

# Toxicological Profile for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

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U.S. Department of Health and Human Services  
Agency for Toxic Substances and Disease Registry

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## FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: [www.regulations.gov](http://www.regulations.gov). Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry  
Office of Innovation and Analytics  
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under Section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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## VERSION HISTORY

Date	Description
May 2024	Draft for public comment toxicological profile released
June 2005	Final toxicological profile released
August 1995	Final toxicological profile released
December 1990	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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## CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

### 1.1 OVERVIEW AND U.S. EXPOSURES

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene occur naturally in fossil fuels such as petroleum and coal, and are produced when organic materials (e.g., fossil fuels, wood, tobacco) are burned (EPA 2002; IARC 2002). Naphthalene is also produced commercially from either coal tar or petroleum. In 2019, the nationally aggregated production volume in the United States was reportedly between 100 and 250 million pounds for naphthalene; 1.9 and 2 million pounds were reported for 1- and 2-methylnaphthalene, respectively (EPA 2022a). Commercially produced naphthalene is predominantly used (over 60% consumption) in the production of phthalic anhydride, which is used as an intermediate for polyvinyl chloride plasticizers such as di(2-ethylhexyl) phthalate. Other uses of naphthalene include production of naphthalene sulfonates (used in concrete additives and synthetic tanning agents), pesticides (e.g., carbaryl insecticides and moth repellents), and dye intermediates (Collin et al. 2012; Mason 2002).

Naphthalene is frequently present in industrial and automobile emissions and effluents, and in various media in the general environment, due to its natural occurrence in coal and petroleum products and emissions and its use in various products and formulations. In 2021, environmental releases of naphthalene reported under the U.S. Environmental Protection Agency (EPA) Toxics Release Inventory (TRI) program were about 1,318,765 pounds in air emissions, 4,727 pounds in surface water discharges, 402,976 pounds in underground injection discharges, and 2,180,478 pounds in releases to land (TRI21 2023). These figures reflect estimates that most naphthalene entering the environment is discharged to soil. Discharges to surface soils may further volatilize to the atmosphere due to the volatility of naphthalene. The second largest environmental compartment naphthalene is discharged to is the atmosphere, with the largest releases to the atmosphere associated with the combustion of plant material and fossil fuels and volatilization from naphthalene-containing consumer products (EPA 2017b; IARC 2002). Naphthalene may also be found in dust from indoor and outdoor sources, although data in the United States are limited.

The most likely route of exposure to naphthalene and the methylnaphthalenes is through inhalation, as the chemicals are highly volatile. Naphthalene has a strong odor of tar or mothballs (see <https://www.atsdr.cdc.gov/odors/> for information on environmental odors). Monitoring studies of outdoor ambient air levels of naphthalene have reported concentrations in the range of about 0.013–115 µg/m<sup>3</sup>, with a mean concentration of 0.04 µg/m<sup>3</sup> reported for urban/suburban air samples collected

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from across the United States (Davey et al. 2014; EPA 2022b; Lu et al. 2005). Higher outdoor air concentrations have been found in cities, during wildfire events, and in the immediate vicinity of certain industrial sources and hazardous waste sites. In indoor air, emissions from cooking, tobacco smoking, or moth repellants are expected to be the predominant sources of naphthalene. The reported average indoor air concentrations range from 0.18 to 2.84  $\mu\text{g}/\text{m}^3$  naphthalene (Jia and Batterman 2011).

Methylnaphthalenes have also been detected in ambient outdoor and indoor air; average concentrations of 1- and 2-methylnaphthalene in ambient outdoor air samples were reported to be 0.21 and 0.37  $\mu\text{g}/\text{m}^3$ , respectively (EPA 2022b). Recent indoor air monitoring data were not located for the methylnaphthalenes. Levels of naphthalene (and methylnaphthalenes), when detected in water, sediments, and soil, tend to be low: usually  $<0.5 \mu\text{g}/\text{L}$  in surface water or groundwater and  $<300 \mu\text{g}/\text{kg}$  in sediments and soil (WQP 2023). However, in the immediate vicinity of point sources of release, such as chemical waste sites, or near nonpoint sources such as in urban environments near fuel combustion and vehicle emissions, concentrations can be higher (Gao et al. 2019).

Naphthalene is rarely detected in drinking water (USGS 2015) and has previously been detected in food at concentrations generally  $<100$  ppb, although many available studies used products bought outside of the United States. Cooking or smoking methods for food preparation have been reported as possible sources of contamination (Polak-Śliwińska et al. 2022; Schauer et al. 1999; Zelinkova and Wenzl 2015).

Naphthalene has also been detected at trace levels in a variety of consumer products bought outside of the United States (Danish EPA 2015). Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are regulated by EPA under the Clean Air Act (CAA) as Hazardous Air Pollutants (HAPs) (EPA 2017a) and naphthalene is identified as hazardous waste under the Resource Conservation and Recovery Act (RCRA) (40 CFR §261).

## 1.2 SUMMARY OF HEALTH EFFECTS

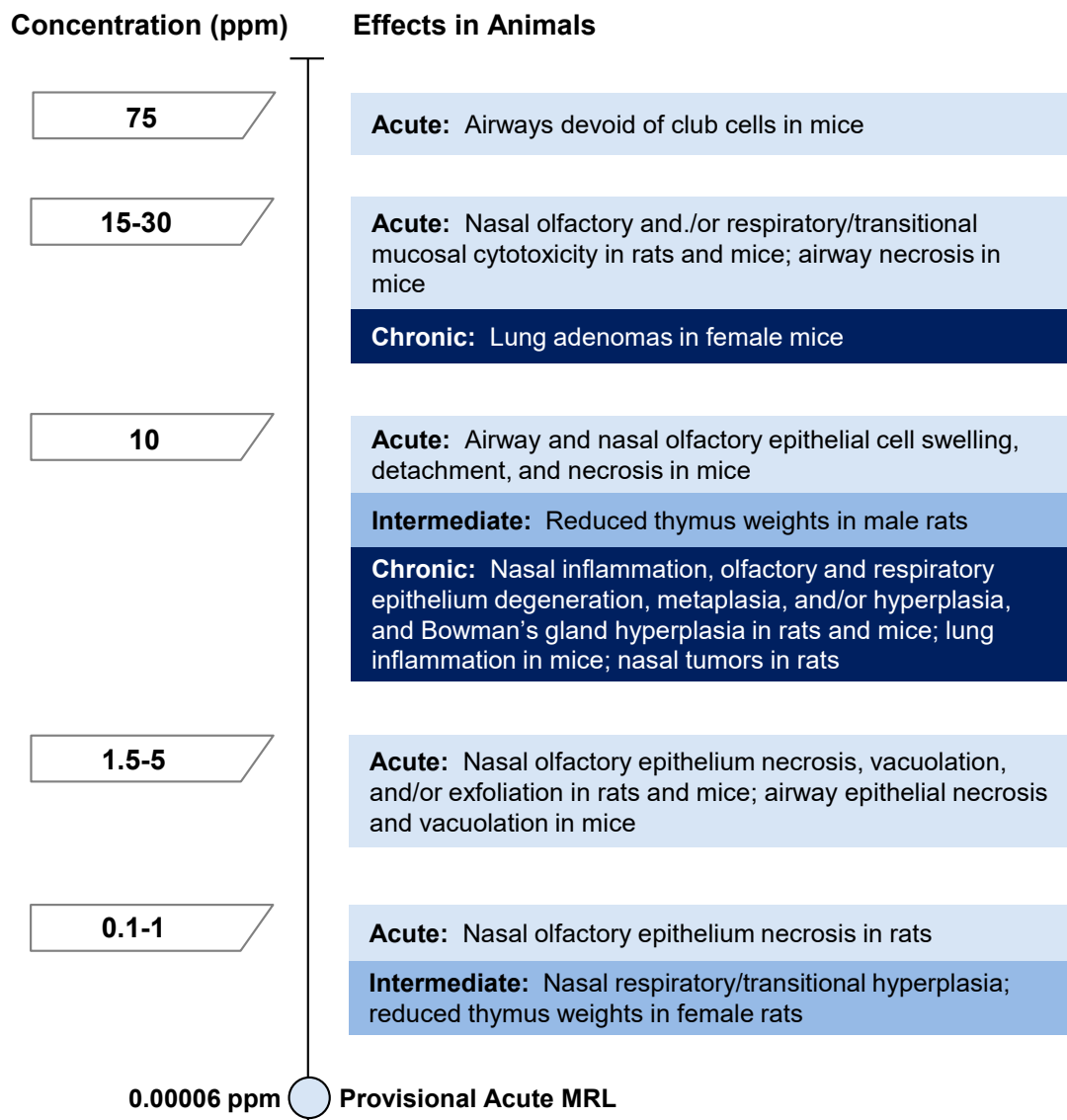
The toxicological database for naphthalene includes case reports, human observational studies of the general population, and studies of animals exposed by inhalation, oral administration, and dermal contact. Studies of exposures to the general population typically evaluated exposure using concentrations of urinary metabolites. Human studies of 1- and 2-methylnaphthalene exposures were not located.

While there is a substantial database of toxicological effects in animals after inhalation, oral, and dermal exposure to naphthalene, fewer studies of animals exposed to 1- and 2-methylnaphthalene are available. Figures 1-1 through 1-6 show the most sensitive effects in animals after inhalation exposure to

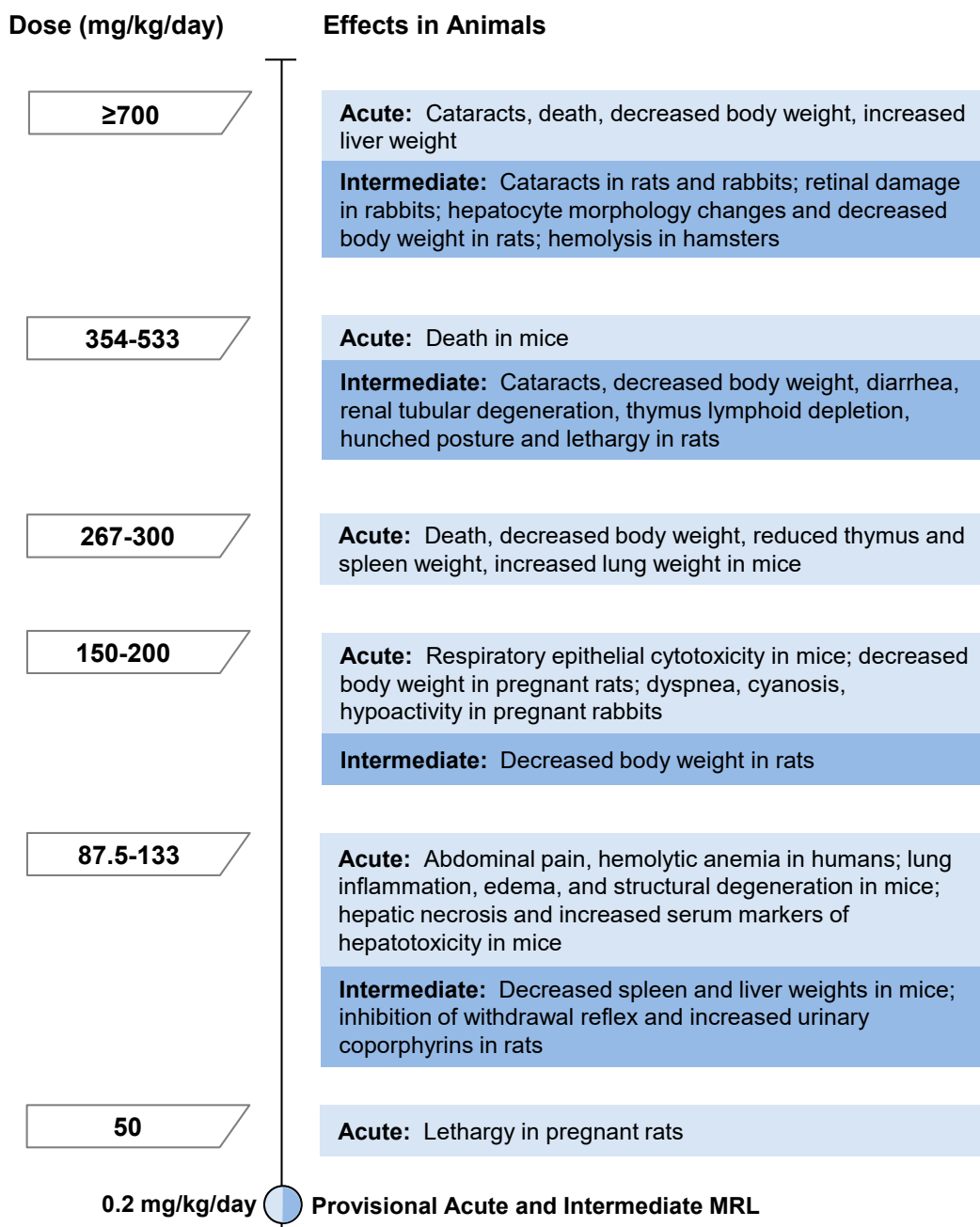
## 1. RELEVANCE TO PUBLIC HEALTH

naphthalene, oral exposure to naphthalene, inhalation exposure to 1-methylnaphthalene, oral exposure to 1-methylnaphthalene, inhalation exposure to 2-methylnaphthalene, and oral exposure to 2-methylnaphthalene, respectively. Each figure also shows provisional minimal risk levels (MRLs) when data were adequate to derive them.

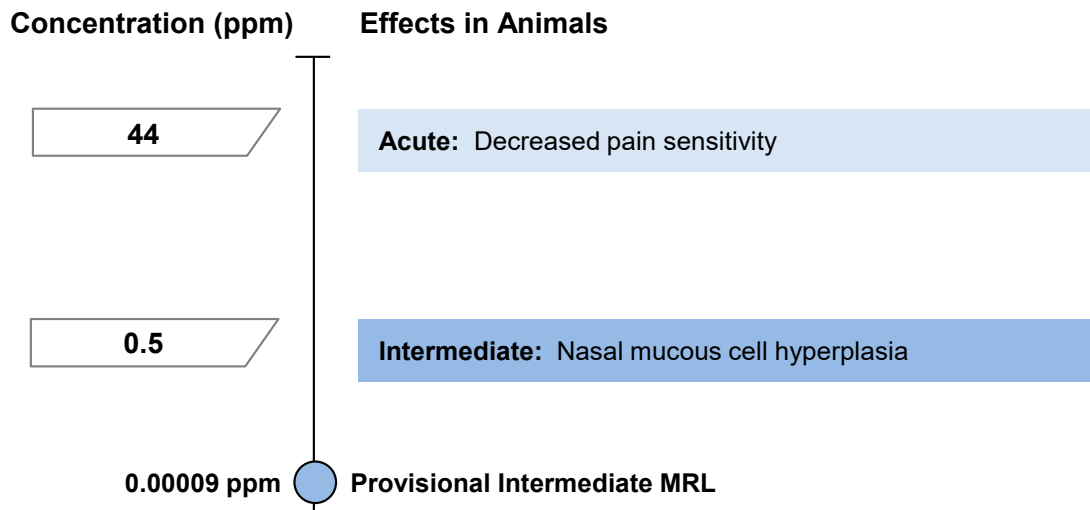
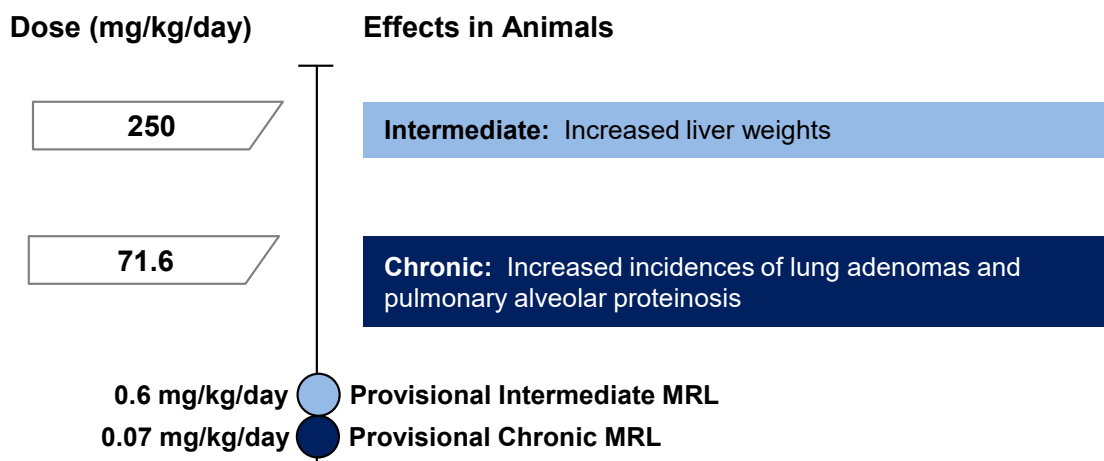
**Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Naphthalene**



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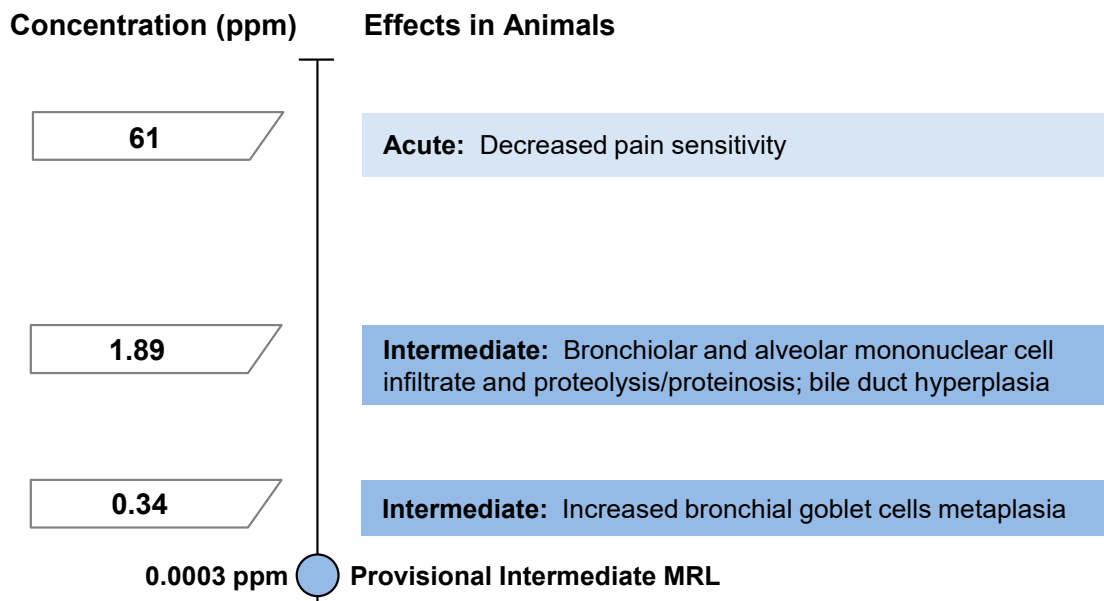
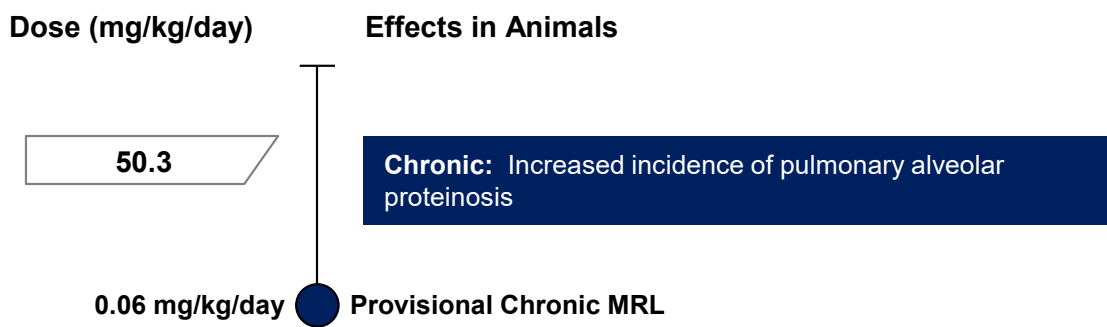
**Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Naphthalene**

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**Figure 1-3. Health Effects Found in Animals Following Inhalation Exposure to 1-Methylnaphthalene****Figure 1-4. Health Effects Found in Animals Following Oral Exposure to 1-Methylnaphthalene**



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**Figure 1-5. Health Effects Found in Animals Following Inhalation Exposure to 2-Methylnaphthalene****Figure 1-6. Health Effects Found in Animals Following Oral Exposure to 2-Methylnaphthalene**

As Figures 1-1 and 1-2 show, the most sensitive effects of oral and inhalation exposure to naphthalene are respiratory, immunological, and neurological toxicity. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Respiratory tract effects are a presumed health effect for humans.
- Neurological effects are a suspected health effect for humans.

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A systematic review was also performed for immunological effects. The hazard identification conclusion was that immunological effects were not classifiable due to inadequate evidence in human studies and low evidence in animal studies.

Figures 1-3 and 1-4 show that the most sensitive effects of exposure to 1-methylnaphthalene in animals are respiratory and hepatic effects. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Respiratory tract effects are a presumed health effect for humans.
- Hepatic effects are a suspected health effect for humans.

Figures 1-5 and 1-6 show that the most sensitive effects of exposure to 2-methylnaphthalene in animals are respiratory and hepatic effects. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Respiratory tract effects are a presumed health effect for humans.
- Hepatic effects are a presumed health effect for humans.

***Respiratory Effects of Naphthalene.*** Human studies of the respiratory tract effects of naphthalene are limited. Occupational exposure to airborne naphthalene was associated with irritation and inflammation in the nose (Sucker et al. 2021). A study of the general population in a community in China suggested an association between particle-bound naphthalene in the air and decreased pulmonary function (Mu et al. 2019). Decreased lung function was also associated with indoor naphthalene vapor concentration among female, but not male adults in a cross-sectional study in Canada (Cakmak et al. 2014).

Studies in animals exposed by inhalation for acute, intermediate, and chronic durations have shown that naphthalene induces pathological changes in the nose of both rats and mice and in the lungs of mice. Acute-duration studies show nasal lesions characterized by degeneration, necrosis, vacuolation, and/or exfoliation of the olfactory and respiratory transitional epithelia (Carratt et al. 2016, 2019a; Cichocki et al. 2014; Dodd et al. 2010; Lee et al. 2005; Li et al. 2017). With intermediate-duration inhalation exposure in rats, additional nasal changes consisting of squamous metaplasia of the respiratory transitional epithelia and goblet cell hyperplasia were observed (Dodd et al. 2012). In studies of rats and mice exposed by inhalation for 2 years, increased incidences of nonneoplastic lesions were observed in the nose of both rats and mice (Abdo et al. 2001; NTP 1992a, 2000), and in the lungs of mice (NTP 1992a). In rats of both sexes, inhalation of 10, 30, or 60 ppm resulted in nasal lesions consisting of hyperplasia, atrophy,

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chronic inflammation, and hyaline degeneration of the olfactory epithelium; and hyperplasia, metaplasia, or degeneration of the nasal respiratory epithelium or glands of the nasal cavity. In mice of both sexes, chronic inhalation of 10 or 30 ppm naphthalene induced inflammation of the nose, metaplasia of the olfactory epithelium, and hyperplasia of the nasal respiratory epithelium (NTP 1992a).

Mice exposed by inhalation showed effects in the lower respiratory tract in addition to the nose. Reported necrosis, epithelial cell swelling and detachment, and squamous cell replacement of club cells were observed in the airways and lungs of mice after 4 hours of exposure to  $\geq 10$  ppm (Kovalchuk et al. 2020; Li et al. 2017; Phimister et al. 2004; West et al. 2001). Inflammation of the lung was observed in the 2-year study of mice at exposure concentrations of 10 or 30 ppm naphthalene (NTP 1992a).

***Neurological Effect of Naphthalene.*** Neurological symptoms of headache, confusion, lethargy, and vertigo have been documented in case reports of human exposure to vapors from mothballs (Linick 1983) or from ingestion of naphthalene (Bregman 1954; Chusid and Fried 1955; Gupta et al. 1979; Kurz 1987; MacGregor 1954; Ojwang et al. 1985; Zuelzer and Apt 1949). In fatal cases of naphthalene ingestion, convulsions and coma have been seen prior to death (Kurz 1987; Gupta et al. 1979; Zuelzer and Apt 1949). Permanent neurological damage observed in humans exposed to high concentrations of naphthalene is associated with jaundice resulting from hemolysis (McMurray 1977; Valaes et al. 1963). Acute oral exposure of pregnant rats to naphthalene doses of 150 or 450 mg/kg/day (but not 50 mg/kg/day) during gestation produced maternal toxicity including clinical signs of neurotoxicity (lethargy and prone position) (NTP 1991). In subchronic studies of rats and mice exposed orally, transient clinical signs of hunched posture and lethargy were seen (NTP 1980a, 1980b).

***Cancer Effects of Naphthalene.*** Chronic inhalation studies found increased incidences of neoplastic lesions in the nose of rats (Abdo et al. 2001; NTP 2000) and in the lungs of mice (NTP 1992a). In female mice (but not male mice), exposure to 30 ppm (but not 10 ppm) increased the incidence of benign lung tumors (alveolar/bronchiolar adenomas) compared with controls. One other female mouse exposed to 30 ppm showed a malignant lung tumor (alveolar/bronchiolar carcinoma). In rats of both sexes, inhalation of 10, 30, or 60 ppm naphthalene induced neoplastic lesions only in the nasal cavity (Abdo et al. 2001; NTP 2000). The nasal tumor types associated with naphthalene exposure in rats were olfactory epithelial neuroblastomas (a rare malignant tumor) and respiratory epithelial adenomas.

The National Toxicology Program (NTP 2021) *15th Report on Carcinogens* considers naphthalene to be *reasonably anticipated to be human carcinogen* based on sufficient evidence from animal studies.

## 1. RELEVANCE TO PUBLIC HEALTH

International Agency for Research on Cancer (IARC 2002) concluded that naphthalene is *possibly carcinogenic to humans* (Group 2B) based on specific evaluations that there is inadequate evidence in humans and sufficient evidence in animals for the carcinogenicity of naphthalene. IARC (2002) considered the findings for nasal tumors in male and female rats and lung tumors in female mice in the NTP (1992a, 2000) bioassays as sufficient evidence, noting that both nasal tumor types (olfactory epithelial neuroblastomas and respiratory epithelial adenomas) are rare in untreated rats.

EPA last assessed the carcinogenicity of naphthalene before the availability of the results from the chronic rat bioassay (Abdo et al. 2001; NTP 2000). In the EPA (1998) *Toxicological Review on Naphthalene*, it was concluded that there was inadequate evidence in humans and limited evidence in animals of naphthalene carcinogenicity (increased incidence of lung tumors in female mice). Under the EPA (1986a) cancer guidelines, naphthalene was assigned to Group C—*possible human carcinogen*. Under the EPA (1996a) proposed cancer guidelines, it was judged that the human carcinogenic potential of naphthalene via the oral or inhalation routes “cannot be determined,” but it was noted that there was suggestive evidence of potential human carcinogenicity based on increased lung tumors in female mice.

***Respiratory Effects of 1- and 2-Methylaphthalene.*** No studies of respiratory effects in humans exposed to 1- or 2-methylnaphthalene were located. In rats exposed to 1-methylnaphthalene for 13 weeks by inhalation, nasal lesions (mucous cell hyperplasia and transitional epithelial cell hyperplasia) occurred at increased incidence at all exposure concentrations ( $\geq 0.52$  ppm) (Kim et al. 2020). Intermediate-duration exposure of rats to 2-methylnaphthalene concentrations  $\geq 0.34$  ppm resulted in histopathology changes in the bronchi consisting of goblet cell metaplasia, proteinosis, and hyperplasia of the peribronchial lymphatic tissue (Świercz et al. 2011). Increased incidences of pulmonary alveolar proteinosis were observed in mice of both sexes exposed via diet for chronic durations to 1-methylnaphthalene (~72–75 and 140–144 mg/kg/day) (Murata et al. 1993) and 2-methylnaphthalene (~50–54 and 108–114 mg/kg/day) (Murata et al. 1997). Histologic examination of major tissues and organs in these studies showed no other exposure-related nonneoplastic or neoplastic lesions at other sites in the respiratory tract (including the bronchiolar regions of the lung). Mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene (a mixture of 1- and 2-methylnaphthalene) for 30–61 weeks also showed increased incidences of pulmonary alveolar proteinosis (Emi and Konishi 1985; Murata et al. 1992).

***Cancer Effects of 1- and 2-Methylaphthalene.*** Studies evaluating cancer effects of 1- and 2-methylnaphthalene in humans were not located. The chronic dietary studies of 1- or 2-methylnaphthalene in animals provide limited evidence for the carcinogenicity of these chemicals. In the

## 1. RELEVANCE TO PUBLIC HEALTH

1-methylnaphthalene study, respective incidences of mice with lung adenomas or carcinomas were 5/50, 2/50, and 5/50 for control through high-dose females, and 2/49, 13/50, and 15/50 for males (Murata et al. 1993). With 2-methylnaphthalene, incidences for lung adenomas or carcinomas were 5/50, 4/49, and 6/48 for females and 2/49, 10/49, and 6/49 for males. The tumorigenic response was predominantly benign and was only consistently seen in male mice exposed to 1-methylnaphthalene. In addition, there are several issues with the performance of these studies, including the potential for simultaneous exposures to 1- and 2-methylnaphthalene: the animals were exposed concurrently in the same room, and the study authors suggested that there may have been inhalation exposure resulting from volatilization of the test compounds.

The NTP (2021) *15th Report on Carcinogens* does not include 1- or 2-methylnaphthalene on its list of chemicals *known to be human carcinogens* or *reasonably anticipated to be human carcinogens*. IARC has not assessed the carcinogenicity potential of the methylnaphthalenes. The EPA (2003) concluded that the available data for 2-methylnaphthalene are *inadequate to assess human carcinogenic potential*, noting that there are no human data and the available evidence of 2-methylnaphthalene in animals is limited and insufficient to determine that 2-methylnaphthalene is carcinogenic to humans. The EPA (2008) Provisional Peer-Reviewed Toxicity Value assessment for 1-methylnaphthalene concluded that the findings of lung adenoma and adenocarcinomas in male mice exposed via the diet for 81 weeks (Murata et al. 1993) provide “Suggestive Evidence of Carcinogenicity.”

### 1.3 MINIMAL RISK LEVELS (MRLs)

**Naphthalene.** Available information of the toxicity of inhaled naphthalene was adequate for derivation of a provisional acute-duration inhalation MRL, but not intermediate- or chronic-duration MRLs. The oral database was adequate to derive provisional acute- and intermediate-duration oral MRLs but no studies of chronic-duration oral exposure were available, precluding derivation of a chronic-duration oral MRL. As shown in Figures 1-7 and 1-8, the most sensitive targets of inhalation exposure to naphthalene are the respiratory tract and immune system, and the most sensitive target of oral exposure is the central nervous system.

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**Figure 1-7. Summary of Sensitive Targets of Naphthalene – Inhalation**

**Available data indicate that the respiratory tract and immune system are the most sensitive targets of naphthalene inhalation exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose response data were available for humans.



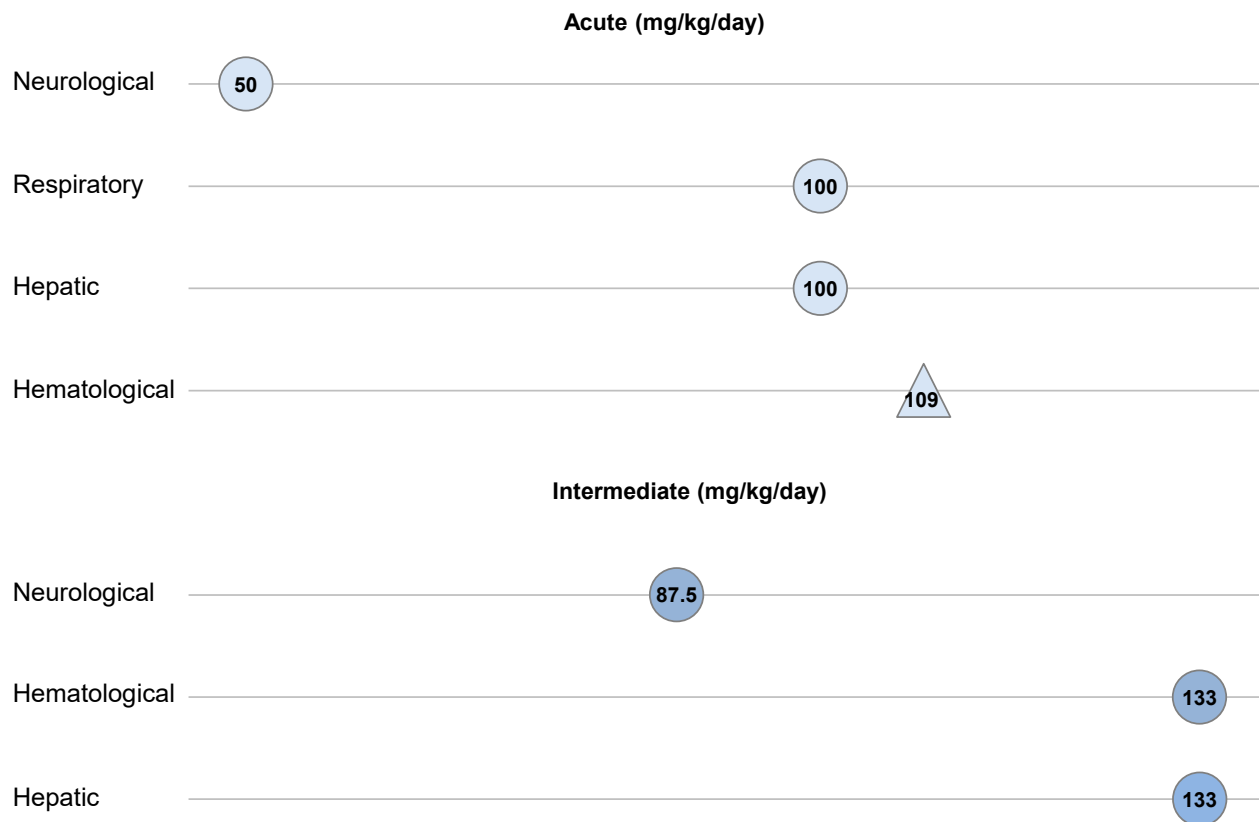
## 1. RELEVANCE TO PUBLIC HEALTH

**Figure 1-8. Summary of Sensitive Targets of Naphthalene – Oral**

**Available data indicate that the nervous system is the most sensitive target of naphthalene oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals.

No reliable dose response data were available for humans.



The MRL values for naphthalene are summarized in Table 1-1 and discussed in greater detail in Appendix A.

## 1. RELEVANCE TO PUBLIC HEALTH

**Table 1-1. Provisional Minimal Risk Levels (MRLs) for Naphthalene<sup>a</sup>**

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/modifying factor	Reference
Inhalation	Acute	<b>6x10<sup>-5</sup> ppm</b> (3x10 <sup>-4</sup> mg/m <sup>3</sup> )	Nasal olfactory epithelial necrosis	BMCL <sub>HEC</sub>	0.0017 ppm	UF: 30	Dodd et al. 2010
	Intermediate	None <sup>b</sup>	—	—	—	—	—
	Chronic	None <sup>b</sup>	—	—	—	—	—
Oral	Acute	<b>0.2 mg/kg/day</b>	Clinical signs of neurotoxicity	LOAEL	50 mg/kg/day	UF: 300	NTP 1991
	Intermediate	<b>0.2 mg/kg/day<sup>c</sup></b>	Clinical signs of neurotoxicity	LOAEL	50 mg/kg/day	UF: 300	NTP 1991
	Chronic	None	—	—	—	—	—

<sup>a</sup>See Appendix A for additional information.

<sup>b</sup>There is some evidence to suggest that the acute-duration inhalation MRL may be protective for inhalation exposures of longer (intermediate and chronic) durations. See Appendix A for discussion of this information.

<sup>c</sup>The acute-duration oral MRL was adopted for the intermediate-duration oral MRL.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

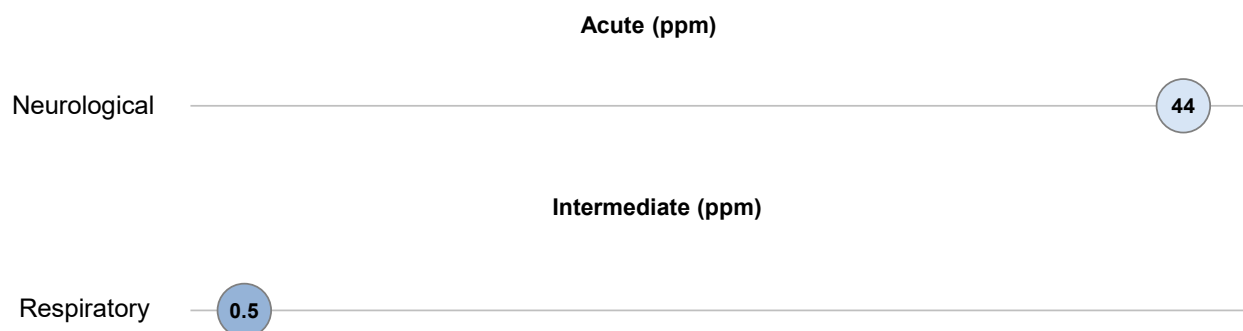


## 1. RELEVANCE TO PUBLIC HEALTH

**1-Methylnaphthalene.** Available information on the toxicity of inhaled 1-methylnaphthalene was adequate for derivation of a provisional intermediate-duration inhalation MRL but was not adequate to derive acute- or chronic-duration inhalation MRLs. Figure 1-3 shows that the respiratory endpoint was a sensitive target following inhalation exposure to 1-methylnaphthalene. The oral database was considered inadequate to derive an acute-duration oral MRL, but adequate to derive provisional intermediate- and chronic-duration oral MRLs. As shown in Figures 1-9 and 1-10, the most sensitive targets of inhalation and oral exposure to 1-methyl naphthalene are the respiratory tract (both routes) and liver (oral).

### Figure 1-9. Summary of Sensitive Targets of 1-Methylnaphthalene – Inhalation

**The respiratory tract is the most sensitive target of 1-methylnaphthalene inhalation exposure.** Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



### Figure 1-10. Summary of Sensitive Targets of 1-Methylnaphthalene – Oral

**The respiratory tract and liver are the most sensitive targets of 1-methylnaphthalene oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals.

No reliable dose response data were available for humans.



## 1. RELEVANCE TO PUBLIC HEALTH

The MRL values for 1-methylnaphthalene are summarized in Table 1-2 and discussed in greater detail in Appendix A.

## 1. RELEVANCE TO PUBLIC HEALTH

**Table 1-2. Provisional Minimal Risk Levels (MRLs) for 1-Methylnaphthalene<sup>a</sup>**

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	<b>9x10<sup>-5</sup> ppm</b> (5x10 <sup>-4</sup> mg/m <sup>3</sup> )	Nasal mucous cell hyperplasia	BMCL <sub>HEC</sub>	0.0027 ppm	UF: 30	Kim et al. 2020
	Chronic	None	–	–	–	–	–
Oral	Acute	None	–	–	–	–	–
	Intermediate	<b>0.6 mg/kg/day</b>	Increased liver weight	BMDL <sub>1SD</sub>	64 mg/kg/day	UF: 100	NITE 2009
	Chronic	<b>0.07 mg/kg/day</b>	Pulmonary alveolar proteinosis	LOAEL	71.6 mg/kg/day	UF: 1,000	Murata et al. 1993

<sup>a</sup>See Appendix A for additional information.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; SD = standard deviation; UF = uncertainty factor

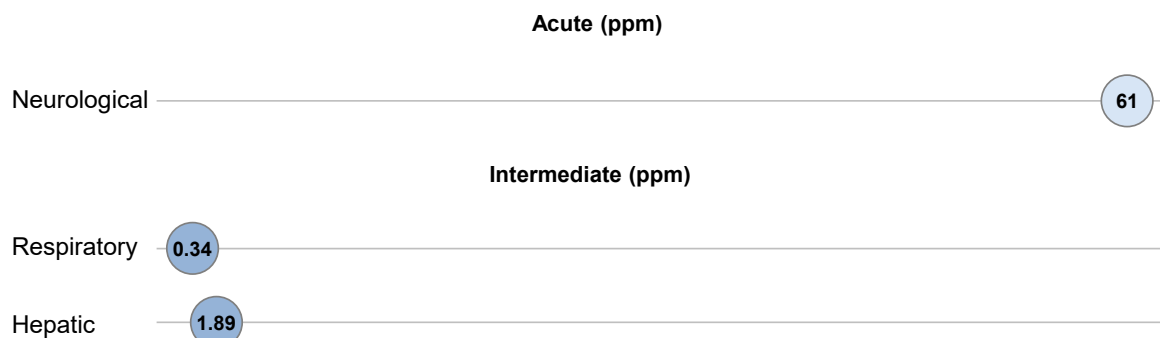
## 1. RELEVANCE TO PUBLIC HEALTH

**2-Methylnaphthalene.** Available information on the toxicity of inhaled 2-methylnaphthalene was adequate for derivation of a provisional intermediate-duration inhalation MRL but was not adequate to derive acute- or chronic-duration inhalation MRLs. The oral database was considered inadequate to derive acute- and intermediate-duration oral MRLs, but adequate to derive a provisional chronic-duration oral MRL. As shown in Figures 1-11 and 1-12, the most sensitive targets of inhalation and oral exposure to 2-methylnaphthalene are the respiratory tract (both routes) and liver (inhalation).

### Figure 1-11. Summary of Sensitive Targets of 2-Methylnaphthalene – Inhalation

**The respiratory tract and liver are the most sensitive targets of 2-methylnaphthalene inhalation exposure.**

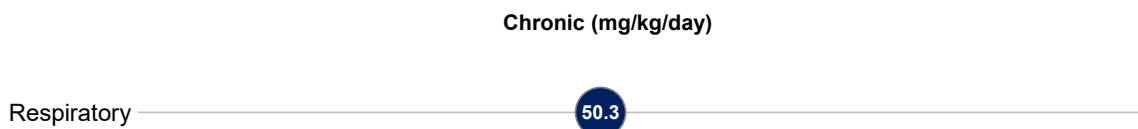
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



### Figure 1-12. Summary of Sensitive Targets of 2-Methylnaphthalene – Oral

**The respiratory tract is the most sensitive target of 2-methylnaphthalene oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



The MRL values for 2-methylnaphthalene are summarized in Table 1-3 and discussed in greater detail in Appendix A.

## 1. RELEVANCE TO PUBLIC HEALTH

**Table 1-3. Provisional Minimal Risk Levels (MRLs) for 2-Methylnaphthalene<sup>a</sup>**

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/modifying factor	Reference
Inhalation	Acute	None	—	—	—	—	—
	Intermediate	<b><math>3 \times 10^{-4}</math> ppm</b> (0.002 mg/m <sup>3</sup> )	Bronchial goblet cell metaplasia	LOAEL <sub>HEC</sub>	0.081 ppm	UF: 300	Świercz et al. 2011
	Chronic	None	—	—	—	—	—
Oral	Acute	None	—	—	—	—	—
	Intermediate	None	—	—	—	—	—
	Chronic	<b>0.06 mg/kg/day</b>	Pulmonary alveolar proteinosis	BMDL <sub>05</sub>	6.4 mg/kg/day	UF: 100	Murata et al. 1997

<sup>a</sup>See Appendix A for additional information.

BMCL<sub>05</sub> = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 05 = dose associated with 5% extra risk); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

## 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 ( $\leq 14$  days), intermediate (15–364 days), and chronic ( $\geq 365$  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.

## 2. HEALTH EFFECTS

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-methylnaphthalene. 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

## 2. HEALTH EFFECTS

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 inadequate evidence in human studies and low evidence in animal studies. 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 finding 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.



