mg/kg/day 1-methyl-naphthalene in the diet was associated with statistically significant increases in bronchiolar/alveolar adenomas in males, but not in females (Murata et al. 1993). Incidences for mice with lung adenomas were 2/49, 13/50, and 12/50, respectively, for control through high-dose male mice, and 4/50, 2/50, and 4/49, respectively, for female mice. Combined incidence for mice with lung adenomas or adenocarcinomas were 2/49, 13/50, and 15/50, respectively, for male mice, and 5/50, 2/50, and 5/50, respectively, for female mice.

2-Methylnaphthalene. In mice exposed to 2-methylnaphthalene in the diet for 81 weeks, incidences for mice with lung adenomas were 2/49, 9/49, and 5/49 in males that ingested 0, 54.3, or 113.8 mg/kg/day,

respectively; and 4/50, 4/49, and 5/48 in females that ingested 0, 50.3, or 107.6 mg/kg/day, respectively (Murata et al. 1997). In males, combined adenomas and adenocarcinomas of the lung incidences were 2/49, 10/49, and 6/49 at 0, 54.3, or 113.8 mg/kg/day, respectively, and only the incidence in the 54.3-mg/kg/day group was statistically significant.

2.20 GENOTOXICITY

Naphthalene and its Metabolites. Naphthalene has been extensively tested for genotoxicity *in vitro*, with more limited testing *in vivo*. *In vitro* studies of genotoxicity are summarized for naphthalene (Table 2-14) and its metabolites (Table 2-15) in bacterial mutation assays and *in vitro* eukaryotic gene mutation, cytogenetic, or DNA damage assays. Tables 2-16 (naphthalene) and 2-17 (naphthalene metabolites) summarize data for *in vivo* eukaryotic gene mutation, cytogenetic, or DNA damage assays in humans and animals.

Table 2-14. Genotoxicity of Naphthalene *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium	Gene mutation	–	–	Bos et al. 1988; Connor et al. 1985;Florin et al. 1980; Gatehouse 1980; Godek et al. 1985; Kaden et al. 1979; McCann et al. 1975; Mortelmans et al. 1986; Narbonne et al. 1987; NTP 1992a; Sakai et al. 1985
S. typhimurium	DNA damage (SOS uma test)	–	–	Nakamura et al. 1987
Escherichia coli	DNA damage (SOS)	–	–	Mamber et al. 1984; Mersch-Sundermann et al. 1993
E. coli	DNA damage (Poly-A)	–	–	Mamber et al. 1983
Vibrio fischeri M169	Gene mutation (mutatox)	+	–	Arfsten et al. 1994
Human lymphoblastoid (MCL-5) cells	Gene mutation	NT	–	Sasaki et al. 1997
Chinese hamster ovary cells	Chromosomal aberrations	+	–	NTP 1992a
Preimplantation whole mouse embryos	Chromosomal aberrations	+	+	Gollahon 1990

Table 2-14. Genotoxicity of Naphthalene *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Human lymphoblasts (TK6)	Micronuclei	+	NT	Recio et al. 2012
Human HepaRG cells	Micronuclei	NT	–	Recio et al. 2023
Human mononuclear leukocytes	Sister chromatid exchange	–	NT	Tingle et al. 1993; Wilson et al. 1995
Chinese hamster ovary cells	Sister chromatid exchange	+/-	+	NTP 1992a
Rat primary hepatocytes	DNA damage	NT	–	Sina et al. 1983
V79 Chinese hamster lung fibroblasts	DNA damage	–	–	Platt et al. 2008
Human lymphocytes	DNA damage	NT	+	Kapuci et al. 2014
Human HepaRG cells	DNA damage	NT	–	Recio et al. 2023
Human hepatoblastoma cells (Hep3B), human epithelial colorectal adenocarcinoma cells (LS-174T), human bronchioalveolar carcinoma (NCI-H358)	DNA damage	NT	–	Tomasetig et al. 2020
Rat primary hepatocytes	Unscheduled DNA synthesis	NT	–	Barfknecht et al. 1985
Fischer rat embryo cells (F1706P96)	Cell transformation	NT	–	Freeman et al. 1973
Syrian baby hamster kidney cells (BHK-21C13)	Cell transformation	NT	–	Purchase et al. 1978
Mouse (BALB/c) whole mammary gland cultures	Cell transformation	NT	–	Tonelli et al. 1979
Mouse BALB/c 3T3 cells	Cell transformation	NT	–	Rundell et al. 1983
Human diploid fibroblasts (WI-38)	Cell transformation	NT	–	Purchase et al. 1978
v-Ha-ras-transfected mouse BALB/c 3T3 cell line (Bhas 42)	Cell transformation	NT	–	Asada et al. 2005