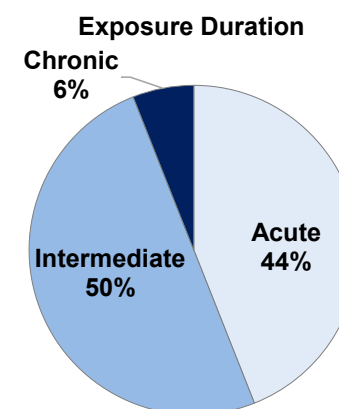
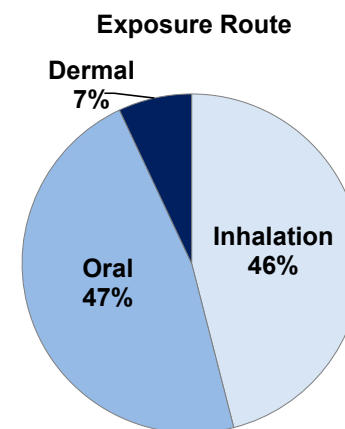
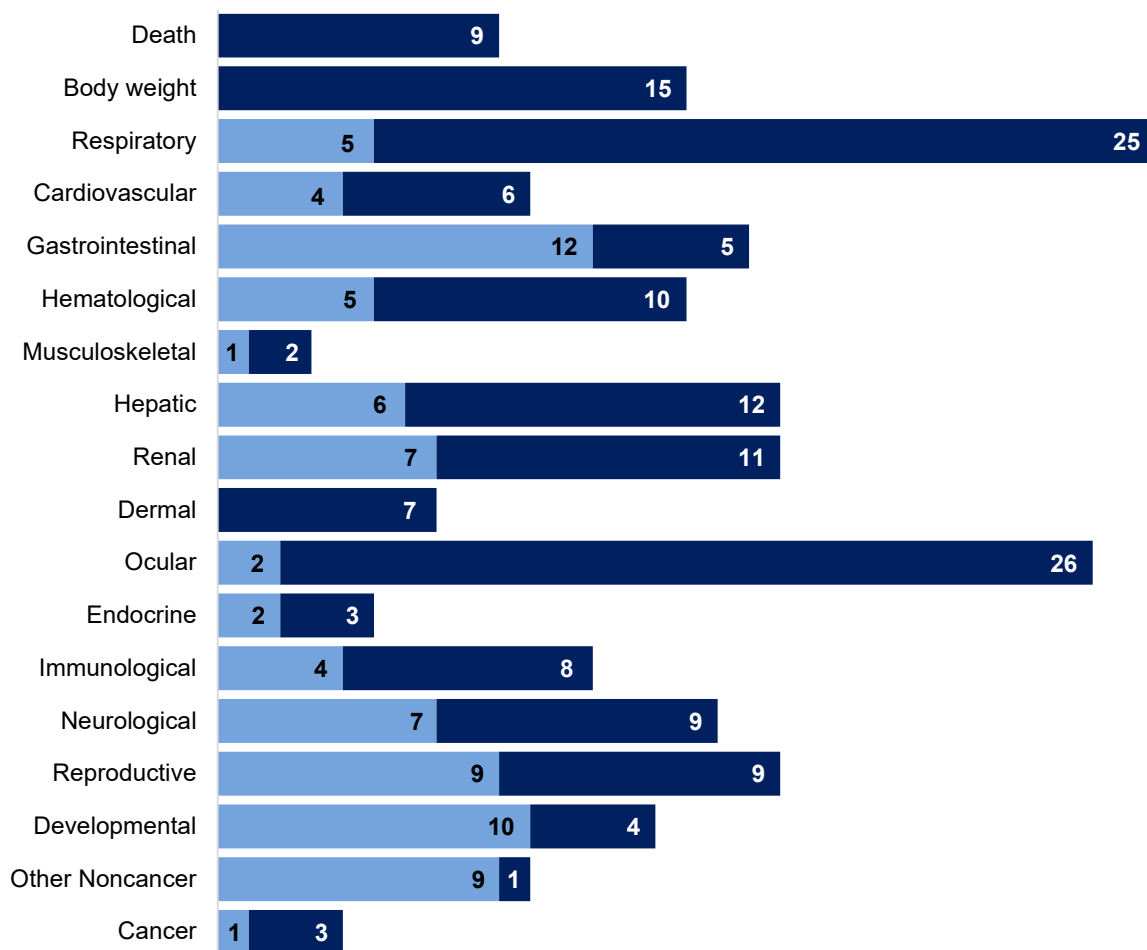
## 2. HEALTH EFFECTS

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 finding 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.

## 2. HEALTH EFFECTS

**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)

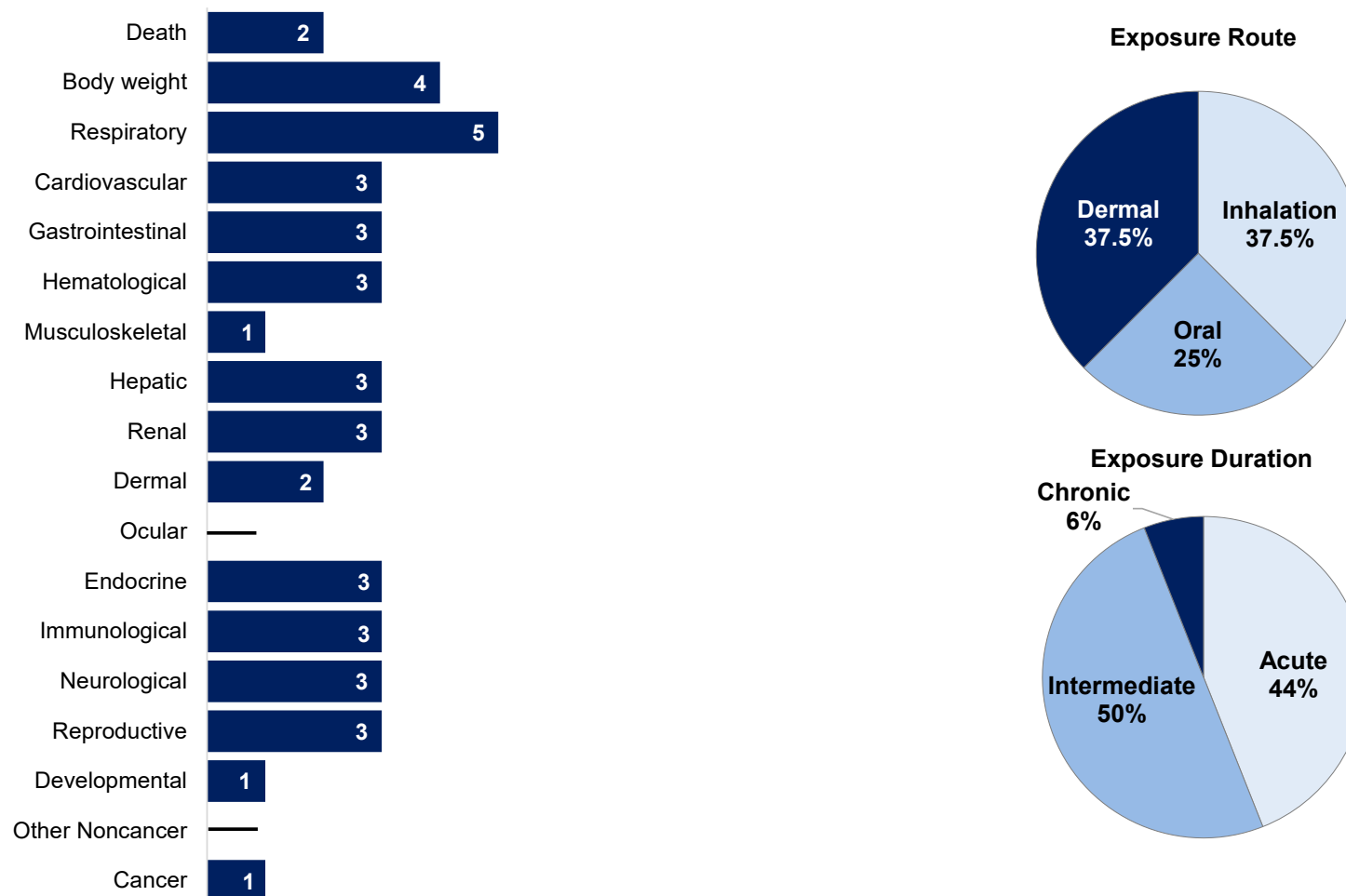
\*Includes studies discussed in Chapter 2. A total of 125 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

## 2. HEALTH EFFECTS

**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)



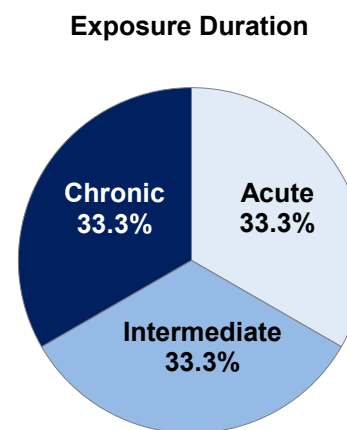
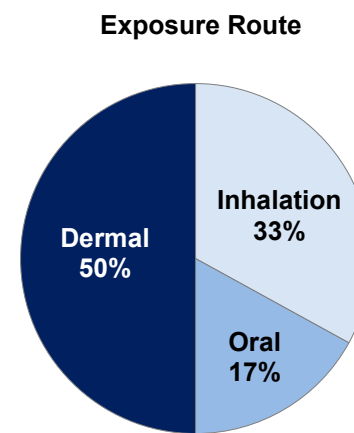
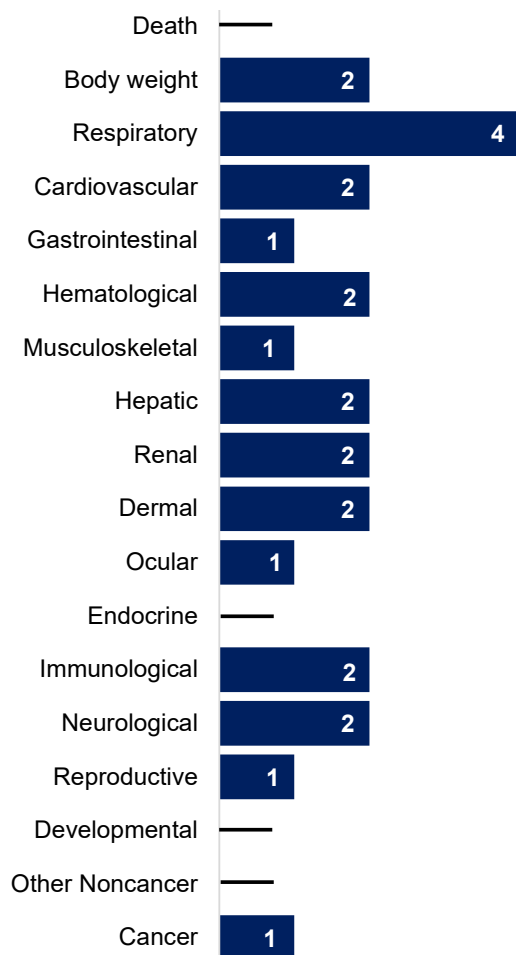
\*Includes studies discussed in Chapter 2. A total of 10 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

## 2. HEALTH EFFECTS

**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 9 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>ACUTE EXPOSURE</b>									
<b>Cichocki et al. 2014</b>									
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
<b>Dodd et al. 2010</b>									
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
<b>Dodd et al. 2010</b>									
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
<b>Dodd et al. 2010</b>									
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 <sup>b</sup>		Minimal severity necrosis of the nasal olfactory epithelium
<b>Dodd et al. 2010</b>									
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
<b>Lee et al. 2005</b>									
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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>West et al. 2001</b>									
7	Rat (Sprague-Dawley) NS/M	Once 4 hours (WB)	0, 2, 10, 30, 75, 100	HP	Resp	100			
<b>Carratt et al. 2016</b>									
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
<b>Carratt et al. 2019b</b>									
9	Mouse (B6:129) NS	Once 4 hours (WB)	0, 5, 10	HP	Resp		5		Epithelial damage (vacuolization and swelling) in proximal airways
<b>Kovalchuk et al. 2020</b>									
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
<b>Li et al. 2017</b>									
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
<b>NTP 1992a</b>									
12	Mouse (B6C3F1) 4–10 M, 4–10 F	14 days 5 days/week 6 hours/day (WB)	0, 10, 30	HE	Hemato	30			

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>Phimister et al. 2004</b>									
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
<b>Phimister et al. 2004</b>									
14	Mouse (Swiss) 4 M	Once 2 hours (WB)	0, 1.5	HP	Resp		1.5		Mild cell loss in olfactory epithelium
<b>West et al. 2001</b>									
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
<b>INTERMEDIATE EXPOSURE</b>									
<b>Dodd et al. 2012</b>									
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 Resp	30 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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>CHRONIC EXPOSURE</b>									
<b>NTP 2000 (Abdo et al. 2001)</b>									
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 Resp	60	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



## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>NTP 1992a</b>									
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

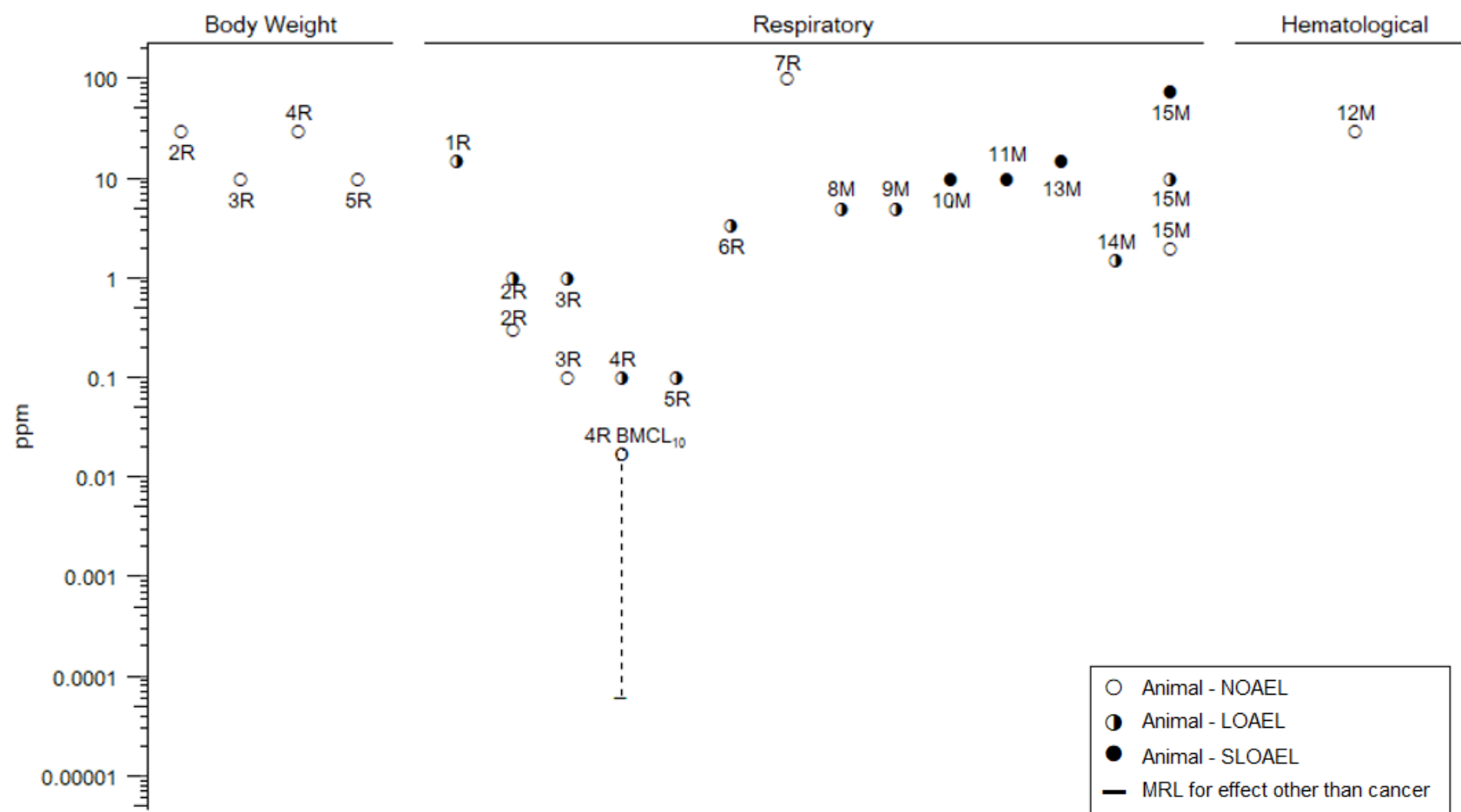
<sup>a</sup>The number corresponds to entries in Figure 2-4.

<sup>b</sup>Used to derive a provisional acute-duration inhalation minimal risk level (MRL) of 0.00006 ppm ( $6 \times 10^{-5}$  ppm) for naphthalene based on benchmark dose modeling of nasal olfactory epithelial necrosis incidences in male and female rats. The BMCL<sub>10</sub> of 0.017 ppm was adjusted for continuous exposure and converted to a BMCL<sub>HEC</sub> of 0.0017 ppm. The BMCL<sub>HEC</sub> 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<sub>10</sub> = 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

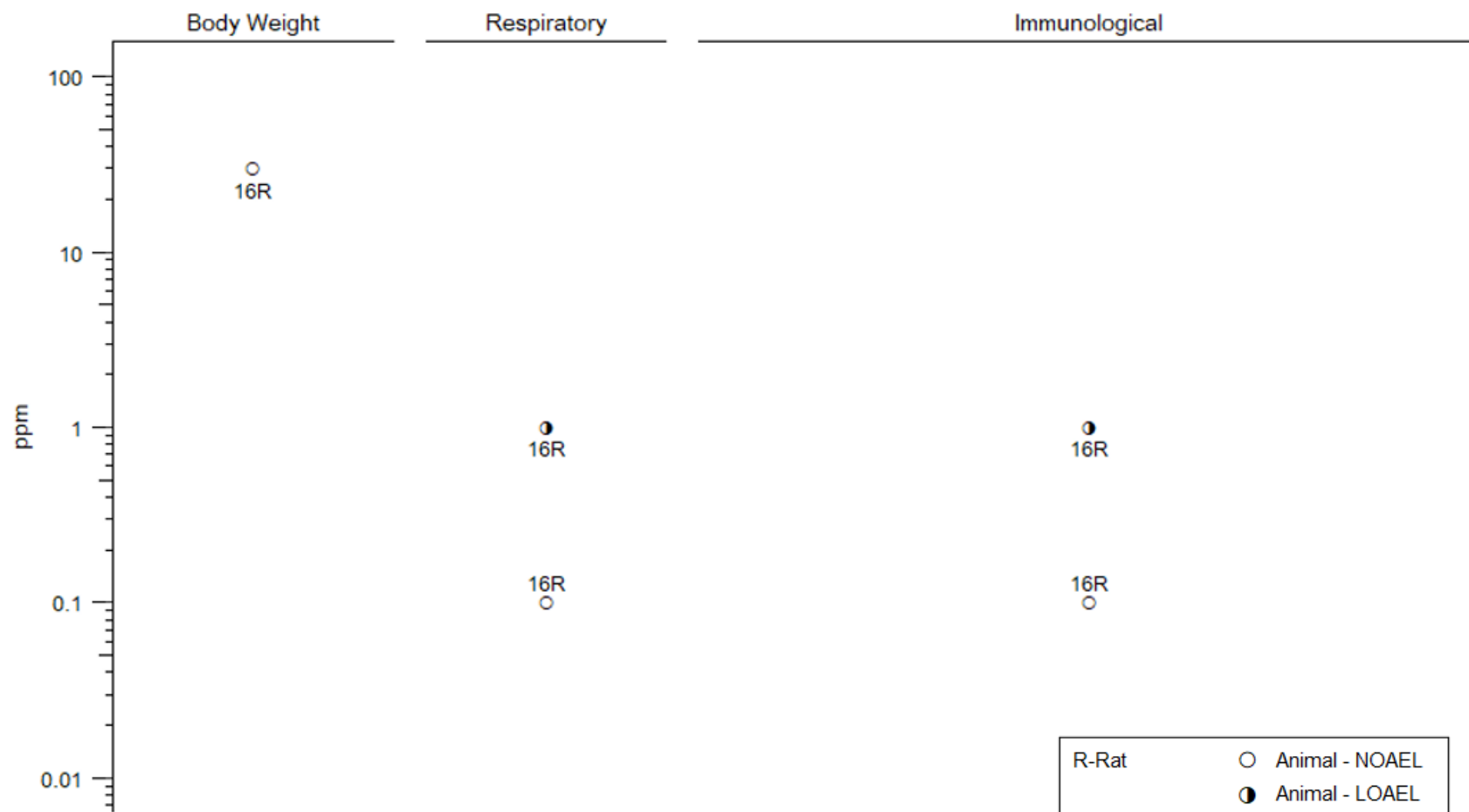
## 2. HEALTH EFFECTS

**Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation**  
Acute ( $\leq 14$  days)



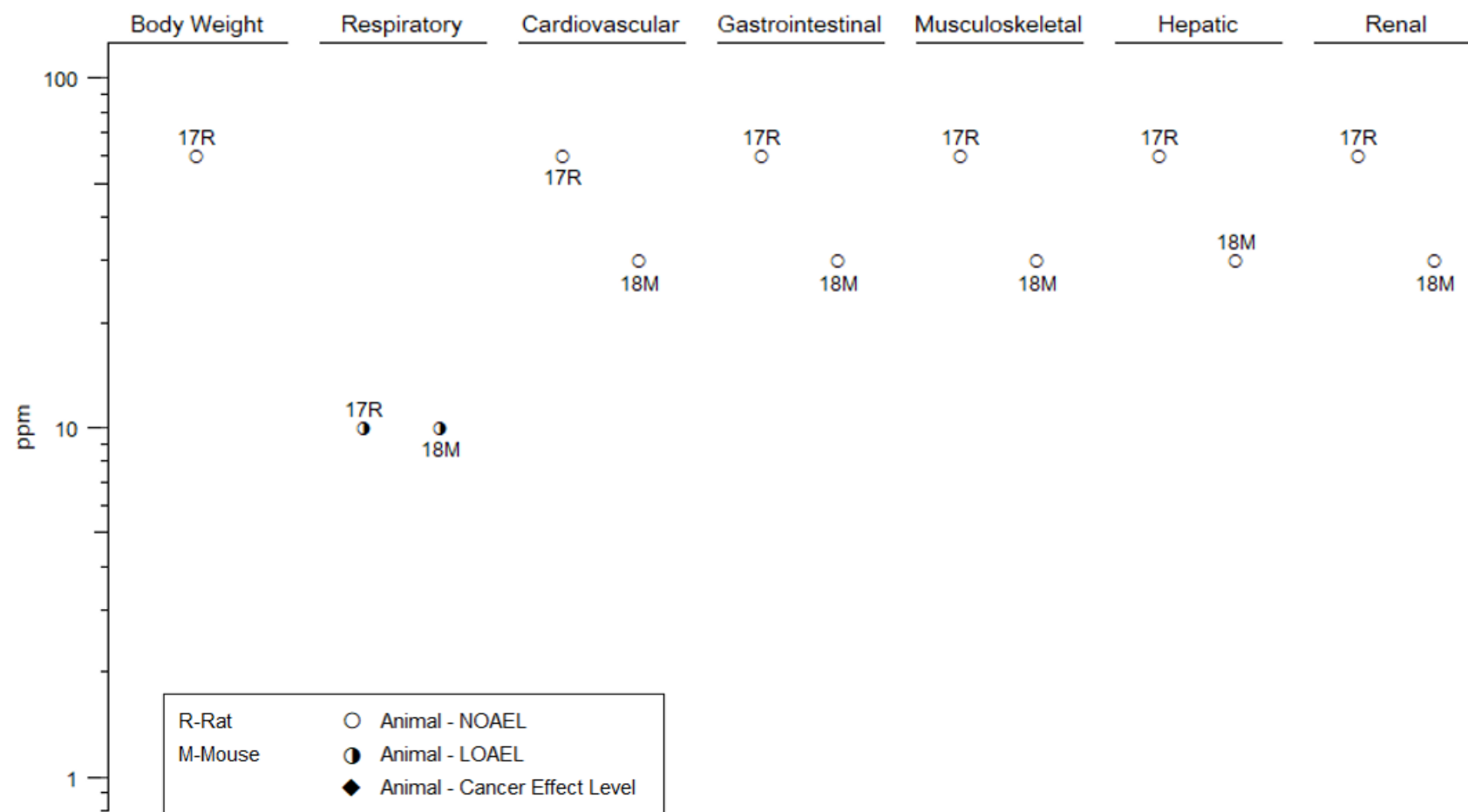
## 2. HEALTH EFFECTS

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



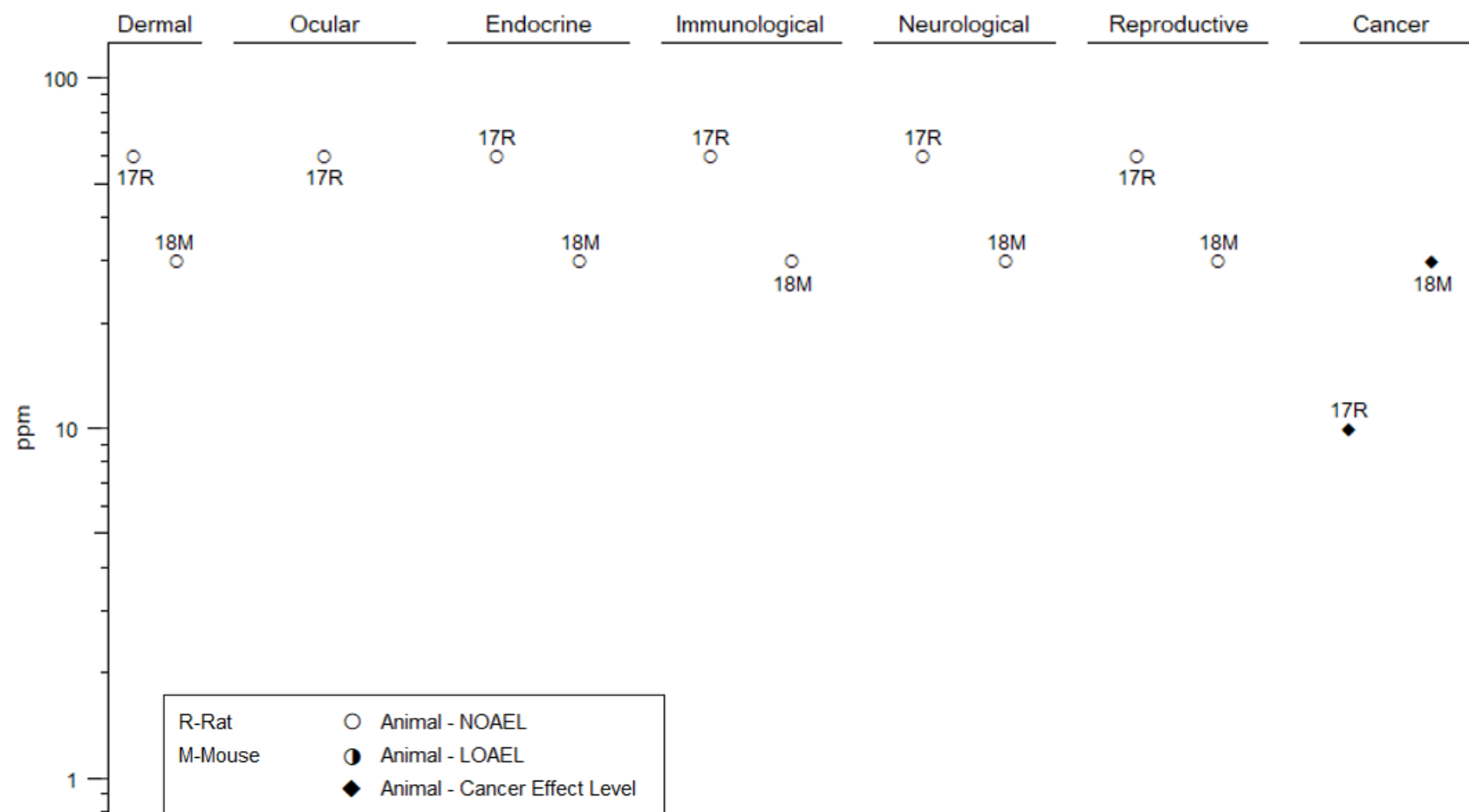
## 2. HEALTH EFFECTS

**Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation**  
Chronic ( $\geq 365$  days)



## 2. HEALTH EFFECTS

**Figure 2-4. Levels of Significant Exposure to Naphthalene – Inhalation**  
Chronic ( $\geq 365$  days)



## 2. HEALTH EFFECTS

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

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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>Kelty et al. 2020</b>									
6	Mouse (B6C3F1) 3–5 M, 3–5 F	Once (GO)	0, 150	HP	Resp		150		Respiratory epithelial cytotoxicity
<b>Plasterer et al. 1985</b>									
7	Mouse (CD-1) 33–45 F	GDs 7–14 (GO)	0, 300	BW, DX, RX	Death Develop	300		300	5/33 died
<b>Plasterer et al. 1985</b>									
8	Mouse CD-1 10 F	8 days (GO)	0, 125, 250, 500, 1,200, 2,000	LE, BW	Death			354	LD <sub>50</sub>
<b>Shopp et al. 1984</b>									
9	Mouse (CD-1) 116–188 M 116–188 F	14 days (GO)	0, 27, 53, 267	BW, HE, BC, OW	Death Bd wt	53	267	267	10/96 males and 3/60 females died 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			
<b>Shopp et al. 1984</b>									
10	Mouse (CD-1) 8 M, 8 F	Once (GO)	200, 400, 600, 800, 1,000	CS, GN	Death			710 F 533 M	LD <sub>50</sub>

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>Zhang et al. 2015</b>									
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
<b>Zhang et al. 2016</b>									
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
<b>NTP 1992b</b>									
13	Rabbit (New Zealand White) 20–23 F	GDs 6–19 (GO)	0, 20, 80, 120	BW, DX	Develop	120			
<b>Texaco 1985d, 1986</b>									
14	Rabbit (New Zealand White) 18 F	GDs 6–18 (G)	0, 40, 200, 400	BW, FI, CS, DX, RX	Resp Neuro		200	200	Maternal dyspnea and cyanosis Maternal body drop and hypoactivity with no pathological changes
					Develop	400			



## 2. HEALTH EFFECTS

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

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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>Murano et al. 1993</b>									
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
<b>NTP 1980b</b>									
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			
<b>Patel and Patel 2018</b>									
23	Rat (Wistar) 6 M, 6 F	28 days (GO)	0, 1,000	OP	Ocular			1,000	Cataracts

## 2. HEALTH EFFECTS

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

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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>NTP 1980a</b>									
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 Resp Cardio Gastro Hemato Hepatic Renal Ocular Neuro Repro	200 200 200 200 200 200 200 200 200 200			
<b>Shopp et al. 1984</b>									
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 Resp Hemato Hepatic Renal Immuno Neuro Repro	133 133 53 F 53 F 133 133 133 133 M	133 F 133 F		Decrease in absolute and relative spleen weight in females Decreased absolute liver weights in females
<b>Darious et al. 2020</b>									
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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>Orzalesi et al. 1994</b>									
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
<b>Rossa and Pau 1988</b>									
35	Rabbit (Chinchilla Bastard New Zealand White) 4 NS	12 weeks 2 days/week (GO)	0, 1,000	OP, CS	Ocular			1,000	Cataracts
<b>van Heyningen and Pirie 1967</b>									
36	Rabbit (NS) NS	4 weeks 7 days/week (GO)	0, 1,000	OP, CS	Ocular			1,000	Cataracts, retinal damage

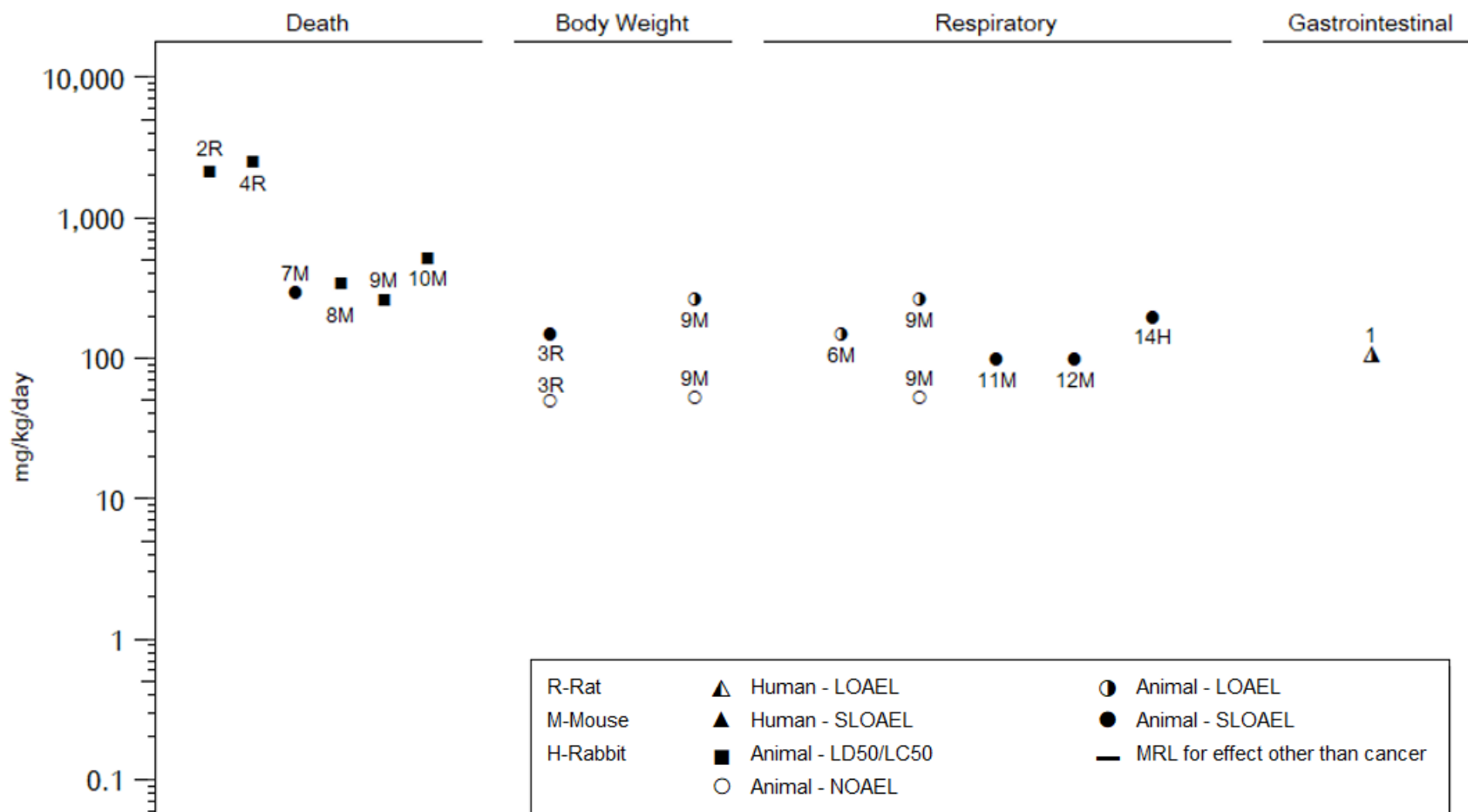
<sup>a</sup>The number corresponds to entries in Figure 2-5.

<sup>b</sup>Used to derive a provisional 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. The acute-duration oral MRL was adopted as the provisional 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<sub>50</sub> = 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

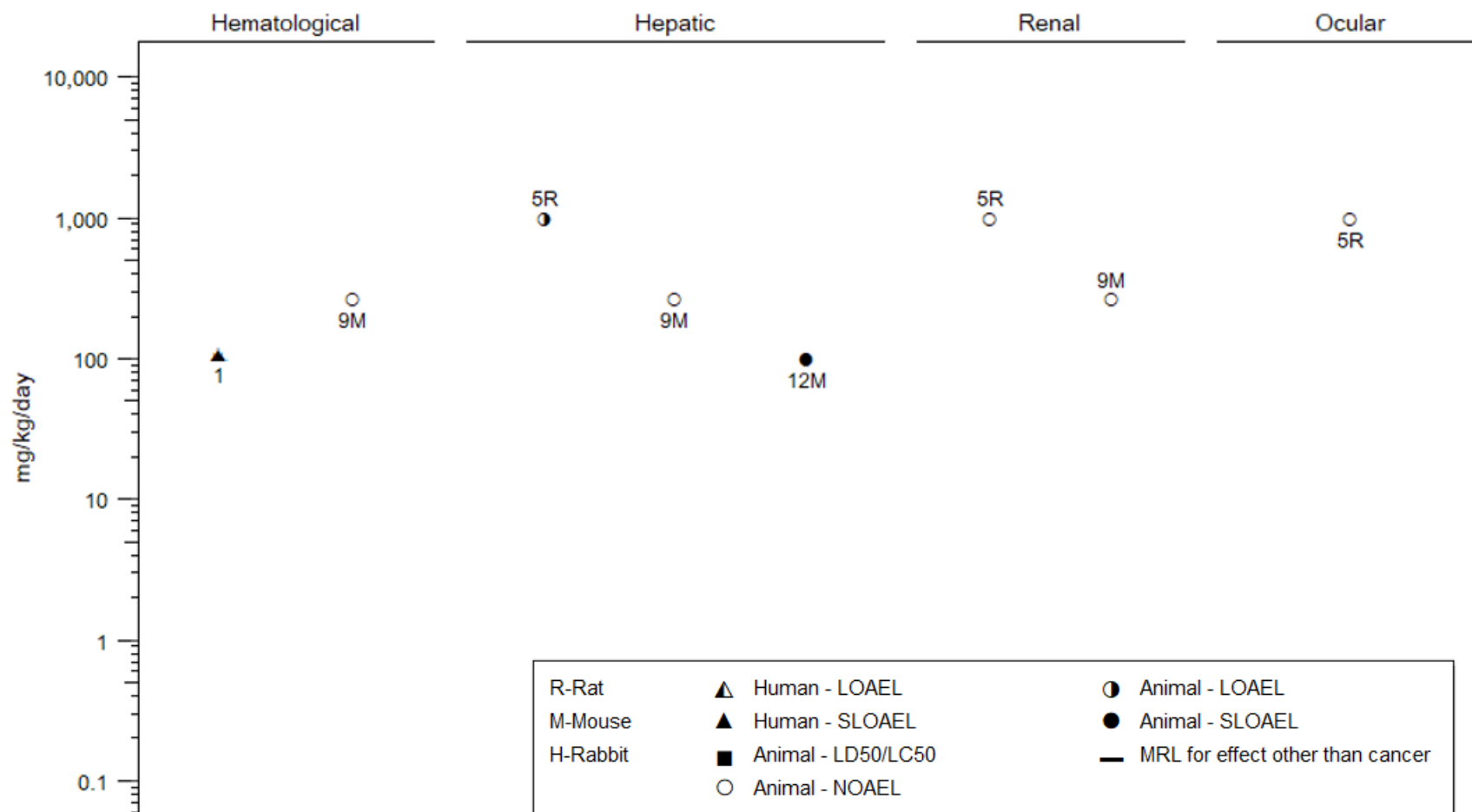
## 2. HEALTH EFFECTS

**Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral**  
Acute ( $\leq 14$  days)



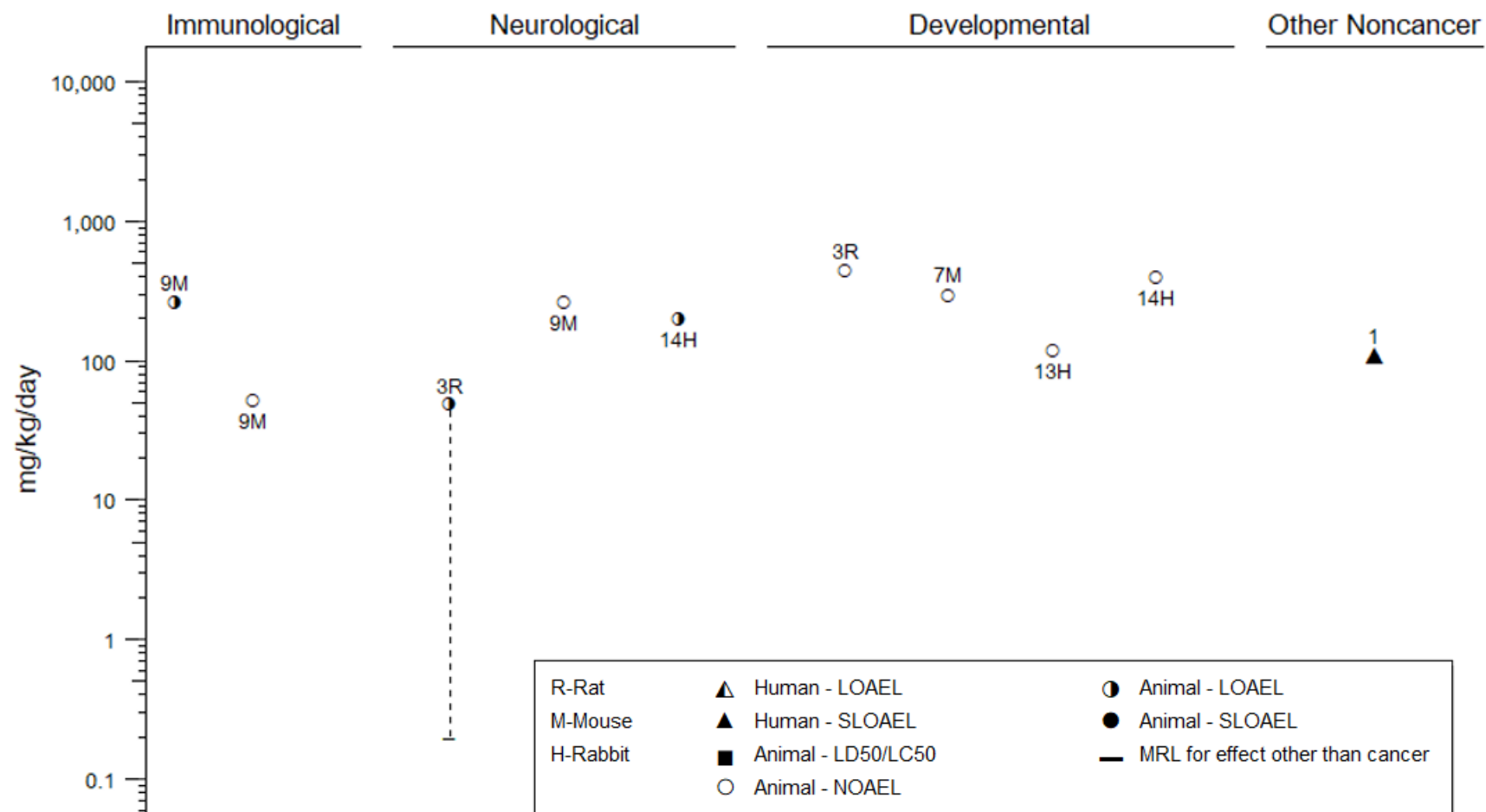
## 2. HEALTH EFFECTS

**Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral**  
Acute ( $\leq 14$  days)



## 2. HEALTH EFFECTS

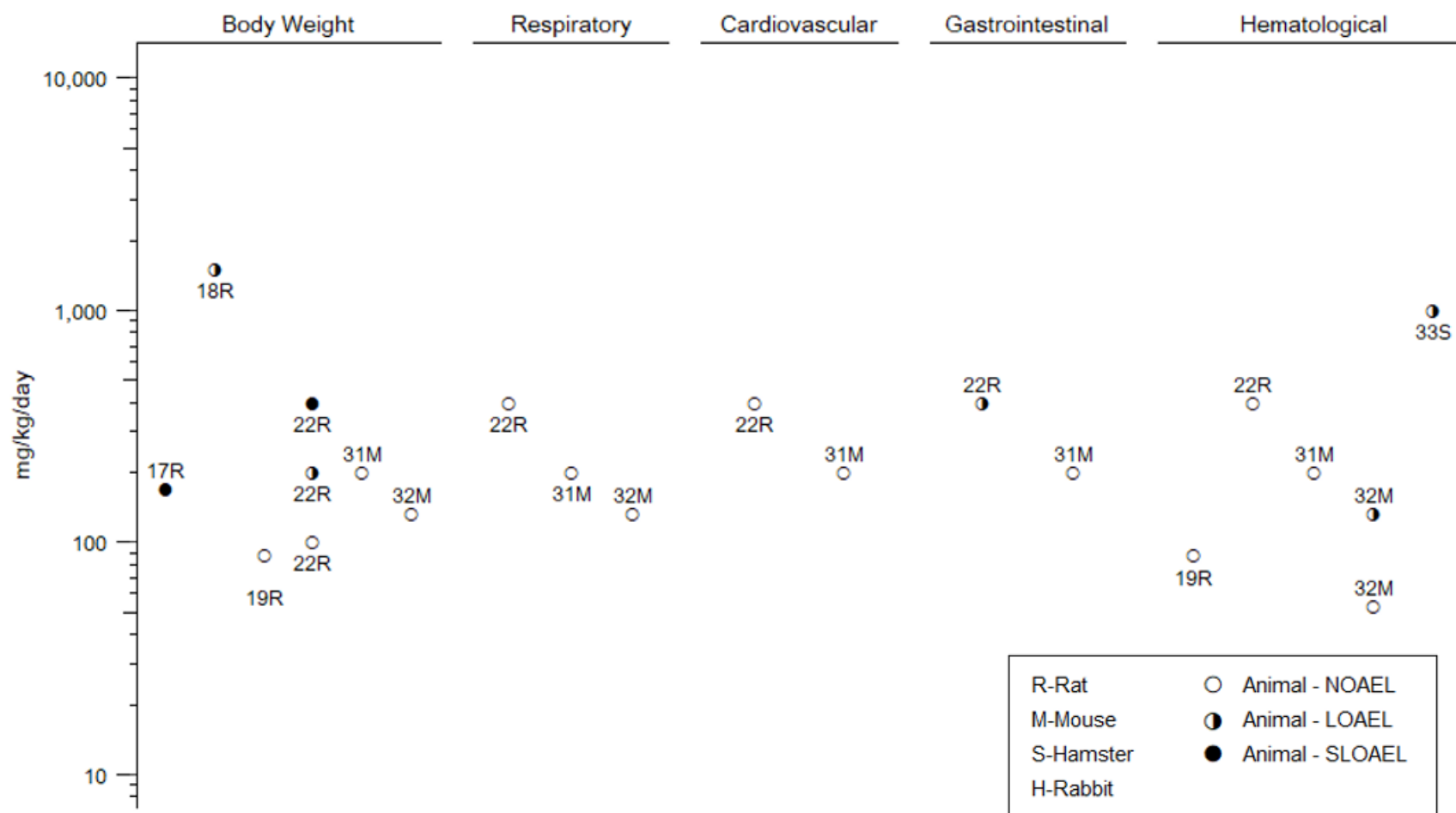
**Figure 2-5. Levels of Significant Exposure to Naphthalene – Oral**  
Acute ( $\leq 14$  days)





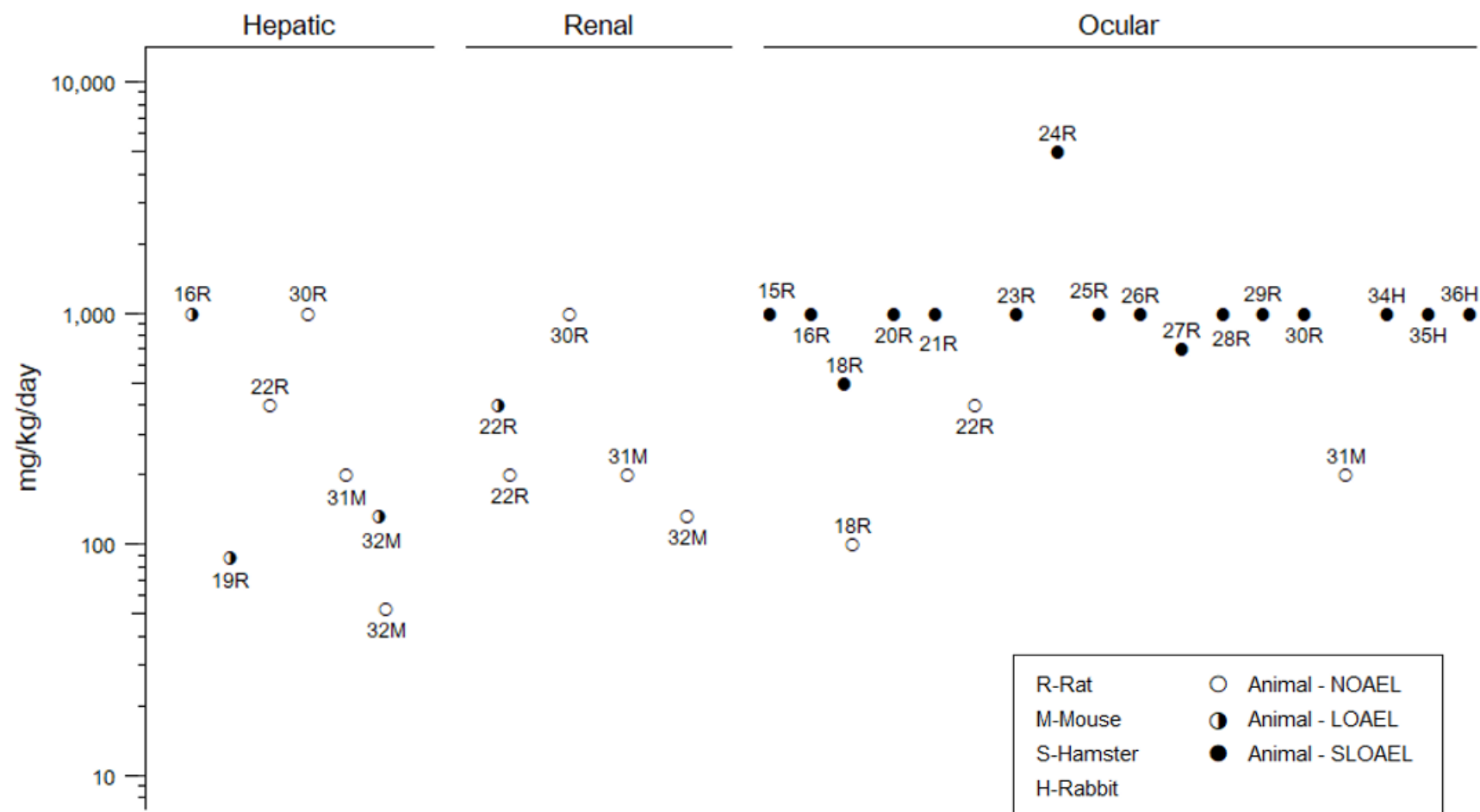
## 2. HEALTH EFFECTS

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



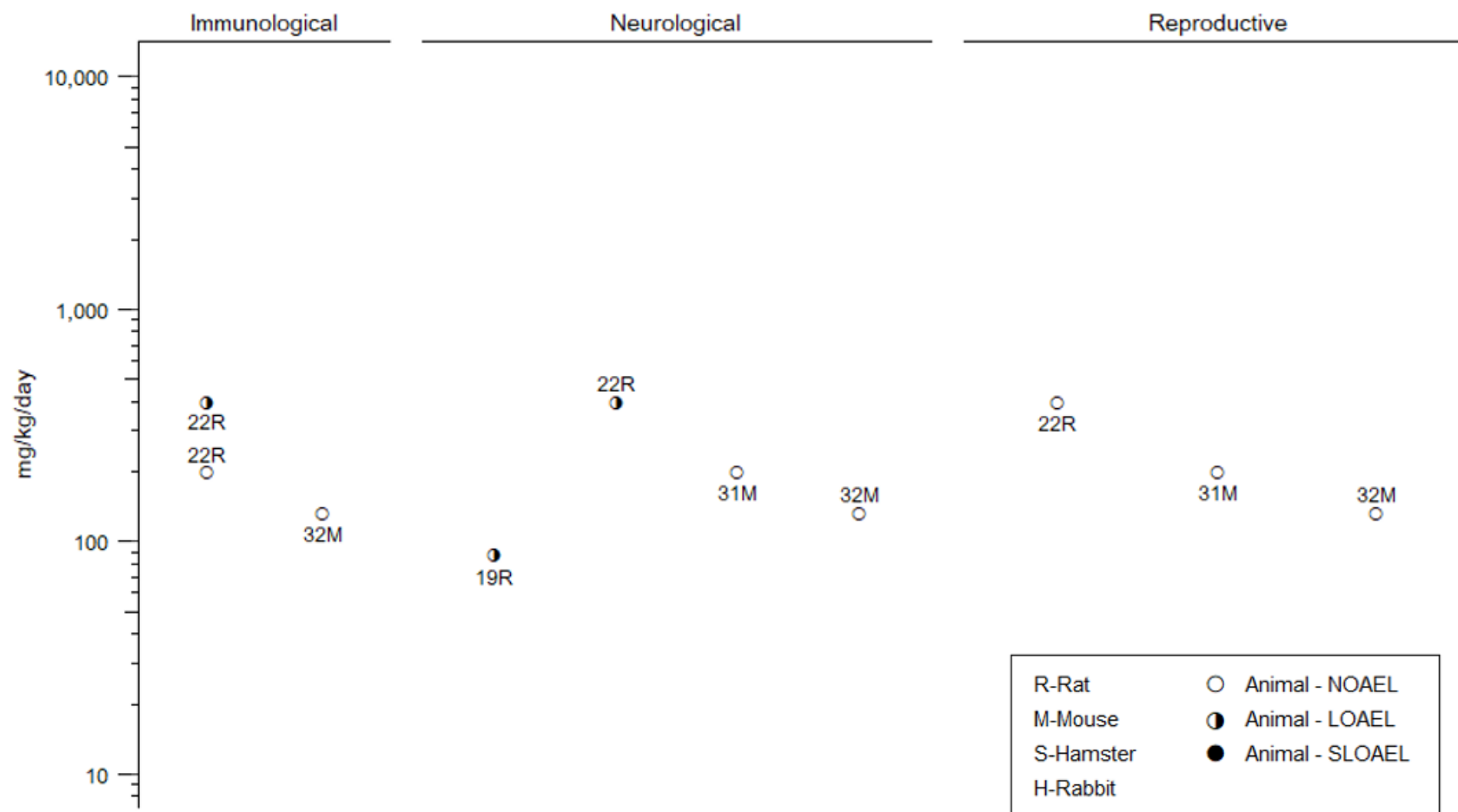
## 2. HEALTH EFFECTS

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



## 2. HEALTH EFFECTS

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



## 2. HEALTH EFFECTS

**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
<b>ACUTE EXPOSURE</b>								
<b>Alalaiwe et al. 2020</b>								
Mouse (NS) NS M	5 days 1 time/day	0, 0.35 mL of 8 mM solution	HP	Dermal	0.35			
<b>Papciak and Mallory 1990; Texaco 1985a</b>								
Rabbit (New Zealand) 3 M, 3 F	4 hours	0, 500 mg	CS	Dermal		500		Reversible erythema
<b>Singh and Singh 2004</b>								
Rabbit (New Zealand) 6 M	24 hours	0, 0.05 mL/3 cm <sup>2</sup> HP		Dermal		0.05		Skin erythema and edema; increased transepidermal water loss, skin temperature, and epidermal thickness; reduced collagen fiber length and thickness
<b>Muhammad et al. 2005</b>								
Pig (NS) 4 NS	1 or 4 days	0, 0.3 mL	HP	Dermal	0.3			
<b>INTERMEDIATE EXPOSURE</b>								
<b>Frantz et al. 1986</b>								
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 Cardio Gastro Hemato Hepatic Renal Dermal	1,000 1,000 1,000 1,000 1,000 1,000 300		1,000	Increased incidence of excoriated skin and papules

## 2. HEALTH EFFECTS

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

						Less		
Species (strain)	Exposure		Parameters			serious	Serious	
No./group	parameters	Doses	monitored	Endpoint	NOAEL	LOAEL	LOAEL	Effects
<b>Papciak and Mallory 1990; Texaco 1985c</b>								
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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>ACUTE EXPOSURE</b>									
<b>Korsak et al. 1998</b>									
1	Rat (Wistar) 10 M	4 hours	0, 26, 44, 70	NX	Neuro	26	44		<b>1-Methylnaphthalene</b> Decreased pain sensitivity
<b>Korsak et al. 1998</b>									
2	Rat (Wistar) 10 M	4 hours	0, 39, 61, 90	NX	Neuro	39	61		<b>2-Methylnaphthalene</b> Decreased pain sensitivity
<b>Świercz and Stępnik 2020</b>									
3	Rat (Wistar) 3 M	5 days 6 hour/day (N)	0, 8.6, 34.4	BW, FI, WI, BC	Bd wt	34.4			<b>1-Methylnaphthalene</b>
<b>INTERMEDIATE EXPOSURE</b>									
<b>Kim et al. 2020</b>									
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 Resp	30 0.5 F	4 F 0.5 <sup>b</sup> M		<b>1-Methylnaphthalene</b> 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			

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
<b>Świercz et al. 2011</b>						<b>2-Methylnaphthalene</b>			
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 <sup>c</sup>		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			

<sup>a</sup>The number corresponds to entries in Figure 2-6.

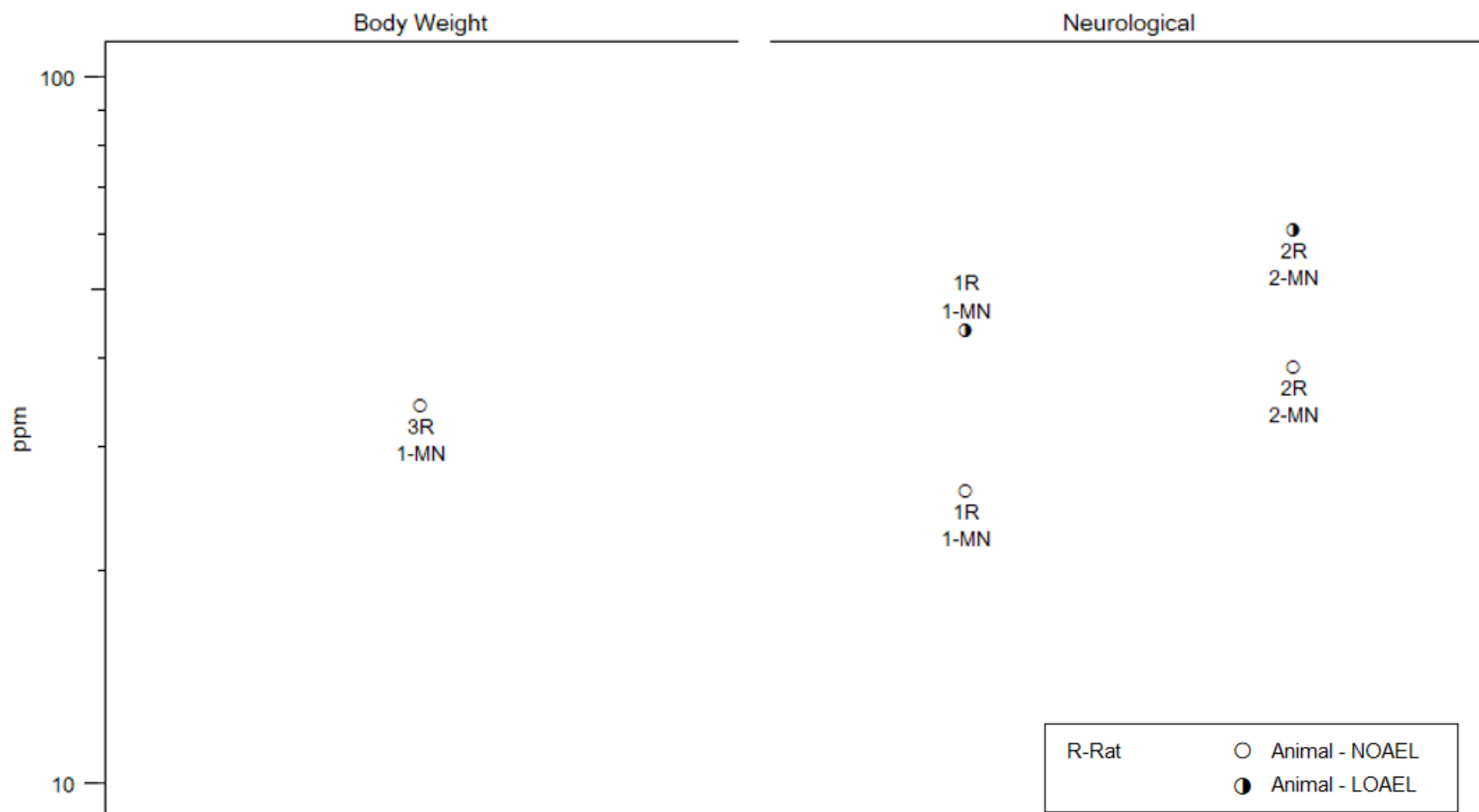
<sup>b</sup>Used to derive a provisional intermediate-duration inhalation minimal risk level (MRL) of 0.00009 ppm ( $9 \times 10^{-5}$  ppm) for 1-methylnaphthalene based on benchmark dose modeling of nasal mucous cell hyperplasia incidences in male rats. The BMCL<sub>10</sub> of 0.06 ppm was adjusted to continuous exposure and converted to a BMCL<sub>HEC</sub> of 0.0027 ppm. The BMCL<sub>HEC</sub> 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.

<sup>c</sup>Used to derive a provisional intermediate-duration inhalation MRL of 0.0003 ppm ( $3 \times 10^{-4}$  ppm) for 2-methylnaphthalene based on the LOAEL. The LOAEL of 0.34 ppm was adjusted to continuous exposure and converted to a LOAEL<sub>HEC</sub> of 0.081 ppm. The LOAEL<sub>HEC</sub> 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<sub>10</sub> = 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

## 2. HEALTH EFFECTS

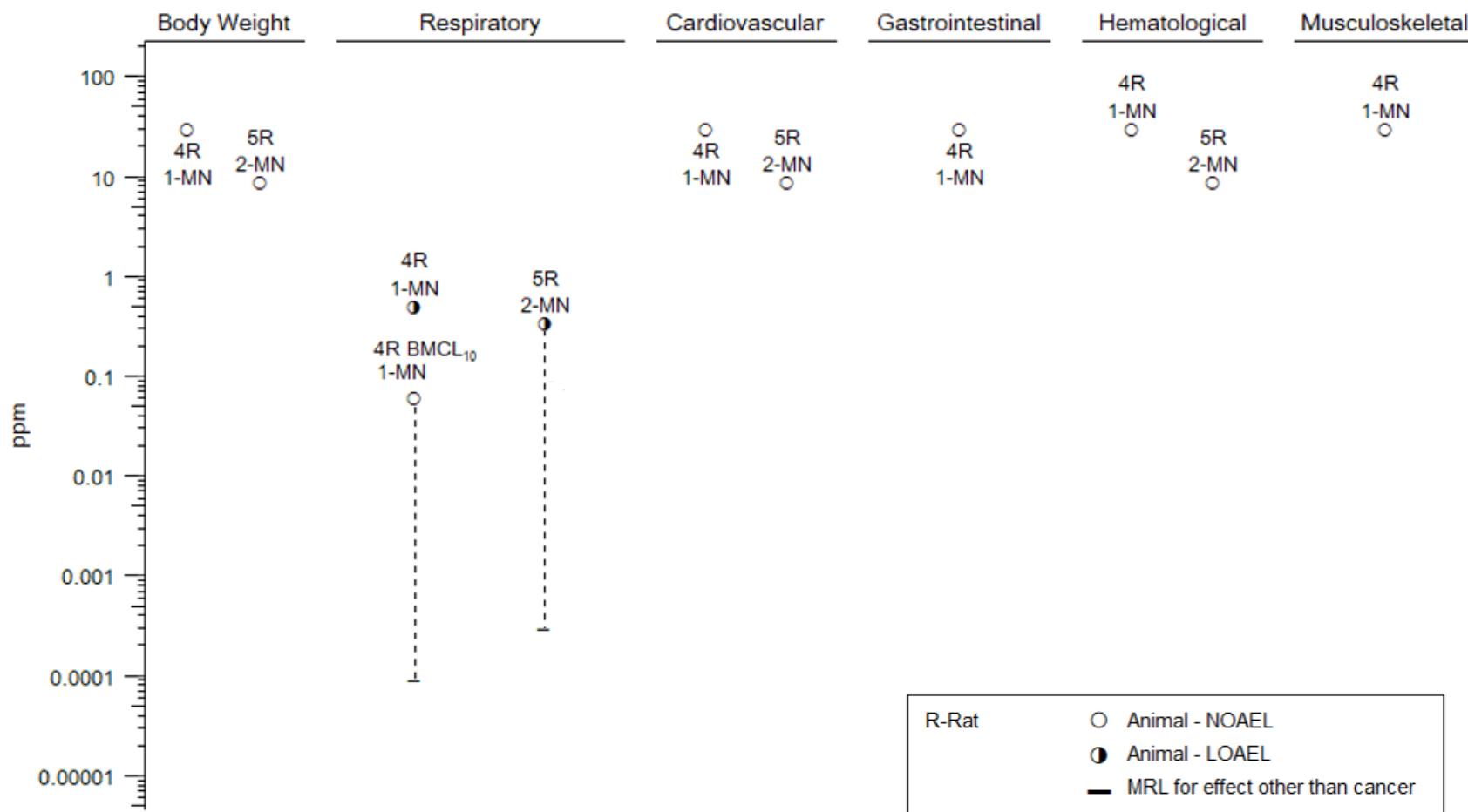
**Figure 2-6. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Inhalation**  
Acute ( $\leq 14$  days)





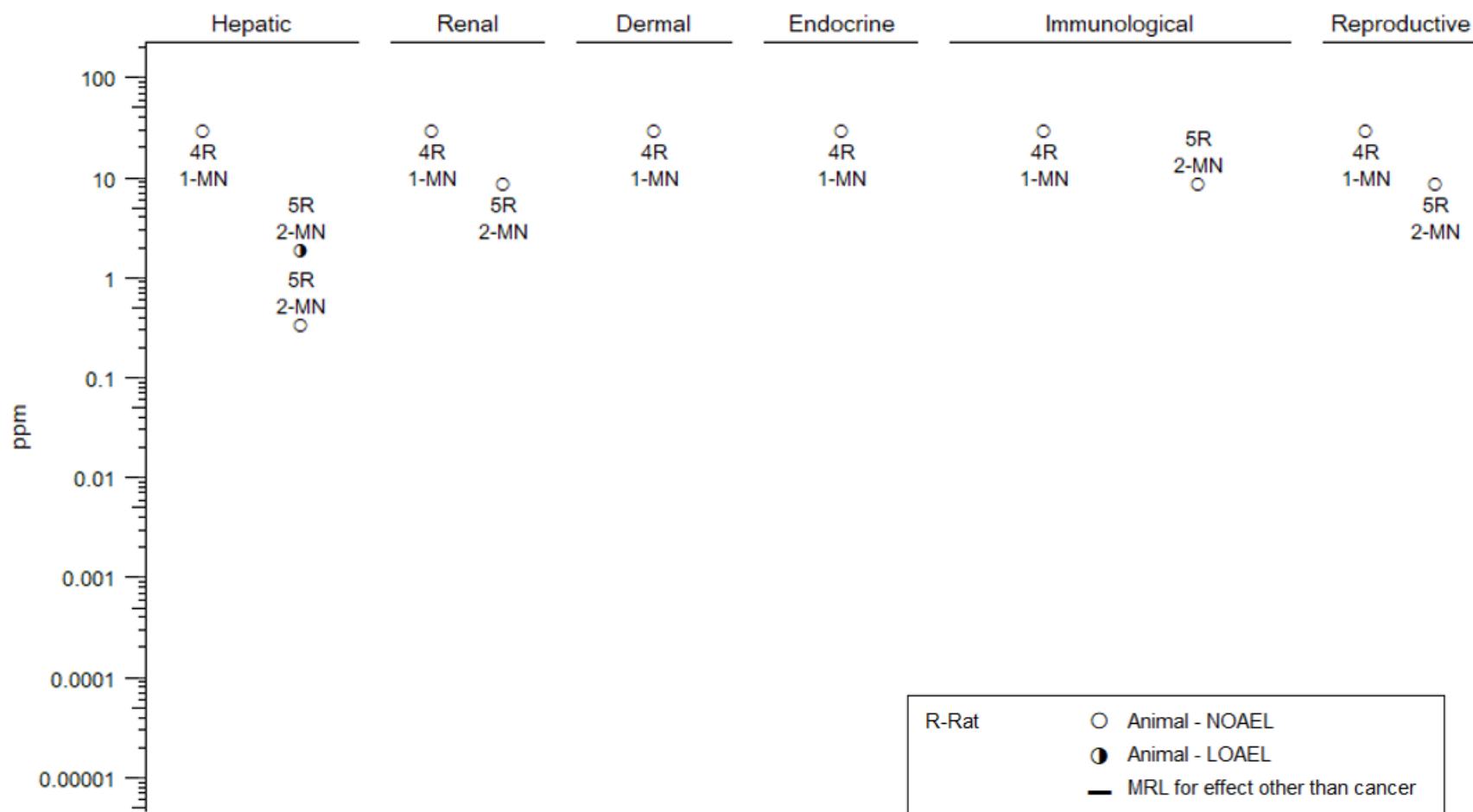
## 2. HEALTH EFFECTS

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



## 2. HEALTH EFFECTS

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



## 2. HEALTH EFFECTS

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

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

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	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
<b>Murata et al. 1997</b>						<b>2-Methylnaphthalene</b>			
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 Resp	113.8	50.3 <sup>d</sup>		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			

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	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

<sup>a</sup>The number corresponds to entries in Figure 2-7.

<sup>b</sup>Used to derive a provisional 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<sub>1SD</sub> 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.

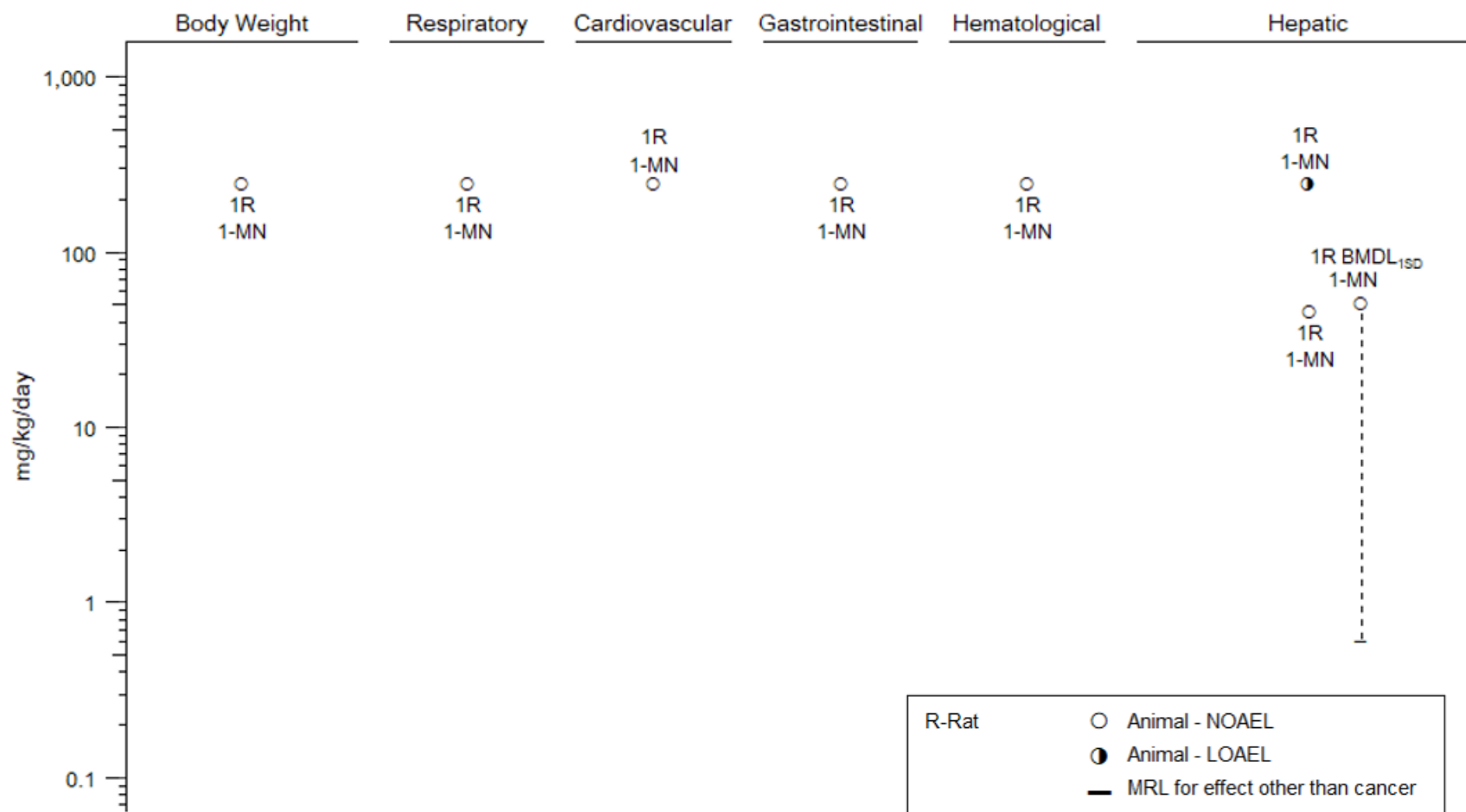
<sup>c</sup>Used to derive a provisional chronic-duration oral MRL of 0.07 mg/kg/day for 1-methylnaphthalene. The LOAEL of 71.6 was divided by an uncertainty factor of 1,000 (10 for animal to human extrapolation, 10 for human variability, and 10 for use of a LOAEL) to derive the MRL; see Appendix A for more detailed information regarding the MRL.

<sup>d</sup>Used to derive a provisional 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<sub>05</sub> 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

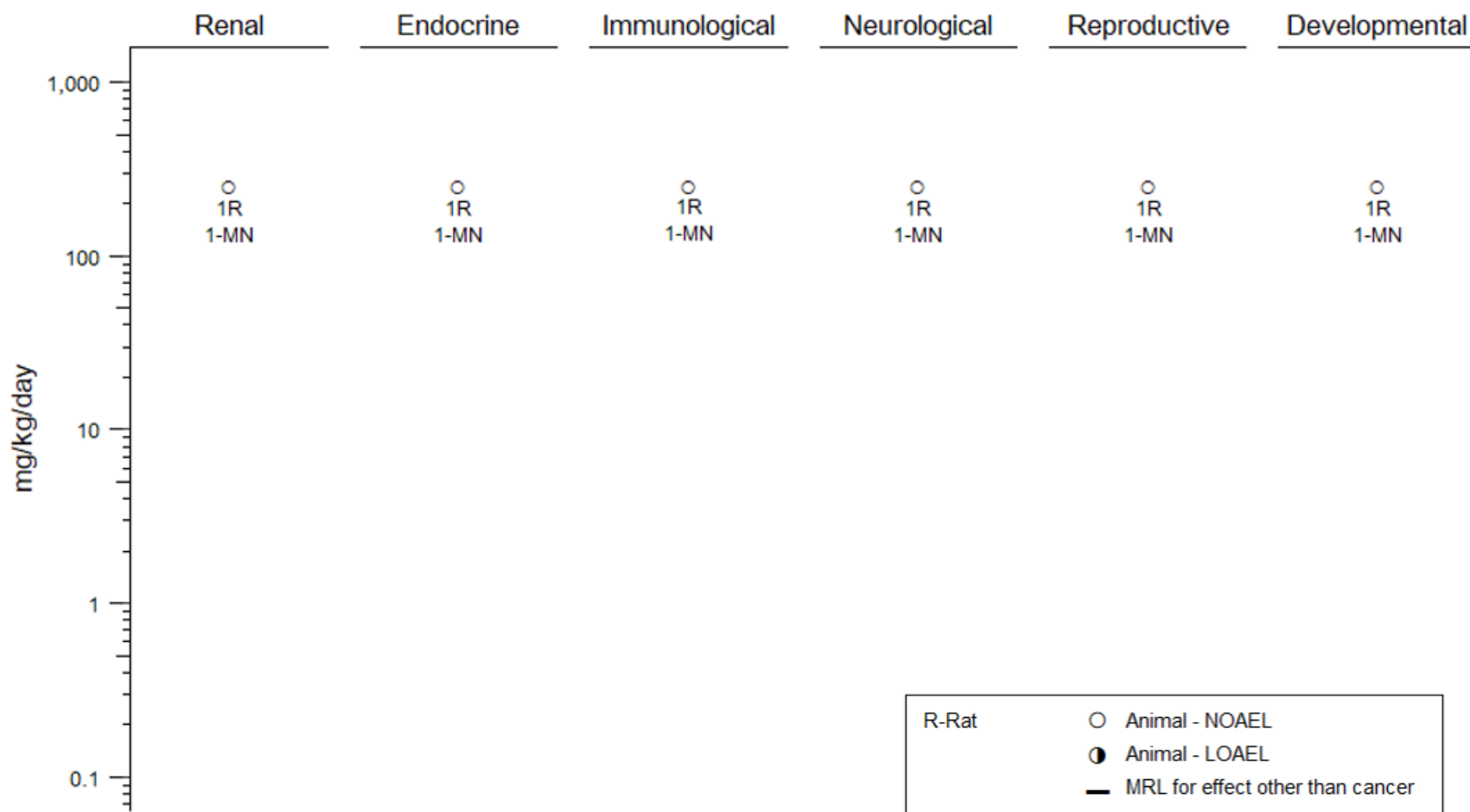
## 2. HEALTH EFFECTS

**Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral**  
Intermediate (15–364 days)



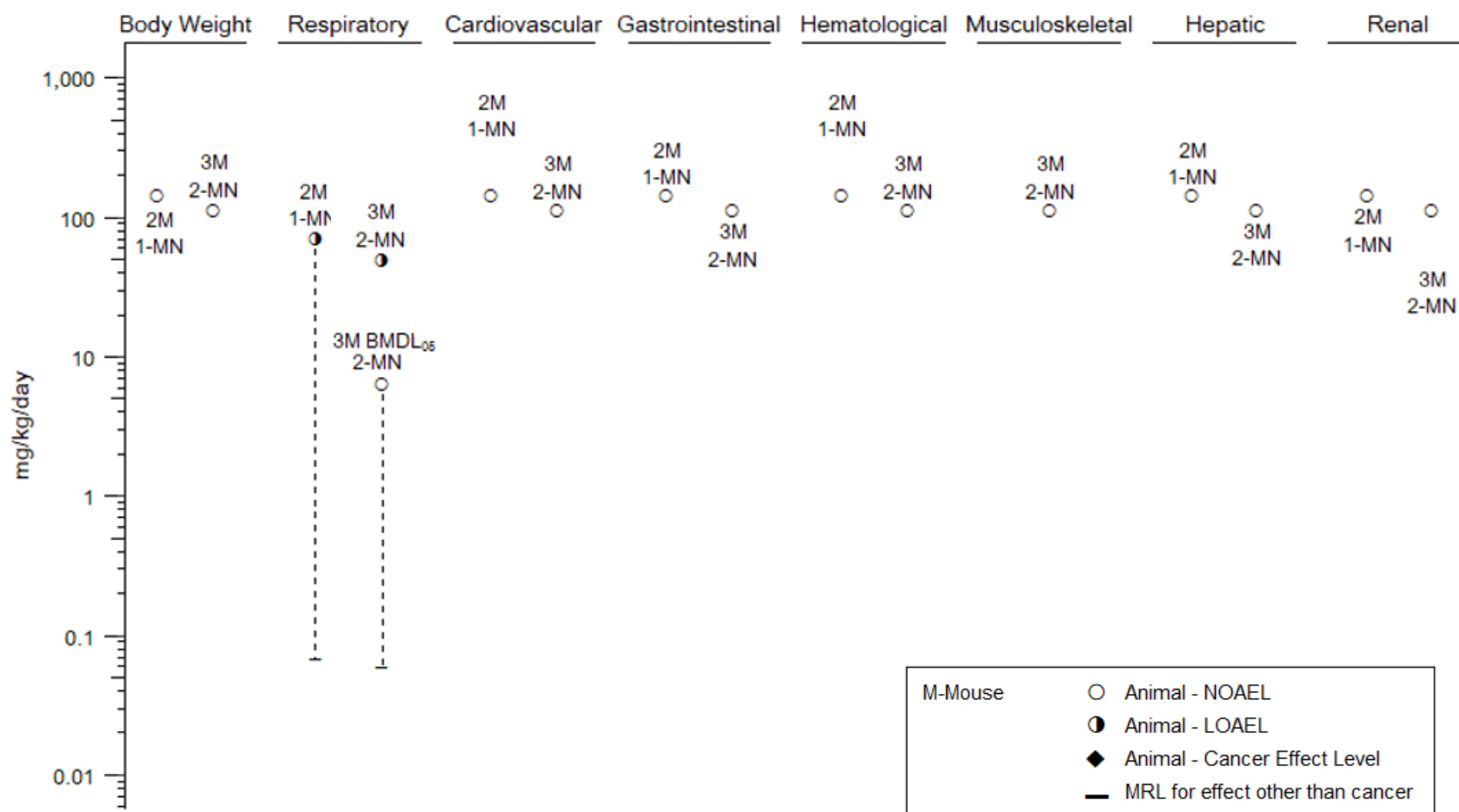
## 2. HEALTH EFFECTS

**Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral**  
Intermediate (15–364 days)



## 2. HEALTH EFFECTS

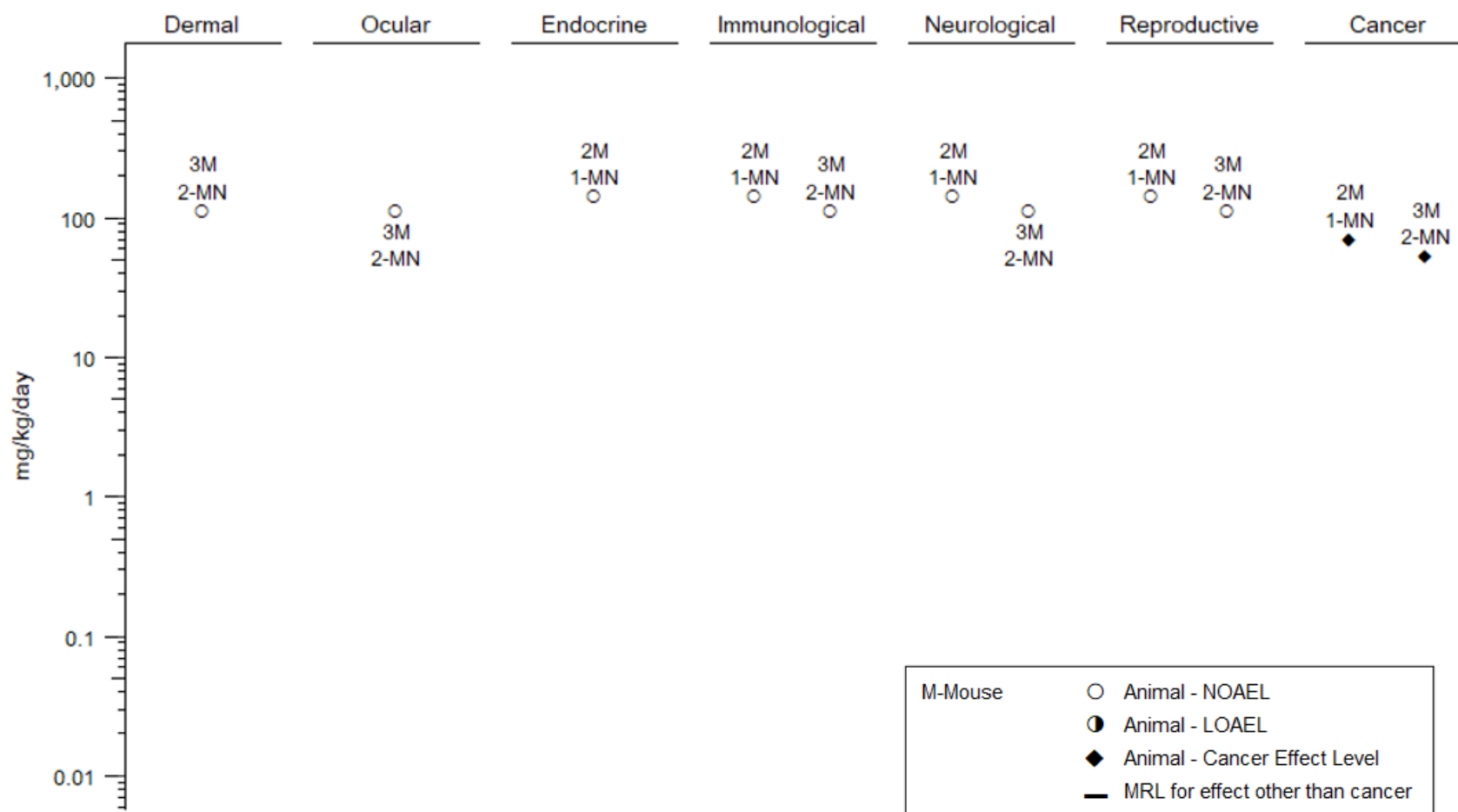
**Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral**  
Chronic ( $\geq 365$  days)





## 2. HEALTH EFFECTS

**Figure 2-7. Levels of Significant Exposure to 1- and 2-Methylnaphthalene – Oral**  
Chronic ( $\geq 365$  days)



## 2. HEALTH EFFECTS

**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
<b>INTERMEDIATE EXPOSURE</b>								
<b>Murata et al. 1992</b>						<b>Mixture of 1- and 2-methylnaphthalene</b>		
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. HEALTH EFFECTS

**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).

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Several animal studies have been conducted to estimate lethal doses of naphthalene. LD<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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

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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.

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 (NTP1992a) 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  $\geq 200$  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-

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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

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2-methylnaphthalene doses  $\geq 276$  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 four studies summarized in Table 2-7. 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<sub>1</sub>], forced vital capacity [FVC], and FEV<sub>1</sub>/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  $\leq 2.5$   $\mu\text{m}$  in diameter [PM<sub>2.5</sub>]) 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<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC or mean forced expiratory flow between 25 and 75% of the FVC [FEF<sub>25-75</sub>]) (Cilluffo et al. 2022).

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**Table 2-7. 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 <sup>3</sup> (mean, [95% CI])	FEV <sub>1</sub> , FVC, and FEV <sub>1</sub> /FVC (all)	↓
			FEV <sub>1</sub> , FVC, and FEV <sub>1</sub> /FVC (females)	↓
			FEV <sub>1</sub> , FVC, and FEV <sub>1</sub> /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 <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC, and FEF <sub>25-75</sub>	↔
	Urinary 2-naphthol	4.84–7.97 µg/g creatinine (range of means over four visits)	Asthma symptom score	↑
			FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC, and FEF <sub>25-75</sub>	↔
Mu et al. 2019 Cohort, 224 adult participants in community-based prospective study, mean age 57 years, China	PM <sub>2.5</sub> particle-bound naphthalene in personal air	3.50 ng/m <sup>3</sup> (mean, all samples)	FVC	↓
			FEV <sub>1</sub>	↔
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 <sup>3</sup> (mean±SD) (referents)	Eye and nasal irritation symptoms; nasal endoscopy score indicative of inflammation	↑
		0.66±0.27 (moderately exposed)		
		6.97±3.10 (highly exposed)		
	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)	Serum club cell secretory protein 16 (CC16)	↓
			Cellular and humoral parameters of nasal lavage fluid and induced sputum	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; CI = confidence interval; FEF<sub>25-75</sub> = mean forced expiratory flow between 25 and 75% of the FVC; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; PM<sub>2.5</sub> = particulate matter ≤2.5  $\mu\text{m}$  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



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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  $\geq 0.1$  ppm resulted in concentration-related increases in the incidences of nasal olfactory epithelial degeneration; in F344 rats, the same lesion was observed at  $\geq 1$  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 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).

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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,

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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

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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

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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, <sup>3</sup>H-thymidine labeling, and/or using immunohistochemistry (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-methylnaphthalene.

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  $\geq 0.34$  ppm, increased incidences of bronchiolar and alveolar mononuclear cell infiltration associated with

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proteinosis at  $\geq 1.89$  ppm, and an increased incidence of peribronchial lymphatic tissue hyperplasia at  $\geq 1.89$  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 methyl-naphthalene 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).

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## 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 2-8. 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). 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 2-8. Summary of Epidemiological Studies of Naphthalene Exposure and Cardiovascular Effects**

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Clark et al. 2012</b> 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	↔
<b>Ranjbar et al. 2015</b> 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	↑

↑ = association with increase; ↓ = association with decrease; ↔ = no association; NHANES = National Health and Nutrition Examination Survey

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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.



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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<sub>50</sub> 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).

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**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 bodies, 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; 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; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Shannon and Buchanan 1982; Tannor and Hutton-Mensah 2019; Uthuman et al. 2019). Changes observed in hematology and blood chemistry in these cases are consistent with

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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 2-9. 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).

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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Kamal et al. 2014</b> 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: $\mu\text{mol/mol-creatinine}$ (mean $\pm$ SD) 3.29 $\pm$ 0.5 (exposed) 0.62 $\pm$ 0.18 (unexposed) 2-naphthol: 1.55 $\pm$ 0.95 (exposed) 0.61 $\pm$ 0.16 (unexposed)	Hemoglobin concentration	↓
			Erythrocyte count	↓
			Mean corpuscular volume	↓
			Leukocyte count	↑
			Platelet count	↔
<b>Sudakin et al. 2011</b> 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 $\pm$ SE) 8.1 $\pm$ 0.5 (males) 8.1 $\pm$ 0.9 (females)	Hemoglobin concentration	↑
			Hematocrit	↑
		2-naphthol (ng/mL) (weighted mean $\pm$ SE) 7.2 $\pm$ 0.5 (males) 6.3 $\pm$ 0.5 (females)	Hemoglobin concentration	↔
			Hematocrit	↔
<b>Wang et al. 2019</b> Cohort, 473 male workers in coke-oven plant and 166 unexposed workers from other facilities, China	Naphthalene in workplace air	21.54 ng/m <sup>3</sup> (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 (Darius et al. 2020). Histopathology of the spleen showed hemolysis in the red pulp and congestion of the white pulp, as well as hemosiderin deposition (Darius et al. 2020).