+ = positive results; – = negative results; +/– = equivocal results; DNA = deoxyribonucleic acid; NT = not tested

Table 2-15. Genotoxicity of Naphthalene Metabolites *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference	Metabolite
Salmonella typhimurium	Gene mutation	–	–	McCann et al. 1975; Narbonne et al. 1987	1-naphthol

Table 2-15. Genotoxicity of Naphthalene Metabolites *In Vitro*

Species (test system)	Endpoint	Results		Reference	Metabolite
		Activation			
		With	Without		
S. typhimurium	Gene mutation	–	–	Sakai et al. 1985	1,4-naphthoquinone
S. typhimurium	Gene mutation	+	+	Flowers-Geary et al. 1996	1,2-naphthoquinone
Human lymphoblastoid (MCL-5) cells	Gene mutation	NT	–	Sasaki et al. 1997	1,4-naphthoquinone
Human mononuclear leukocytes	Sister chromatid exchange	NT	+	Wilson et al. 1996	1,2- and 1,4-naphthoquinone
32P-labeled DNA fragments of human tumor-relevant genes	DNA damage	NT	+	Ohnishi et al. 2018	1,2-dihydroxynaphthalene, 1,4-dihydroxynaphthalene, and 1,2-naphthoquinone
32P-labeled DNA fragments of human tumor-relevant genes	DNA damage	NT	–	Ohnishi et al. 2018	1, 4- naphthoquinone
Human lymphocytes	DNA damage	NT	+	Kapuci et al. 2014	1-naphthol and 2-naphthol
Rat primary hepatocytes	Unscheduled DNA synthesis	NT	–	Probst et al. 1981	1-naphthol and 2-naphthol
Cell-free DNA	DNA adduct formation	NT	+	Saeed et al. 2007	1,2-naphthoquinone and 1,2-dihydroxynaphthalene

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

Table 2-16. Genotoxicity of Naphthalene *In Vivo*

Species and tissue	Endpoint	Results	Reference
Drosophila melanogaster	Mutations	+	Delgado-Rodriquez et al. 1995
F344 rat nasal olfactory and nasal respiratory epithelium	Mutations (p53)	–	Meng et al. 2011
Mouse bone marrow cells (ICR Swiss, CD-1)	Micronuclei	–	Harper et al. 1984; Sorg et al. 1985
Salamander larvae (Pleurodeles waltl): erythrocytes	Micronuclei	+	Djomo et al. 1995
Human peripheral white blood cells (occupational)	DNA damage (8-OHdG)	+	Marczynski et al. 2011; Marczynski et al. 2005; Lin et al. 2022
Human peripheral white blood cells (occupational)	DNA damage	–	Krieg et al. 2012