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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 G6PDH deficiency are more susceptible to naphthalene-induced hemolytic anemia because they are unable to rapidly replenish reduced glutathione. G6PDH 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.

## 2. HEALTH EFFECTS

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  $\geq 1.89$  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

## 2. HEALTH EFFECTS

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  $\geq 10$  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.

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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) 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).



## 2. HEALTH EFFECTS

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.

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.

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

## 2. HEALTH EFFECTS

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.** 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; Ojwang et al. 1985; 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) were noted in two case reports, although urine output was normal in a third (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).

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

## 2. HEALTH EFFECTS

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 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.

## 2. HEALTH EFFECTS

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 (PGE<sub>2</sub>) 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.

## 2. HEALTH EFFECTS

Dietary administration of 1-methylnaphthalene doses up to 140.2 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  $\mu$ L, 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  $\mu$ L, 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,

## 2. HEALTH EFFECTS

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 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

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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

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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).



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***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) or creatinine-adjusted urinary levels of 1- or 2-hydroxynaphthalene in a cohort of Chinese men (Zhu et al. 2009).

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).

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**2-Methylnaphthalene.** No studies of endocrine effects in humans or animals 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 2-10. Lehmann et al. (2001) found an inverse association between air concentrations of naphthalene in children's bedrooms and interferon- $\gamma$  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- $\gamma$ , or tumor necrosis factor  $\alpha$  in cord blood (Lehmann et al. 2002). 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).

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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Lehmann et al. 2001</b> Cohort, 200 children 3 years of age at study initiation, Germany	Naphthalene in child's bedroom air	0.73 $\mu\text{g}/\text{m}^3$ (median)	Sensitization to egg white and/or milk allergens	$\leftrightarrow$
			IFN- $\gamma$ -producing CD8+ T-cells	$\downarrow$
			IL-4-producing T-cells	$\leftrightarrow$

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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Lehmann et al. 2002</b> 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 <sup>3</sup> (median)	IL-4 in cord blood IL-2, IFN-γ, and TNF-α in cord blood	↑ ↔
<b>Lin et al. 2018</b> 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	↑ ↔ ↔
<b>Rhodes et al. 2003</b> 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 <sup>3</sup> (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	↑ ↔

↑ = 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; 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

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100 mg/kg had increased serum levels of inflammatory markers (tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ] 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- Methylanththalene.** 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-Methylanththalene.** 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.

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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-methylnaphthalene 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).

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

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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). There were no changes in the brain weights in mice exposed to naphthalene at

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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<sup>3</sup> 1-methylnaphthalene (44 or 70 ppm), but not after exposure to 152 mg/m<sup>3</sup> (26 ppm) 1-methylnaphthalene (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<sup>3</sup> 2-methylnaphthalene (61 or 90 ppm), but not 229 mg/m<sup>3</sup> (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 2-11. In a cohort of male college students in China, there was a positive association between concentrations of naphthalene bound to airborne particulate matter (PM<sub>2.5</sub>) 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

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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. 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 2-11. Summary of Epidemiological Studies of Naphthalene Exposure and Reproductive Effects**

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Chen et al. 2021</b> Cohort, 656 male college students (median age 20 years), China	PM <sub>2.5</sub> particle-bound naphthalene	0.653 ng/m <sup>3</sup> (mean in 2013; not detected in 2014 samples)	Sperm motility	↑
			Normal sperm morphology	↓
			Sperm concentration, count, DNA stainability, and DNA fragmentation index	↔
			Semen volume	↔



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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
			Serum estradiol	↑
			Serum FSH, LH, prolactin, progesterone, and testosterone	↔
<b>Meeker et al. 2004a</b> 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	↑
<b>Meeker et al. 2004b</b> 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	↑
<b>Meeker et al. 2006</b> 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	↔
<b>Meeker et al. 2008</b> Cross-sectional, 322 adult males, United States	Urinary 1-naphthol	3.23 µg/L (geometric mean, adjusted for specific gravity)	Serum estradiol	↓
			Serum prolactin	↔
<b>Xia et al. 2009</b> 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)		↔
<b>Yang et al. 2017</b> 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	↓
<b>Ye et al. 2020</b> 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	↓
<b>Yin et al. 2017</b>	Umbilical cord serum	30.5 (22.1–40.6) ng/g lipid (median [IQR])	Umbilical cord blood serum anti-mullerian hormone	↓

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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
Cohort, 109 mother-child pairs, China	naphthalene		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<sub>2.5</sub> = 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).

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**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-methylnaphthalene 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 2-12. 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

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(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. 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).

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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Agarwal et al. 2022</b> Cross-sectional, 110 pregnant women aged 18–40 years, India	Naphthalene in placental tissue	0.54±1.62 µg/L (mean±SD)	Birth weight	↔
<b>Bushnik et al. 2020</b> 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	↑
<b>Dehghani et al. 2022</b> Birth cohort, 126 pregnant women aged 18–44 years, Iran	Naphthalene in maternal serum	327.91 ng/g lipid (mean±SD)	Birth weight, length, head circumference, and Apgar score	↔
<b>Khalili Doroodzani et al. 2021</b> Cross-sectional, 199 pregnant women, average age 39 years, Iran	Naphthalene in cord serum	66.17 µg/L (mean, petrochemical area)	Birth length	↓
		61.97 µg/L (mean, urban area)	Birth weight and head circumference	↔
	Naphthalene in maternal serum	96.18 µg/L (mean, petrochemical area)	Birth weight, length, and head circumference	↔
<b>Nie et al. 2018</b> 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	↔
<b>Scinicariello and Buser 2014</b> 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)	BMI z-score	↑
		2-naphthol: 2,530.30 ng/L	Waist circumference	↑
			Overweight	↔
			Obesity	↑

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

Reference, study type, and population	Exposure metric	Concentration	Outcome evaluated	Result
<b>Wang et al. 2014</b> 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	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; BMI = body mass index; NHANES = National Health and Nutrition Examination Survey; SD = standard deviation

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- Methyl naphthalene.** 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).

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**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).

A meta-analysis 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). Association 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 industry (Garcia-Perez et al. 2020).

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;

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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

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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 tract 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. 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). 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. Results from genotoxicity tests for naphthalene have been predominately (but not completely) negative, and, mechanistic understanding of naphthalene's carcinogenic mode of action is too incomplete to rule out the possibility of a genotoxic mode of action. Key issues that remain unexplained or unstudied include:

- the possible significance of the positive genotoxicity results that have been obtained, including: induction of reverse mutations in *Salmonella typhimurium* by 1,2-naphthoquinone (Flowers-Geary et al. 1994); DNA adducts detected by accelerator mass spectrometry in mouse and primate airways exposed to naphthalene or 1,2-naphthoquinone *ex vivo* (Buchholz et al. 2019; Carratt et al. 2019a); *in vitro* formation of N-7 guanine adducts of DNA by 1,2-naphthoquinone (McCoull et al. 1999); reverse mutations for luminescence in the marine bacteria, *Vibrio fischeri*, by naphthalene (Arfsten et al. 1994); induction of sister chromatid exchanges in Chinese hamster ovary cells by naphthalene (NTP 1992a) and in human mononuclear leukocytes by 1,2- or 1,4-naphthoquinone (Wilson et al. 1996); induction of micronuclei in human lymphoblasts (Recio et al. 2012); induction of chromosomal aberrations in Chinese hamster ovaries (NTP 1992a) and preimplantation mouse embryos by naphthalene (Gollahon 1990); induction of somatic mutations and recombination in *Drosophila melanogaster* by naphthalene (Delgado-Rodriguez et al. 1995); induction of DNA damage in Chinese hamster lung fibroblasts by naphthalene (Platt et al. 2008) and in human lymphocytes by naphthalene, 1-naphthol, and 2-naphthol (Kapuci et al. 2014); induction of DNA damage in the liver, brain, and lung of mice exposed *in vivo* (Bagchi et al. 1998, 2000, 2002; Karagiannis et al. 2012); and weak (about 2-fold) induction of micronuclei in red blood cells from *Pleurodeles waltl* larvae by naphthalene (Djomo et al. 1995).



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- the lack of a mechanistic explanation of why nearly all rats and mice develop nasal nonneoplastic lesions following chronic-duration exposure to naphthalene at concentrations  $\geq 10$  ppm, but only some rats develop nasal tumors.
- the lack of a mechanistic explanation of why both male and female mice exposed to naphthalene show similar incidences of chronic lung inflammation following chronic-duration exposure to 10 or 30 ppm, but only female mice showed statistically significant increased incidence of lung tumors.

**1-Methylnaphthalene.** Long-term exposure (81 weeks) of mice to 71.6 or 140.2 mg/kg/day 1-methylnaphthalene 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.** *In vitro* studies of genotoxicity are summarized for naphthalene (Table 2-13) and its metabolites (Table 2-14) in bacterial mutation assays, *in vitro* eukaryotic gene mutation, cytogenetic, or DNA damage assays. Tables 2-15 (naphthalene) and 2-16 (naphthalene metabolites) summarize data for *in vivo* eukaryotic gene mutation, cytogenetic, or DNA damage assays in humans and animals.

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**Table 2-13. Genotoxicity of Naphthalene *In Vitro***

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
<i>Salmonella typhimurium</i>	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
<i>S. typhimurium</i>	DNA damage (SOS uma test)	–	–	Nakamura et al. 1987
<i>Escherichia coli</i>	DNA damage (SOS)	–	–	Mamber et al. 1984; Mersch-Sundermann et al. 1993
<i>E. coli</i>	DNA damage (Poly-A)	–	–	Mamber et al. 1983
<i>Vibrio fischeri</i> 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 (abstract only)
Human lymphoblasts (TK6)	Micronuclei	+	NT	Recio et al. 2012
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	NT	+	Platt et al. 2008
Human lymphocytes	DNA damage	NT	+	Kapuci et al. 2014
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

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**Table 2-13. Genotoxicity of Naphthalene *In Vitro***

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Mouse (BALB/c) whole mammary gland cultures	Cell transformation	NT	–	Tonelli et al. 1979
Mouse BALB/c 3T3 cell culture	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 2-14. Genotoxicity of Naphthalene Metabolites *In Vitro***

Species (test system)	Endpoint	Results		Reference	Metabolite
		Activation			
		With	Without		
<i>Salmonella typhimurium</i>	Gene mutation	–	–	McCann et al. 1975; Narbonne et al. 1987	1-naphthol
<i>S. typhimurium</i>	Gene mutation	–	–	Sakai et al. 1985	1,4-naphthoquinone
<i>S. typhimurium</i>	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
Commercially purchased DNA	DNA adduct formation	NT	+	Saeed et al. 2007	1,2-naphthoquinone
Commercially purchased DNA	DNA adduct formation	NT	+	Saeed et al. 2007	1,2-dihydroxynaphthalene
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, 2-naphthol

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

Species (test system)	Endpoint	Results		Reference	Metabolite
		Activation			
		With	Without		
Rat primary hepatocytes	Unscheduled DNA synthesis	NT	–	Probst et al. 1981	1-naphthol, 2-naphthol

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

**Table 2-15. Genotoxicity of Naphthalene *In Vivo***

Species and tissue	Endpoint	Results	Reference
<i>Drosophila melanogaster</i>	Mutations	+	Delgado-Rodriguez 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
SENCAR mice, epidermis	DNA adducts	+	Saeed et al. 2009
Mouse and primate lungs (exposed ex vivo)	DNA adducts	+	Carratt et al. 2019a
Mouse lung	DNA adducts	–	Buchholz et al. 2019
Human peripheral lymphocytes	DNA adducts	+	Zhu et al. 2016
Human peripheral White blood cells	DNA adducts (8-OHdG)	+	Marczynski et al. 2011; Marczynski et al. 2005
Human urine	DNA adducts	+	Baek et al. 2021; Hanchi et al. 2017
Rat liver	DNA damage (single-strand breaks)	+	Kitchin et al. 1992, 1994
Mouse liver, brain	DNA damage	+	Bagchi et al. 1998, 2000, 2002
Mouse lung	DNA damage	+	Karagiannis et al. 2012
Human peripheral white blood cells	DNA damage	+	Marczynski et al. 2011; Marczynski et al. 2005
Human peripheral white blood cells	DNA damage	–	Krieg et al. 2012
F344 partially hepatectomized rats, liver	Neoplastic transformation	–	Tsuda et al. 1980

– = negative result; + = positive result; DNA = deoxyribonucleic acid

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

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

+ = positive result; DNA = deoxyribonucleic acid

*Bacterial assays.* Naphthalene was not mutagenic in *S. 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). 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). 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).

1,2-Naphthoquinone induced reverse mutations in several *S. typhimurium* strains without a metabolic activation system (Flowers-Geary et al. 1996), and naphthalene, in the presence of rat liver metabolic activation, induced reverse mutations in the marine bacterium *Vibrio fischeri* (Arfsten et al. 1994).

*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). However, naphthalene (in the presence of rat liver metabolic activation) induced chromosomal aberrations in Chinese hamster ovary cells (NTP 1992a) and preimplantation whole mouse embryos (Gollahon 1990). Naphthalene also induced sister chromatid exchanges (in the presence or absence of rat liver metabolic activation) in Chinese hamster ovary 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). In contrast,

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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  $\mu$ M) that depleted cellular glutathione levels and induced about 35-45% cell death (Wilson et al. 1996). Naphthalene did not induce cell transformations in several mammalian cell types (see Table 2-13) or DNA single-strand breaks (Sina et al. 1983) or unscheduled DNA synthesis (Barfknecht et al. 1985; Probst et al. 1981) in rat hepatocytes.

*Cell-free systems.* In cell-free test systems (not included in Table 2-13), 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, naphthalene caused DNA strand scission 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 vivo mammalian assays.* *In vivo* studies of genotoxicity endpoints after exposure to naphthalene and its metabolites are summarized in Tables 2-15 and 2-16.

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; Marczyński et al. 2005, 2011;). However, 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 (Marczyński et al. 2011). 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). In addition, a correlation between DNA methylation levels and urinary 2-naphthol was reported in a cohort of male smokers in China (Zhu et al. 2016).

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

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single oral doses of 359 mg/kg (Kitchin et al. 1992, 1994) or transformation foci ( $\gamma$ -glutamyl transpeptidase-positive) in livers of F344 partially hepatectomized rats given single 100 mg/kg doses, but did cause DNA fragmentation in brain and liver tissue from rats exposed to 110 mg/kg/day for up to 120 days (Bagchi et al. 1998). In the DNA fragmentation assays, the effect was accompanied by increased lipid peroxidation in the same tissues. 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  $\gamma$ -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).

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

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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  $\mu$ M) 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-Rodriguez 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 2-17. 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 2-17. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene *In Vitro***

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
1-Methylnaphthalene				
Prokaryotic organisms				
<i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537)	Gene mutation	—	—	Florin et al. 1980
Mammalian cells				
Human lymphocytes	Chromosomal aberration, sister chromatid exchange	—	—	Kulka et al. 1988



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**Table 2-17. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene *In Vitro***

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
2-Methylnaphthalene				
Prokaryotic organisms				
<i>S. typhimurium</i> (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

## CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

### 3.1 TOXICOKINETICS

- Adverse effects in humans exposed by inhalation and oral routes show that naphthalene is readily absorbed across the respiratory and gastrointestinal tracts. In addition, dermal absorption has been proposed as an explanation for naphthalene toxicity in human infants exposed to diapers stored with naphthalene mothballs. In animals exposed by inhalation, uptake across the respiratory tract is dependent on concentration. Based on urinary excretion of radioactivity, at least 76% of a gavage dose was absorbed in rats.
- Systemic effects in animals exposed to 1-methylnaphthalene by inhalation or oral administration demonstrate absorption.
- 2-Methylnaphthalene is rapidly absorbed in rats exposed by inhalation. Oral absorption of 1-methylnaphthalene by guinea pigs was at least 80% of the administered dose based on urinary excretion of radioactivity.
- Naphthalene has been detected in adipose tissues and breast milk of humans and is known to cross the placenta at sufficient doses to cause toxicity in newborns.
- Naphthalene and 1-methylnaphthalene are widely distributed in animals after oral and dermal exposure.
- Naphthalene metabolism begins with cytochrome P450 (CYP)-mediated epoxidation to 1,2-naphthalene epoxide. This electrophilic intermediate may be further metabolized by one of three competing pathways: glutathione conjugation and excretion as mercapturic acids, spontaneous hydration to 1- or 2-naphthol and urinary excretion, or hydration by epoxide hydrolase, yielding naphthalene 1,2-dihydrodiol. Naphthalene 1,2-dihydrodiol may be transformed via dihydrodiol reductase to 1,2-dihydroxynaphthalene, which is subsequently oxidized to 1,2-naphthoquinone.
- *In vitro* and animal studies suggest that, unlike naphthalene, 1- and 2-methylnaphthalenes are preferentially metabolized via oxidation of the methyl group, yielding hydroxymethylnaphthalenes. Ring oxidation occurs at lower rates and results in low quantities of dihydrodiol and naphthol metabolites.
- Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are primarily excreted in urine as metabolites; small quantities are excreted in exhaled air and feces.

#### 3.1.1 Absorption

**Naphthalene.** Based on the presence of adverse effects following exposure, humans and animals can absorb naphthalene by pulmonary, gastrointestinal, and cutaneous routes.

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The rate and extent of naphthalene absorption in humans exposed by inhalation have not been determined, but there is evidence for uptake via inhalation from case reports and occupational health studies. Clinical reports suggest that prolonged exposure to naphthalene vapors can cause adverse health effects in humans (Harden and Baetjer 1978; Linick 1983; Valaes et al. 1963). In addition, naphthalene has been detected in the expired air of workers exposed to naphthalene-containing jet fuels, and naphthalene metabolites have also been detected in the urine of these workers (Egeghy et al. 2003; Rodrigues et al. 2014; Serdar et al. 2003, 2004). Presumably, naphthalene moves across the alveolar membrane by passive diffusion through the lipophilic matrix.

The absorption of naphthalene across the upper respiratory tract was studied in rats and mice exposed by nose-only inhalation (Morris 2013; Morris and Buckpitt 2009). In both studies, the upper respiratory tract was isolated by inserting an endotracheal tube in an incision below the larynx, and air was drawn from the exposure chamber, through the isolated upper respiratory tract, and into the endotracheal tube at two different flow rates. Uptake was calculated as the difference between the naphthalene concentration in the exposure chamber and the concentration in the endotracheal tube. In both male and female rats, uptake across the upper respiratory tract was dependent on concentration (when flow rate was held constant) (Morris and Buckpitt 2009). At exposure concentrations of 1, 4, 10, and 30 ppm, uptake efficiencies were 56–57, 40–49, 34–37, and 28–36%, respectively, at a flow rate of 150 mL/minute (Morris and Buckpitt 2009). At the higher flow rate (300 mL/minute), uptake rates were reduced by about half, but the concentration dependence remained. When rats were pretreated with a suicide CYP inhibitor (5-phenyl-1-pentene), the dependence on concentration was abolished, and uptake estimates were in the range of 25–29% at concentrations from 4 to 30 ppm (Morris and Buckpitt 2009). The higher uptake seen in rats that retained CYP metabolic capacity indicates that naphthalene is metabolized by CYP enzymes in the nasal cavity, leading to greater scrubbing of naphthalene from the air.

In mice, uptake from the upper respiratory tract followed a similar pattern of dependence on concentration when flow rate was held constant (Morris 2013). At concentrations of 0.5, 3, 10, and 30 ppm, uptake efficiencies of 89.3–91.4, 77.6–82.1, 61.6–64.8, and 51.6–58.3%, respectively, were observed in male and female mice at an inspiratory flow rate of 25 mL/minute (Morris 2013). Doubling the flow rate reduced uptake estimates, but not as much as it did in rats. As with rats, pretreatment of mice with 5-phenyl-1-pentene resulted in decreased uptake efficiencies and abolished the dependence on exposure concentration (Morris 2013).

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The bioaccessibility of naphthalene adsorbed to PM<sub>2.5</sub> particles measured *in vitro* in simulated lung fluid was 68–76% (Luo et al. 2021). The PM<sub>2.5</sub> particles were collected from indoor microenvironments in China and had naphthalene concentrations ranging between 0.33 and 6.87 ng/m<sup>3</sup>. The estimated bioaccessibility was higher in the system simulating an inflammatory lung condition (artificial lysosomal fluid) than in the system simulating a healthy lung (gamble's solution) (Luo et al. 2021).

Several case reports indicate that naphthalene ingested by humans can be absorbed in quantities sufficient to elicit toxicity (Ahmad et al. 2019; Bregman 1954; Chusid and Fried 1955; Dela Cruz et al. 2019; Ekambaram et al. 2017; Eskandarani and Alghamdi 2020; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; Kuwada et al. 2022; MacGregor 1954; Mackell et al. 1951; Ojwang et al. 1985; Santhanakrishnan et al. 1973; Shannon and Buchanan 1982; Tang 2017; Tannor and Hutton-Mensah 2019; Uthuman et al. 2019; Zuelzer and Apt 1949). However, no studies have been located that report the rate or extent of absorption.

In one patient who died as a result of naphthalene ingestion, 25 mothballs were found in the stomach 5 days after her death (Kurz 1987). A single naphthalene mothball reportedly weighs between 0.5 and 5 g depending on its size (Ambre et al. 1986; Siegel and Wason 1986). The gastric contents of a person who mistakenly ingested naphthalene flakes still smelled strongly of naphthalene at least 2 days following ingestion (Ojwang et al. 1985). These findings suggest that dissolved naphthalene is transported slowly into the intestines. Uptake from the intestines is governed by the partition coefficient between the materials in the intestinal lumen and the membrane lipids. Ingestion of mothballs or other forms of particulate naphthalene will lead to continued absorption over a period of several days as the solid dissolves. Unfortunately, none of the human data permit a quantitative evaluation of absorption coefficients or rates.

Limited data in animals indicate that naphthalene is rapidly absorbed across the gastrointestinal tract. In rats administered <sup>14</sup>C naphthalene by gavage, ~76% of the administered radioactivity was recovered in urine within 24 hours (Bakke et al. 1985). When <sup>14</sup>C naphthalene was instilled in the lumen of isolated rat intestinal loops, 97% of the radioactivity was detected in portal blood 0.5 hours later (Bock et al. 1979).

Several cases of naphthalene toxicity in neonates have been reported in which the proposed route of exposure was dermal (Dawson et al. 1958; Schafer 1951). Each case involved the use of diapers that had been stored in contact with naphthalene (mothballs or naphthalene flakes). The study authors proposed that the naphthalene was absorbed through the skin, causing hemolytic anemia. It was suggested that this

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absorption may have been enhanced by the presence of oils that had been applied to the babies' skin (Schafer 1951). Inhalation of vapors from the treated diapers probably contributed to the total exposure.

$^{14}\text{C}$ -Naphthalene was rapidly absorbed when the neat material (43  $\mu\text{g}$ ) was applied for a 48-hour period under a sealed glass cap to shaved 13- $\text{cm}^2$  areas of rat skin. Half of the sample (3.3  $\mu\text{g}/\text{cm}^3$ ) was absorbed in 2.1 hours (Turkall et al. 1994). When the naphthalene was mixed with either a sandy soil or a clay soil prior to contact with the skin, the presence of the soil slowed the absorption (Turkall et al. 1994). The absorption half-times from the clay and sandy soil samples were 2.8 and 4.6 hours, respectively. The rate of absorption did not influence the total amount of naphthalene absorbed in 48 hours since the areas under the plasma concentration curve did not differ significantly with any of the three exposure scenarios (0.42–0.63%/mL hour). The study authors proposed that naphthalene was absorbed more slowly from the sandy soil than from the clay soil because the sandy soil had a higher organic carbon content (Turkall et al. 1994). The sandy soil contained 4.4% organic matter and the clay soil contained 1.6% organic matter.

**1-Methylnaphthalene.** No information has been located that documented the absorption of 1-methylnaphthalene in humans by any exposure route or in animals after oral or dermal exposure. Systemic effects observed after the ingestion of 1-methylnaphthalene demonstrate that intestinal absorption does occur in rats (Murata et al. 1993; NITE 2009). In rats exposed to 1-methylnaphthalene (50 or 200  $\text{mg}/\text{m}^3$ ) by inhalation (nose only) for 6 hours, 1-methylnaphthalene was detected in blood within minutes after the end of the exposure period (Świercz and Wąsowicz 2018).

**2-Methylnaphthalene.** Data on the absorption of 2-methylnaphthalene in humans were not located, and information on absorption in animals is limited to one study of rats exposed by inhalation and one study of guinea pigs exposed orally. In rats exposed nose-only to concentrations of 200 or 400  $\text{mg}/\text{m}^3$ , 2-methylnaphthalene was detected in blood after the first hour of a 6-hour exposure period, increased during hour 2, and then remained fairly constant through the remainder of the exposure (Świercz et al. 2010). Blood concentrations were roughly proportional to exposure levels. In guinea pigs, rapid absorption was seen after oral exposure. At least 80% of a 10  $\text{mg}/\text{kg}$  oral dose of 2-methylnaphthalene was absorbed within 24 hours based on recovery of the radiolabel in the urine (Teshima et al. 1983).

### 3.1.2 Distribution

**Naphthalene.** There are limited data concerning the distribution of naphthalene in human tissues. Naphthalene was present in 40% of the adipose tissue samples that were analyzed as part of the National

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Human Adipose Tissue Survey (EPA 1986b). The maximum concentration observed was 63 ng/g. Naphthalene was also detected in human milk samples (concentration not reported) (Pellizzari et al. 1982). The sources of naphthalene in these milk and body fat samples are not known.

Naphthalene can cross the human placenta in concentrations high enough to cause red cell hemolysis and lead to anemia in newborn infants of mothers who consumed naphthalene during pregnancy (Anziulewicz et al. 1959; Sahni et al. 2019; Shafer et al. 2020; Zinkham and Childs 1957, 1958).

The distribution of naphthalene and its metabolites in young pigs given a single dose of 0.123 mg/kg (4.8 Ci/kg)  $^{14}\text{C}$ -labeled naphthalene was monitored at 24 and 72 hours (Eisele 1985). At 24 hours, the highest percentage of the label ( $3.48 \pm 2.16\%$  dose/mg tissue) was in the adipose tissue. The kidneys had the next highest concentration of label ( $0.96\%$  dose/mg tissue), followed by the liver ( $0.26 \pm 0.06\%$  dose/mg tissue) and lungs ( $0.16\%$  dose/mg tissue). The heart contained  $0.09 \pm 0.04\%$  dose/mg tissue and the spleen contained  $0.07 \pm 0.01\%$  dose/mg tissue. At 72 hours, the amount of label in the fat had fallen to  $2.18 \pm 1.16\%$  dose/mg tissue, the amount in the liver decreased to  $0.34 \pm 0.24\%$  dose/mg tissue, and the kidneys and lungs contained the same concentration ( $0.26\%$  dose/mg tissue).

Pigs were also given oral doses of 0.006 mg/kg/day ( $0.22 \text{ Ci/kg/day}$ )  $^{14}\text{C}$ -labeled naphthalene for 31 days (Eisele 1985). With repeated administration of the radiolabel, the tissue distribution differed considerably from that observed with a single dose of the compound. The highest concentration of label was in the lungs ( $0.15\%$  dose/mg tissue), followed by the liver and heart ( $0.11\%$  dose/mg tissue). There was very little label in the fat tissue ( $0.03\%$  dose/mg tissue). The spleen had  $0.09 \pm 0.05\%$  dose/mg tissue and the kidney had  $0.09\%$  dose/mg tissue.

In one dairy cow, naphthalene distributed to milk with both single and repeated doses of  $^{14}\text{C}$ -labeled naphthalene. The label was distributed between the milk and the milk fat (Eisele 1985). When the cow was given naphthalene for a 31-day period, the amount of label found in the milk remained relatively constant throughout the exposure period. The amount in the milk fat was lower for the first 7 days than it was for the remainder of the exposure.

In rats, radiolabel from naphthalene distributed to the ileum, duodenum, and kidney ( $0.01\text{--}0.02\%$  of initial dose) when tissues were analyzed 48 hours after naphthalene contact with the skin (Turkall et al. 1994). The largest concentration was found at the site of application ( $0.56\%$  of initial dose). A total of 20 tissues were evaluated; the percentage of label in all other tissues was minimal.

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***1-Methylnaphthalene.*** Information on the tissue distribution of 1-methylnaphthalene in humans was not located. Świercz and Wąsowicz (2018) measured the concentration of 1-methylnaphthalene in blood and tissues of rats after single or repeated (5 days) exposures to 50 or 200 mg/m<sup>3</sup> 1-methylnaphthalene for 6 hours via nose-only inhalation. In blood, 1-methylnaphthalene was detected minutes after the end of exposure at peak concentrations of ~1 and 0.1 mg/L at concentrations of 200 and 50 mg/m<sup>3</sup>, respectively. Concentrations in blood declined rapidly after the end of exposure. After single or repeated exposures, the tissue concentrations were highest in kidney and fat, followed by lungs, spleen, liver, and brain. For example, after a single exposure to 50 mg/m<sup>3</sup>, tissue concentrations were 1.88, 1.29, 0.41, 0.26, 0.21, and 0.16 µg/g in the kidney, fat, lungs, brain, spleen, and liver, respectively. Tissue concentrations were lower after five daily exposures to 1-methylnaphthalene than after a single day of exposure (Świercz and Wąsowicz 2018). When measured 24 hours after the end of exposure, 1-methylnaphthalene was not detected in any of these tissues from rats exposed to 50 mg/m<sup>3</sup> (single or repeated exposures) and was detected only in kidney and fat from rats exposed to 200 mg/m<sup>3</sup> (Świercz and Wąsowicz 2018).

***2-Methylnaphthalene.*** Data on the distribution of 2-methylnaphthalene in exposed humans were not located. The tissue distribution of 2-methylnaphthalene was measured in guinea pigs 3, 6, 24, and 48 hours after oral administration of tritium-labeled 2-methylnaphthalene (10 mg/kg; 59 µCi/kg) (Teshima et al. 1983). The highest concentration of label was present in the gallbladder, with 20.17 µg at 3 hours and 15.72 µg at 6 hours. (All concentrations are expressed in µg equivalents of <sup>3</sup>H/g wet tissue.) The value fell to 0.43 µg at 24 hours and 0.04 µg at 48 hours. The presence of label in the gallbladder presumably reflects the excretion of hepatic metabolites in the bile. The values for the kidney were 5.64 µg at 3 hours, 7.62 µg at 6 hours, 0.29 µg at 24 hours, and 0.09 µg at 48 hours.

Radiolabeled compound was detected in the liver immediately after exposure (Teshima et al. 1983). When converted to units of mass, hepatic concentrations were 1.71 µg at 3 hours and 2.66 µg at 6 hours, falling to 0.18 µg at 24 hours. Lung concentrations were similar to those for blood at all time points. The amounts were 0.75 µg in blood and 0.69 µg in lungs at 3 hours; at 6 hours, concentrations were 0.71 µg in the blood and 0.76 µg in the lung. The half-life of 2-methylnaphthalene in the blood was 10.4 hours. The decay of 2-methylnaphthalene and metabolites in the other tissues examined was described as biphasic.

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After i.p. administration in mice,  $^{14}\text{C}$ -labeled 2-methylnaphthalene distribution was measured in the fat, kidney, liver, and lung for 24 hours (Griffin et al. 1982). The amount of label in the fat peaked 3 hours after exposure and remained higher than the amount of label in other tissues at 8 hours. The liver, kidney, and lung followed the fat in order of decreasing concentration. The maximum concentration in the fat was 13 nmol equivalents/mg wet weight. The maximum value for the liver was 3.5 nmol equivalents/mg wet weight at 1 hour. Maximum values were about 1.75 nmol equivalents/mg wet weight for the kidneys at 2 hours and 0.8 nmol equivalents/mg wet weight for the lungs at 4 hours.

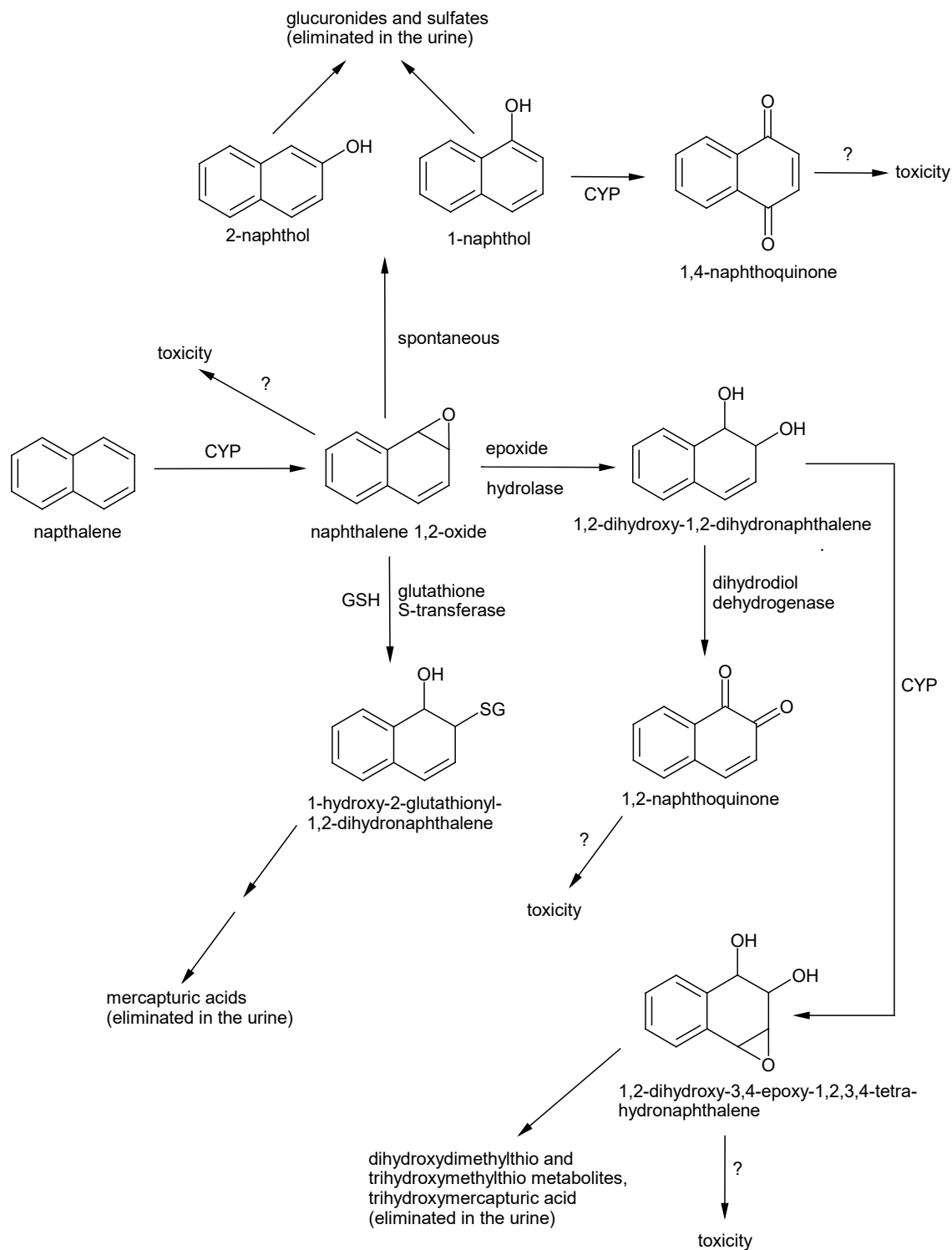
### 3.1.3 Metabolism

**Naphthalene.** The metabolism of naphthalene in mammalian systems has been studied extensively and is depicted in Figure 3-1. The metabolic scheme in Figure 3-1 illustrates that there are multiple reactive metabolites formed from naphthalene: 1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene. This section presents an overview of the metabolic scheme and the evidence for the involvement of the 1,2-epoxide and the naphthoquinones in naphthalene toxicity. The fourth metabolite listed above is expected to be reactive, but its potential role in naphthalene toxicity has not been investigated. A review of the metabolism and bioactivation of naphthalene has been published by Buckpitt et al. (2002).

The first step in naphthalene metabolism is catalyzed by CYP oxygenases and produces a reactive electrophilic arene epoxide intermediate, 1,2-naphthalene oxide. In mammalian systems, several CYP isozymes have been demonstrated to metabolize naphthalene, including 1A1, 1A2, 1B1, 3A7, 3A5 (Juchau et al. 1998), 2E1 (Wilson et al. 1996), 2F2 (Buckpitt et al. 1995; Shultz et al. 1999), and 2B4 (Van Winkle et al. 1996). The epoxide can spontaneously rearrange to form naphthols (predominantly 1-naphthol) and subsequently conjugate with glucuronic acid or sulfate to form conjugates, which are excreted in urine (Ayala et al. 2015; Bock et al. 1976).



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**Figure 3-1. Scheme for Naphthalene Metabolism and Formation of Multiple Reactive Metabolites, that may be Involved in Naphthalene Toxicity**

CYP = cytochrome P450 enzyme(s); GSH = reduced glutathione; SG = glutathione

Sources: Buckpitt et al. (2002); Waidyanatha et al. (2002)

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Alternatively, the 1,2-epoxide can react with tissue macromolecules. This reaction is thought to be involved in several aspects of naphthalene toxicity, especially injury to club cells (non-ciliated cells in the epithelium of proximal and distal airways of the lung) from acute exposure to naphthalene (Buckpitt et al. 2002; Zheng et al. 1997). In pH 7.4 buffer, the epoxide has been shown to have a half-life of approximately 2–3 minutes, which is extended by the presence of albumins to about 11 minutes (Buckpitt et al. 2002; Kanekal et al. 1991). Mice are markedly more susceptible than rats to acute naphthalene-induced club cell injury (Buckpitt et al. 1992; West et al. 2001). The susceptibility difference apparently extends to chronic exposure scenarios. Mice exposed by inhalation to 10 or 30 ppm naphthalene for 2 years showed lung inflammation, but rats exposed to concentrations up to 60 ppm showed no lung inflammation (Abdo et al. 2001; NTP 1992a, 2000). The species difference in lung susceptibility has been correlated with higher rates of formation of a specific enantiomeric epoxide (1*R*,2*S*-naphthalene oxide) in lung microsomes and isolated dissected airways of mice compared with rats (Buckpitt et al. 1992, 1995). Rat, hamster, and monkey lung microsomes preferentially formed the 1*S*,2*R*-naphthalene oxide enantiomer and showed lower rates of formation of epoxides than mouse lung microsomes (Buckpitt et al. 1992). Microsomes from human lymphoblastoid cells expressing recombinant human CYP2F1 also showed preferential formation of the 1*S*,2*R*-naphthalene oxide enantiomer, providing some evidence that human transformation of naphthalene to reactive epoxides in lung tissue may be more like rats than mice (Lanza et al. 1999).

In contrast to the lung, species differences in susceptibility at another sensitive target of naphthalene, the olfactory and respiratory epithelia of the nose, do not correlate with differences in rates of transformation to 1,2-epoxide derivatives in extracts of olfactory tissue (Buckpitt et al. 1992; Plopper et al. 1992). Metabolic rates (units of nmol naphthalene converted to epoxide derivatives/minute/mg protein) in olfactory tissue extracts showed the following order: mouse (87.1) > rat (43.5) > hamster (3.9). However, rats were more susceptible to naphthalene-induced cell injury than mice or hamsters. The lowest single i.p. doses producing necrosis and exfoliation in olfactory epithelium were 200 mg/kg in rats and 400 mg/kg in mice and hamsters. These observations suggest that the reasons for species differences in susceptibility to naphthalene toxicity are complex and do not solely involve the formation of the 1,2-epoxide metabolites. Although CYP monooxygenases, which are involved in naphthalene metabolism and bioactivation, have been demonstrated to exist in nasal respiratory epithelial and olfactory epithelial tissue from rodents and humans (Thornton-Manning and Dahl 1997), studies designed to specifically characterize metabolism of naphthalene in nasal tissue are restricted to those by Buckpitt et al. (1992) and Plopper et al. (1992).

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In addition to being converted to the naphthols, the 1,2-epoxide can be conjugated with glutathione via glutathione-S-transferase catalysis. Figure 3-1 shows one such conjugate, 1-hydroxy-2-glutathionyl-1,2-dihydronaphthalene. The glutathionyl conjugates are converted in several steps to mercapturic acids, which are excreted in the urine. The conjugation of the epoxide is thought of as a detoxication mechanism, as evidenced by studies showing that glutathione depletion increased the degree of acute naphthalene-induced club cell injury in mice (Warren et al. 1982; West et al. 2000). In addition, elevated activities of  $\gamma$ -glutamylcysteine synthetase, the enzyme catalyzing the rate-limiting step in glutathione synthesis, were observed in dissected airways from mice that developed tolerance to acute naphthalene club cell cytotoxicity (West et al. 2000).

The 1,2-epoxide can also be enzymatically hydrated by epoxide hydrolase to form 1,2-dihydroxy-1,2-dihydronaphthalene (Figure 3-1). This 1,2-dihydrodiol derivative was the major stable metabolite of naphthalene produced by human liver microsomes, whereas the major stable metabolite formed by mouse liver microsomes was 1-naphthol (Tingle et al. 1993). In the presence of an inhibitor of epoxide hydrolase (trichloropropene oxide), the major stable metabolite with human liver microsomes was 1-naphthol. How this species difference in liver metabolism may relate to the human relevance of toxicity of inhaled naphthalene in sensitive target tissues in the nose and lungs of mice is unknown.

The 1,2-dihydrodiol can be catalytically transformed by dihydrodiol dehydrogenase to 1,2-naphthoquinone (also known as naphthalene-1,2-dione). 1,2-Naphthoquinone is both reactive itself and capable of producing reactive oxygen species through redox cycling (Flowers et al. 1997) and has been shown to be mutagenic in several strains of *S. typhimurium* (Flowers-Geary et al. 1996). In isolated club cells incubated with 0.5 mM naphthalene, 1,2-naphthoquinone was the major naphthalene derivative covalently bound to proteins, although covalent binding with the 1,2-epoxide was also observed (Zheng et al. 1997). The formation of the other naphthoquinone, 1,4-naphthoquinone, from 1-naphthol, presumably via a CYP monooxygenase, has been proposed based on the finding that, following incubations of liver microsomes with 1-naphthol, ethylene diamine (a compound that reacts readily with 1,2-naphthoquinone), did not trap reactive metabolites (Doherty et al. 1984). Cysteinyl adducts of both 1,2-naphthoquinone and 1,4-naphthoquinone (and of 1,2-naphthalene oxide) with hemoglobin and albumin have been detected in blood of rats given single oral doses of naphthalene ranging from 100 to 800 mg/kg (Troester et al. 2002; Waidyanatha et al. 2002). Levels of 1,2-naphthalene oxide adducts were greater than levels of 1,2-naphthoquinone adducts, which were greater than levels of 1,4-naphthoquinone adducts (Troester et al. 2002; Waidyanatha et al. 2002). In *in vitro* studies with whole human blood samples, 1,2- or 1,4-naphthoquinone induced increased frequencies of sister chromatid exchanges at concentrations

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$\geq 10$   $\mu\text{M}$ , whereas naphthalene 1,2-epoxide did not at concentrations up to 100  $\mu\text{M}$  (Wilson et al. 1996). Similarly, incubation of human mononuclear leukocytes with 1,2-naphthoquinone or 1,4-naphthoquinone caused significant depletion of cellular glutathione levels and significant cytotoxicity at concentrations between 1 and 100  $\mu\text{M}$ , whereas naphthalene 1,2-epoxide did not display these toxic actions in this concentration range (Wilson et al. 1996).

1,2-Naphthoquinone formed in lens tissue is thought to be involved in naphthalene-induced cataracts in rats and rabbits. The enzyme involved in the transformation of the 1,2-dihydrodiol to 1,2-naphthoquinone in lens tissue is thought to be aldose reductase (this enzyme, also known as aldehyde reductase, is not specified in Figure 3-1). Support for this hypothesis includes findings that aldose reductase inhibitors prevent cataract formation in naphthalene-fed rats (Tao et al. 1991; Xu et al. 1992a), dihydrodiol dehydrogenase is apparently absent in rat lens (Greene et al. 2000), and aldose reductase appears to be the only enzyme in rat lens that can transform 1,2-dihydroxy-1,2-dihydronaphthalene to 1,2-naphthoquinone (Sugiyama et al. 1999).

Support for the *in vivo* formation of another potentially reactive metabolite, 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene, comes from the identification of several urinary metabolites, including a number of trihydroxytetrahydromethylthio derivatives (Horning et al. 1980) and a trihydroxytetrahydro-mercapturic acid (Pakenham et al. 2002). These urinary metabolites, however, are minor, and the importance of their common proposed precursor in naphthalene toxicity is unstudied to date. Figure 3-1 proposes an oxidative transformation of dihydrodiol derivative to the tetrahydrodiol epoxide derivative via CYP catalysis.