Table 2-16. Genotoxicity of Naphthalene *In Vivo*

Species and tissue	Endpoint	Results	Reference
Rat liver	DNA damage	+	Kitchin et al. 1992, 1994
Mouse liver, brain	DNA damage	+	Bagchi et al. 1998, 2000, 2002
Mouse lung	DNA damage	+	Karagiannis et al. 2012
F344 partially hepatectomized rats, liver	Neoplastic transformation	–	Tsuda et al. 1980
Human urine (occupational)	DNA adducts	+	Baek et al. 2021; Hanchi et al. 2017
Human peripheral lymphocytes (occupational)	DNA adducts	+	Zhu et al. 2016
SENCAR mice, epidermis	Stable and depurinating DNA adducts	+	Saeed et al. 2009
Mouse and primate lungs (ex vivo)	DNA adducts	+	Carratt et al. 2019a
Mouse lung (ex vivo)	DNA adducts	+	Buchholz et al. 2019

– = negative result; + = positive result; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; DNA = deoxyribonucleic acid

Table 2-17. Genotoxicity of Naphthalene Metabolites *In Vivo*

Species (exposure route)	Endpoint	Results	Reference	Metabolite
SENCAR mice, epidermis	Stable and depurinating DNA adducts	+	Saeed et al. 2009	1-naphthol, 1,2-dihydrodiolnaphthalene, 1,2-dihydroxynaphthalene, 1,2-naphthoquinone
Mouse and primate lungs (*ex vivo*)	DNA adducts	+	Carratt et al. 2019a	1,2-naphthoquinone
Human peripheral lymphocytes (occupational)	Chromosomal aberrations	+	Orjuela et al. 2012	1-naphthol, 2-naphthol

+ = positive result; DNA = deoxyribonucleic acid

Overview. *In vitro* studies suggest that while naphthalene itself is not genotoxic, it can be metabolized to genotoxic compounds, especially 1,2-naphthoquinone and 1,2-dihydroxynaphthalene. Oxidative DNA damage induced by naphthalene metabolites appears to stem from NADH-dependent redox cycling. In some *in vitro* test systems, the addition of exogenous glutathione has prevented or reduced the genotoxic effects of naphthalene metabolites. *In vivo* studies are limited, but include reports that naphthalene induced mutations in fruit flies and micronuclei in salamander larvae. DNA damage has been observed in the liver, lung, and/or brain of rats or mice after oral or i.p. exposure to naphthalene. One study

documented severe tissue (lung) injury that temporally preceded the most significant DNA damage. An *in vivo* study showed that naphthalene can form stable and depurinating DNA adducts in mouse skin.

Bacterial assays. In the presence of rat liver metabolic activation, naphthalene induced reverse mutations in the marine bacterium, *Vibrio fischeri* (Arfsten et al. 1994). Naphthalene was not mutagenic in *Salmonella typhimurium* assays in the presence or absence of rat liver metabolic preparations (Bos et al. 1988; Connor et al. 1985; Florin et al. 1980; Gatehouse 1980; Godek et al. 1985; Kaden et al. 1979; McCann et al. 1975; Mortelmans et al. 1986; Nakamura et al. 1987; Narbonne et al. 1987; NTP 1992a; Sakai et al. 1985). Naphthalene was not mutagenic, with or without metabolic activation, in the Pol A- or Rec assays in several *Escherichia coli* strains (Mamber et al. 1983). Naphthalene did not damage DNA (as assayed by the induction of the SOS-repair system) in *E. coli* PQ37 (Mersch-Sundermann et al. 1993), in *E. coli* K12 (Mamber et al. 1984), or in *S. typhimurium* TA1535/p5K1002 (Nakamura et al. 1987).

The metabolites, 1-naphthol and 1,4-naphthoquinone, were not mutagenic in several *S. typhimurium* strains in the presence or absence of metabolic activation (McCann et al. 1975; Narbonne et al. 1987; Sakai et al. 1985). 1,2-Naphthoquinone induced reverse mutations in several *S. typhimurium* strains without a metabolic activation system (Flowers-Geary et al. 1996).

In vitro mammalian assays. In vitro eukaryotic gene mutation assays are restricted to a single report that naphthalene and 1,4-naphthoquinone (1,2-naphthoquinone was not tested) did not induce mutations at the hprt and tk loci in human lymphoblastoid cells (Sasaki et al. 1997).

In vitro studies have suggested that the availability of glutathione influences the genotoxicity of naphthalene metabolites. Recio et al. (2012) reported that naphthalene exposure in the presence of rat liver S9 resulted in a concentration-related increase in frequency of micronuclei along with a concentration-related decrease in survival in human TK6 cells. Survival was ~70% at the naphthalene concentration (20 μM) that yielded a 2-fold increase in micronuclei. The increase in micronuclei and the decrease in survival were both abolished when the cells were cultured in the presence of 5 mM glutathione (Recio et al. 2012). In a subsequent study, Recio et al. (2023) assessed the induction of micronuclei and DNA damage in HepaRG™ cells. HepaRG ™ cells, unlike human TK6 cells or rat liver S9, have intact phase II enzyme activity (Recio et al. 2023). In this test system, naphthalene exposure did not increase DNA damage or micronuclei except at concentrations that reduced relative survival to <60%. The study authors postulated that the presence of Phase II enzymes in HepaRG ™ enabled efficient detoxification of reactive naphthalene metabolites, preventing a genotoxic response.

Naphthalene (in the presence of rat liver metabolic activation) induced chromosomal aberrations in Chinese hamster ovary (CHO) cells (NTP 1992a) and in preimplantation whole mouse embryos (Gollahon 1990). Naphthalene also induced sister chromatid exchanges (in the presence or absence of rat liver metabolic activation) in CHO cells (NTP 1992a), but did not do so in human mononuclear leukocytes in the presence or absence of human liver microsomes (Tingle et al. 1993; Wilson et al. 1995).

Mixed results were reported in studies of DNA damage in cells exposed to naphthalene. Kapuci et al. (2014) reported increased DNA fragmentation (terminal deoxynucleotidyl transferase dUTP nick end labeling [TUNEL] assay) in human lymphocytes exposed to naphthalene in the absence of metabolic activation, while Platt et al. (2008) observed no increase in DNA damage (comet assay) when Chinese hamster lung fibroblasts were exposed with or without activation. A study of naphthalene exposure in three different human tumor cell lines (Tomasetig et al. 2020) detected no DNA damage (measured as γ-H2AX).

Naphthalene did not induce DNA single-strand breaks (Sina et al. 1983) or unscheduled DNA synthesis (Barfknecht et al. 1985; Probst et al. 1981) in rat hepatocytes. In addition, naphthalene did not induce cell transformations in several mammalian cell types (see Table 2-14).

In a study of naphthalene metabolites, both 1,2-naphthoquinone and 1,4-naphthoquinone (but not 1,2-naphthalene oxide), in the absence of metabolic activation, induced sister chromatid exchanges in human leukocytes at concentrations (10 and about 50 μM) that depleted cellular glutathione levels and induced about 35–45% cell death (Wilson et al. 1996).

Cell-free systems. Naphthalene caused DNA strand scission in a cell-free assay in the presence of NADPH and copper via reactive oxygen species from a Cu(II)/Cu(I) oxidation/reduction cycle (Flowers et al. 1997).

In studies of metabolites, 1,2-naphthoquinone formed depurinating N7 adducts with deoxyguanosine (McCoull et al. 1999; Saeed et al. 2007) and N3 adducts with adenine (Saeed et al. 2007). Further, when DNA was reacted with 1,2-dihydroxynaphthalene in the presence of tyrosinase (which oxidizes 1,2-dihydroxynaphthalene to 1,2-naphthoquinone), greater quantities of these adducts were formed compared with DNA reacted with 1,2-naphthoquinone (Saeed et al. 2007). In another cell-free experiment, 1,2- and 1,4-dihydroxynaphthalenes and 1,2-naphthoquinone each induced DNA damage (in

the presence of CuII) in ^{32}P-labeled DNA fragments from tumor-suppressor genes (TP53 and p16) and the HRAS protooncogene; in contrast, 1,4-naphthoquinone did not (Ohnishi et al. 2018).