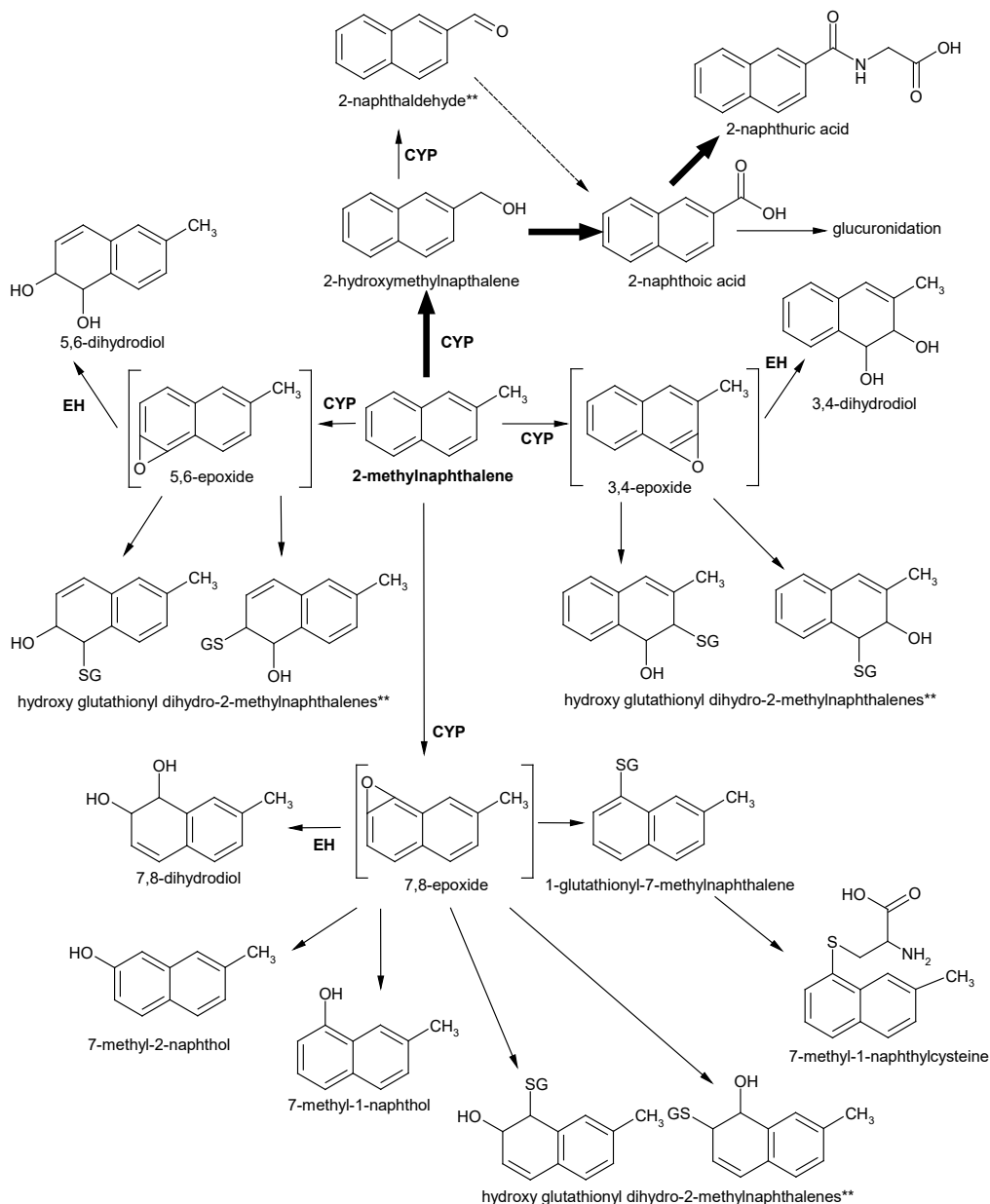
**1-Methylnaphthalene.** Information on the metabolism of 1-methylnaphthalene in humans and animals was not located. In both human and rat liver microsomes incubated with 1-methylnaphthalene, the primary metabolite resulted from oxidation of the methyl group, yielding 1-(hydroxymethyl)naphthalene (Wang et al. 2020). Minor metabolites included dihydro-1-methyl-naphthalenediols and 1-methyl-naphthols (Wang et al. 2020). The rates of ring- and side-chain-oxidation differed between rat and human liver microsomes. In human liver microsomes, Wang et al. (2020) observed higher intrinsic clearance of 1-methylnaphthalene via aromatic ring oxidation compared with side chain oxidation, while the opposite was observed in rat liver microsomes.

**2-Methylnaphthalene.** As with 1-methylnaphthalene, the methyl substituent of 2-methylnaphthalene presents the opportunity for side chain oxidation reactions in addition to the ring oxidation, which is the

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sole initial step in naphthalene metabolism. A proposed metabolic scheme for 2-methylnaphthalene is shown in Figure 3-2. Oxidation at the methyl group (the predominant path), or at several competitive positions on the rings, is catalyzed by CYP monooxygenases (Figure 3-2).

**Figure 3-2. Metabolism of 2-Methylnaphthalene**



[ ] = putative metabolite; CYP = cytochrome P450 enzyme(s); EH = epoxide hydrolase; GS = glutathione

\*\*Metabolites identified *in vitro* only

Sources: Buckpitt and Franklin (1989); EPA (2003); Shultz et al. (2001); Teshima et al. (1983)

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In rats and mice, about 50–80% of 2-methylnaphthalene is oxidized at the 2-methyl group to produce 2-hydroxymethylnaphthalene (Breger et al. 1983; Teshima et al. 1983). This 2-hydroxymethylnaphthalene metabolite is further oxidized to 2-naphthoic acid (Grimes and Young 1956; Melancon et al. 1982; Teshima et al. 1983), and this step proceeds either directly or through the intermediate, 2-naphthaldehyde (Figure 3-2). Detection of 2-naphthaldehyde has only been reported following *in vitro* incubation of 2-methylnaphthalene with recombinant mouse CYP2F2 (Shultz et al. 2001). 2-Naphthoic acid may be conjugated with either glycine or glucuronic acid (Figure 3-2). The glycine conjugate of 2-naphthoic acid forms 2-naphthuric acid, which is the most prevalent urinary metabolite of 2-methylnaphthalene detected in exposed animals (Grimes and Young 1956; Melancon et al. 1982; Teshima et al. 1983).

Ring epoxidation at the 7,8-, 3,4-, or 5,6- positions occurs in approximately 15–20% of 2-methylnaphthalene (Breger et al. 1983; Melancon et al. 1985). These epoxidation reactions are catalyzed by CYP isozymes that include CYP1A and CYP1B. These epoxides are proposed intermediates based on experimentally observed metabolites but have not been individually isolated (Figure 3-2). These epoxides may be further oxidized by epoxide hydrolase to produce dihydrodiols (the 7,8-dihydrodiol, 3,4-dihydrodiol, or 5,6-dihydrodiol of 2-methylnaphthalene) or may be conjugated with glutathione (Griffin et al. 1982; Melancon et al. 1985) by glutathione S-transferase catalysis or can proceed spontaneously. The hydroxy glutathionyl dihydro-2-methylnaphthalenes (Figure 3-2) have been detected after incubation of 2-methylnaphthalene with hepatic microsomes from Swiss-Webster mice or with isolated recombinant mouse CYP2F2 enzyme and glutathione S-transferase (Shultz et al. 2001). Figure 3-2 indicates six hydroxy glutathionyl 2-methylnaphthalenes; two are formed for each of the epoxide intermediates (3,4-, 5,6-, and 7,8-epoxides), and each can exist in two enantiomeric forms not shown in Figure 3-2 (Shultz et al. 2001).

Three other minor metabolites formed via the 7,8-epoxide pathway are shown in Figure 3-2. Urinary 1-glutathionyl-7-methylnaphthalene was identified in guinea pigs and by *in vitro* experiments with guinea pig microsomes (Teshima et al. 1983). 7-Methyl-1-naphthol and 7-methyl-2-naphthol were identified in the urine of rats, mice, guinea pigs, and rabbits following oral exposure (Grimes and Young 1956).

In rats administered subcutaneous injections of 2-methylnaphthalene (0.3 mg/kg 2-methyl-[8-<sup>14</sup>C]-naphthalene), 2-naphthoic acid and naphthoic acid conjugates were identified in the urine (Melancon et al. 1982). The naphthoic acid and various conjugates of the acid were estimated to account for 36–43% of the radiolabel in collected urine. Most of this (30–35% of radiolabel in urine) was found as a glycine

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conjugate. The urine contained 3–5% unreacted 2-methylnaphthalene; free dihydrodiols accounted for 6–8% of the label. Unidentified highly polar metabolites comprised another 36–45% of the excreted label. At least three diol derivatives of 2-methylnaphthalene were produced by hepatic microsomes from mice (Griffin et al. 1982), suggesting that the ring oxidation reactions of 2-methylnaphthalene are similar to those for naphthalene. Rat liver microsomes also produced 2-hydroxymethylnaphthalene and three diols from 2-methylnaphthalene (Breger et al. 1981, 1983; Melancon et al. 1985; Wang et al. 2020). The three diols were identified as 3,4-dihydrodiol, 5,6-dihydrodiol, and 7,8-dihydrodiol (Breger et al. 1983; Wang et al. 2020). Both rat and human liver microsomes cleared 2-methylnaphthalene primarily via side-chain oxidation, with lower intrinsic clearance via ring oxidation (Wang et al. 2020).

Metabolites isolated in the urine of guinea pigs after oral dosing with tritium labeled 2-methylnaphthalene (10 mg/kg) were 2-naphthoic acid and its glycine and glucuronic acid conjugates (Teshima et al. 1983). These metabolites accounted for 76% of the label in collected urine. Glucuronic acid and sulfate conjugates of 7-methyl-1-naphthol, along with *S*-(7-methyl-1-naphthyl)cysteine, accounted for 18% of the excreted label. No diol metabolites were identified.

Glutathione conjugation appears to be an important detoxication pathway for 2-methylnaphthalene. Pretreatment of male C57BL/6J mice with 625 mg/kg of diethylmaleate (a depletor of glutathione) 1 hour prior to i.p. administration of 400 mg/kg of 2-methylnaphthalene resulted in mortality in four of five mice, whereas treatment without glutathione depletion was not fatal (Griffin et al. 1982). Bronchiolar necrosis was not observed in male ddY mice given single i.p. injections of 200 mg/kg of 2-methylnaphthalene; pretreatment with the glutathione depletor diethylmaleate (600 µL/kg) 1 hour prior to injections caused “extensive sloughing and exfoliation of bronchiolar epithelial cells” in all five animals (Honda et al. 1990). In contrast, pretreatment of male DBA/2J mice (5/group) with 625 mg/kg of diethylmaleate did not increase the severity of pulmonary necrosis induced by 400 mg/kg of 2-methylnaphthalene (Griffin et al. 1983). The observed differences among mouse strains in response to depletion of glutathione remain unexplained. Other experiments (without pretreatment) observed decreased tissue or intracellular levels of glutathione in response to exposure to high acute doses of 2-methylnaphthalene, demonstrative of glutathione conjugation (Griffin et al. 1982, 1983; Honda et al. 1990). Similarly, depletion of glutathione (by 35% compared to controls) was detected in primary cultures of female Sprague-Dawley rat hepatocytes treated with 1,000 µM of 2-methylnaphthalene (Zhao and Ramos 1998).

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**3.1.4 Excretion**

**Naphthalene.** Little information is available pertaining to the excretion of naphthalene in humans after inhalation exposure to naphthalene. Workers employed in the distillation of naphthalene oil and at a coke plant had peak levels of urinary 1-naphthol 1 hour after finishing a shift (Bieniek 1994). Of three workers and a nonoccupationally exposed group, naphthalene oil distribution plant workers had the highest concentrations of urinary 1-naphthol, with a mean excretion rate of 0.57% mg/hour. Investigators calculated the half-life for the urinary excretion of 1-naphthol as approximately 4 hours (Bieniek 1994). This urinary metabolite may indicate both exposure to naphthalene and low concentrations of 1-naphthol during naphthalene oil distillation (Bieniek 1994). Several other studies have shown urinary excretion of naphthalene metabolites in humans occupationally exposed to vapors or emissions from jet fuel, creosote, coke oven, asphalt, iron foundry, and aluminum production industries (Chao et al. 2006; Rappaport et al. 2004; Rodrigues et al. 2014; Serdar et al. 2003, 2004, 2016).

In rats and mice exposed by inhalation, naphthalene metabolites are primarily excreted as mercapturate conjugates (Ayala et al. 2015; Pakenham et al. 2002). In mice treated with seven daily 4-hour exposures to 15 ppm, ~60% of the urinary metabolites in each 24-hour sample consisted of mercapturates (from glutathione conjugation of naphthalene oxide), while glucuronide and sulfate conjugates (of 1-naphthol) made up nearly 20% each. A small fraction ( $\leq 3\%$ ) of the metabolites was excreted as N-acetyl glutathione conjugates (Ayala et al. 2015). Pakenham et al. (2002) compared the urinary mercapturate levels in mice and rats exposed by inhalation to concentrations of 0.8–100 ppm and observed concentration-dependent increases in mercapturate excretion in both species. Mice excreted more urinary mercapturates than rats at comparable exposure concentrations. At low concentrations (0.8 and 1 ppm in rats and mice, respectively), excreted mercapturates were similar (0.6 and 1  $\mu\text{mol/kg}$ , respectively), but at the highest concentration tested (100 ppm), mice excreted 240  $\mu\text{mol/kg}$  while rats excreted only 67  $\mu\text{mol/kg}$  as urinary mercapturates (Pakenham et al. 2002). Species differences were also observed in the diastereomers excreted, with mice excreting more 1R,2S- than 1S,2R-epoxide derived mercapturates at all exposure levels (Pakenham et al. 2002). Ratios of mercapturates derived from 1R,2S- than 1S,2R-epoxides ranged from 1:1 to 0.5:1 from low to high exposure concentrations in rats, while the corresponding ratios ranged from 5:1 to 3:1 in mice (Pakenham et al. 2002).

Limited data were located on excretion of ingested naphthalene by humans. The urine of one patient was tested for naphthalene and its derivatives. Naphthol was found at the time of hospital admission (4 days post-ingestion). Smaller quantities were present 1 day later, but naphthalene was not detected in later



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specimens (Zuelzer and Apt 1949). In another instance, the urine of an 18-month-old child was found to contain 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone (but no naphthalene) 9 days after exposure (Mackell et al. 1951). With the exception of the 1,4-naphthoquinone, these metabolites were still detectable on day 13, but not on day 17. These data indicate that urinary excretion of metabolites may be prolonged following exposure. It is important to note, however, that delayed dissolution and absorption from the gastrointestinal tract may also be a contributing factor. Unabsorbed naphthalene was visible in the fecal matter after ingestion of naphthalene flakes or mothballs in several individuals (Zuelzer and Apt 1949).

In nonhuman primate studies, Rhesus monkeys given naphthalene at oral doses up to 200 mg/kg did not excrete naphthalene as thioethers in urine or feces (Rozman et al. 1982). In a similar study, chimpanzees orally administered naphthalene at 200 mg/kg did not excrete naphthalene as thioethers in urine (Summer et al. 1979). These data suggest that glutathione conjugation of naphthalene may not occur to any great extent in nonhuman primates. Data from two chimpanzees indicate that most of the naphthalene excreted in this species is excreted as glucuronic acid and sulfate conjugates (Summer et al. 1979).

In rats administered radiolabeled naphthalene, the amount of label recovered in 24 hours was 77–93% in urine and 6–7% in feces (Bakke et al. 1985). There was a dose-dependent increase in urinary thioether excretion following gavage doses of naphthalene at 30, 75, and 200 mg/kg within 24 hours (Summer et al. 1979). The levels of thioethers excreted accounted for approximately 39, 32, and 26% of the three dose levels tested.

The dermal exposure of rats to  $^{14}\text{C}$ -labeled naphthalene was evaluated over a 48-hour period (Turkall et al. 1994). Naphthalene (43  $\mu\text{g}$ ) samples were applied to shaved 13- $\text{cm}^2$  areas on the skin under a sealed plastic cap. Neat naphthalene or naphthalene adsorbed to the surface of sandy soil or clay soil was tested. In all three cases, excretion of the label was primarily through the urine (70–87%). With the pure naphthalene and naphthalene adsorbed to clay soil, the exhaled air accounted for 6–14% of the administered label. Exhaled air contained only 0.9% of the label in the sandy soil group. This finding was presumably related to the slower adsorption of naphthalene from the sandy soil and its more rapid metabolism to nonvolatile metabolites. Less than 0.02% of the label was exhaled as carbon dioxide in all groups. The feces contained 2–4% of the label.

The primary metabolites in the urine after dermal application of naphthalene were 2,7-dihydroxy-naphthalene, 1,2-dihydroxynaphthalene, and 1,2-naphthoquinone (Turkall et al. 1994). The ratio of these

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metabolites for pure naphthalene and naphthalene adsorbed to clay soil were roughly 3:2:1. For the sandy soil, the corresponding ratio was 3:2:1.5. Small amounts of 1-naphthol and 2-naphthol were also excreted. In all cases, the amount of urinary free naphthalene was <0.4% of the administered label.

In mouse studies using the i.p. or subcutaneous exposure routes, several naphthalene metabolites were excreted in the urine. After i.p. administration of 100 mg/kg naphthalene, conjugates accounted for 80–95% of the urinary metabolites (Horning et al. 1980; Stillwell et al. 1982). Much of the conjugated material was present as thioethers (glutathione conjugates and their derivatives). The major oxidation products of naphthalene metabolism were 1-naphthol and trans-1,2-dihydro-1,2-naphthalenediol.

***1-Methylnaphthalene.*** Information on the excretion of 1-methylnaphthalene in humans exposed by any route or in animals exposed via oral or dermal administration was not located. In a study of rats exposed via nose-only inhalation to 50 or 200 mg/m<sup>3</sup> 1-methylnaphthalene for 6 hours/day on 1 day or 5 consecutive days, elimination of 1-methylnaphthalene from blood was rapid (Świercz and Wąsowicz 2018). The study authors calculated rates of elimination from blood using an open two-compartment model, yielding phase I and phase II half-lives of ~1 and ~40 minutes for 1 and 5 days of exposure to 50 mg/m<sup>3</sup>, respectively, and ~2.5 and 90–100 minutes for 1 and 5 days of exposure to 200 mg/m<sup>3</sup>, respectively. While the area under the curve (AUC) for blood concentration over time (first hour after exposure ended) was similar for single and repeated exposures to 50 mg/m<sup>3</sup>, repeated exposures to 200 mg/m<sup>3</sup> resulted in a significantly lower AUC than a single exposure did (0.58 hours x mg/L compared with 2.65 hours x mg/L in the first 6 hours after exposure ended). The study authors suggested that 1-methylnaphthalene induced its own metabolism, resulting in faster elimination after repeated exposures (Świercz and Wąsowicz 2018).

In this study, urinary excretion of 1-methylnaphthalene was greatest during the first 24 hours after exposure ended (Świercz and Wąsowicz 2018). Urine concentrations during this time period were similar after single and repeated exposures to the same concentration. Concentrations of 0.069 and 0.051 µg/L were measured after 1 and 5 days of exposure to 50 mg/m<sup>3</sup>, respectively and concentrations of 0.385 and 0.377 µg/L were measured after 1 and 5 days at 200 mg/m<sup>3</sup>, respectively. Urine concentrations were much lower during subsequent 24-hour collection periods (Świercz and Wąsowicz 2018)

***2-Methylnaphthalene.*** In guinea pigs, 80% of a 10 mg/kg tritium-labeled 2-methylnaphthalene dose was excreted in the urine within 24 hours and about 10% was recovered in the feces (Teshima et al. 1983). Most of the excreted material (76%) was found as 2-naphthoic acid or its conjugates. About 18% of the

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recovered label was found as conjugates of 7-methyl-1-naphthol. Following subcutaneous administration of 0.3 mg/kg  $^{14}\text{C}$ -labeled 2-methylnaphthalene, 55% was found in the urine of rats (Melancon et al. 1982). Naphthoic acid and its glycine conjugate were identified. Three other metabolites were tentatively identified as isomeric diols.

**3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models**

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Research on PBPK models of naphthalene have focused on simulating characteristics of the anatomy and physiology of the rodent and human that are thought to contribute to interspecies differences in dose-response relationships for nasal cavity lesions. Important features of naphthalene toxicity and kinetics that are relevant to interspecies extrapolation include: (1) necrotic lesions of the nasal cavity, most prominent in the olfactory epithelium (Dodd et al. 2010, 2012); (2) first-pass extraction of naphthalene by nasal cavity tissues, which decreases as the inhalation exposure concentration increases (Morris and Buckpitt 2009); and (3) production of reactive intermediates from CYP-mediated saturable metabolism of naphthalene in olfactory and nasal respiratory epithelia (Morris and Buckpitt 2009).

Several models have been developed to simulate the kinetics of naphthalene uptake and metabolism of inhaled naphthalene (Campbell et al. 2014; Kapraun et al. 2020; Willems et al. 2001). Two models are described in detail in the following discussion because they provide a means to simulate the nasal cavity

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and systemic kinetics of naphthalene in rats and humans (Campbell et al. 2014; Kapraun et al. 2020); and the models have been used to predict nasal tissue and systemic doses for interspecies dosimetry extrapolation (Campbell et al. 2014; EPA 2022c; Kapraun et al. 2020).

**Campbell et al. 2014 Model**

**Description.** Campbell et al. (2014) developed a model to simulate the kinetics of inhaled naphthalene in rats and humans. The model consists of a nasal cavity and systemic model. The nasal cavity model simulates the kinetics of naphthalene uptake and metabolism in the nasal cavity and transfer of naphthalene to blood (absorption) and to distal regions of the respiratory tract. The systemic model simulates absorption, distribution, and elimination of naphthalene transferred from the nasal cavity to the lung. The structure of the nasal cavity model was based on models for vinyl acetate and acetaldehyde (Bogdanffy et al. 1999; Teeguarden et al. 2008). The systemic model was based on a model developed by Willems et al. (2001).

*Nasal cavity model.* The nasal cavity model divides the nasal tissues into compartments representing: (1) dorsal medial respiratory tissue; (2) dorsal/medial olfactory tissue; and (3) lateral/ventral respiratory tissue. The rat model includes two dorsal medial olfactory tissue compartments; the human model includes a single dorsal medial olfactory tissue compartment. Each tissue compartment is represented by layered subcompartments that provide a diffusion pathway for naphthalene between the surface mucus layer and deeper epithelial, basal cell, and submucosal layers. In the Campbell et al. (2014) model, the mucous and epithelial layers are represented by a single compartment. This simplification was justified on the basis that metabolism of naphthalene is not expected to occur in the mucous layer. Inhaled naphthalene deposits in the surface mucus layer of each tissue compartment and then diffuses to deeper subcompartments where it is cleared by metabolism and absorption to blood. The model simulates two air flow patterns in the nasal cavity. A dorsal/medial flow contacts the dorsal olfactory and respiratory compartments and a lateral/ventral flow that contacts the lateral ventral respiratory tissue. Naphthalene is assumed to be homogeneously distributed in the air flows and move through the nasal cavity by convection. Exchanges between naphthalene in air and the mucus surfaces are assumed to occur by diffusion, governed by the air-mucus concentration gradient, the mucus surface area, a mass transfer coefficient (cm/minute), and a tissue:air partition coefficient. Exchanges between nasal tissue subcompartments are governed by diffusion coefficients (cm<sup>2</sup>/hour) and the concentrations gradient between subcompartments. Metabolism of naphthalene through the 1,2-epoxide pathway is simulated as a Michaelis-Menten processes ( $V_{\max}$ ,  $K_M$ ), with parameter values assigned to the nasal respiratory and

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olfactory epithelial cell compartments. The dispositions of metabolites are not simulated. Absorption of naphthalene from the submucosa is assumed to be flow-limited and governed by the mass of each chemical in the submucosa, blood flow to the submucosa, and a tissue:blood partition coefficient. Naphthalene that is not extracted into nasal cavity tissues is transferred to the lung, where flow-limited absorption occurs (see description of systemic model).

*Systemic model.* The systemic model includes compartments representing the upper respiratory tract (excluding the nasal cavity), lung, liver, fat, and two lumped compartments representing other richly perfused and poorly perfused tissues, respectively. Transfer of naphthalene from the lung to blood is assumed to be flow-limited, governed by the concentration in pulmonary air, ventilation rate, cardiac output, and the blood:air partition coefficient. Transfers between blood and other tissues are also assumed to be flow-limited, governed by tissue blood flow, the arterial blood concentration, and the tissue:blood partition coefficient. Metabolism of naphthalene through the 1,2-epoxide pathway is simulated as a Michaelis-Menten processes ( $V_{\max}$ ,  $K_M$ ), with parameter values assigned to lung and liver. The dispositions of metabolites are not simulated.

***Parameter Estimates and Calibration.*** Values for nasal cavity physiological parameters (air flow, blood flow, subcompartment dimensions) were adopted from previously published nasal cavity models (Bogdanffy et al. 1999; Frederick et al. 1998; Morris 1999; Plowchalk et al. 1997). Values for nasal cavity blood flow in humans were based on estimates made in human clinical studies (Holmberg et al. 1989; Paulson et al. 1985). Physiological parameters for the systemic model were adopted from Brown et al. (1997). The value for the blood:air partition coefficient was reported in a naphthalene carcinogenicity assay (NTP 2000). Values for tissue:blood partition coefficients were cited to personal communications from A.R. Buckpitt.

Parameters ( $V_{\max}$ ,  $K_M$ ) for metabolism of naphthalene in the nasal cavity and lung were from Buckpitt et al. (2013). The  $K_M$  for liver was from Willems et al. (2001) and the liver  $V_{\max}$  was calibrated to the naphthalene blood-time profile following intravenous dosing of rats (Campbell et al. 2014). Human metabolism parameters for the nasal cavity and lung were based on estimates made in Rhesus monkeys (Buckpitt et al. 2013). The  $V_{\max}$  for the monkey nasal cavity (olfactory and respiratory tissues combined) from Buckpitt et al. (2013) was proportioned between olfactory and respiratory tissue in a 4:1 ratio based on estimates made in rats (Buckpitt et al. 2013). Nasal cavity olfactory and respiratory tissue  $K_M$  values for humans were assigned values estimated for rats (Buckpitt et al. 2013). The  $K_M$  for human lung was from (Buckpitt et al. 2013) and the  $V_{\max}$  from Buckpitt and Bahnson (1986). Values for  $K_M$  and  $V_{\max}$  of

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human liver were based on Cho et al. (2006). All *in vitro* estimates of  $V_{\max}$  were scaled to whole-tissue microsomal protein content.

After calibration of the liver  $V_{\max}$ , the model predicted the overall dose-dependent time course for blood naphthalene concentrations in rats following a single intravenous dose of naphthalene (1, 3, or 10 mg/kg, Campbell et al. 2014). In general, the predicted concentrations were within a factor of 2 of observations. For the 1 mg/kg dose, most predictions were within 1 standard deviation (SD) of the observed means (shown in Figure 2 of Campbell et al. 2014).

A sensitivity analysis of the model showed that predictions of steady-state blood naphthalene concentrations and metabolism rates were most sensitive to values assigned to ventilation rate and cardiac output (reported in Tables 4 and 5 of Campbell et al. 2014). Within the nasal cavity, predicted tissue naphthalene concentrations and metabolism rates were most sensitive to values assigned to blood:air and tissue:blood partition coefficients and to the  $K_M$  and  $V_{\max}$  for metabolism of naphthalene.

**Evaluation.** The model was evaluated against observations of blood naphthalene concentrations in rats following 6-hour inhalation exposures to 10, 30 or 60 ppm naphthalene (NTP 2000). The model predicted the time course for the post-exposure decline in blood naphthalene levels, with all predictions within 1 SD of the observed means (shown in Figure 3 of Campbell et al. 2014). Model predictions of extraction of inhaled naphthalene in the nasal cavity were evaluated against observations made in rats following a 1-hour inhalation exposure to 3, 10, or 30 ppm naphthalene (Morris and Buckpitt 2009). Nasal cavity extraction was estimated based on the inhalation rate and naphthalene concentration in air sampled with a laryngeal cannula placed at the anterior end of the nasal cavity. The model predicted the observed dose-dependent decline in nasal cavity extraction predicted for saturable metabolism of naphthalene in the nasal cavity. Predictions were within 1 SD of the observed means (shown in Figure 4 of Campbell et al. 2014). The model also predicted a constant nasal cavity extraction that was independent of dose in rats pre-treated with 5-phenyl pentene to inhibit metabolism of naphthalene (Morris and Buckpitt 2009). The model was not evaluated against data from studies conducted in humans.

**Applications to Dosimetry.** The model was used to predict naphthalene concentrations and rates of metabolism in rat and human dorsal olfactory epithelium, ventral nasal respiratory epithelium, lung, and liver for 6-hour inhalation exposures ranging from 0.1 to 60 ppm. Across this range of exposures, naphthalene concentrations in the dorsal olfactory epithelium were predicted to be 3–4 times higher in the

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human compared to the rat. Rates of metabolism in the human dorsal olfactory epithelium were predicted to be approximately 20% of the rates predicted for rats (reported in Tables 6 and 7 of Campbell et al. 2014). Internal dose metrics were used to predict human equivalent exposure concentrations (HECs) corresponding to the same internal doses in rats and humans (reported in Table 9 of Campbell et al. 2014). The HEC based on dorsal olfactory epithelium naphthalene concentrations or rate of metabolism increased with dose, reflecting different assumptions about saturable metabolism of naphthalene in the rat and human nasal cavity. The HECs based on dorsal olfactory naphthalene concentration ranged from 0.0046 ppm (0.1 ppm rat exposure) to 4.47 ppm (60 ppm rat exposure). The HECs based on naphthalene metabolism in the dorsal olfactory epithelium ranged from 0.12 (0.1 ppm rat exposure) to 9.85 ppm (3 ppm rat exposure). These outcomes predict that HECs would be dependent on the exposure concentration and the internal dose metric selected.

**Kapraun et al. 2020 Model**

**Description.** Kapraun et al. (2020) developed a human model to simulate the kinetics of naphthalene absorbed from an application of JP-8 to the skin surface. The model is an extension of the Campbell et al. (2014) model with the addition of parameters describing the transfer of naphthalene from the exposure site (“exposure well”) to blood. Two approaches to modeling skin penetration were explored, referred to in Kapraun et al. (2020) as a 2-compartment (2C) model and a partial differential equation (PDE) model. In the 2C model, transfer of naphthalene from the exposure well to the stratum corneum (SC) and from SC to viable epidermis (VE) are governed by the concentration gradient between compartments, a permeability coefficient (cm/minute) and tissue:well partition coefficient. Transfer of naphthalene from the VE to blood is assumed to be flow-limited and governed by tissue blood flow, the arterial blood concentration, and the tissue-blood partition coefficient. In the PDE model, transfer of naphthalene through the SC is simulated as diffusion through a series of 10 subcompartments representing progressively deeper layers of the SC and the outer layer of the VE. Each transfer is governed by the concentration gradient between layers and a diffusion coefficient (cm<sup>2</sup>/minute). The PDE model predicts a SC depth profile for naphthalene concentrations in the SC, which is useful for simulating the loss of naphthalene from the SC resulting from tape stripping (Kim et al. 2006).

**Parameter Estimates and Calibration.** Values for SC and VE thickness, SC:VE and BE: blood partition coefficients, and diffusion coefficients of naphthalene in the VE were from McCarley and Bunge (2001). Values for the SC:JP-8 and VE:JP-8 partition coefficients and the blood naphthalene dose rate from background sources of exposure were calibrated to blood naphthalene observations in humans. In these

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studies, 10 adult subjects received 30-minute dermal applications of JP-8 to a 20-cm<sup>2</sup> area of the forearm (Kim et al. 2006). Parameters were calibrated against data from individual subjects and against the combined observations from all subjects. The two approaches yielded similar mean values for the three parameters (reported in Tables 5 and 6 of Kapraun et al. 2020). The calibrated 2C and PDE models predicted the time-course of blood naphthalene concentrations observed, with most predictions being less than a factor of 2 from observations (shown in Figure 3 of Kapraun et al. 2020)

A sensitivity analysis of the model evaluated predictions for average, peak, and steady-state blood naphthalene concentrations. In general, blood naphthalene concentrations were most sensitive to values assigned to parameters that determined the naphthalene dose to the skin surface such as the naphthalene concentration in JP-8, exposure surface area, and SC:JP-8 partition coefficient (shown in Figure 4 of Kapraun et al. 2020). The model was also sensitive to other systemic parameters such as cardiac output and blood flow to the liver and body weight. Predictions of blood naphthalene concentrations were relatively insensitive to values assigned to the nasal cavity parameters and to systemic metabolism parameters.

***Evaluation.*** Kapraun et al. (2020) did not report evaluations of performance of the model against observations that were not used for calibrating the model.

***Applications to Dosimetry.*** The model was used to predict naphthalene HECs to support derivation of an acute inhalation reference dose (EPA 2022c). The approach taken to deriving HECs was similar to the approach reported in Campbell et al. (2014). The study that formed the basis for the HECs exposed rats to air concentrations of naphthalene ranging from 0.1 to 30 ppm for a period of 6 hours. The cumulative amount of naphthalene metabolized in the dorsal olfactory epithelium during the 6-hour exposure period was selected as the internal dose metric for HEC calculations based on the rationale that lesions observed in the nasal cavity are likely to have resulted from reactive naphthalene metabolites formed in dorsal olfactory tissues. The point of departure (POD) based on benchmark dose (BMD) modeling of the rat internal doses was 24.2 µg metabolized/mL tissue. The Kapraun et al. (2020) human model was used to predict HECs corresponding to the rat internal doses. The corresponding HECs were 19.6 µg/m<sup>3</sup> (1-hour exposure), 1.41 µg/m<sup>3</sup> (8-hour exposure), and 0.451 µg/m<sup>3</sup> (24-hour exposure).



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**3.1.6 Animal-to-Human Extrapolations**

**Naphthalene.** Naphthalene-induced lesions in nasal epithelia of mice and rats appear to be the critical nonneoplastic effect (i.e., the effect occurring at the lowest exposure level) associated with inhalation exposure to naphthalene, while effects in the lung occur at higher exposures. Comparison of species susceptibility to naphthalene-induced nonneoplastic lung damage suggests that mice are much more sensitive than rats (e.g., nonneoplastic or neoplastic lung lesions were not found in chronically exposed rats in the NTP [2000] study) and that differences in rates and stereoselectivity of naphthalene metabolism to epoxide intermediates may be involved in this species difference (Buckpitt et al. 1992, 2002). Acute (4-hour) inhalation exposure of mice to naphthalene concentrations as low as 2–10 ppm induced lung injury, whereas rats exposed to naphthalene concentrations as high as 110 ppm showed no signs of lung injury (West et al. 2001). Some evidence has been reported that rates and stereoselectivity of naphthalene metabolism in primate lung tissue may be more like rats than mice (Buckpitt and Bahnson 1986; Buckpitt et al. 1992, 1995). In *in vitro* studies with microsomes from lymphoblastoid cells, which expressed recombinant human CYP2F1, metabolism of naphthalene to epoxide intermediates was demonstrated, but the predominant enantiomeric form produced (1*S*,2*R*-oxide) was different from the form (1*R*,2*S*-oxide) produced by mouse CYP2F2 (Lanza et al. 1999). Although these observations on epoxide formation may suggest that mice may be more sensitive than humans to acute naphthalene lung toxicity from epoxide intermediates, the possible role of other potentially reactive metabolites of naphthalene (e.g., the naphthoquinone metabolites) is unknown with chronic exposure scenarios.

In contrast to the lung, the olfactory epithelium and respiratory epithelium of the nose of rats and mice do not appear to differ in sensitivity to naphthalene nonneoplastic toxicity from inhalation exposure. Nonneoplastic nasal lesions were found in nearly all exposed animals of both species at the lowest exposure level, 10 ppm, in both chronic studies (NTP 1992a, 2000). *In vitro* and *ex vivo* data suggest that human nasal tissues may be susceptible to naphthalene toxicity. Kedderis et al. (2014) compared the cytotoxicity of naphthalene in freshly isolated cells from target tissues (lung and nasal epithelium) and nontarget tissues of F344 rats, B6C3F1 mice, and humans. Cytotoxicity in nasal respiratory epithelium, measured as cellular LDH, ATP, and reduced glutathione, was most severe in human nasal tissues (compared with rat and mouse), with dose-dependent decreases in all three measures, even though high-performance liquid chromatography (HPLC) analysis did not detect any naphthalene metabolites (Kedderis et al. 2014). The study authors suggested that human nasal respiratory epithelium may have a smaller pool of available reduced glutathione than rat or mouse. DeStefano-Shields et al. (2010) provided additional support for relevance of nasal lesions in rats to effects in humans. These investigators

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compared the levels of adducted proteins in rat olfactory and septal turbinates with those in Rhesus monkey maxilloturbinates and ethmoturbinates incubated with  $^{14}\text{C}$ -naphthalene. No significant differences in the covalently bound radioactivity were detected between the rat and monkey tissues. Identification of the adducted proteins showed a wider variety in rat nasal tissue compared with monkey nasal tissue. In rats, adducted proteins included structural proteins (actin and tubulin), proteins involved in energy metabolism, and proteins involved in the unfolded protein response; in monkeys, the adducted proteins were primarily structural, but also included a multifunctional protease inhibitor (DeStefano-Shields et al. 2010).

Evidence for human susceptibility to naphthalene-induced nasal and pulmonary effects was provided in a study of transgenic mice expressing human CYP2A13 and CYP2F1 (Li et al. 2017). Mice expressing the humanized enzymes exhibited nasal and lung toxicity, while mice that lack CYP2 isozyme expression (Cyp2abfgs-null) did not. These findings support the human relevance of naphthalene toxicity seen in mice.

As described further in Section 2.20, Carratt et al. (2019a) observed greater quantities of radiolabeled naphthalene and 1,2-naphthoquinone DNA adducts in primate (Rhesus macaque) lung tissue explants compared with mouse lung tissue explants, and rat nasal tissue explants showed the smallest adduct levels. Carratt et al. (2019a) did not identify the specific adducts but did show that radiolabeled naphthalene and 1,2-naphthoquinone were covalently bound to DNA. The relevance of the DNA adducts to nasal and lung toxicity is uncertain.

Species differences in the effects of naphthalene may also be influenced by differing rates of hepatic metabolism, which contributes to circulating naphthalene and metabolites. Kovalchuk et al. (2017) compared airway histopathology changes in wild-type mice with those in liver-Cpr-null (LCN) mice after inhalation exposure to 5 or 10 ppm naphthalene for 4 hours. The LCN strain lacks hepatic microsomal P450 activity due to deletion of the *Cpr* gene. After inhalation exposure to naphthalene, the volume of damaged airway epithelial cells was significantly lower in LCN mice compared with wild-type mice, indicating that bioactivation of naphthalene in the liver contributes to lung tissue damage in mice.

***1- and 2-Methylnaphthalene.*** Pulmonary alveolar proteinosis induced in mice following chronic-duration oral exposure to 1- or 2-methylnaphthalene is assumed to be relevant to humans, in the absence of data to indicate otherwise. Pulmonary alveolar proteinosis is a condition that has been described in

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humans, although reports noting associations with human exposure to 1- or 2-methylnaphthalene were not located.

*In vitro* studies comparing metabolism of naphthalene and alkylated naphthalenes by human and rat liver microsomes showed higher overall intrinsic clearance in human microsomes compared to rat microsomes (Wang et al. 2020). For naphthalene, metabolism by human microsomes yielded more 1,2-dihydro-1,2-naphthalenediol than 1-naphthol, while the opposite was true of rat microsomes (Wang et al. 2020).

### 3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are discussed in Section 5.7, Populations with Potentially High Exposures.

***Naphthalene.*** Newborns and infants are thought to be more susceptible to adverse health effects from naphthalene (e.g., hemolytic anemia from acute exposure) because hepatic enzyme systems involved in conjugation and excretion of naphthalene metabolites are not well developed shortly after birth (EPA 1987). No studies were located, however, that specifically examined the influence of age on naphthalene toxicokinetic capabilities in humans.

Although the occurrence of hemolytic anemia in neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al.

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1959; Zinkham and Childs 1957, 1958), oral-exposure developmental toxicity studies in animals do not provide evidence that naphthalene was fetotoxic or impaired fetal development, even at maternally toxic dose levels as high as 450 mg/kg/day (NTP 1991; Plasterer et al. 1985; Texaco 1986).

Naphthalene has been detected in human milk samples (concentration not reported) (Pellizzari et al. 1982), but no studies were located that have specifically examined the rate or extent of naphthalene distribution to breast milk in exposed humans or animals.

The hemolytic response to naphthalene is enhanced by the presence of inherited erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. Although any human may experience acute hemolysis if exposed to a sufficiently high dose of naphthalene, this enzyme deficiency may cause some persons to be unusually sensitive. The incidence of the deficiency among Caucasians of European origin is relatively low, while there is a higher incidence among certain groups of Asians and Middle Eastern populations. A study of hemolytic anemia in African-American children with G6PD deficiency by Shannon and Buchanan (1982) suggests that this is a population that may be susceptible to the hemolytic effects of naphthalene exposure. It was also reported that 16% of African-American males are G6PD-deficient (Calabrese 1986). According to Shannon and Buchanan (1982), a syndrome of acute severe hemolysis following exposure to oxidative stress is associated with the Mediterranean variant of the deficiency, whereas the hemolytic anemia seen in African Americans is generally mild.

Children with genetically determined G6PD deficiency are expected to be especially susceptible to the hemolytic action of naphthalene (Owa 1989; Owa et al. 1993; Santucci and Shah 2000; Valaes et al. 1963). In support of this hypothesis, in 21 cases of hemolytic anemia in Greek infants exposed to naphthalene, 10 of the children had a genetically determined deficiency in G6PD (Valaes et al. 1963). In a 10-year chart review of 24 African-American children hospitalized with acute hemolytic anemia, 14 were noted to have been exposed to naphthalene-containing moth repellants (Santucci and Shah 2000). Deficiency in G6PD makes red blood cells more susceptible to oxidative damage from a wide range of causes including naphthalene exposure. Relatively high rates of genetically determined G6PD deficiency have been reported in males of certain subpopulations of Asian, Arabic, Caucasian, African, and African-American ancestry (EPA 1987).

The limited mobility of infants when they are wearing naphthalene-treated clothing or when they are near other naphthalene-treated articles (e.g., blankets treated with naphthalene-containing moth repellants) may maximize exposure due to the development of a microenvironment with a high level of naphthalene

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vapor in the space around the infant. The tendency for infants and small children to place small objects, such as mothballs, in their mouths also increases their risk.

Studies in animals have demonstrated greater susceptibility of young mice compared with adult mice to naphthalene-induced lung effects. Juvenile animals have been shown to be more susceptible to the lung toxicity of naphthalene after inhalation exposure than either adults or neonates. Carratt et al. (2019b) exposed 7-day old, 3-week-old, and adult mice to 5 or 10 ppm naphthalene in air for 4 hours and examined airway histology. Histopathology changes (club cell swelling and vacuolation) occurred in all of the examined airways and groups but were most severe in the proximal airways of juvenile females. The enhanced susceptibility of juvenile females was not explained by levels of glutathione-conjugated naphthalene in the lungs, which were higher in neonatal females than juveniles. Gene expression analysis showed that juvenile female mice were predisposed to upregulation of DNA damage and cancer pathways, suggesting a possible mechanism for the susceptibility (Carratt et al. 2019b).

In contrast, neonatal mice were more susceptible than juvenile or adult mice to lung injury from single i.p. doses of 25, 50, or 100 mg/kg naphthalene (Fanucchi et al. 1997). Epithelial damage in terminal bronchioles (principally in the club cells) was observed in 7-day-old mice exposed to 25 mg/kg but was absent in adult mice at the same dose level. In adult mice exposed to 50 mg/kg, injury was only mild and variable (from mouse to mouse) and only became consistent with exposure to 100 mg/kg. Epithelial damage in 14-day-old mice was less severe than the damage in 7-day-old mice. Activities of CYP-mediated naphthalene metabolism in bronchiolar tissues were 2.5 times lower in neonatal mice than in adult mice, suggesting that the difference in susceptibility is not explained by differences in ability to form reactive metabolites alone (e.g., 1,2-naphthalene oxide). Differences between neonates and adults in the balance between formation of reactive naphthalene metabolites and downstream transformations could potentially explain the difference in susceptibility to naphthalene toxicity, but the possibilities for specific, age-related differences in downstream enzyme activities for naphthalene (e.g., epoxide hydrolase, dihydrodiol dehydrogenase) have not been studied to date. Alternatively, toxicodynamic differences may exist between neonatal and adult mice (e.g., different target macromolecules). Based on findings that *in utero* exposure to other chemicals (which are bioactivated by CYP), caused club cell tumors in adult offspring, Fanucchi et al. (1997) postulated that naphthalene exposure during the neonatal period (when increased susceptibility to naphthalene-induced cytotoxicity occurs) may lead to loss of regulatory mechanisms resulting in club cell proliferation and tumor formation in adult animals. However, direct evidence for naphthalene in support of this hypothesis is not available (e.g.,

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demonstration that *in utero* or neonatal naphthalene exposure will cause increased incidence of lung tumors in adult mice).