In vivo mammalian assays. *In vivo* studies of genotoxicity endpoints after exposure to naphthalene and its metabolites are summarized in Tables 2-16 and 2-17, respectively.

Studies of genotoxicity endpoints in humans exposed to naphthalene are confounded by coexposure to other chemicals, limiting their ability to assess whether there is a causal relationship. In studies of occupationally exposed populations, increases in DNA damage and DNA adducts have been reported in peripheral blood and in urine (Baek et al. 2021; Hanchi et al. 2017; Lin et al. 2022; Marczynski et al. 2005, 2011). Some studies that evaluated correlations between these findings and measures of naphthalene exposure did not find relationships between DNA damage or adducts and naphthalene concentration in breath (Krieg et al. 2012) or urinary naphthol levels (Marczynski et al. 2011). A study of 546 petrochemical workers in China identified an association between urinary naphthalene metabolite levels and oxidative DNA damage (measured as urinary 8-hydroxy-2'-deoxyguanosine [8-OHdG]), but potential confounding by smoking was not considered in the analysis (Lin et al. 2022). A correlation between DNA methylation levels and urinary 2-naphthol was reported in a cohort of male smokers in China (Zhu et al. 2016). One study of 5-year-old U.S. children in urban areas reported correlations between urinary naphthol levels and the frequency of stable chromosomal aberrations and translocations (Orjuela et al. 2012).

No increase in p53 mutations at codon 271 was observed in the nasal epithelium (olfactory or respiratory) of F344 rats exposed by inhalation to naphthalene concentrations up to 30 ppm for 13 weeks (Meng et al. 2011). Naphthalene did not cause increased single-stranded DNA breaks in hepatocytes of rats given single oral doses of 359 mg/kg (Kitchin et al. 1992, 1994) or transformation foci (γ-glutamyl transpeptidase-positive) in livers of F344 partially hepatectomized rats given single 100 mg/kg doses. DNA fragmentation accompanied by increased lipid peroxidation was observed in brain and liver tissue from rats exposed to 110 mg/kg/day for up to 120 days (Bagchi et al. 1998). It is unclear whether the apparent DNA damage in these assays was due to direct effects of naphthalene metabolites or reactive oxygen species or was secondary to cell death induced at an extranuclear site. Naphthalene did not induce neoplastic transformation in the liver of partially hepatectomized F344 rats (Tsuda et al. 1980).

In mice exposed by i.p. injection, naphthalene induced DNA double strand breaks (measured as γ-H2Ax foci) in lung tissue at doses known to result in lung toxicity (Karagiannis et al. 2012; Zhou et al. 2011).

Karagiannis et al. (2012) reported that the greatest degree of DNA damage occurred later (24 and 48 hours after dosing) than the most severe histopathology findings in the lung epithelium (12 and 24 hours after dosing), suggesting that toxicity may have occurred prior to DNA damage. Naphthalene was reported to induce DNA fragmentation in brain and liver tissue from mice given single oral doses of 32 or 158 mg/kg (Bagchi et al. 2000, 2002). No increase in the frequency of micronuclei was observed in bone marrow of mice given single oral (50, 250, or 500 mg/kg) or i.p. doses of naphthalene (250 mg/kg) (Harper et al. 1984; Sorg et al. 1985).

In SENCAR mice treated topically with naphthalene or its metabolites, depurinating (N3 adenine and N7 guanine adducts) and stable DNA adducts were detected in the epidermis (Saeed et al. 2009). With exposures to 500 nmol, the greatest quantity of N7 guanine adducts in the epidermis was observed after exposure to 1,2-naphthoquinone, followed by 1,2-dihydroxynaphthalene and 1-naphthol; naphthalene did not produce detectable N7 guanine adducts at this exposure level, but did with exposure to 1,200 nmol (Saeed et al. 2009).