Female mice, but not male mice, developed lung tumors after chronic exposure to naphthalene (NTP 1992a). Several studies have suggested that female mice are more susceptible to lung injury than male mice after exposure to naphthalene. In the study of age-dependent lung toxicity in mice described above, Carratt et al. (2019b) observed the most severe damage to airway epithelium in juvenile females. These investigators also conducted studies examining DNA adducts in mouse and primate lung explants exposed to naphthalene, and in both species, the adduct levels were significantly (2–5-fold) higher in females than in males. In male and female Swiss-Webster mice given i.p. injections of 0 or 200 mg/kg naphthalene in corn oil, club cell injury in terminal bronchioles occurred earlier, affected cells farther up the airway tree, and showed a different temporal pattern of changes in female mice compared with male mice (Van Winkle et al. 2002). Twenty-four hours after injection, club cell injury in the lobar bronchus of female mice was evidenced by numerous vacuolated cells, whereas normal bronchiolar epithelium containing club and ciliated cells was found in vehicle-control males and females, as well as in exposed male mice. Assessment of *in vitro* naphthalene metabolism in micro-dissected regions of airways from male and female mice indicated that the rate of formation of a dihydrodiol metabolite (1,2-dihydroxy-1,2-dihydronaphthalene) was greater in female tissue than in male tissue (Van Winkle et al. 2002). Sutherland et al. (2012) showed that the higher susceptibility of female mice persisted when both sexes were exposed to a naphthalene regimen designed to induce tolerance. After seven daily i.p. injections of 10 µL/g body weight naphthalene followed by a challenge i.p. injection of 300 mg/kg, both males and females showed less damage than control animals given the challenge injection, but histopathology findings in female airways remained more extensive than in airways of males (Sutherland et al. 2012). Measurement of CYP2F2 messenger ribonucleic acid (mRNA) and protein levels showed that expression of this enzyme was lower in airways of tolerant females than tolerant males. However, protein expression of glutamate-cysteine ligase, a critical enzyme in glutathione synthesis that is believed to be upregulated in tolerant males, was also lower in females (Sutherland et al. 2012).

Sex differences in susceptibility to nasal tumors in rats were also observed; male rats developed respiratory adenomas, while female rats developed olfactory neuroblastomas (Abdo et al. 2001; NTP 2000). Cichocki et al. (2014) observed no difference in cytotoxicity in the nasal respiratory or olfactory epithelium in F344 rats exposed nose-only to naphthalene vapor concentrations up to 30 ppm for 4 or 6 hours. However, the study authors also observed greater induction of glutamate-cysteine ligase catalytic subunit gene expression in the olfactory epithelium of males compared to females (~2.5–4-fold

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higher), and higher induction of heme oxygenase 1 gene expression. The study authors proposed that the reduced ability of female rat olfactory epithelium to induce antioxidant-responsive genes may play a role in the susceptibility of this tissue to tumor formation (Cichocki et al. 2014).

Other factors that could influence the susceptibility to naphthalene toxicity may include nutritional status and genetic differences in the form or expression of enzymes involved in the bioactivation and/or detoxification of naphthalene. Nutritional status can influence detoxification pathways such as glutathione conjugation and antioxidant capacity; however, no studies examining the role of nutrition in naphthalene toxicity were located. Some studies have shown that polymorphisms in genes encoding CYP2E1 and glutathione-S-transferase can modify the excretion of urinary naphthols in humans exposed to naphthalene (Rodrigues et al. 2014; Yang et al. 1999), but the relationship to naphthalene toxicity is uncertain.

***1- and 2-Methylnaphthalene.*** No direct information was located on the relative susceptibility of children or young animals to 1- or 2-methylnaphthalene toxicity, compared with adults. However, clinical experience with humans displaying pulmonary alveolar proteinosis of unknown etiology has indicated that children with this condition experience more severe symptoms and a worse prognosis for survival than adults (EPA 2003; Mazzone et al. 2001).

### 3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see <http://www.cdc.gov/exposurereport/>). If available, biomonitoring data for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance

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itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. Biomarkers of susceptibility are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

### 3.3.1 Biomarkers of Exposure

**Naphthalene.** In cases where humans have swallowed one or more mothballs, it is possible to identify the undissolved naphthalene in the stomach or duodenum by radioluminescence (Woolf et al. 1993). Thus, radiography of the abdominal area is of value in determining if exposure has occurred, especially in children who are often unreliable sources of exposure information. Of the 2,400 cases on naphthalene ingestion reported to 72 Poison Control Centers in the United States, 2,100 involve children <6 years old. Radioluminescence has the advantage of differentiating naphthalene-containing solids in the gastrointestinal tract from paradichlorobenzene or other materials used in moth repellants and deodorizers.

Methods are available for the determination of naphthalene in human adipose tissue (EPA 1986b; Liao et al. 1988). In the National Human Adipose Tissue Survey, 40% of the subjects surveyed had measurable levels of naphthalene with concentrations of up to 63 ng/g. Naphthalene and its metabolites can be detected in human and animal urine (Horning et al. 1980; Mackell et al. 1951; Stillwell et al. 1982). Investigators have reported strong correlations between 1-naphthol concentrations in the urine of exposed



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workers and naphthalene concentrations in the breathing zone air (Bieniek 1994). Peak naphthalene concentrations in the urine occurred immediately after the end of the exposure period and declined thereafter. In some instances, 1-naphthol concentrations had returned to baseline 8 hours later. Few current data are available relating naphthalene levels in adipose tissue or urine with the human exposure concentrations.

In swine, a good correlation existed between 1-naphthol levels in hydrolyzed urine samples collected in the first and second 24 hours after dosing with as little as 7 µg/kg/day naphthalene (Keimig and Morgan 1986). Thus, 1-naphthol may be an appropriate biomarker for monitoring naphthalene exposures in the occupational setting. Some caution must be exercised in using 1-naphthol as a biomarker of naphthalene exposure in the general population since this metabolite is also excreted after exposure to the common insecticide, carbaryl (Benson and Dorrough 1984).

Early work to develop biomarkers of exposure, such as naphthalene mercapturic acid derivatives in urine (Marco et al. 1993) and naphthalene hemoglobin adducts in blood (Cho et al. 1994b), has been extended to develop techniques to measure cysteinyl adducts formed from reactions of hemoglobin and albumin with reactive metabolites of naphthalene (Troester et al. 2002; Waidyanatha et al. 2002). One of the reasons for developing these techniques is that it is difficult to measure reactive metabolites of naphthalene *in vivo*. Using these techniques, hemoglobin and albumin adducts of 1,2-naphthalene oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone were shown to increase with increasing dose in F344 rats given single oral doses of 0, 100, 200, 400, or 800 mg/kg naphthalene (Waidyanatha et al. 2002). The stabilities of the adducts were measured in rats following exposure to naphthalene (Troester et al. 2002). Some were found to be stable and others unstable, although they all were more stable than the reactive metabolites themselves. As such, the adducts are expected to be useful in estimating internal doses of these metabolites.

***1- and 2-Methylnaphthalene.*** An analytical method is available to determine levels of 2-methylnaphthalene and its derivatives in rat urine (Melancon et al. 1982). This method would probably also be useful in measuring 2-methylnaphthalene levels in human urine. Because of the lack of information for 1-methylnaphthalene, it is not possible to identify a biomarker of exposure for this substance.

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**3.3.2 Biomarkers of Effect**

***Naphthalene.*** Hemolytic anemia has been frequently reported to be a consequence of exposure to naphthalene. However, this effect can also occur without exposure to naphthalene, and may not be useful as a specific biomarker of effect. Club cell damage may be identified by the presence of naphthalene/protein adducts in lung lavage fluids (Cho et al. 1994a). Additional research is needed to improve the specificity of this technique as a biomarker of effect. Similarly, naphthalene DNA adducts may serve as biomarkers of naphthalene effects (Carratt et al. 2019a), but data on adduct identity, abundance, and fate in various animal and human tissues are needed to ascertain specificity.

***1- and 2-Methylnaphthalene.*** Because of the lack of information for 1- or 2-methylnaphthalene, it is not possible to identify a biomarker of effects for these chemicals.

**3.4 INTERACTIONS WITH OTHER CHEMICALS**

Roberts et al. (2018) showed that concurrent exposure to naphthalene and carbon particles increased the deposition of naphthalene in the respiratory tract of male rats compared with naphthalene vapor alone. Significantly higher tissue concentrations of radioactivity were found in the bronchioles and lung of rats co-exposed to 20 ppm <sup>3</sup>H-naphthalene and 5 mg/m<sup>3</sup> carbon particles compared with naphthalene alone. No effect of co-treatment with particles was seen in the radioactivity levels in the nasopharynx or trachea (Roberts et al. 2018).

When naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene was applied dermally in combination with benzo[a]pyrene (BaP), there was an inhibitory effect on the induction of skin tumors in female mice (Schmeltz et al. 1978). These investigators also reported that a mixture containing naphthalene (0.02%), 2-methylnaphthalene (0.02%), and 10 other methylated and ethylated naphthalenes (each at 0.02%) also appeared to inhibit the development of BaP-induced skin tumors. The study authors suggested that it is likely that certain naphthalenes compete with BaP for the same enzyme sites, resulting in alteration of the BaP metabolic pathway and decreased production of the active BaP metabolite. This hypothesis is consistent with the observation that benzo(a)pyrene hydroxylase is inhibited by naphthalene (Shopp et al. 1984). Dermal application of the naphthalene mixture did not induce tumors in the absence of BaP. The results of these studies were not analyzed statistically.

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Several studies have been conducted to assess factors that influence the toxicity of naphthalene. For the most part, these studies have evaluated the effects of mixed function oxidase activity (MFO) and alterations in glutathione levels on pulmonary and ocular toxicities. The effects of cyclooxygenase activity, antioxidants, and epoxide hydrolase inhibitors on the cataractogenic effect of naphthalene have also been evaluated. The administration of MFO inhibitors (SKF-525A, metyrapone) and antioxidants (caffeic acid and vitamin E) decreased ocular toxicity in mice (Wells et al. 1989). Use of ALO1576, an inhibitor of the enzyme aldose reductase (also known as aldehyde reductase), prevented cataract formation in both *in vivo* and *in vitro* studies (Xu et al. 1992a, 1992b). On the other hand, naphthalene-induced cataracts were enhanced by pretreatment with a MFO inducer (phenobarbital) and a glutathione depletor (diethyl maleate) (Wells et al. 1989). Pulmonary damage was decreased by prior treatment with a MFO inhibitor (piperonyl butoxide), but enhanced by prior treatment with a glutathione depletor (diethyl maleate) (Warren et al. 1982). For the most part, these studies support the role for MFO activity and glutathione conjugation in naphthalene-induced pulmonary and ocular lesions.

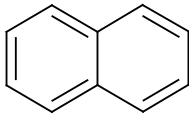
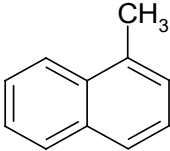
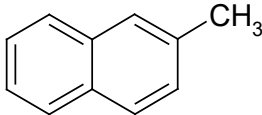
MFO inducers also affect the metabolism of 2-methylnaphthalene. Inducers that influence CYP increase the oxidation of the side chain and the concentration of one dihydrodiol. Induction of CYP increased the production of two other dihydrodiols (Melancon et al. 1985). The production of naphthoic acid in preference to the diols may explain why acute exposure to 2-methylnaphthalene is less toxic to club cells than acute exposure to naphthalene.

In general, interactions with environmental contaminants, such as other polycyclic aromatic hydrocarbons (PAHs), heavy metals, and organic solvents, may be expected at hazardous waste sites. For example, many such sites contain arsenic, which is well known to increase oxidative stress and deplete GSH levels, and thus may influence naphthalene toxicity.

## CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

### 4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is presented in Table 4-1.

<b>Table 4-1. Chemical Identity of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene</b>				
Characteristic	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Reference
Synonyms and registered trade name(s)	Tar camphor; albocarbon; naphthene; mothballs; moth-flakes; white tar; and others; Caswell No. 587®	Alpha-methylnaphthalene; naphthalene, 1-methyl; naphthalene, alpha-methyl	Beta-methylnaphthalene; naphthalene, 2-methyl; naphthalene, beta-methyl	NLM 2023a, 2023b, 2023c
Chemical formula	C <sub>10</sub> H <sub>8</sub>	C <sub>11</sub> H <sub>10</sub>	C <sub>11</sub> H <sub>10</sub>	NLM 2023a, 2023b, 2023c
SMILES	C1=CC=C2C=CC=CC2=C1	CC1=CC=CC2=CC=CC=C12	CC1=CC2=CC=CC=C2C=C1	NLM 2023a, 2023b, 2023c
Chemical structure				NLM 2023a, 2023b, 2023c
CAS Registry Number	91-20-3	90-12-0	91-57-6	NLM 2023a, 2023b, 2023c

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

### 4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is presented in Table 4-2.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

Property	Naphthalene	1-Methyl-naphthalene	2-Methyl-naphthalene	Reference
Molecular weight	128.17	142.20	142.20	NLM 2023a, 2023b, 2023c
Color	White	Colorless	No data	NLM 2023a, 2023b, 2023c
Physical state	Solid	Liquid	Solid	NLM 2023a, 2023b, 2023c
Melting point	80.2°C	-22°C	34.6°C	NLM 2023a, 2023b, 2023c
Boiling point	217.9°C	244°C	241.1°C	NLM 2023a, 2023b, 2023c
Density at 20°C	1.162 g/mL	1.0202 g/mL	1.0058 g/mL	NLM 2023a, 2023b, 2023c
Vapor density (air = 1)	4.42	4.91	No data	NLM 2023a, 2023b, 2023c
Odor	Strong (tar or mothballs)	No data	No data	NLM 2023a, 2023b, 2023c
Odor threshold:				
Water	0.021 mg/L; 6.80 mg/L	0.0075 mg/L	0.01 mg/L	Amoore and Hautala 1983; NLM 2023a; Verschueren 1983
Air	0.44 mg/m <sup>3</sup>	0.12 mg/m <sup>3</sup>	0.0581– 0.2905 mg/m <sup>3</sup>	NLM 2023a, 2023b, 2023c
Solubility:				
Water at 25°C	31 mg/L	25.8 mg/L	24.6 mg/L	NLM 2023a, 2023b, 2023c
Organic solvents	Soluble in benzene, alcohol, ether, acetone	Soluble in alcohol, ether, benzene	Soluble in alcohol, ether, benzene	NLM 2023a, 2023b, 2023c
Partition coefficients:				
Log K <sub>ow</sub>	3.30	3.87	3.86	NLM 2023a, 2023b, 2023c
Log K <sub>oc</sub>	2.05–3.97	3.36; 3.64	3.00–5.96	NLM 2023a, 2023b, 2023c
Vapor pressure at 25°C	0.085 mmHg	0.067 mmHg	0.055 mmHg	NLM 2023a, 2023b, 2023c
Henry's law constant at 25°C	4.4x10 <sup>-4</sup> atm-m <sup>3</sup> /mol	5.14x10 <sup>-4</sup> atm-m <sup>3</sup> /mol	5.18x10 <sup>-4</sup> atm-m <sup>3</sup> /mol	NLM 2023a, 2023b, 2023c
Autoignition temperature	526°C	529°C	No data	NLM 2023a, 2023b, 2023c
Flashpoint (closed cup)	79°C	82°C	98°C	NLM 2022a, 2022b, 2022c

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

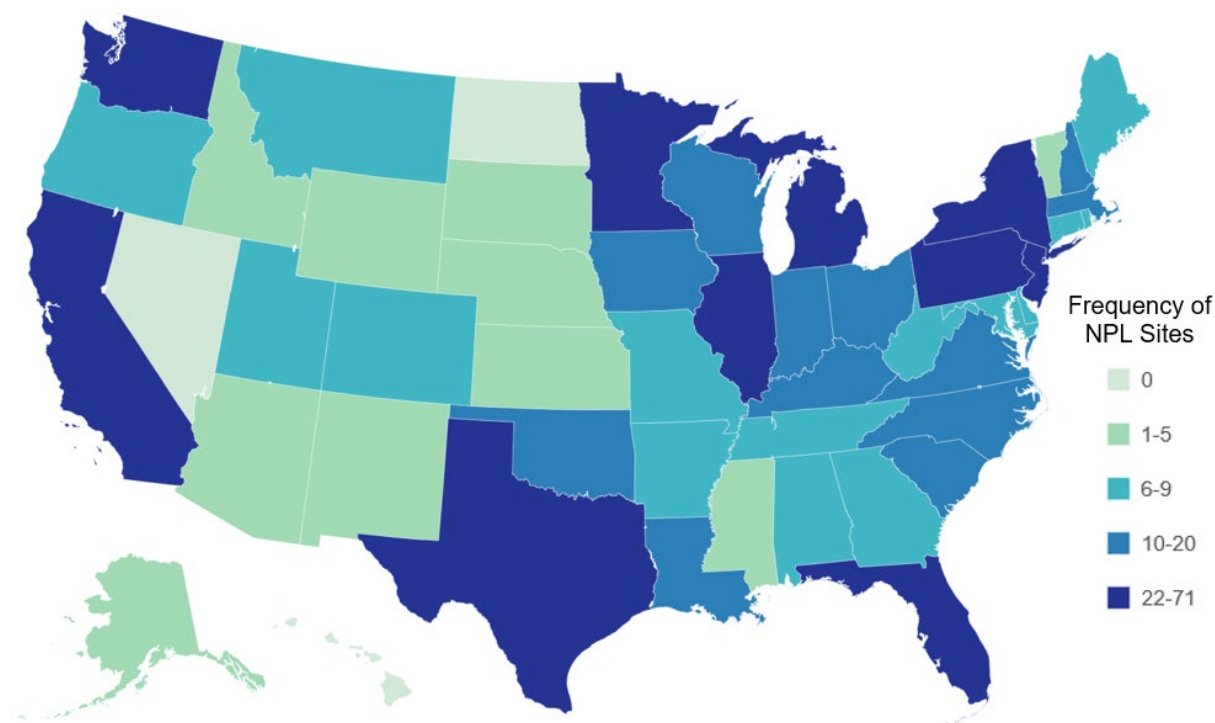
Flammability limits	0.9–5.9%	No data	No data	NLM 2023a, 2023b, 2023c
Conversion factors	1 ppm=5.24 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> =0.191 ppm	1 ppm=5.91 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> =0.17 ppm	1 ppm=5.91 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> =0.17 ppm	Verschueren 1983
Explosive limits	No data	No data	No data	

## CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.1 OVERVIEW

Naphthalene or methylnaphthalene has been identified in at least 682 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022a). However, the number of sites in which naphthalene or methylnaphthalene has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 681 are located within the United States, and 1 is located in the Virgin Islands (not shown).

**Figure 5-1. Number of NPL Sites with Naphthalene and Methylnaphthalene**



Source: ATSDR 2022a

- People who use products which contain naphthalene (e.g., mothballs, inks, plastics), smoke tobacco, or burn organic material indoors may be exposed to naphthalene.
- For the general public, the most likely route of exposure to naphthalene and methylnaphthalenes is through inhalation. Most people will not be exposed to concentrations  $>2$  ppbv ( $10 \mu\text{g}/\text{m}^3$ ) in ambient air.

## 5. POTENTIAL FOR HUMAN EXPOSURE

- Naphthalene and methylnaphthalenes are expected to primarily volatilize to air. They may be removed from the water column by sorption or retained in soil and sediment, especially where solids have a high organic carbon content.
- Naphthalene and methylnaphthalenes are readily degraded by indirect photolysis in air and water. Biodegradation in water, soil, and sediment is slow, but proceeds readily in historically contaminated media where microorganisms are adapted.

Most of the naphthalene entering the environment is discharged to the air. The largest releases result from the combustion of wood and fossil fuels; the largest amount to indoor air is from the off-gassing of naphthalene-containing moth repellents. Smaller amounts of naphthalene are introduced to water as the result of discharges from coal-tar production and distillation processes. The coal-tar industry is also a major source of the small amounts of naphthalene that are directly discharged to land. A large amount of naphthalene (often considerably >1,000 mg/kg) is present in soils contaminated with wastes from manufactured-gas plants. Urban soils may also have increased concentrations of naphthalene.

Naphthalene in the atmosphere is subject to a number of degradation processes, including reaction with photochemically produced hydroxyl radicals. Naphthalene has a short half-life in most natural waters and soils because of its tendency to volatilize and biodegrade, although biodegradation may be slow if the site was not previously contaminated and microorganisms are not adapted to naphthalene. As a consequence of these processes, there is little tendency for naphthalene to build up in the environment over time.

The concentration of naphthalene in air tends to be low in rural areas, but is elevated in urban areas. The highest atmospheric concentrations have been found in the immediate vicinity of specific industrial sources and hazardous waste sites, and around forest fires. Naphthalene is also a common indoor contaminant in households using naphthalene-containing moth repellents or where tobacco is smoked. Electronic cigarettes may also release naphthalene, but at lower concentrations than conventional cigarettes. Levels in water, sediments, and soil tend to be low, except in the immediate vicinity of point sources of release, such as chemical waste sites.

The most likely pathway by which the general public is exposed to naphthalene is by inhalation due to the release of this substance from combustion fuels, moth repellents, and cigarette smoke. The estimated average per capita daily intake from ambient air is 0.8 µg. Exposure by other routes is not likely.

High naphthalene exposure levels could occur near industrial sources or chemical waste sites, but the extent of such exposure to individuals can only be evaluated on a site-by-site basis. High naphthalene exposure levels could also occur in certain work environments in industries that produce and use



## 5. POTENTIAL FOR HUMAN EXPOSURE

naphthalene such as wood preserving, tanning, coal distillation, and ink and dye production, or workers who are in close proximity to naphthalene release during combustion, such as firefighters.

Based on limited data, potential human exposure to 1- or 2-methylnaphthalene is expected to be mainly by inhalation from ambient air. Exposure to these chemicals from tobacco smoke is likely.

Both 1- and 2-methylnaphthalene have also been detected in the environment, particularly in air. These are released from many of the same natural and industrial sources as naphthalene (combustion of wood and fossil fuels, tobacco smoke, coal distillation), but in smaller quantities.

## 5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

### 5.2.1 Production

Table 5-1 summarizes information on companies that reported the production, import, or use of naphthalene for the Toxics Release Inventory (TRI) in 2021 (TRI21 2023). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Naphthalene and methylnaphthalenes occur naturally in fossil fuels such as petroleum and coal, and are produced when organic materials (e.g., fossil fuels, wood, tobacco) are burned (EPA 2002; IARC 2002). Commercially, naphthalene may be produced from either coal tar or petroleum. Distillation and fractionation of coal tar was the most common production process until the late 1950s (Mason 2002). The middle fraction (containing most of the naphthalene) is cooled, crystallizing the naphthalene. The crude naphthalene may be refined by distillation, washing, and sublimation (EPA 1982; Hughes et al. 1985). 1-Methylnaphthalene and 2-methylnaphthalene are also produced from coal tar by first extracting the heteroaromatics and phenols, then filtering off the crystallized 2-methylnaphthalene and redistilling the filtrate to yield 1-methylnaphthalene (GDCH 1992; Sax and Lewis 1987). The individual isomers are not often isolated for commercial purposes in the United States; a methylnaphthalene-rich fraction of the coal tar or petroleum is distributed instead (Mason 2002).

From 1960, recovery of naphthalene from petroleum by dealkylation of methyl naphthalenes in the presence of hydrogen at high temperature and pressure had become a major commercial production process, accounting for over 40% of total naphthalene production (Mason 2002). The naphthalene is then recovered by fractionation, decolorized, and purified by crystallization. Naphthalene produced from

## 5. POTENTIAL FOR HUMAN EXPOSURE

petroleum is about 99% pure. In the United States, most naphthalene was produced from petroleum, but due to decreasing demand and production, this changed when the last petroleum processing plant for naphthalene was closed in 1991 (EPA 1982; Hughes et al. 1985; Mason 2002). Petroleum sources made a modest rebound later, however. In 2001, petroleum sources accounted for 20% of naphthalene production capacity, leaving 80% production capacity to coal tar (Collin et al. 2012). It is not known which is the current dominant process.

The 2019 nationally aggregated production volume for naphthalene was between 100,000,000 and <250,000,000 pounds (EPA 2022a). The same production volumes were reported for 2016 and 2017, but there was a temporary increase to  $\geq 1,000,000,000$  pounds in 2018. The 2019 nationally aggregated production volume for 1-methylnaphthalene was about 1,900,000 pounds, comparable to reporting from 2016 to 2018; about 2,000,000 pounds were reported for 2-methylnaphthalene, also comparable to previous reporting years (EPA 2022a).

There are currently five companies that reported manufacturing naphthalene in 2019: Coopers Creek Chemical Corporation, Equilon Enterprises LLC dba Shell Oil Products US (a subsidiary of Shell Oil Company), Koppers Inc., Monument Chemical LLC, and Shell Chemical LP (EPA 2022a). Only one company, Shell Chemical LP, reported manufacturing 1- and 2-methylnaphthalene. This may not be an exhaustive list; companies must meet a reporting threshold per site to trigger reporting to the Chemical Data Reporting (CDR) rule.

Table 5-1 lists information on United States companies that reported the manufacture and use of naphthalene in 2020 (TRI21 2023). The Toxics Release Inventory (TRI) data should be used with caution since only certain types of facilities are required to report. The TRI is not an exhaustive list. No information is available in the TRI database on facilities that manufacture or process 1- or and 2-methylnaphthalene because these chemicals are not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

**Table 5-1. Facilities that Produce, Process, or Use Naphthalene**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AK	28	1,000	9,999,999	1, 3, 4, 5, 7, 8, 9, 10, 12, 14
AL	23	100	9,999,999	1, 2, 3, 4, 5, 7, 9, 10, 12, 13, 14

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-1. Facilities that Produce, Process, or Use Naphthalene**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AR	9	1,000	999,999	1, 5, 7, 9, 10, 12, 14
AZ	22	100	999,999	1, 5, 7, 9, 12
CA	79	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	9	100	49,999,999	1, 5, 7, 9, 10, 12, 13, 14
CT	6	10,000	9,999,999	1, 5, 6, 7, 9, 12, 14
DE	5	10,000	9,999,999	1, 2, 3, 5, 7, 12, 13, 14
FL	37	0	49,999,999	1, 5, 7, 9, 12, 13, 14
GA	25	100	9,999,999	1, 5, 6, 7, 8, 9, 10, 12, 13, 14
GU	6	100	9,999,999	1, 5, 7, 9, 12
HI	19	0	9,999,999	1, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
IA	16	1,000	999,999	1, 4, 5, 7, 8, 9, 10, 11, 12
ID	6	1,000	999,999	1, 5, 7, 9, 12, 14
IL	45	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
IN	39	0	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
KS	18	0	99,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
KY	27	100	9,999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
LA	67	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	12	1,000	9,999,999	1, 2, 4, 5, 7, 8, 9, 12
MD	16	10,000	999,999	1, 5, 7, 9, 12
ME	8	0	9,999,999	2, 3, 4, 7, 9, 12
MI	31	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	7	0	999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
MO	27	0	9,999,999	1, 2, 5, 7, 8, 9, 10, 11, 12, 13
MP	2	10,000	999,999	1, 5, 7, 9
MS	18	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MT	6	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
NC	19	1,000	999,999	1, 5, 6, 7, 8, 9, 10, 12
ND	6	100	9,999,999	1, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
NE	4	10,000	99,999	9, 12
NH	7	1,000	9,999,999	1, 2, 3, 4, 5, 7, 9, 12
NJ	15	1,000	49,999,999	1, 3, 4, 5, 6, 7, 9, 12, 14
NM	12	100	999,999	1, 3, 5, 6, 7, 9, 12
NV	23	100	9,999,999	1, 2, 5, 7, 9, 12, 13, 14
NY	29	0	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-1. Facilities that Produce, Process, or Use Naphthalene**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
OH	56	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	17	100	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	8	100	999,999	1, 5, 7, 9, 12
PA	39	100	9,999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	21	0	49,999,999	1, 2, 3, 4, 5, 9, 12
RI	5	10,000	9,999,999	1, 5, 7, 9, 12, 13, 14
SC	19	100	9,999,999	1, 5, 6, 8, 9, 10, 12, 14
SD	1	100,000	999,999	1, 12, 13
TN	26	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	180	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	17	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
VA	28	10,000	49,999,999	1, 5, 7, 9, 12
VI	4	1,000	49,999,999	1, 5, 7, 9, 12
WA	25	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	17	0	999,999	1, 5, 7, 9, 10, 11, 12, 14
WV	16	100	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
WY	11	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

<sup>a</sup>Post office state abbreviations used.<sup>b</sup>Amounts on site reported by facilities in each state.<sup>c</sup>Activities/uses:

- |                      |                             |                          |
|----------------------|-----------------------------|--------------------------|
| 1. Produce           | 6. Reactant                 | 11. Manufacture Aid      |
| 2. Import            | 7. Formulation Component    | 12. Ancillary            |
| 3. Used Processing   | 8. Article Component        | 13. Manufacture Impurity |
| 4. Sale/Distribution | 9. Repackaging              | 14. Process Impurity     |
| 5. Byproduct         | 10. Chemical Processing Aid |                          |

Source: TRI21 2023 (Data are from 2021)

**5.2.2 Import/Export**

Around 74,000,000 pounds of naphthalene were reported as imported in 2019; around 1,900,000 pounds were reported as exported the same year (EPA 2022a). No imports of 1- or 2-methylnaphthalene were included in the CDR for 2019 and exported quantities of around 440,000 pounds of 1-methylnaphthalene and 650,000 pounds of 2-methylnaphthalene were reported. These values may be lower than the actual

## 5. POTENTIAL FOR HUMAN EXPOSURE

total amounts imported or exported; companies must meet a threshold to trigger reporting to the CDR reporting rule, and some quantities were not available in the public dataset.

### 5.2.3 Use

The principal end use for naphthalene is as an intermediate in the production of phthalic anhydride (>60% of consumption), which is used as an intermediate in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellents, and other materials (Collin et al. 2012; Mason 2002). It is also used in the production of the insecticide carbaryl, synthetic leather-tanning agents, and surface-active agents (naphthalene sulfonates and derivatives, which are used as dispersants or wetting agents in paint, dye, and paper-coating formulations), and miscellaneous organic chemicals, including dyes and resins (Collin et al. 2012; EPA 2022a). Crystalline naphthalene is also used as a moth repellent; about 7% of total U.S. consumption in 2000 was used for this purpose (Mason 2002). Naphthalene is an active ingredient in 22 pesticide products with active registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (EPA 2023a). These products include moth, small mammal, snake, and bat repellants.

It is anticipated that consumption of naphthalene for phthalic anhydride and production of naphthalene sulfonates will increase due to increased demand for these products, although some decline may occur based on increased usage of *o*-xylene feedstock for phthalic anhydride production (Mason 2002).

Mixtures rich in methylnaphthalenes have been used as dye carriers and as feedstock for naphthalene or phthalic anhydride production (Mason 2002). 1-Methylnaphthalene is used as a solvent, as feedstock in the synthesis of 1-methylnaphthoic acid, and, to a lesser degree, as a dyeing agent and as a test substance for determining the ignition capability of diesel fuels. 2-Methylnaphthalene is used in vitamin K production by oxidation to 2-methyl-1,4-naphthoquinone, which can then be reacted to yield phytymenadione (vitamin K). It can also be chlorinated and oxidized to form dyes and small amounts in sulfonated form are used as textile aids, wetting agents, and emulators (GDCH 1992).

### 5.2.4 Disposal

Naphthalene and waste containing naphthalene are classified as hazardous wastes by EPA and its disposal is regulated under RCRA (40 CFR §261). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for these wastes (EPA 1988a, 1989a).

## 5. POTENTIAL FOR HUMAN EXPOSURE

No information was located on disposal methods or quantities of wastes containing 1- or 2-methylnaphthalene. However, these chemicals have been detected at hazardous waste sites (see Section 5.1).

**5.3 RELEASES TO THE ENVIRONMENT**

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ  $\geq 10$  full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022).

Most of the naphthalene entering environmental media is from combustion of wood and fossil fuels, and is released to the air (EPA 2017b). Methylnaphthalenes are released from similar sources (EPA 2017b). Smoking tobacco also releases small amounts of naphthalene and methylnaphthalenes into the environment.

**5.3.1 Air**

Estimated releases of 1,318,765 pounds (~598 metric tons) of naphthalene to the atmosphere from 1,202 domestic manufacturing and processing facilities in 2021, accounted for about 33% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2. There is no information on releases of 1- or 2-methylnaphthalene to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2022).

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Naphthalene<sup>a</sup>**

State <sup>c</sup>	RF <sup>d</sup>	Reported amounts released in pounds per year <sup>b</sup>							
		Air <sup>e</sup>	Water <sup>f</sup>	UI <sup>g</sup>	Land <sup>h</sup>	Other <sup>i</sup>	Total release		
							On-site <sup>j</sup>	Off-site <sup>k</sup>	On- and off-site
AL	23	20,961	37	0	42,949	472	20,997	43,421	64,418
AK	28	377,605	63	0	12	71	377,669	82	377,751
AZ	22	828	0	0	507	458	1,078	715	1,793
AR	9	1,142	1	0	3	0	1,142	3	1,145
CA	74	9,507	187	0	1,620,925	443	1,629,018	2,043	1,631,061
CO	9	303	1	0	14	76	318	76	394
CT	6	144	1	0	0	0	145	0	145
DE	5	1,844	6	0	0	571	1,849	572	2,421
FL	37	18,623	3	0	30	153	18,627	182	18,809
GA	25	5,525	3	0	5	258	5,529	263	5,792
HI	19	3,466	0	4	634	21	3,470	655	4,125
ID	6	68	0	0	6	0	71	3	74
IL	45	72,823	28	0	52	390	72,850	443	73,292
IN	38	23,815	11	11,722	39,517	2,799	54,742	23,122	77,864
IA	16	21,384	99	0	229	3	21,483	233	21,716
KS	18	4,671	67	14	4,091	2	4,754	4,090	8,845
KY	27	205,560	48	0	195	1,657	205,609	1,852	207,461
LA	64	96,730	446	739	33,818	216	97,437	34,512	131,949
ME	8	33	1	0	11	219	34	230	264
MD	16	44	1	0	0	312	45	312	357
MA	12	280	0	0	122	47	280	169	449
MI	30	9,951	232	0	2,769	481	10,186	3,247	13,433
MN	7	1,307	33	0	13	0	1,340	13	1,353
MS	18	22,881	513	0	8,802	758	23,584	9,370	32,954
MO	27	24,395	5	0	0	350	24,400	350	24,750
MT	6	4,160	34	0	4	15	4,170	42	4,213
NE	4	217	0	0	210	0	217	210	427
NV	21	2,275	0	0	1,710	1,066	2,337	2,714	5,051
NH	7	32	2	0	5	0	34	5	39
NJ	15	5,537	334	0	8	23,454	5,871	23,462	29,333
NM	12	1,337	0	4	13	1,714	1,354	1,714	3,068
NY	29	2,593	28	0	12	38	2,627	43	2,670
NC	19	495	10	0	542	500	495	1,052	1,547
ND	5	3,010	2	5	3	0	3,020	0	3,020
OH	56	45,258	53	0	31,716	1,634	60,303	18,359	78,662
OK	16	21,869	44	0	0	0	21,913	0	21,913
OR	8	417	1	0	1,285	0	1,702	1	1,703

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Naphthalene<sup>a</sup>**

State <sup>c</sup>	RF <sup>d</sup>	Reported amounts released in pounds per year <sup>b</sup>					Total release		
		Air <sup>e</sup>	Water <sup>f</sup>	UI <sup>g</sup>	Land <sup>h</sup>	Other <sup>i</sup>	On-site <sup>j</sup>	Off-site <sup>k</sup>	On- and off-site
PA	39	26,284	120	0	1,001	509	26,516	1,398	27,914
RI	5	21	1	0	0	97	22	97	119
SC	19	39,179	1	0	501	94	39,179	596	39,775
SD	1	26	0	0	0	0	26	0	26
TN	26	20,276	3	0	134	0	20,276	137	20,414
TX	180	138,897	1,155	390,485	70,312	29,889	561,194	69,544	630,739
UT	16	2,502	105	0	2,759	206	2,525	3,047	5,572
VA	28	43,826	1,012	0	18	1,248	44,838	1,265	46,103
WA	24	3,240	8	0	313,212	311	316,312	458	316,770
WV	16	25,379	0	3	803	84	25,380	889	26,269
WI	17	4,358	0	0	1,453	801	4,364	2,248	6,613
WY	11	756	0	0	59	15	798	32	830
GU	6	1,363	0	0	0	0	1,363	0	1,363
MP	2	24	0	0	0	0	24	0	24
PR	21	1,028	1	0	0	33	1,029	33	1,062
VI	4	514	28	0	14	0	553	2	556
Total	1,202	1,318,765	4,727	402,976	2,180,478	71,465	3,725,104	253,307	3,978,411

<sup>a</sup>The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

<sup>b</sup>Data in TRI are maximum amounts released by each facility.

<sup>c</sup>Post office state abbreviations are used.

<sup>d</sup>Number of reporting facilities.

<sup>e</sup>The sum of fugitive and point source releases are included in releases to air by a given facility.

<sup>f</sup>Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

<sup>g</sup>Class I wells, Class II-V wells, and underground injection.

<sup>h</sup>Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

<sup>i</sup>Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.

<sup>j</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>k</sup>Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2023 (Data are from 2021)

Nearly all naphthalene entering the environment is released directly to the air. The largest source of emission is expected to be through inadvertent releases due to combustion of wood and fossil fuels (EPA 2017b). Naphthalene emissions from unvented kerosene space heaters have been reported (Traynor et al.



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1990). Releases to indoor air include tobacco smoking, use of moth repellents containing naphthalene, and proximity to motor vehicles (Jia and Batterman 2011). Methylnaphthalenes may be released to air from fuel and wood combustion and from tobacco smoke (EPA 2017b; Schmeltz et al. 1978).

Naphthalene may also enter the atmosphere during coal-tar production and distillation processes, through volatilization processes (aeration) in publicly owned treatment works (POTWs), from the use of naphthalene in the manufacture of phthalic anhydride, during the production and use of naphthalene, from forest fires, and from tobacco smoke. Off-gassing of treated wood was shown to release <10 tons of naphthalene/year at the Denver Koopers, Inc., facility in Colorado (Morgan et al. 2015). The facility is also permitted to emit 8,160 kg/year volatile naphthalene from the wastewater treatment effluent tank and 59 kg/year volatile naphthalene from the creosote storage tank (Morgan et al. 2015). Naphthalene may also be released from formulations containing naphthalene such as printer ink (Arı 2020). Relatively small emissions of naphthalene occur through the combustion of fireworks, even during heavy holiday usage on the 4<sup>th</sup> of July (Jia et al. 2020).

Naphthalene has been detected in the emissions from motor vehicles. A gasoline-powered vehicle equipped with a catalytic converter reportedly emits 1,600 µg naphthalene per mile, and heavy-duty diesel vehicles emit between 10.2 and 505 µg naphthalene per mile, depending on whether the vehicle is idling or driving (Jia and Batterman 2011; Schauer et al. 2002). A gasoline-powered vehicle equipped with a catalytic converter emits approximately 800 µg 1-methylnaphthalene per mile and 1,600 µg 2-methylnaphthalene per mile (Schauer et al. 2002). Average concentrations of 137–1714, 92–1,458, and 154–2,129 ng/m<sup>3</sup> of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively, were detected during various flight related and ground-support activities of C-130H aircraft at an Air National Guard base (Childers et al. 2000).

Naphthalene was previously detected in ash from municipal refuse and hazardous waste incinerators (EPA 1989b; Shane et al. 1990). More recent monitoring studies were not located. More than 960,000 pounds of naphthalene and 260,000 pounds of 2-methylnaphthalene were estimated to be released by waste disposal in 2017 (EPA 2020). In a lab-scale incineration experiment with municipal solid waste, emission factors determined for naphthalene were 287 ng/g for gas, 30.4 ng/g for airborne particles (diameter not reported), 24.9 ng/g for fine particles (0.4–10 µm diameter), and 36.7 ng/g for bottom ash emissions (Li et al. 2019).

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Smoking tobacco products or using electronic cigarettes releases naphthalene and methylnaphthalenes to the air; about 46, 30, and 32 µg/cigarette was released for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively (Schmeltz et al. 1976). Cigarette butts littered to the environment can continue to emit naphthalene (Poppendieck et al. 2020). In the aerosol from electronic cigarettes, naphthalene was detected at 61.5–92.2 pg/puff (Dusautoir et al. 2021).

The National Emissions Inventory (NEI) reports air emissions estimates sector for criteria pollutants and precursors and hazardous air pollutants. The estimates are created over a 3-year period; the estimates for 2017 are reported in Table 5-3.

**Table 5-3. National Emission Inventory (NEI) Total National Emissions (pounds) for Naphthalene and Methylnaphthalenes Estimated by Sector 2017**

Sector	Naphthalene emissions	1-Methylnaphthalene emissions	2-Methylnaphthalene emissions
Agriculture; livestock waste	0.09	–	49,582.19
Bulk gasoline terminals	8,296.77	27.20	57.61
Commercial cooking	201,519.72	–	–
Dust; construction dust	1	–	–
Fires; prescribed fires	37,374,454.72	–	–
Fires; wildfires	85,672,702.66	–	–
Fuel combustion; commercial/institutional; biomass	17,321.75	684.33	970.29
Fuel combustion; commercial/institutional; coal	1,919.78	–	–
Fuel combustion; commercial/institutional; natural gas	4,125.92	–	89.52
Fuel combustion; commercial/institutional; oil	2,151.99	–	0.01
Fuel combustion; commercial/institutional; other	1,334.69	–	0.20
Fuel combustion; electric generation; biomass	10,656.77	–	7.70
Fuel combustion; electric generation; coal	3,765.66	–	61.15
Fuel combustion; electric generation; natural gas	10,376.81	–	38.28
Fuel combustion; electric generation; oil	6,931.90	–	0.69
Fuel combustion; electric generation; other	594.78	–	3.37
Fuel combustion; industrial boilers, ICEs; biomass	174,452.84	6,206.78	8,816.91

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**Table 5-3. National Emission Inventory (NEI) Total National Emissions (pounds) for Naphthalene and Methylnaphthalenes Estimated by Sector 2017**

Sector	Naphthalene emissions	1-Methylnaphthalene emissions	2-Methylnaphthalene emissions
Fuel combustion; industrial boilers, ICEs; Coal	4,127.96	–	0.28
Fuel combustion; industrial boilers, ICEs; Natural Gas	54,973.81	0.19	15,611.25
Fuel combustion; industrial boilers, ICEs; Oil	18,861.43	–	20.62
Fuel combustion; industrial boilers, ICEs; Other	767,535.55	–	70.27
Fuel combustion; residential; natural gas	2,733.93	–	0.60
Fuel combustion; residential; oil	3,663.43	–	–
Fuel combustion; residential; other	276.16	–	–
Fuel combustion; residential; wood	5,172,159.62	–	–
Gas stations	29,234.43	0.009	4.44
Industrial processes; cement manufacturing	51,356.07	–	76.30
Industrial processes; Chemical Manufacturing	185,758.64	0.01	61.09
Industrial processes; Ferrous Metals	54,204.35	998.75	474.88
Industrial processes; Mining	583.79	–	–
Industrial processes; NEC	439,728.82	0.002	4,579.67
Industrial processes; non-ferrous metals	18,671.10	–	1.86
Industrial processes; oil and gas production	210,055.59	–	0.35
Industrial processes; petroleum refineries	168,207.30	229.73	447.11
Industrial processes; pulp and paper	141,694.13	57.37	2,190.82
Industrial processes; storage and transfer	128,486.79	102.34	502.77
Miscellaneous non-industrial NEC	23,494.82	–	604.42
Mobile; aircraft	1,231,718.57	3,317.82	207,506.43
Mobile; commercial marine vessels	236,093.00	–	–
Mobile; locomotives	147,855.37	–	–
Mobile; non-road equipment; diesel	574,528.59	–	–
Mobile; non-road equipment; gasoline	3,065,367.09	–	–
Mobile; non-road equipment; other	3,291.00	82.63	1,155.69
Mobile; on-road diesel heavy duty vehicles	2,112,775.51	–	–
Mobile; on-road diesel light duty vehicles	742,174.26	–	–

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**Table 5-3. National Emission Inventory (NEI) Total National Emissions (pounds) for Naphthalene and Methylnaphthalenes Estimated by Sector 2017**

Sector	Naphthalene emissions	1-Methylnaphthalene emissions	2-Methylnaphthalene emissions
Mobile; on-road non-diesel heavy duty vehicles	79,914.05	–	–
Mobile; on-road non-diesel light duty vehicles	4,249,210.65	–	–
Solvent; consumer and commercial solvent use	7,901,059.66	–	–
Solvent; degreasing	20,442.35	–	–
Solvent; dry cleaning	15.45	–	–
Solvent; graphic arts	16,150.25	–	18.88
Solvent; industrial surface coating and solvent use	227,385.95	9.736	20.34
Solvent; non-industrial surface coating	307,872.48	–	–
Waste disposal	963,730.65	–	260,507.89

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA 2017b

**5.3.2 Water**

Estimated releases of 4,727 pounds (~2.1 metric tons) of naphthalene to surface water from 1,202 domestic manufacturing and processing facilities in 2021, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2023). These releases are summarized in Table 5-2. There is no information on releases of 1- or 2-methylnaphthalene to surface water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2022).

Most of the naphthalene released to water is attributable to coal-tar production and distillation processes. Some naphthalene from these sources is discharged directly to surface waters; the remainder is distributed to POTWs. The effluent and oil-spills from the wood-preserving industry is the only other source of consequence that releases naphthalene into the nation's waterways (EPA 1982).

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Naphthalene was below the limits of quantification ( $<0.094\text{--}259\text{ ng/L}$ ) in 99 wastewater treatment plant effluent samples collected by the State of Oregon Department of Environmental Quality between 2010 and 2013 (WQP 2023). More robust effluent monitoring data were not located.

The detection of naphthalene and methylnaphthalenes in groundwater in the vicinity of industrial facilities and landfills (see Section 5.5.2) (Masoner et al. 2014) indicates that these chemicals are released to water from these sources. Methylnaphthalenes have also been detected in effluents from industrial sources.

1-Methylnaphthalene and 2-methylnaphthalene were reported in process sewage and production water samples from coal gasification plants at concentrations of  $78\text{--}278$  and  $66\text{--}960\text{ }\mu\text{g/L}$ , respectively (GDCH 1992).

### 5.3.3 Soil

Estimated releases of 2,180,478 pounds ( $\sim 989$  metric tons) of naphthalene to soil from 1,202 domestic manufacturing and processing facilities in 2021, accounted for about 55% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). An additional 402,976 pounds ( $\sim 183$  metric tons), constituting about 10% of the total environmental emissions, were released via underground injection (TRI21 2023). These releases are summarized in Table 5-2. There is no information on releases of 1- or 2-methylnaphthalene to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2022).

Sources of naphthalene emissions to soil include coal-tar production and minor contributions from naphthalene production, POTW sludge disposal, the use of organic chemicals that include naphthalene, and landfill disposal of municipal waste (EPA 1982).

The residuals produced in gas production by coal carbonization, carbureted water gas production, or oil gas production at manufactured gas plants (MGPs) included PAHs (naphthalene, anthracene, phenanthrene, and benzo[1]pyrene). These residuals were deposited on site in tar wells, sewers, nearby pits, or streams resulting in widespread soil and groundwater contamination (Luthy et al. 1994).

Discarded cigarette butts, particularly in large amounts as in urban environments, may contribute to local contamination with naphthalene (Dobaradaran et al. 2019).

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**5.4 ENVIRONMENTAL FATE****5.4.1 Transport and Partitioning**

**Air.** Naphthalene released to the atmosphere may be transported to surface water and/or soil by wet or dry deposition. Since most airborne naphthalene and methylnaphthalenes will be in the vapor phase based on their vapor pressures, deposition is expected to be very slow (about 0.04–0.06 cm/second). It has been estimated that about 2–3% of naphthalene emitted to air is transported to other environmental media, mostly by dry deposition (EPA 1982). Atmospheric transportation and partitioning data for the methylnaphthalenes were not located.

**Water.** Naphthalene in surface water may volatilize to the atmosphere. With a vapor pressure of 0.085 mm Hg, a water solubility of 31 mg/L at 20 °C, and a Henry's law constant of  $4.4 \times 10^{-4}$  atm-m<sup>3</sup>/mol (NLM 2023a), it is likely that volatilization will be an important route of naphthalene loss from water. The rate of volatilization also depends upon several environmental conditions, including temperature, wind velocity, and mixing rates of the air and water columns (EPA 1982). The highest measured volatilization flux of naphthalene from Gulf of Mexico sites of the Deepwater Horizon oil spill were 52,200 and 27,500 ng/m<sup>2</sup>/day (Tidwell et al. 2016). The half-life of naphthalene in the Rhine River was 2.3 days, based on monitoring data (Zoeteman et al. 1980). In an experiment using a mesocosm, that simulated Narragansett Bay, the half-life in water was 12 days during winter, with loss primarily due to volatilization (Wakeham et al. 1983).

Limited data were located on transport and partitioning of methylnaphthalenes in the environment. The respective vapor pressures (0.067 and 0.055 mm Hg), water solubilities (25.8 and 24.6 mg/L), and Henry's law constants ( $5.14 \times 10^{-4}$  and  $5.18 \times 10^{-4}$  atm-m<sup>3</sup>/mol) for 1- and 2-methylnaphthalene are of similar magnitude to these properties for naphthalene (NLM 2023a). Thus, it is likely that loss of methylnaphthalenes from ambient water occurs by volatilization. In a mesocosm experiment, that simulated Narragansett Bay, the half-life of 2-methylnaphthalene in water was 13 days in winter, with loss primarily due to volatilization (Wakeham et al. 1983).

The log octanol/water partition coefficient ( $K_{ow}$ ) for naphthalene is 3.30 and the log organic carbon coefficients ( $K_{oc}$ ) range from 2.05 to 3.97 (NLM 2023b, 2023c). Based on the magnitude of these values, it is expected that a moderate fraction of naphthalene in typical surface water would be associated with

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particulate matter. Thus, some naphthalene discharged to surface waters would remain in solution, with some quantity removed by sorption to suspended solids and benthic sediments.

Based on the magnitude of log  $K_{ow}$  values for 1- and 2-methylnaphthalene (3.87 and 3.86, respectively) (NLM 2023b, 2023c) and the experimental log  $K_{oc}$  values of 3.36 and 3.64 for 1-methylnaphthalene and 3.00–5.96 for 2-methylnaphthalene (NLM 2023b, 2023c), these chemicals may partition similarly to naphthalene in environmental media and may be removed from the water column by sorption to solids.

**Sediment and Soil.** Naphthalene is easily volatilized from aerated soils (Park et al. 1990) and is adsorbed to a moderate extent (10%) (Karickhoff 1981; Schwarzenbach and Westall 1981). The extent of sorption depends on the organic carbon content of the soil, with rapid movement expected through sandy soils (Howard 1989). The estimated soil adsorption coefficient for naphthalene in a soil with <0.6% organic carbon is 1.8 (Klecka et al. 1990). In soils with 0.4, 1.7, and 0.1% organic carbon, naphthalene had calculated partition coefficients of 0.0034, 0.18, and 0.13 L/kg, respectively (Stagge et al. 2016). Because it adsorbs to aquifer material (Ehrlich et al. 1982), naphthalene's passage through groundwater will be somewhat retarded. Nevertheless, naphthalene frequently appears in effluent drainage from disposal sites (Rittman et al. 1980; Roberts et al. 1980; Schwarzenbach et al. 1983). However, sorption of naphthalene to aquifer materials with low organic carbon content (<0.03%) may be enhanced by the presence of nonionic low-polarity organics, such as tetrachloroethene, commonly found at hazardous waste sites (Brusseau 1991). Similarly, the presence of solvents such as cetylpyridinium chloride may affect sorption capacity of the soils, increasing sorptive capacities for low organic carbon and cation exchange capacity (CEC) soils or decreasing capacity for higher organic carbon and CEC soils (Stagge et al. 2016).

Based on the magnitude of log  $K_{ow}$  values for 1- and 2-methylnaphthalene (3.87 and 3.86, respectively) (NLM 2023b, 2023c) and the experimental log  $K_{oc}$  values of 3.36 and 3.64 for 1-methylnaphthalene and 3.00–5.96 for 2-methylnaphthalene (NLM 2023b, 2023c), these chemicals may partition similarly to naphthalene in environmental media and are expected to be slightly mobile to immobile in soils.

**Other Media.** Bioconcentration factors (BCFs) for naphthalene have been measured and calculated from the  $K_{ow}$ ,  $K_{oc}$ , or water solubility. BCFs of 36.5–168 have been measured in carp (NITE 2010a), and 692 and 714 wet-weight (9,230 and 10,307 lipid-weight adjusted) were measured in Sheepshead minnows (Jonsson et al. 2004). Previous studies reported BCFs ranging from about 40 to 1,000 (Banerjee and Baughman 1991; Bysshe 1982; Geyer et al. 1982; Kenaga 1980; Southworth et al. 1978; Veith et al.

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1979). Based on the magnitude of the  $K_{ow}$ , bioaccumulation in the food chain is not expected to occur (Thomann 1989). However, naphthalene exposure of cows and chickens could lead to the presence of naphthalene in milk and eggs (Eisele 1985).

In an Organisation for Economic Cooperation and Development (OECD) guideline terrestrial plant bioaccumulation study, BCFs in lettuce (*Lactuca sativa*) via simulated uptake through atmospheric deposition were 184.62 for naphthalene, 77.00 for 1-methylnaphthalene, and 120.26 for 2-methylnaphthalene (Teke et al. 2020).

BCFs for 1- and 2-methylnaphthalene in oysters ranged from about 500 to 12,590 (GDCH 1992). Methylnaphthalenes are also metabolized and excreted rapidly by fish and shellfish when they are removed from polluted waters (Breger et al. 1981; GDCH 1992). In Sheepshead minnows, BCFs of 2,800 and 2,900 (wet-weight), and 37,00 and 44,000 (lipid-weight adjusted) were determined kinetically for 2-methylnaphthalene, with elimination occurring in 2–8 days (Jonsson et al. 2004).

In landfill leachate, a partition coefficient ( $K_{DOC}$ ) of 22,000 mL/g dissolved organic carbon (DOC) was determined for naphthalene, which correlated with the substance's high water solubility, and supports the possibility for leaching from landfills and other waste sites (Kalmykova et al. 2013). Most of the naphthalene was dissolved in the aqueous phase rather than bound to the dissolved organics in the leachate.

#### 5.4.2 Transformation and Degradation

**Air.** The most important atmospheric removal process for naphthalene is reaction with photochemically produced hydroxyl radicals (Howard 1989). The rate constant for this reaction is  $2.17\text{--}2.39 \times 10^{-11}$  cm<sup>3</sup>/molecule-second (Atkinson et al. 1987; Phoungphouang and Arey 2002) and the atmospheric half-life for naphthalene based on this reaction is 5.8 hours < 1 day. The major products are 1- and 2-naphthol and 1- and 2-nitronaphthalene (Atkinson et al. 1987). Atmospheric oxidation with other species such as nitrate radicals and ozone, occurs at a slower rate. Naphthalene reacts with N<sub>2</sub>O<sub>5</sub>, with an experimentally determined rate constant of  $1.4 \times 10^{-17}$  cm<sup>3</sup>/molecule-second (Atkinson et al. 1987). Using an ambient 12-hour nighttime concentration for N<sub>2</sub>O<sub>5</sub> of  $2 \times 10^{10}$  molecules/cm<sup>3</sup>, an estimated half-life of approximately 29 days was calculated. Naphthalene also reacts with nighttime nitrate radicals, with an estimated atmospheric half-life of about 60 hours calculated from its experimentally determined rate constant of  $6.4 \times 10^{-15}$  cm<sup>3</sup>/molecule-second and a nitrate radical concentration of  $5 \times 10^8$  molecules/cm<sup>3</sup>.



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(Atkinson 1984). The reaction of naphthalene with ozone is insignificant as compared to its reaction with hydroxyl radicals. Direct photolysis is expected to occur, although no experimental data were located (Howard 1989).

Methylnaphthalenes react with hydroxyl radicals. The reported rate constants are  $5.30 \times 10^{-11}$  and  $5.23 \times 10^{-11} \text{ cm}^3/\text{molecule-second}$  for 1- and 2-methylnaphthalene, respectively (NLM 2023b, 2023c). Based on an atmospheric hydroxyl radical concentration of  $1.5 \times 10^6/\text{cm}^3$ , the corresponding atmospheric half-lives are 2.4 and 2.5 hours. Reactions of 1- and 2-methylnaphthalene with  $\text{N}_2\text{O}_5$  radicals have half-lives of 24 and 19 days, respectively (GDCH 1992). These chemicals also react with atmospheric ozone and nitrate radicals. In a rural setting, where the concentration of nitrate radicals is lower, calculated atmospheric lifetimes for monosubstituted naphthalenes based on reactions with nitrate radicals range from 2.5 to 3.6 years; in urban and polluted environments, where the concentration of nitrate radicals is higher, the calculated lifetimes range from 22 to 31 hours (Phousongphouang and Arey 2003).

**Water.** Naphthalene and methylnaphthalenes are degraded in water by photolysis and biological processes. The half-life for direct photolysis of naphthalene in surface water is estimated to be about 71 hours, but the half-life in deeper water (5 m) is estimated at 550 days (Zepp and Schlotzhauer 1979). The half-lives for photolysis of 1- and 2-methylnaphthalene were estimated at 22 and 54 hours, respectively (GDCH 1992). Reduced indirect photolytic rates for naphthalene were observed with increasing salinity, an important consideration when estimating fate in marine environments after oil spills (Jing et al. 2014). Ions in seawater such as  $\text{Br}^-$ ,  $\text{CO}_3^{2-}$ , and  $\text{HCO}_3^-$  act as scavengers of hydroxyl radicals, reducing indirect photolysis of naphthalene and methylnaphthalenes.

Biodegradation of naphthalene may be sufficiently rapid for it to be a significant fate process in aquatic systems when acclimated organisms are present. Data on biodegradation of naphthalene in biodegradability tests and natural systems suggest that biodegradation occurs after a relatively short period of acclimation (half-life of about 7 days in oil-polluted water) and the biodegradation rate increases with the naphthalene concentration. Biodegradation occurs slowly (half-lives up to 1,700 days) in unpolluted water (Herbes 1981; Herbes and Schwall 1978; Herbes et al. 1980; Howard 1989; Kappeler and Wuhrmann 1978). Reported biodegradation half-lives range from 3 to 1,700 days in various water systems, occurring more rapidly in PAH- and oil-polluted environments (Howard 1989). In a static-flask-screening test, naphthalene showed rapid acclimation and 100% loss from the test medium in 7 days (Tabak et al. 1981). In another flask-screening test with unacclimated organisms, negligible loss (2%) was observed (NITE 2010b). In an experiment with Narragansett Bay seawater, the half-life of

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naphthalene in late summer was reported at 0.8 days, mainly due to biodegradation (Wakeham et al. 1983). The half-life of 2-methylnaphthalene was 0.7 days in the same experiment.

Methylnaphthalenes are biodegraded under aerobic conditions after adaptation. The highest degradation rates were reported in water constantly polluted with petroleum (GDCH 1992).

**Sediment and Soil.** Biodegradation is expected to proceed more rapidly in sediments with acclimated organisms. Half-lives reported in sediment include 4.9 hours and >88 days in oil-contaminated and uncontaminated sediment, respectively (Herbes and Schwall 1978), 9 days in sediment near a coal-coking discharge (Herbes 1981), 3, 5, and >2,000 hours in sediments with high, medium, and low PAH levels, respectively (Herbes et al. 1980), and ranging from 2.4 weeks in sediments exposed to petroleum hydrocarbons to 4.4 weeks in sediments from a pristine environment (Howard 1989). Methyl-naphthalenes biodegrade more slowly. Reported half-lives in sediments were 46 weeks for 1-methylnaphthalene and ranged from 14 to 50 weeks for 2-methylnaphthalene (GDCH 1992).

Biodegradation potential is important to biological remediation of soil. Studies on biodegradation of PAHs suggest that adsorption to the organic matter significantly reduces the bioavailability for microorganisms, and thus the biodegradability, of PAHs, including naphthalene (Heitzer et al. 1992; Weissenfels et al. 1992). There is considerable variability in reported naphthalene soil half-lives. The estimated half-life of naphthalene reported for a solid waste site was 3.6 months (Howard 1989). In soils with 0.2–0.6% organic carbon and 92–94% sand, the half-lives were 11–18 days (Klecka et al. 1990). In another study, sandy loams with 0.5–1% organic carbon had naphthalene half-lives of 2–3 days (Park et al. 1990). The half-life in an unimpacted soil with 0.78% organic matter was 34.7 days (Agarry and Oghenejoboh 2015). Biodegradation is accomplished through the action of aerobic microorganisms and declines precipitously when soil conditions become anaerobic (Klecka et al. 1990). Studies indicate that naphthalene biodegrades to carbon dioxide in aerobic soils, with salicylate as an intermediate product (Heitzer et al. 1992).

Abiotic degradation of naphthalene seldom occurs in soils. In one study, only about 10% of the naphthalene added to two soil samples treated with mercuric chloride to kill microorganisms was degraded over a 105- or 196-day period (Park et al. 1990).

In contaminated subsurface soils often found at former MGP sites, naphthalene is present as a component in coal tar, a dense nonaqueous-phase liquid (DNAPL). It may exist in the subsurface in the form of

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trapped pools of organic liquid or as immobilized macroporous ganglia. Slow partitioning of naphthalene and other PAHs from DNAPLs into the aqueous phase causes them to be unavailable to the microorganism, thus resulting in the partitioning of the PAHs being the rate-limiting step in their biodegradation (Thomas et al. 1986). Using phenanthrene as a test substance, Birman and Alexander (1996) showed that the viscosity of the nonaqueous-phase liquid (NAPL) may reflect a slower diffusion of the aromatic substrate in the more viscous NAPLs and its subsequent slower mass transfer to water. Ghoshal and Luthy (1996) demonstrated that a very large fraction of naphthalene can be biodegraded from an accessible coal-tar-NAPL (free flowing) by microorganisms in bioslurry systems. Metabolically active microflora were detected beneath the water table at former MGP sites from 2.6 to 30.8 m below the ground surface. The subsurface microflora appeared to be acclimated to the presence of PAHs and were found to mineralize naphthalene (8–55%) in sediment-water microcosms under aerobic conditions. Naphthalene biodegradation half-lives ranged from 18 to 480 days (Durant et al. 1994).

Partitioning to soil organic matter may also limit biodegradation in uncontaminated soils. Naphthalene remaining in soil for extended periods of time was shown to become less available to bacteria and earthworms (Kelsey and Alexander 1997).

**Other Media.** Naphthalene is reported to be rapidly eliminated from invertebrates when the organisms are placed in pollutant-free water (Eastmond et al. 1984; Tarshis 1981). Naphthalene is readily metabolized in fish (Howard 1989), and was eliminated within 2–8 days when placed in pollutant-free water (Jonsson et al. 2004).

## 5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

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Table 5-4 shows the lowest limits of detection that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in ambient environmental media sampled from a variety of site types (e.g., rural, urban) is presented in Table 5-5.

**Table 5-4. Lowest Limit of Detection Based on Standards for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene<sup>a</sup>**

Media	Detection limit <sup>b</sup>	Reference
Air	4.40 ng/m <sup>3</sup>	Jia et al. 2020
Drinking water	0.012 µg/L	EPA 2009a
Surface water and groundwater	0.03 µg/L	USGS 2006
Surface water	0.00014–0.027 µg/L 0.000056 (1-methylnaphthalene) 0.0001 (2-methylnaphthalene)	USGS 2018, 2019
Soil	4 µg/kg	USGS 2004
Sediment (pore water)	4 µg/kg 5.7 mg/mL 2.4 ng/mL (1- and 2-methylnaphthalene)	USGS 2004 EPA 2007a
Whole blood	0.0758 ng/g	Hao et al. 2020

<sup>a</sup>Detection limits are based on using appropriate preparation and analytics. These limits may not be possible in all situations.

<sup>b</sup>All detection limits are for naphthalene unless otherwise noted.

**Table 5-5. Summary of Environmental Levels of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

Media	Naphthalene		1-Methyl naphthalene		2-Methyl naphthalene		For more information
	Low	High	Low	High	Low	High	
Outdoor air (ppbv)	0.0025	22.1	0.036	0.0908	0.000574	0.132	Section 5.5.1
Indoor air (ppbv)	0.034	1.9	–	–	–	–	Section 5.5.1
Surface water (ppb)	0.00018	0.52	0.00034	0.2	0.00054	0.2	Section 5.5.2
Ground water (ppb)	>0.2	4,070	0.01	19	36.1	431	Section 5.5.2
Drinking water (ppb)	–	>0.2	–	–	–	–	Section 5.5.2
Food (ppb)	<0.61	561.4	<0.4	306.0	<0.36	286.9	Section 5.5.4
Soil (ppb)	2.0	25,900	2.2	4,400	1.3	11,500	Section 5.5.3

Concentration (ppbv) = 24.45 x concentration (µg/m<sup>3</sup>) ÷ molecular weight; ppb = µg/L = µg/kg

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Detections of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in air, water, and soil at NPL sites are summarized in Table 5-6.

**Table 5-6. Naphthalene and Methylnaphthalene Levels in Water, Soil, and Air of National Priorities List (NPL) Sites**

Medium	Median <sup>a</sup>	Geometric mean <sup>a</sup>	Geometric standard deviation <sup>a</sup>	Number of quantitative measurements	NPL sites
<b>Naphthalene</b>					
Water (ppb)	59.5	124	58.1	168	110
Soil (ppb)	32,000	38,100	43.2	272	174
Air (ppbv)	2.48	2.14	20.0	43	30
<b>1-Methylnaphthalene</b>					
Water (ppb)	0.0245	1.07	1,230	6	3
Soil (ppb)	63,000	19,000	32.8	12	4
Air (ppbv)	No data	No data	No data	No data	No data
<b>2-Methylnaphthalene</b>					
Water (ppb)	21	32.4	56.8	57	41
Soil (ppb)	15,000	14,000	32.2	191	118
Air (ppbv)	0.0258	0.130	46.5	7	6
<b>Methylnaphthalene</b>					
Water (ppb)	6	6	1	2	1
Soil (ppb)	5,300	11,900	18.0	7	5
Air (ppbv)	No data	No data	No data	No data	No data

<sup>a</sup>Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022a). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

### 5.5.1 Air

Naphthalene and methylnaphthalenes have been reported in ambient air at several locations in the United States. While concentrations of naphthalene in air in the United States have been well-studied, more limited data are available on the methylnaphthalenes. The Air Quality System (AQS) reports that the average naphthalene concentration from 2018 to 2021 has remained constant between 0.4 and 0.5 µg/m<sup>3</sup>, with maximum concentrations reported in 2018, dropping over time. Data on methylnaphthalenes are too limited to observe any longitudinal trends in concentration (EPA 2022b). These data are summarized in Table 5-7.

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**Table 5-7. Summary of Annual Concentrations of Naphthalene and Methylnaphthalenes ( $\mu\text{g}/\text{m}^3$ ) Measured in Ambient Air at Locations Across the United States<sup>a,b</sup>**

Year	Number of monitoring locations	Number of samples	Average	Maximum
<b>Naphthalene</b>				
2018	32	1,739	0.04	2.66
2019	36	1,776	0.04	2.21
2020	34	1,801	0.06	1.7
2021	43	2,032	0.04	1.16
2022 <sup>c</sup>	32	720	0.02	0.66
<b>1-Methylnaphthalene</b>				
2018	—	—	—	—
2019	—	—	—	—
2020	1	130	0.0023	0.00581
2021	1	65	0.0026	0.0108
2022 <sup>c</sup>	—	—	—	—
<b>2-Methylnaphthalene</b>				
2018	1	71	0	0
2019	—	—	—	—
2020	1	130	0.0040	0.00843
2021	1	63	0.0039	0.00922
2022 <sup>c</sup>	—	—	—	—

<sup>a</sup>Values were originally reported in parts per billion carbon (ppbC) or  $\text{ng}/\text{m}^3$  and converted to  $\mu\text{g}/\text{m}^3$ .

<sup>b</sup>24-hour sampling period.

<sup>c</sup>As of October 14th, 2022.

Source: EPA 2022b

A Norfolk Southern train derailed near East Palestine, Ohio, on February 3, 2023, with hazardous material being released to the local environment (NTSB 2023). Air monitoring and sampling data have been reported by the EPA (EPA 2023b). Data collected from February 4 to August 18, 2023 resulted in 1,444 samples analyzed for naphthalene (EPA 2023b). A maximum value of 4.58 ppbv was detected on February 28, 2023 (EPA 2023b).

Naphthalene concentrations in air can vary widely depending on the uses of the site, the site's proximity to sources of naphthalene, and atmospheric conditions. A summary of studies monitoring naphthalene and methylnaphthalenes in outdoor air is provided in Table 5-8. During atmospheric stagnation periods in January and July, 2009, ambient air samples were collected from mobile samplers in neighborhoods

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adjacent to three fixed air toxic sites in Tacoma, Washington. Pollutant sources were identified as traffic-related or wood smoke-related. Wood-burning sources had calculated overall means of  $16.5 \mu\text{g}/\text{m}^3$  in summer and  $10.6 \mu\text{g}/\text{m}^3$  in winter; traffic sources had calculated overall means of  $69.5 \mu\text{g}/\text{m}^3$  in summer and  $16.1 \mu\text{g}/\text{m}^3$  in winter (Davey et al. 2014).

**Table 5-8. Summary of Naphthalene and Methylnaphthalenes ( $\mu\text{g}/\text{m}^3$ ) Measured in Outdoor Air**

Date	Location	Average <sup>a</sup>	Range	Percent detected <sup>b</sup>	Notes	Source
<b>Naphthalene</b>						
2001–2003	Riverside, California	0.259	0.013–0.767	–	Urban air	Lu et al. 2005
	San Dimas, California	0.265	0.041–0.652	–		
	Mira Loma, California	0.249	0.027–1.035	–		
	Upland, California	0.207	0.026–0.306	–		
	Long Beach, California	0.091	0.046–0.178	–		
	Los Angeles, California	0.697	0.094–2.543	–		
January 2009; July 2009	Tacoma, Washington	10.6; 16.5	8.44–13.1; 7.18–22.6	–	Wood-burning sources during two air stagnation events	Davey et al. 2014
		16.1; 69.5	12.1–20.3; 31.8–116	–	Traffic sources during two air stagnation events	
1990–2014	United States	0.178	NS–9.092	–	Urban air	Liu et al. 2017
		0.135	NS–1.309	–	Rural air	
June 2013–June 2015	Mille Lacs Band of Ojibwe Land	0.012±0.006	–	–	Rural air	Ellickson et al. 2017
	Minneapolis, Minnesota	0.075±0.016	–	–	Urban air	
August, 2018	Eugene, Oregon	0.08 <sup>c,d</sup>	0.005 (LOD)–0.3 <sup>d</sup>	50%	Air during wildfire	Messier et al. 2019
<b>1-Methylnaphthalene</b>						
August, 2018	Eugene, Oregon	0.009 <sup>c,d</sup>	0.0009 (LOD)–0.03 <sup>d</sup>	52%	Air during wildfire	Messier et al. 2019
<b>2-Methylnaphthalene</b>						
June 2013–June 2015	Mille Lacs Band of Ojibwe Land	0.00334±0.00165	–	–	Rural air	Ellickson et al. 2017
	Minneapolis, Minnesota	0.0339±0.00784	–	–	Urban air	

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**Table 5-8. Summary of Naphthalene and Methylnaphthalenes ( $\mu\text{g}/\text{m}^3$ ) Measured in Outdoor Air**

Date	Location	Average <sup>a</sup>	Range	Percent detected <sup>b</sup>	Notes	Source
August, 2018	Eugene, Oregon	0.01 <sup>b,d</sup>	0.001 (LOD) –0.08 <sup>d</sup>	55%	Air during wildfire	Messier et al. 2019

<sup>a</sup>Value is an average unless otherwise noted.

<sup>b</sup>Percent detection on a per sample basis.

<sup>c</sup>Value is reported as the median of values above the limit of detection (LOD).

<sup>d</sup>Values estimated from a figure and should be treated as approximates.

NS = not specified

Urban air may have higher concentrations of naphthalene and methylnaphthalenes. Rural and urban air monitoring was conducted between June 2013 and June 2015 on the Mille Lacs Band of Ojibwe Land and in south Minneapolis, respectively. Naphthalene was detected at  $0.012 \mu\text{g}/\text{m}^3$  in Mille Lacs and at  $0.075 \mu\text{g}/\text{m}^3$  in Minneapolis; 2-methylnaphthalene was detected at  $0.00334 \mu\text{g}/\text{m}^3$  in Mille Lacs and at  $0.0339 \mu\text{g}/\text{m}^3$  in Minneapolis (Ellickson et al. 2017). The highest naphthalene concentrations were observed at a site near a foundry and asphalt production facility. Average air concentrations between 2001 and 2003 in cities in California were between  $0.091$  and  $0.697 \mu\text{g}/\text{m}^3$  for cities in California (Lu et al. 2005). Mean long-term trends analyzed from AQS data between 1990 and 2014 were  $0.178 \mu\text{g}/\text{m}^3$  naphthalene in urban air and  $0.135 \mu\text{g}/\text{m}^3$  naphthalene in rural air (Liu et al. 2017).

Naphthalene concentrations in indoor air may be higher than outdoor air, depending on ventilation, tobacco use, and use of naphthalene releasing products or burning wood or fuel. Concentrations of naphthalene detected in indoor and outdoor air measured in 24 low-income homes in North Carolina were  $0.33$ – $9.7$  and  $0.57$ – $1.82 \mu\text{g}/\text{m}^3$  respectively (Chuang et al. 1999). In urban and suburban homes in Southeast Michigan, Syracuse, New York, and Chicago, Illinois, median concentrations of naphthalene detected were  $0.84$ ,  $2.84$ , and  $0.18 \mu\text{g}/\text{m}^3$ , respectively (Jia and Batterman 2011). For rural homes in Missoula, Montana, the median naphthalene concentration detected was  $0.3 \mu\text{g}/\text{m}^3$ . Indoor air concentrations of naphthalene of residences in Ottawa, Canada, ranged from  $0.68$  to  $1.83 \mu\text{g}/\text{m}^3$  (Wheeler et al. 2014). In homes with smokers, indoor and outdoor air concentrations were measured to be  $2.2$  and  $0.3 \mu\text{g}/\text{m}^3$ , respectively. Comparable values in homes without smokers were  $1.0$  and  $0.1 \mu\text{g}/\text{m}^3$ , respectively (EPA 1991; Gold et al. 1993). Vapor intrusion is not expected to be a source of indoor air naphthalene pollution. Naphthalene was detected in indoor air at  $2.6$  and  $49 \mu\text{g}/\text{m}^3$ , in soil gas at  $0.5 \mu\text{g}/\text{m}^3$ , and in outdoor air at  $6.3 \mu\text{g}/\text{m}^3$  at a daycare investigated for vapor intrusion by ATSDR (2007b); a consumer product was reported as a more likely source of the indoor pollution. Naphthalene



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was detected at a maximum of  $9.7 \mu\text{g}/\text{m}^3$  in apartments investigated for vapor intrusion, however soil gas samples were not reported (ATSDR 2008). Indoor air concentrations may also be impacted by wildfires; the median indoor air concentration of naphthalene was approximately  $0.1 \mu\text{g}/\text{m}^3$  in comparison to  $0.08 \mu\text{g}/\text{m}^3$  for outdoor air, and indoor air ranged higher and had a higher percent detection (detected in 79% of indoor air samples) (Messier et al. 2019). Similar trends were observed for the methylnaphthalenes, and median indoor air concentrations of approximately  $0.06 \mu\text{g}/\text{m}^3$  1-methylnaphthalene and  $0.09 \mu\text{g}/\text{m}^3$  2-methylnaphthalene were reported (detected in 67 and 64% of samples, respectively).

Limited recent data reporting naphthalene concentrations at industrial and hazardous waste sites were located. Naphthalene was detected in the air of a wood creosote-treatment facility at  $1.50 \mu\text{g}/\text{m}^3$  (Morgan et al. 2015). At sites near another wood creosote-treatment facility, naphthalene ranged from 0.4 to  $12.9 \mu\text{g}/\text{m}^3$ , 1-methylnaphthalene ranged from 0.2 to  $2.3 \mu\text{g}/\text{m}^3$ , and 2-methylnaphthalene ranged from 0.2 to  $5.7 \mu\text{g}/\text{m}^3$ , during 24-hour sampling periods (ATSDR 2007a). Sampling periods of 1–3 hours had larger maximum concentrations: 25.6, 7.2, and  $19.4 \mu\text{g}/\text{m}^3$ , respectively. Based on use and reported emissions of naphthalene, detections at sites producing or using naphthalene would be expected.

Limited monitoring data were available for methylnaphthalenes. 1-Methylnaphthalene and 2-methylnaphthalene have been reported in ambient air at average concentrations of 0.21 and  $0.37 \mu\text{g}/\text{m}^3$ , respectively (EPA 2022b).

### 5.5.2 Water

The EPA maintains a Water Quality Portal (WQP) database that aggregates environmental monitoring data from the National Water Information System (NWIS) and STORage and RETrieval (STORET) system, providing ample data for assessment of current conditions and trends in naphthalene and methylnaphthalene concentrations in waters of the United States. A summary of the data for ambient surface and groundwater from recent years are reported in Table 5-9 (WQP 2023). Naphthalene and methylnaphthalenes have been detected in surface water and groundwater in the United States.

Detections were generally infrequent and at trace levels, although limited sampling was conducted for the methylnaphthalenes. Concentrations present in groundwater were generally higher than surface water, where volatilization may occur.

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**Table 5-9. Summary of Concentrations of Naphthalene and Methylnaphthalenes (µg/L) Measured in Surface and Groundwater Across the United States**

Year	Average	Maximum	Number of samples	Percent detected
Surface water				
Naphthalene				
2018	0.06	0.3	930	2.2%
2019	0.02	0.02	709	1.0%
2020	0.05	0.15	242	2.1%
2021	0.04	0.16	184	5.4%
2022	0.04	0.52	90	44%
2023 <sup>a</sup>	0.04	0.06	22	41%
1-Methylnaphthalene				
2018	0.03	0.2	182	13%
2019	0.02	0.1	176	7.4%
2020	0.02	0.02	56	1.8%
2021	0.01	0.01	72	4.2%
2022	0.03	0.03	23	4.3%
2023 <sup>a</sup>	—	—	4	0%
2-Methylnaphthalene				
2018	0.05	0.2	431	4.4%
2019	0.04	0.2	348	2.3%
2020	0.04	0.04	93	1.1%
2021	0.01	0.01	74	4.1%
2022	0.03	0.03	23	4.3%
2023 <sup>a</sup>	—	—	4	0%
Groundwater				
Naphthalene				
2018	36.1	365	1,286	1.8%
2019	51.2	522	1,648	1.8%
2020	94.1	700	1,275	3.8%
2021	109	4,070	1,821	9.4%
2022	105	980	2,823	9.4%
2023 <sup>a</sup>	115	740	716	10%
1-Methylnaphthalene				
2018	0.02	0.028	38	7.9%
2019	0.01	0.01	19	5.2%
2020	—	—	39	0%
2021	4.67	19	59	25%
2022	0.077	0.077	22	4.5%
2023 <sup>a</sup>	—	—	—	—

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**Table 5-9. Summary of Concentrations of Naphthalene and Methylnaphthalenes (µg/L) Measured in Surface and Groundwater Across the United States**

Year	Average	Maximum	Number of samples	Percent detected
<b>2-Methylnaphthalene</b>				
2018	20.1	66	68	8.8%
2019	42.4	379	53	26%
2020	41.4	200	119	16%
2021	36.1	431	216	31%
2022	63.6	1,830	184	35%
2023 <sup>a</sup>	55.2	91.5	36	25%

<sup>a</sup>As of August, 2023.

Source: WQP 2023

In a study of surface water in Southern Lake Powell, recreational waters in Arizona and Utah, naphthalene concentrations ranged from 0.00065 to 0.0029 µg/L in summer 2016 and were below the detection limits (0.022 and 0.027 µg/L, respectively, which were an order of magnitude higher than detection limits for other sampling campaigns) for spring and summer 2017 (USGS 2018, 2019).

1-Methylnaphthalene was detected at concentrations of 0.00058–0.0024, 0.00034–0.0017, and 0.00071–0.0011 µg/L for summer 2016, spring 2017, and summer 2017, respectively; 2-methylnaphthalene was detected at 0.0009–0.0035, 0.00054–0.0019, and 0.00088–0.0021 µg/L for summer 2016, spring 2017, and summer 2017, respectively (USGS 2019).

In a study of contaminants of an urban watershed of Chesapeake Bay, naphthalene was detected in the northeast and northwest branches of Anacostia River (an urban watershed of Chesapeake Bay) at a concentration range of 0.00018–0.0216 µg/L. 2-Methylnaphthalene was also detected at a concentration of 0.00057–0.0627 µg/L (Foster et al. 2000).

Naphthalene is rarely detected in drinking water. In a large-scale monitoring study of principal aquifers in the United States between 1991 to 2010, naphthalene was detected at >0.2 µg/L in 7 of the 40 aquifer areas used for drinking water (USGS 2015). For these aquifers, percent detections ranged from only 0.22 to 5.26%. Current data regarding the presence of methylnaphthalenes in drinking water were not located.

Concentrations of naphthalene and methylnaphthalenes in groundwater are expected to be higher near industrial sites using naphthalene and landfills. In a landfill leachate sampling campaign collected in

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2011, naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were detected in leachate at median concentrations of 5.05, 1.70, and 1.92 µg/L, respectively, from landfills across the United States (Masoner et al. 2014). Detections in leachate and groundwater plumes have been reported previously from industrial and municipal landfills and waste disposal sites (Barbee 1994; Brown and Donnelly 1988; Kinman et al. 1995). Naphthalene and 2-methylnaphthalene were detected in groundwater at five wood treatment facilities (Rosenfeld and Plumb 1991). Naphthalene was reported in 35% of samples at all five sites at an average concentration of 3,312 µg/L. 2-Methylnaphthalene was reported in 27% of samples at four sites at an average concentration of 563 µg/L. Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have been detected in groundwater at Gas Works Park, Seattle, Washington, in the range of 20–12,000, 20–1,100, and 30–1,400 µg/L, respectively (Turney and Goerlitz 1990). Gas Works Park is located on the site of a coal and oil gasification plant that ceased operation in 1956. Naphthalene and 2-methylnaphthalene were detected in the groundwater of a former petroleum bulk plant at 147 and 1,420 µg naphthalene/L and 392 µg 2-methylnaphthalene/L (ATSDR 2006). Naphthalene was below the ATSDR child and adult intermediate environmental media evaluation guide (EMEG) values; EMEGs were not available for 2-methylnaphthalene. Naphthalene and 2-methylnaphthalene were detected in groundwater at the Superfund Portland Harbor Site at an average of 1,150 µg/L (n=644, 71% detected) and 69.3 µg/L (n=438, 77% detected), respectively, between 2004 and 2007 (WQP 2023). Detections in surface water were much lower, with averages of 45.2 and 0.03 µg/L, respectively (percent detections around 13–27%). Naphthalene was not detected in groundwater at the Palermo Wellfield Superfund site between 2018 and 2020 (WQP 2023).

Limited data are available for marine environments. Naphthalene has been reported at a mean concentration of 0.0063 µg/L in seawater in the south Atlantic Ocean (Cripps 1992).

### 5.5.3 Sediment and Soil

Naphthalene and methylnaphthalenes were generally commonly detected in soil/sediment samples, at average concentrations typically between 100 and 200 µg/kg (WQP 2023). A summary of the data for ambient soil/sediment monitoring is reported in Table 5-10. Samples were not specified as sediment or soil.

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**Table 5-10. Summary Naphthalene and Methylnaphthalenes (µg/kg) Measured in Soil/Sediment Across the United States, Reported in the Water Quality Portal**

Year	Average	Maximum	Number of samples	Percent detected
<b>Naphthalene</b>				
2018	361	25,900	694	56%
2019	80.0	707	372	27%
2020	139	2,600	214	19%
2021	141	5,900	176	51%
2022	4.08	69	108	56%
2023 <sup>a</sup>	—	—	—	—
<b>1-Methylnaphthalene</b>				
2018	87.8	1,010	277	48%
2019	108	1,360	237	32%
2020	—	—	142	0%
2021	8.72	214.8	118	43%
2022	1.22	5	55	38%
2023 <sup>a</sup>	—	—	—	—
<b>2-Methylnaphthalene</b>				
2018	170	11,500	500	63%
2019	144	2,990	314	30%
2020	216	1,600	193	7.7%
2021	79.7	4,400	152	45%
2022	5.96	140	80	48%
2023 <sup>a</sup>	—	—	—	—

<sup>a</sup>As of August, 2023.

Source: WQP 2023

Naphthalene concentrations have been well characterized in urban soils. The results of several soil and sediment monitoring studies are provided in Table 5-11. In samples taken across Manhattan from 2005 to 2006, median concentrations of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in surface soils were 23, 16, and 17 µg/kg, respectively (Azzolina et al. 2016). Concentrations were decreased in subsurface soils. Soils collected from small cities in Florida had approximate median naphthalene concentrations of 75–100 µg/kg (Gao et al. 2019). PAH sources were hypothesized to be from biomass, coal and coke combustion, and vehicle emissions. Naphthalene and methylnaphthalene analysis was conducted for surface and subsurface soil samples that were collected from parks in Milwaukee, Wisconsin, where the only expected pollutant source was atmospheric deposition. In 0–7 cm soil, the

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mean concentrations were 69 µg/kg naphthalene, 37.3 µg/kg 1-methylnaphthalene, and 39.7 µg/kg 2-methylnaphthalene (Siemering and Thiboldeaux 2021). Subsurface concentrations decreased.

**Table 5-11. Summary of Naphthalene and Methylnaphthalenes (µg/kg) Measured in Ambient Soil and Sediment**

Date	Location	Average <sup>a</sup>	Range	Percent detected	Notes	Source
Naphthalene						
2005–2006	Manhattan, New York	23 <sup>b</sup>	2.4–210	100	Urban surface soil, 0–5 cm	Azzolina et al. 2016
		17 <sup>b</sup>	2.0–22,000	100	Urban subsurface soil, >15 cm	
2017	Milwaukee, Wisconsin	69	20.6–190	5	Soil from parks, 0–7 cm	Siemering and Thiboldeaux 2021
		–	–	0%	Soil from parks, 15–30 cm	
2018	Clay County, Florida	75 <sup>b</sup>	–	–	Soil from small cities	Gao et al. 2019
	Ocala, Florida	83 <sup>b</sup>	–	–		
	Pensacola, Florida	95 <sup>b</sup>	–	–		
	West Palm Beach, Florida	100 <sup>b</sup>	–	–		
1992–1995	United States	–	NS–4,900	7%	496 streambeds sampled	Lopes and Furlong 2001
–	Richardson Bay, California	–	–	–	Decreased from 33 to 2.1 with increasing depth (0–148 cm)	Pereira et al. 1999
–	San Pablo Bay, California	–	–	–	Decreased from 18 to 4.1 with increasing depth (0–239 cm)	
2012–2016	Northern Colorado Plateau, Colorado	–	61	4%	Sediment from bodies of water in and near national parks; detected at 2 of 18 sites	Weissinger et al. 2018
2017	Great Lakes tributaries in Minnesota, Wisconsin, Indiana,	7.04	NS–1,340	100%	Streambeds of tributaries to the Great Lakes	Baldwin et al. 2022

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**Table 5-11. Summary of Naphthalene and Methylnaphthalenes (µg/kg) Measured in Ambient Soil and Sediment**

Date	Location	Average <sup>a</sup>	Range	Percent detected	Notes	Source
<b>1-Methylnaphthalene</b>						
2005–2006	Ohio, and New York Manhattan, New York	16 <sup>b</sup>	1.4–150	100%	Urban surface soil, 0–5 cm	Azzolina et al. 2016
		13 <sup>b</sup>	2.2–4,400	100%	Urban subsurface soil, >15 cm	
2017	Milwaukee, Wisconsin	37.3	2.7–233	11%	Soil from parks, 0–7 cm	Siemering and Thiboldeaux 2021
		18.6	14.5–22.4	15%	Soil from parks, 15–30 cm	
2012–2016	Northern Colorado Plateau, Colorado	–	41	8%	Sediment from bodies of water in and near national parks; Detected at 2 of 18 sites	Weissinger et al. 2018
2017	Great Lakes tributaries in Minnesota, Wisconsin, Indiana, Ohio, and New York	11.0	NS–3,050	60%	Streambeds of tributaries to the Great Lakes	Baldwin et al. 2022
<b>2-Methylnaphthalene</b>						
2005–2006	Manhattan, New York	17 <sup>b</sup>	1.3–130	100%	Urban surface soil, 0–5 cm	Azzolina et al. 2016
		11 <sup>b</sup>	1.8–5,500	96%	Urban subsurface soil, >15 cm	
2017	Milwaukee, Wisconsin	39.7	2.3–281	13%	Soil from parks, 0–7 cm	Siemering and Thiboldeaux 2021
		21.8	17.3–24.9	12%	Soil from parks, 15–30 cm	
2012–2016	Northern Colorado Plateau, Colorado	–	62	7%	Sediment from bodies of water in and near national parks; detected at 2 of 18 sites	Weissinger et al. 2018
2017	Great Lakes tributaries in Minnesota, Wisconsin,	18.0	NS–2,460	60%	Streambeds of tributaries to the Great Lakes	Baldwin et al. 2022

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**Table 5-11. Summary of Naphthalene and Methylnaphthalenes (µg/kg) Measured in Ambient Soil and Sediment**

Date	Location	Average <sup>a</sup>	Range	Percent detected	Notes	Source
	Indiana, Ohio, and New York					

<sup>a</sup>Value is an average unless otherwise noted.