Two studies examined total DNA adduct formation in lung tissues exposed to naphthalene *ex vivo* (Buchholz et al. 2019; Carratt et al. 2019a). These studies did not identify the specific DNA adducts formed or evaluate their potential relationship to mutagenesis. In addition, there is uncertainty regarding the relevance of the explants (exposure conditions and detoxification capability) to *in vivo* conditions. Buchholz et al. (2019) evaluated whether exposure resulted in fewer DNA adducts in mice that had developed tolerance to naphthalene (through repeated i.p. exposures) compared with those that had not. Lungs of tolerant and untreated mice were exposed *ex vivo* to ^{14}C naphthalene and total DNA adducts were analyzed using accelerator mass spectrometry. A slightly lower level of DNA adducts was observed in tolerant mice, but the difference from mice that had not been pretreated was not statistically significant.

Carratt et al. (2019a) compared DNA adducts in mouse and primate (Rhesus macaque) lung tissue and rat nasal tissue explants cultured with naphthalene or 1,2-naphthoquinone. In experiments with naphthalene, adduct levels in rat nasal olfactory epithelium were below the limit of quantitation, and levels in the nasal respiratory epithelium were only slightly higher (69 adducts/pg DNA). In contrast, both mouse and primate lung showed significant levels of naphthalene DNA adducts, with slightly higher quantity in primate lung (~2,000 adducts/pg DNA) than in mouse (1,706 adducts/pg DNA). A marked sex difference in adducts in the lung was seen: female mice and primates both exhibited significantly higher mean adduct levels in lung tissue cultured with naphthalene than similarly treated tissues from males. The mean adduct level in female mouse lung tissue was ~4.7 times as high as the level in male mouse lung

tissue, and in female primate lung tissue the level was about twice that of males. Female primates and mice showed similar levels of adducts (2,220 and 2,160 adducts/pg DNA, respectively), while male primates had a mean adduct level about double that of male mice (~1,000 versus ~500 adducts/pg DNA). DNA adduct levels increased with naphthalene dose (25 and 250 μM) in experiments in explants of both male and female macaques, and higher levels were seen in females at both doses. Incubation of the primate explants with 1,2-naphthoquinone resulted in markedly higher adduct levels compared with those induced by naphthalene. While Carratt et al. (2019a) did not identify the specific adducts in this study, they showed that naphthalene and 1,2-naphthoquinone were covalently bound to DNA, as the adducts were still detected in enzymatically-digested DNA.

Other in vivo assays. Naphthalene was mutagenic in *D. melanogaster* (Delgado-Rodriquez et al. 1995), and induced micronuclei in erythrocytes of salamander (*P. waltl*) larvae exposed to concentrations of 0.5 mM.

1- and 2-Methylnaphthalene. No studies were located that documented genotoxic effects of 2-methylnaphthalene in humans or animals exposed by any route. In an *in vitro* study, 1- and 2-methylnaphthalene failed to induce chromosomal aberrations or sister chromatid exchanges in human peripheral lymphocytes (Kulka et al. 1988). In another study, an *in vitro* microbial assay employing *S. typhimurium*, mutagenic activity was not detected with either compound, with either the presence or absence of microsomal activation (Florin et al. 1980). These studies are presented in Table 2-18. In transgenic *gpt* delta B6C3F1 mice exposed to 1-methylnaphthalene in the diet at concentrations up to 0.15% for 13 weeks, no increase in the frequencies of point mutations in the *gpt* gene or deletion mutations in the red/gam genes were detected in the lungs (Jin et al. 2012).

Table 2-18. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
1-Methylnaphthalene				
Prokaryotic organisms				
Salmonella typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Florin et al. 1980

Table 2-18. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mammalian cells				
Human lymphocytes	Chromosomal aberration, sister chromatid exchange	–	–	Kulka et al. 1988
2-Methylnaphthalene				
Prokaryotic organisms				
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Florin et al. 1980
Mammalian cells				
Human lymphocytes	Chromosomal aberration, sister chromatid exchange	–	–	Kulka et al. 1988

– = negative result