<sup>b</sup>Value is the median.

Streambed sediments collected from Great Lakes tributaries in several states in the summer of 2017 had median concentrations of 7.04 µg/kg naphthalene, 11.0 µg/kg 1-methylnaphthalene, and 18.0 µg/kg 2-methylnaphthalene detected (Baldwin et al. 2022). Surface sediment samples were collected between 2012 and 2016 from locations in and near national parks on the northern Colorado Plateau for naphthalene analysis. Naphthalene and methylnaphthalenes were detected in 2 of the 18 sites, with maximum concentrations of 61, 41, and 62 µg/kg, for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively (Weissinger et al. 2018). Naphthalene was detected in 7% of 496 streambed sediment sites across the United States tested for the presence of semi-volatile organic compounds; the maximum concentration was 4,900 µg/kg dry weight (Lopes and Furlong 2001). Like soil, concentrations of naphthalene have been observed to decrease with depth in sediments. Concentrations of naphthalene decreased from 33 to 2.1 µg/kg dry weight with increasing depth (0–148 cm) in the sediment core in Richardson Bay and from 18 to 4.1 µg/kg dry weight with increasing depth (0–239 cm) in the sediment core in San Pablo Bay (Pereira et al. 1999). These bays are located in the San Francisco Bay, which is the largest urbanized estuary on the west coast of the United States.

Naphthalene and methylnaphthalenes have been reported at higher concentrations near or within sources of contamination, although recent data were not located. Previously, reported naphthalene concentrations in contaminated soils included 6,100 µg/kg in coal-tar contaminated soil (Yu et al. 1990), 16,700 µg/kg in soil from a former tar-oil refinery (Weissenfels et al. 1992), and up to 66 µg/kg in sludge-treated soils (Wild et al. 1990). Methylnaphthalenes (isomer not specified) were reported at a concentration of 2,900 µg/kg in coal-tar contaminated soil (Yu et al. 1990). Hawthorne et al. (2001) reported the concentration of naphthalene to be 48,000 µg/kg in the soil from an unspecified MGP in the midwestern United States. Naphthalene and 2-methylnaphthalene were detected in soil samples collected from a former petroleum bulk plant at 46,700 and 68,600 µg naphthalene/kg and 13,400 µg 2-methylnaphthalene/kg (ATSDR 2006). These pollutants were not reported in soil gas samples, and naphthalene



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was below the ATSDR child and adult reference media evaluation guide (RMEG) values; RMEGs were not available for 2-methylnaphthalene. The mean concentration of naphthalene found in the sediment samples taken from 31 freshwater and estuarine sites adjacent to, nearby, or downstream from potential pollutant sources in Florida was 33,000 µg/kg (Miles and Delfino 1999).

No studies evaluating indoor or residential dust concentrations of naphthalene or methylnaphthalenes in the United States were located. Naphthalene was detected in dusts collected from inside 20 homes in Greece (Stamatelopoulou et al. 2021) and 31 homes in China (Liu et al. 2021). Mean concentrations of naphthalene were 0.339 and 1.984 µg/kg, respectively. Stamatelopoulou et al. (2021) included analyses for 1- and 2-methylnaphthalene and reported mean concentrations of 0.126 and 0.242 µg/kg, respectively. Van Metre et al. (2009) measured PAHs including naphthalene in pavement dust from sealcoated and unsealcoated parking lots in six cities across the United States. The study authors presented the results as the sum of 12 PAHs; results for naphthalene alone were not reported. The summed concentrations of PAHs were substantially higher (on the order of 100-fold) in dust from parking lots that had been sealcoated than those that had not been, indicating that coal tar-sealcoating mixture was likely an important source of PAHs in the dust (Van Metre et al. 2009).

#### 5.5.4 Other Media

Naphthalene and methylnaphthalenes have been detected in trace amounts in fish and unspecified bivalves and polychaetas, although sample sizes were not very large. Most detections were <100 µg/kg. A summary of the available data reported by the WQP is presented in Table 5-12. Data for other taxa groups were not located, although naphthalene has been previously detected in shellfish. Reported naphthalene concentrations were 5–176 µg/kg in oysters, 4–10 µg/kg in mussels, and <1–10 µg/kg in clams from U.S. waters (Bender and Huggett 1989). In shore crabs collected from the San Francisco Bay area, average naphthalene concentrations were 7.4 µg/kg (Miles and Roster 1999). Naphthalene and methylnaphthalene (isomer not specified) were also detected in the muscle (1.5–3.1 µg/kg wet weight), kidney (1.4–4.3 µg/kg wet weight), liver (1.4–4.7 µg/kg wet weight), and blubber (8.3–23.5 µg/kg wet weight) of harp seals caught in southern Labrador on the eastern coast of Canada (Zitko et al. 1998).

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**Table 5-12. Summary of Concentrations of Naphthalene and Methylnaphthalenes (µg/kg) Measured in Biota Samples Across the United States**

Year	Species	Mean	Maximum	Number of samples	Percent detected
<b>Naphthalene</b>					
2018		3.2	79	140	99%
	<i>Ambloplites rupestris</i>	1.1	2.1	25	100%
	<i>Ameiurus nebulosus</i>	1.1	2.5	30	100%
	<i>Cyprinus carpio</i>	10	79	29	100%
	<i>Micropterus salmoides</i>	2	7.6	22	100%
Other species sampled with n<10: <i>Lepomis gibbosus</i> , <i>Lepomis macrochirus</i> , <i>Lutjanus kasmira</i> , <i>Micropterus dolomieu</i> , <i>Oncorhynchus mykiss</i> , <i>Perca flavescens</i> , <i>Selar crumenophthalmus</i>					
2019		2.7	4.83	19	42%
	<i>L. kasmira</i>	2.4	4.1	6	33%
	<i>Salvelinus namaycush</i>	3.3	4.83	5	100
	<i>S. crumenophthalmus</i>	0.7	0.66	6	17%
Not detected in: <i>Bivalvia</i> , <i>Polycheta</i>					
2020		8.8	73.7	27	59%
	<i>C. carpio</i>	13.9	73.7	9	89%
	<i>L. kasmira</i>	1.7	2.1	6	50%
	<i>M. salmoides</i>	9.9	15.6	2	100%
	<i>S. crumenophthalmus</i>	1.7	2	6	50%
Not detected in: <i>Onchorhynchus tshawytscha</i>					
2021		25.8	240	27	70%
	<i>Ameiurus natalis</i>	20.4	38.7	3	67%
	<i>Bivalvia</i>	16.4	18	5	100%
	<i>Castomus commersonii</i>	4.8	4.77	2	50%
	<i>Polycheta</i>	3.4	3.41	1	100%
	<i>S. crumenophthalmus</i>	91.3	240	3	100%
	<i>Vertebrata</i>	21.3	57.8	3	100%
Not detected in: <i>M. dolomieu</i> , <i>Semotilus atromaculatus</i>					
2022		3.19	12.643	57	91%
	<i>Catostomus latipinnis</i>	5.58	12.643	9	100%
	<i>Pantosteus discobolus</i>	4.82	6.467	7	100%
	<i>C. commersonii</i>	3.87	5.014	4	100%
	<i>O. mykiss</i>	4.74	5.608	6	100%
	<i>C. commersonii</i> x <i>C. latipinnis</i>	4.3	4.792	2	100%
	<i>Salmo trutta</i>	2.8	2.895	2	100%
	<i>C. commersonii</i> x <i>Catostomus discobolus</i>	4.3	4.306	1	100%
	<i>Macoma nasuta</i>	0.621	0.77	10	100%
	<i>S. crumenophthalmus</i>	1.73	2.3	3	100%

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**Table 5-12. Summary of Concentrations of Naphthalene and Methylnaphthalenes (µg/kg) Measured in Biota Samples Across the United States**

Year	Species	Mean	Maximum	Number of samples	Percent detected
	<i>Alitta virens</i>	0.6	0.76	10	50%
	<i>L. kasmira</i>	1.63	2.4	3	100%
2023 <sup>a</sup>	No data				
1-Methylnaphthalene					
2018		4.5	9.23	6	100%
	<i>O. mykiss</i>	4.5	8.23	6	100%
2019		1.3	2.09	7	71%
	<i>S. namaycush</i>	1.3	2.09	5	100%
Not detected in: <i>Bivalvia</i> , <i>Polycheta</i>					
2020		15.8	95.8	15	60%
	<i>C. carpio</i>	17.4	95.8	9	89%
	<i>O. tshawytscha</i>	3.54	3.54	4	25%
Not detected in: <i>M. salmoides</i>					
2021		9.9	55	22	68%
	<i>A. natalis</i>	24.7	24.7	3	33%
	<i>Bivalvia</i>	4.8	5.4	5	100%
	<i>C. commersonii</i>	5.4	5.44	3	33%
	<i>Polychaeta</i>	23.3	55	3	100%
	<i>S. atromaculatus</i>	14.2	14.2	3	33%
	<i>Vertebrata</i>	2.6	5.771	4	100%
Not detected in: <i>M. dolomieu</i>					
2022		3.63	11.09	31	97%
	<i>C. commersonii</i>	2.48	3.054	4	75%
	<i>C. latipinnis</i>	4.67	11.09	9	100%
	<i>P. discobolus</i>	4.02	5.517	7	100%
	<i>C. commersonii</i> x <i>C. discobolus</i>	4.12	4.123	1	100%
	<i>O. mykiss</i>	3.04	3.754	6	100%
	<i>C. commersonii</i> x <i>C. latipinnis</i>	2.59	2.847	2	100%
	<i>S. trutta</i>	1.94	2.309	2	100%
2023 <sup>a</sup>	No data				
2-Methylnaphthalene					
2018		3.6	28	128	100%
	<i>A. rupestris</i>	1.7	3.5	25	100%
	<i>A. nebulosus</i>	1.1	3.1	30	100%
	<i>C. carpio</i>	7.4	28	29	100%
	<i>M. salmoides</i>	4.5	23	22	100%
Other species sampled with n<10: <i>L. gibbosus</i> , <i>L. macrochirus</i> , <i>M. dolomieu</i> , <i>O. mykiss</i> , <i>P. flavescens</i>					
2019		1.8	2.65	7	71%

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**Table 5-12. Summary of Concentrations of Naphthalene and Methylnaphthalenes (µg/kg) Measured in Biota Samples Across the United States**

Year	Species	Mean	Maximum	Number of samples	Percent detected
	<i>S. namaycush</i>	1.8	2.65	5	100%
Not detected in: <i>Bivalvia</i> , <i>Polycheta</i>					
2020		7.8	41	15	80%
	<i>C. carpio</i>	9.6	41	9	100%
	<i>O. tshawytscha</i>	2.7	6.22	4	75%
Not detected in: <i>M. salmoides</i>					
2021		14.6	84	22	73%
	<i>A. natalis</i>	41.7	41.7	3	33%
	<i>Bivalvia</i>	6.86	7.3	5	100%
	<i>C. commersonii</i>	5.25	8.05	3	67%
	<i>Polychaeta</i>	38	84	3	100%
	<i>S. atromaculatus</i>	19.8	19.8	3	33%
	<i>Vertebrata</i>	3.197	5.784	4	100%
Not detected in: <i>M. dolomieu</i>					
2022		3.36	7.361	51	84%
	<i>C. latipinnis</i>	5.2	6.726	9	100%
	<i>C. commersonii</i> x <i>C. discobolus</i>	4.91	4.906	1	100%
	<i>C. commersonii</i>	3.59	4.271	4	75%
	<i>O. mykiss</i>	4.32	4.792	6	100%
	<i>P. discobolus</i>	5.27	7.361	7	100%
	<i>C. commersonii</i> x <i>C. latipinnis</i>	3.45	3.521	2	100%
	<i>S. trutta</i>	2.78	3.76	2	100%
	<i>M. nasuta</i>	0.525	0.64	10	100%
	<i>A. virens</i>	0.507	0.68	10	30%
2023 <sup>a</sup>	No data				

<sup>a</sup>As of August, 2023.

Source: WQP 2023

Higher concentrations of naphthalene and 1- and 2-methylnaphthalene in biota are expected to be caused by nearby pollution. Naphthalene and methylnaphthalenes (isomer not specified) were detected at concentrations of 7.15 and 65.11 µg/kg of salmon tissue, respectively, and at 12.9 and 17.3 µg/kg of mussels, respectively. Both the salmon and mussels were caught in Exxon Valdez spill affected Snug Harbor in the Prince William Sound (Neff and Burns 1996). Methylnaphthalenes have occasionally been detected in fish from polluted waters. 2-Methylnaphthalene was reported at concentrations ranging from

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0.4 to 320 µg/kg in fish from Ohio waters, but neither isomer of methylnaphthalene was detected in liver or muscle tissue of fish from polluted areas of Puget Sound (GDCH 1992).

Table 5-13 presents a summary of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene concentrations in food, beverages, and supplements. Naphthalene was reported to be below the limit of quantification in oil extracted from menhaden fish, a source of commercial fish oil, caught off the coasts of New Jersey, Delaware, and Louisiana (Chopra et al. 2019). Naphthalene and methylnaphthalenes were detected in commercial coffee beans at 8.2–561.4 µg/kg for naphthalene, 24.0–306.0 µg/kg for 1-methylnaphthalene, and 7.2–286.9 µg/kg for 2-methylnaphthalene (Jimenez et al. 2014). Higher concentrations were associated with darker roasts, due to contamination likely occurring during the roasting process. Other current data regarding naphthalene contamination of food in the United States were not located. Naphthalene was not included in the Food and Drug Administration (FDA) Total Diet Study between 2003 to 2017 (FDA 2022a). Naphthalene may contaminate food from atmospheric deposition of naphthalene in air, or partitioning from soil and water. Previously, naphthalene was detected in 2 of 13,980 samples of foods analyzed in six states (Minyard and Roberts 1991). In a Lower Rio Grande Valley environmental study, naphthalene (median concentration, 2.159 µg/kg body weight) was detected in five of the nine duplicate-diet samples (Berry et al. 1997). Naphthalene (1–7 µg/kg) was also detected in fresh tree-ripened apricots, plums, and their interspecific hybrids (Gomez et al. 1993).

**Table 5-13. Summary of Naphthalene and Methylnaphthalenes Measured in Food, Beverages, and Supplements**

Location	Product	Average	Range	Notes	Source
<b>Naphthalene</b>					
Coasts of New Jersey, Delaware, and Louisiana	Oil from Menhaden fish	<3 µg/kg	–	Not detected	Chopra et al. 2019
United States	Instant coffee beans	<0.61 µg/kg	–	Not detected in 2 of 2 products	Jimenez et al. 2014
	Espresso coffee beans	<0.61 µg/kg; 22.8 µg/kg	–	Not detected in 1 of 2 products	
	Light blend coffee beans	8.2 µg/kg; 13.4 µg/kg	–		
	Medium blend coffee beans	27.9 µg/kg; 79.1 µg/kg	–		
	Dark blend decaffeinated beans	101.7 µg/kg	–		
	Dark blend coffee beans	–	27.8–561.4 µg/kg	4 products analyzed	

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**Table 5-13. Summary of Naphthalene and Methylnaphthalenes Measured in Food, Beverages, and Supplements**

Location	Product	Average	Range	Notes	Source
United States; 10 states	–	–	–	Detected in 2 of 13,980 food samples	Minyard and Roberts 1991
–	Apricots, plums, and their hybrids	–	1–7 µg/kg		Gomez et al. 1993
Spain	Cereal-based foodstuffs; cookies, breakfast cereal, flour, pasta, rice, bread	–	0.013–5.500 µg/kg	22 foods analyzed	Sampaio et al. 2021
Spain	Beer	–	0.340–1.500 µg/L		Sampaio et al. 2021
	Wine	–	0.075–3.600 µg/L		
	Juice	–	0.00029– 0.0036 µg/L		
Canada	Farmed salmon	1.98 µg/kg	–		Easton et al. 2002
Pacific coast	Wild salmon	2.15 µg/kg	–		
1-Methylnaphthalene					
United States	Instant coffee beans	<0.4 µg/kg	–	Not detected in 2 of 2 products	Jimenez et al. 2014
	Espresso coffee beans	<0.47 µg/kg; 24.0 µg/kg	–	Not detected in 1 of 2 products	
	Light blend coffee beans	<0.47 µg/kg	–	Not detected in 2 of 2 products	
	Medium blend coffee beans	28.1 µg/kg; 39.7 µg/kg	–		
	Dark blend decaffeinated beans	97.6 µg/kg	–		
	Dark blend coffee beans	–	27.2–306.0 µg/kg	4 products analyzed	
Canada	Farmed salmon	0.96 µg/kg	–		Easton et al. 2002
Pacific cost	Wild salmon	1.53 µg/kg	–		
Poland	Unsmoked cheese	10.5 µg/kg	8.8–12.3 µg/kg	5 products analyzed	Polak- Śliwińska et al. 2022
	Smoked cheese	5.0 µg/kg	1.5–11.3 µg/kg	10 products analyzed	
2-Methylnaphthalene					
United States	Instant coffee beans	<0.36 µg/kg	–	Not detected in 2 of 2 products	Jimenez et al. 2014
	Espresso coffee beans	9.9 µg/kg; <0.36 µg/kg	–	Not detected in 1 of 2 products	
	Light blend coffee beans	<0.36 µg/kg; 28.2 µg/kg	–	Not detected in 1 of 2 products	

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-13. Summary of Naphthalene and Methylnaphthalenes Measured in Food, Beverages, and Supplements**

Location	Product	Average	Range	Notes	Source
	Medium blend coffee beans	<0.36 µg/kg	–	Not detected in 2 of 2 products	
	Dark blend decaffeinated beans	7.2 µg/kg	–		
	Dark blend coffee beans	–	10.5–286.9 µg/kg	4 products analyzed	
Canada	Farmed salmon	1.98 µg/kg	–		Easton et al. 2002
Pacific coast	Wild salmon	2.93 µg/kg	–		

Outside of the United States, naphthalene was detected in 22 cereal-based foodstuffs, such as flour, pasta, rice, and bread, at 0.013–5.5 µg/kg (Sampaio et al. 2021). Naphthalene was detected at 0.340–1.500 µg/L in beer, 0.075–3.600 µg/L in wine, and 0.00029–0.0026 µg/L in juice (Sampaio et al. 2021).

Food grown near sources of naphthalene may have higher concentrations. Naphthalene was detected in all leafy vegetable samples (e.g., garden egg leaves and Chinese cabbage) grown in the city center of Accra, Ghana (Sampaio et al. 2021). Vegetables grown in an industrial area of Thessaloniki, Greece had naphthalene concentrations measured to be 0.37–15 µg/kg dry weight in cabbage; 8.9–30 µg/kg dry weight in carrots; 6.3–35 µg/kg dry weight in leeks; 4.9–53 µg/kg dry weight in lettuce; and 27–63 µg/kg dry weight in endive (Kipopoulou et al. 1999). Naphthalene was among the volatile organic compounds (VOCs) identified in whole and ground sorghum (Seitz et al. 1999).

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were detected at mean concentrations of 1.98, 0.96, and 1.98 µg/kg, respectively, in whole gutted farmed salmon and at 2.15, 1.53, and 2.93 µg/kg, respectively, in whole gutted wild salmon from the Pacific coast (Easton et al. 2002).

Naphthalene may contaminate food if cooked by a source that releases naphthalene. Naphthalene was detected in the gas phase (5,860 µg emitted per kg of meat cooked) as well as the particle phase (1,440–1,690 µg emitted per kg of meat cooked) in the emissions from the process of charbroiling hamburger meat over a natural gas grill (Schauer et al. 1999). Measurements in the meat were not conducted in this study. Naphthalene was detected in traditionally smoked cheeses (5.0 µg/kg), but at higher average concentrations in unsmoked cheeses (10.5 µg/kg) (Polak-Śliwińska et al. 2022). Naphthalene has also been detected in smoked salmon (Zelinkova and Wenzl 2015).

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Studies conducted in the 1990s suggested that naphthalene contamination could also occur from food packaging. Naphthalene levels in sterilized milk drinks contained in low-density polyethylene (LDPE) bottles were shown to be low (20 µg/L) at the time of purchase, increasing to 100 µg/L 30 days later, and averaging 250 µg/L at the expiration date of the milk (Lau et al. 1994). Residual naphthalene present in the LDPE packaging was hypothesized to be the contamination source. A later study by the same study authors observed that the level of naphthalene in LDPE milk bottle material had been reduced to 100–400 µg/kg due to the use of new packaging material (Lau et al. 1995). More recent data on naphthalene leaching from food packaging were not located.

Naphthalene has been detected in a variety of other consumer products. Table 5-14 reproduced from a report by the Danish Environmental Protection Agency, reports naphthalene concentrations detected in products available commercially in Denmark (Danish EPA 2015). Similar analysis of products sold in the United States were not located.

**Table 5-14. Summary of Naphthalene Measured in Consumer Products**

Product	Value	Notes
Window glass colors	5.7–11 mg/kg	Red paint
Toothbrush	0.04–0.53 mg/kg	0.0053 mg/toothbrush
Incense smoke	403 µg/m <sup>3</sup>	
Printed matter	0.122–0.389 mg/kg; 18–90 µg/m <sup>3</sup> emitted	
Textiles	0.04–2.4 mg/kg	
Bathing shoes	0.2–0.5 mg/kg	
Bicycle tires	0.5–1.0 mg/kg	
Rubber figurine	0.2–0.5 mg/kg	
Balloons	0.2–0.5 mg/kg	
Toy car	0.2–0.5 mg/kg	
Tattoo ink	0.8–81 mg/kg	Black ink
	1.9–2.8 mg/kg	Blue ink
	1.6 mg/kg	Red ink
	1.3 mg/kg	Orange ink
Wood tar	510 mg/kg	
Silicone based pacifiers	>0.1 mg/kg	
<b>Products with &lt;0.2 mg/kg:</b> rubber shoes, bracelet, scooter and bicycle handles, eraser, doll, teething ring, swimming equipment, bib, bags, alarm horn, and pen		

Source: Danish EPA 2015



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Naphthalene was detected at a concentration of 227 mg/kg of wood burned from the fireplace combustion of pine wood. 1-Methylnaphthalene was detected at concentrations of 10.6, 6.39, and 4.31 mg/kg of wood burned from the combustion of pine, oak, and eucalyptus wood respectively (Schauer et al. 2001). 2-Methylnaphthalene was detected at concentrations of 15.0, 9.31, and 5.69 mg/kg of wood burned from combustion of pine, oak, and eucalyptus wood, respectively. Naphthalene was not measured from the oak and eucalyptus fires (Schauer et al. 2001). In another study, the respective median concentrations of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were determined to be 22.57, 4.14, and 4.76 mg/kg of burned Ponderosa pine in the fireplace; 60.86, 12.71, and 15.55 mg/kg for mixed hardwoods in the fireplace; and 34.96, 5.23 and 6.32 mg/kg for mixed hardwoods burned in a woodstove (McDonald et al. 2000).

Naphthalene and methylnaphthalene detections in tobacco products are reported in Table 5-15.

Naphthalene was not detected in main-stream smoke from filtered “low nicotine” research cigarettes, but was emitted at a rate of 18.11 ug/cigarette into sidestream smoke (Charles et al. 2007). In a study from 1978, reported levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in the smoke from U.S. commercial unfiltered cigarettes were 3, 1, and 1 µg, respectively (Schmeltz et al. 1978). Levels in sidestream smoke were found to be higher: 46, 30, and 32 µg/cigarette, respectively (Schmeltz et al. 1976). In the emissions from electronic cigarettes, naphthalene was detected at  $6.15 \times 10^{-5}$ – $9.22 \times 10^{-5}$  µg/puff, significantly lower than 3,598.6 µg/puff in a reference conventional cigarette (Dusautoir et al. 2021). Naphthalene and the methylnaphthalenes have been detected at approximately between 10 and 100 µg/kg dry weight in smokeless tobacco products (McAdam et al. 2013).

**Table 5-15. Summary of Naphthalene and Methylnaphthalenes Measured in Tobacco Products**

Product	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Source
Smoke of unfiltered cigarettes	3 µg/cigarette	1 µg/cigarette	1 µg/cigarette	Schmeltz et al. 1978
Sidestream smoke of unfiltered cigarettes	46 µg/cigarette	30 µg/cigarette	32 µg/cigarette	
Smoke of filtered “low nicotine” research cigarettes	Below detection limit	–	–	Charles et al. 2007
Sidestream smoke of filtered “low	18.11 µg/cigarette	–	–	

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**Table 5-15. Summary of Naphthalene and Methylnaphthalenes Measured in Tobacco Products**

Product	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Source
nicotine” research cigarettes				
Electronic cigarette	6.15x10 <sup>-5</sup> – 9.22x10 <sup>-5</sup> µg/puff	–	–	Dusautoir et al. 2021
Reference conventional cigarette	3,598.6 µg/puff	–	–	
Chewing tobacco	54.0 µg/kg dw	20.1 µg/kg dw	10.4 µg/kg dw	McAdam et al. 2013
Dry snuff	84.9 µg/kg dw	75.2 µg/kg dw	60.0 µg/kg dw	
Hard pellet	69.7 µg/kg dw	19.2 µg/kg dw	10.5 µg/kg dw	
Soft pellet	76.5 µg/kg dw	74.2 µg/kg dw	65.6 µg/kg dw	
Moist snuff	110 µg/kg dw	62.0 µg/kg dw	46.9 µg/kg dw	
Plug products	53.4 µg/kg dw	18.3 µg/kg dw	9.51 µg/kg dw	

dw = dry weight

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were among the chemicals detected in air in Lower Manhattan in the aftermath of the destruction of the World Trade Center, New York City, New York on September 11, 2001. Concentration of naphthalene ranged from 699 ng/m<sup>3</sup> on September 26–27, 2001, to 42 ng/m<sup>3</sup> on October 21–22, 2001. The concentration of 1-methylnaphthalene ranged from 178 to 100 ng/m<sup>3</sup> and that of 2-methylnaphthylene ranged from 267 to 165 ng/m<sup>3</sup> for the same days (Swartz et al. 2003).

**5.6 GENERAL POPULATION EXPOSURE**

The general population is most likely to be exposed to naphthalene by inhalation of ambient and indoor air. The use of naphthalene-containing moth repellents and smoke from cigarettes are the main sources of naphthalene in indoor air. Other indoor sources include kerosene heaters, wood burning, and formulations containing naphthalene, such as printer ink (Arı 2020).

Based on an urban/suburban average air concentration of 0.04 µg/m<sup>3</sup> (8.0x10<sup>-6</sup> ppmv) (EPA 2022b) and an inhalation rate of 20 m<sup>3</sup>/day, it has been estimated that the average daily intake from ambient air is 0.8 µg (Howard 1989). Intake from indoor air may be higher, depending on the presence of indoor sources. The estimated average daily intakes from ambient air may be about 4.2 µg for 1-methylnaphthalene and 7.4 µg for 2-methylnaphthalene. These estimates are based on ambient air samples taken

## 5. POTENTIAL FOR HUMAN EXPOSURE

from an average air concentration of  $0.21 \mu\text{g}/\text{m}^3$  (0.036 ppmv) 1-methylnaphthalene,  $0.37 \mu\text{g}/\text{m}^3$  (0.064 ppmv) 2-methylnaphthalene (EPA 2022b), and an assumed human daily intake of  $20 \text{ m}^3$ .

Inhalation exposure is a major source of exposure in both adults and children, particularly in homes where repellents and deodorant blocks containing naphthalene are used or tobacco is smoked in the home. Under experimental conditions, a box of moth balls placed in a closet had naphthalene emissions between 8 and 12 mg/hour, decreasing over time to  $\sim 5$  mg/hour (Guerrero and Corsi 2012). Naphthalene was one of the PAHs detected in an eight-home pilot study that was conducted in Columbus, Ohio to measure the PAH concentration profiles in house dust. The average concentration of naphthalene was found to be dependent upon the method of extraction ( $2.8 \text{ mg}/\text{m}^3$  by Soxhlet extraction and  $1.8 \text{ mg}/\text{m}^3$  by sonication extraction) (Chuang et al. 1995). Concentrations of naphthalene detected in the indoor and outdoor air measured in 24 low-income homes in North Carolina were 0.33–9.7 and  $0.57\text{--}1.82 \mu\text{g}/\text{m}^3$ , respectively (Chuang et al. 1999). In a study reporting the concentrations of VOCs in a wide range of environments (i.e., homes, offices, restaurants, pubs, department stores, train and bus stations, heavily trafficked roadside locations, buses, trains and automobiles) in Birmingham, United Kingdom, naphthalene concentrations were found to range from  $0.1 \mu\text{g}/\text{m}^3$  (laboratories) to  $12.1 \mu\text{g}/\text{m}^3$  (heavily trafficked roadside) (Kim et al. 2001). A mean concentration of naphthalene was found to be  $2.3 \mu\text{g}/\text{m}^3$  in a German environmental survey that monitored 113 adults aged 25–69 years, selected at random, for personal exposure to VOCs including naphthalene (Hoffmann et al. 2000). Low levels of naphthalene (average concentration,  $0.44 \mu\text{g}/\text{m}^3$ ) and 1-methylnaphthalene (average concentration,  $0.08 \mu\text{g}/\text{m}^3$ ) were found in the indoor air of 92% of single-family homes and 81% of apartments monitored (Kostianen 1995). Naphthalene has been detected in the smoke from charbroiling meat (Schauer et al. 1999) and from the smoke from domestic fireplaces and wood-burning stoves (McDonald et al. 2000; Schauer et al. 2001).

Exposure to naphthalene may occur from ingestion of drinking water and/or food, but these exposures are expected to be much less than inhalation exposures for the general population. Estimated exposure from drinking water, assuming a worst-case water concentration of about  $0.2 \mu\text{g}/\text{L}$  (USGS 2015), is  $0.4 \mu\text{g}/\text{day}$  (Howard 1989). However, naphthalene was rarely detected in drinking water. No recent dietary exposure estimates were available.

Dermal exposure to naphthalene may occur from handling or wearing clothing stored in naphthalene-containing moth repellents. However, no data were located concerning the level of human exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene via this exposure route. Experimental studies

## 5. POTENTIAL FOR HUMAN EXPOSURE

have shown that naphthalene can be dermally absorbed and systemically metabolized in rats (Turkall et al. 1994).

The Centers for Disease Control and Prevention (CDC) creates ongoing assessments on Human Exposure to Environmental Chemicals that were derived from data obtained from NHANES. The biomonitoring data report urinary levels of two metabolites of naphthalene, 1-hydroxynaphthalene (or 1-naphthol) and 2-hydroxynaphthalene (2-naphthol), from a sample of people who represent the noninstitutionalized, civilian U.S. population during 2-year study periods. The data for the most recent study period (2015–2016) are summarized in Table 5-16. In studies on worker exposures, naphthalene air concentrations were correlated with 1- and 2-hydroxynaphthalene; 1-hydroxynaphthalene, may also be a metabolite of the insecticide carbaryl (CDC 2017). Urinary levels reflect recent exposure, and higher levels are typically found in smokers and workers who are in industries that expose them to naphthalene. Table 5-17 provides the urinary levels of 1- and 2-hydroxynaphthalene in U.S. adult ( $\geq 18$  years old) smokers, who had means higher than adult ( $\geq 20$  years old) nonsmokers.

**Table 5-16. Geometric Mean of the Urine Concentration ( $\mu\text{g/L}$ ) of 1- and 2-Hydroxynaphthalene in the U.S. Population (2015–2016)**

Population group	Geometric mean	95% CL	Sample size
<b>1-Hydroxynaphthalene</b>			
Total population	1.36	1.29–1.43	2,926
Age 3–5 years	0.83	0.78–1.01	471
Age 6–11 years	0.88	0.78–1.00	373
Age 12–19 years	0.95	0.85–1.07	392
Age 20+ years	1.86	1.72–2.01	1,690
Males	1.53	1.42–1.65	1,463
Females	1.20	1.11–1.30	1,463
Mexican Americans	1.07	0.96–1.20	556
Non-Hispanic Blacks	1.96	1.75–2.19	640
Non-Hispanic Whites	1.48	1.32–1.64	879
<b>2-Hydroxynaphthalene</b>			
Total population	5.23	5.02–5.45	2,926
Age 3–5 years	4.02	3.95–4.95	471
Age 6–11 years	4.42	3.95–4.96	373
Age 12–19 years	5.57	5.01–6.19	392
Age 20+ years	5.74	5.44–6.07	1,690
Males	5.36	5.06–5.66	1,463
Females	5.07	4.78–5.38	1,463

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-16. Geometric Mean of the Urine Concentration (µg/L) of 1- and 2-Hydroxynaphthalene in the U.S. Population (2015–2016)**

Population group	Geometric mean	95% CL	Sample size
Mexican Americans	7.21	6.62–7.85	556
Non-Hispanic Blacks	7.13	6.59–7.71	640
Non-Hispanic Whites	4.03	3.73–4.36	879

CL = confidence limit

Source: CDC 2023

**Table 5-17. Geometric Mean of the Urine Concentration (µg/L) of 1-Hydroxynaphthalene and 2-Hydroxynaphthalene in the U.S. Adult Smoking Population (2015–2016)**

Population group	Geometric mean	95% CL	Sample size
<b>1-Hydroxynaphthalene</b>			
Total population	2.73	2.57–2.90	3,010
Males	3.17	2.89–3.48	1,114
Females	2.32	2.08–2.58	1,079
Mexican Americans	1.64	1.40–1.93	335
Non-Hispanic Blacks	4.61	4.05–5.23	504
Non-Hispanic Whites	3.23	2.82–3.71	743
<b>2-Hydroxynaphthalene</b>			
Total population	7.10	6.81–7.39	3,010
Males	7.48	7.01–7.98	1,114
Females	6.62	6.17–7.10	1,079
Mexican Americans	8.74	7.87–9.70	335
Non-Hispanic Blacks	10.43	9.63–11.29	504
Non-Hispanic Whites	6.04	5.52–6.61	743

CL = confidence limit

Source: CDC 2023

Naphthalene was detected in 40% of human adipose tissue samples at concentrations ranging from <9 to 63 µg/kg in a National Human Adipose Tissue Survey (NHATS) (EPA 1986b). More recent large-scale biomonitoring studies were not available. Naphthalene was detected between 0.618 and 5.14 ng/g in 10 whole blood samples obtained from a blood donation center in the San Francisco Bay area (Hao et al. 2020). In a study of 52 women in Ottawa, Canada, naphthalene was detected in breastmilk, with a median concentration of 7.55 ng/g lipid (range, 3.86–79.36 ng/g lipid) (Wheeler et al. 2014). The study authors also concluded that urinary concentrations of naphthalene metabolites tended to be similar to

## 5. POTENTIAL FOR HUMAN EXPOSURE

(1-naphthol) or lower (2-naphthol) than those reported in another Canadian survey of women of reproductive age and only urinary metabolite 1-naphthol and naphthalene levels in breast milk were correlated.

A personal air monitoring study of 17 pregnant women in their third trimester, conducted in the McAllen-Edinburg-Mission area of Texas, utilized both air-sampler backpacks and passive-sampler silicone wristbands to measure methylnaphthalene exposure across 3 nonconsecutive days. The backpack reported exposure to 57.26 ng/m<sup>3</sup> 1-methylnaphthalene and the wristband reported exposure to 139.93 ng/m<sup>3</sup> 1-methylnaphthalene; 93.50 ng/m<sup>3</sup> 2-methylnaphthalene and 174.78 ng/m<sup>3</sup> 2-methylnaphthalene were reported by the backpack and wristband samplers, respectively (Mendoza-Sanchez et al. 2022). Personal air monitoring of pregnant women in Ottawa, Canada, reported median naphthalene concentrations of 0.73 and 0.79 µg/m<sup>3</sup> during pregnancy on weekdays and weekends, respectively, and 1.74 µg/m<sup>3</sup> 2–3 months after birth (Wheeler et al. 2014). Air samples were collected from a sampler attached to the collar.

Children are likely to be exposed to naphthalene via the same routes that affect adults, such as inhalation of contaminated air, ingestion of contaminated drinking water or contaminated food, and dermal contact with contaminated soils or products treated with the compound. Small children are more likely than adults to come into intimate contact with yard dirt, lawns, and dust from carpets. Dislodgeable pesticide residues in carpets or on uncovered floors may present a relatively important exposure route for infants and toddlers through dermal contact and oral ingestion. The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented. These behavioral traits can result in ingestion of naphthalene present in soil and dust. Naphthalene has been detected in the house-dust in an eight-home pilot study (Chuang et al. 1995).

Accidental ingestion of household products containing naphthalene such as mothballs or deodorant blocks frequently occurs in children. In 2020, 527 cases of accidental naphthalene moth repellent ingestion were reported to Poison Control Centers in the United States (Gummin et al. 2021). About 50% of these cases occurred in children under 5 years of age.

Naphthalene was among the chemicals detected at nine day care centers in Durham, Raleigh, and Chapel Hill, North Carolina (Wilson et al. 1999). Indoor and outdoor air was found to contain naphthalene at concentrations of 205 and 89.6 ng/m<sup>3</sup>, respectively. The concentrations were 0.011 ppm in soil, 0.008 ppm in dust, 0.94 ppb in liquid food, and 0.25 ppb in solid food samples. The differences in PAH

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concentrations between daycare centers serving low-income clients and those serving middle-income clients were found to be small.

Naphthalene (mothballs) is commonly used as a moth repellent in clothes during storage and as a deodorizer in diaper pails. Acute hemolysis was reported in 21 children following a period of inhalation exposure of naphthalene. The source of naphthalene was woolen clothes and blankets that had been stored with mothballs over the summer (Valaes et al. 1963).

A potential source of exposure in infants is from the presence of naphthalene in breast milk or formula. Naphthalene was detected (concentrations not reported) in six of eight breast milk samples from women in four U.S. cities (Pellizzari et al. 1982). Children may also be exposed to naphthalene from milk drinks that have been stored in LDPE bottles (Lau et al. 1994).

Naphthalene may volatilize from water; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily TWA exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to [showermodel@cdc.gov](mailto:showermodel@cdc.gov). Using representative values from drinking water aquifers as discussed in Section 5.5.2 and representative outdoor air levels discussed in Section 5.5.1, Reasonable Maximum Exposure (RME) levels for naphthalene were calculated for different exposure groups (see Table 5-18). Data regarding methylnaphthalene concentrations in drinking water sources were not available, and estimates could therefore not be calculated.

**Table 5-18. Reasonable Maximum Estimate of Naphthalene Daily Inhalation and Dermal Doses from Showering by Exposure Group**

Exposure group	Inhalation ( $\mu\text{g}/\text{m}^3$ )	Dermal ( $\mu\text{g}/\text{kg}/\text{day}$ )
Birth–<1 year	0.096	0.0063
1–<2 years	0.096	0.0058
2–<6 years	0.096	0.0050
6–<11 years	0.096	0.0041
11–<16 years	0.096	0.0033
16–<21 years	0.096	0.0030
Adult	0.096	0.0030

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-18. Reasonable Maximum Estimate of Naphthalene Daily Inhalation and Dermal Doses from Showering by Exposure Group**

Exposure group	Inhalation ( $\mu\text{g}/\text{m}^3$ )	Dermal ( $\mu\text{g}/\text{kg}/\text{day}$ )
Pregnant and breastfeeding women	0.096	0.0030

Source: ATSDR 2022b

**5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES**

Naphthalene concentrations can vary widely based on the site conditions, source of naphthalene, and proximity to the source, resulting in large variations in the levels of exposure, even for populations with expected high exposures. Members of the general population most likely to have high levels of exposure to naphthalene are users of naphthalene-containing moth repellents (including infants exposed to blankets or clothing stored in naphthalene-containing mothballs), smokers, and those in proximity to smokers. Workers in naphthalene-producing or naphthalene-using industries, and workers exposed to burning wood or coal, and fuels, could be subject to heightened exposure. Individuals living or working near hazardous waste sites at which naphthalene has been detected could also be exposed to higher naphthalene concentrations if they came into contact with contaminated media. Potentially high exposure to naphthalene and other PAHs are possible for people working with or using coal tar or coal tar creosote products.

NIOSH (2009) evaluated environmental tobacco smoke exposure in Las Vegas casino dealers, including measurements of naphthalene concentrations in personal breathing zone samples and area samples. The geometric mean concentration naphthalene in personal breathing zone samples across three casinos was  $0.78 \mu\text{g}/\text{m}^3$ , with a range of  $0.21\text{--}1.4 \mu\text{g}/\text{m}^3$ . In area samples, the concentrations were similar, with a geometric mean concentration of  $0.729 \mu\text{g}/\text{m}^3$  (range  $0.19\text{--}1.6 \mu\text{g}/\text{m}^3$ ).

In a personal monitoring study collecting dermal wipes primarily from the lower arms, hands, and neck, U.S. Air Force fuel-cell maintenance workers had an average estimate whole body dermal exposure of  $2,020 \text{ ng}/\text{m}^2$  (range,  $100\text{--}4.88 \times 10^6 \text{ ng}/\text{m}^2$ ) to naphthalene (Chao et al. 2005). The highest dermal exposures were seen in workers who entered fuel tanks (to perform cleaning or maintenance tasks); those whose work did not involve entry into the tanks had lower dermal exposure levels (Chao et al. 2005).



## 5. POTENTIAL FOR HUMAN EXPOSURE

People living near industrial sites may have increased exposure to naphthalene and methylnaphthalenes. Naphthalene has also been detected in household dust, at  $0.083 \mu\text{g}/\text{m}^2$  from wipes collected in 25 homes in Houston, Texas, near an oil refinery. (Horney et al. 2018).

Firefighters may be exposed to naphthalene and methylnaphthalenes when around the combustion of wood. Naphthalene was detected at  $<4\text{--}21,439 \text{ ng}/\text{m}^3$  via personal air monitoring during wildfire and prescribed burning events (Navarro et al. 2017). During overhaul events, naphthalene was detected in air at up to  $89.91 \mu\text{g}/\text{m}^3$  (Baxter et al. 2014), and at an average of  $0.010 \mu\text{g}/\text{m}^3$  in the air during a wildfire (Simms et al. 2021). Another personal air monitoring study reported  $7,460\text{--}344,000 \mu\text{g}/\text{m}^3$  naphthalene detected from monitors outside the firefighter's jackets and from less than the limit of detection to  $6,250 \mu\text{g}/\text{m}^3$  naphthalene detected within the firefighters' jackets (Mayer et al. 2022) suggesting that firefighters may have higher dermal exposure to naphthalene than the general population. In addition, firefighters or other workers exposed to naphthalene may carry it home or elsewhere with them on their clothing. Naphthalene was detected at  $9.24$  and  $9.22 \mu\text{g}/\text{m}^3$  in the kitchen and truck bay (respectively) of one firehouse but was below the quantification limit in the same areas of another firehouse (Baxter et al. 2014). Skin wipes of firefighters on their hands and jaw/throat showed an increase in naphthalene post shift:  $3.27\text{--}4.24 \text{ ng}/\text{wipe}$  for hands and  $3.89\text{--}5.16 \text{ ng}/\text{wipe}$  of the jaw/throat area (Cherry et al. 2021).

The highest naphthalene exposure is anticipated to be in naphthalene-producing industries and naphthalene-using industries such as wood preserving, tanning, and ink and dye production; however, no current American workplace monitoring studies for these specific industries were located. Liu and Jia (2015) compared PAH exposures across different occupations using urinary metabolite levels from NHANES surveys between 2001 and 2008. Urinary levels of naphthalene metabolites in the study population of 4,162 adults were highest among individuals whose jobs were categorized as "extractive, construction, and repair" occupations (Liu and Jia 2015). The weighted geometric mean urinary naphthalene metabolite concentration for this group was ~40% higher than the corresponding value in the group categorized as "management" (the reference group). In a study of German and Austrian abrasive manufacturing sites, personal air measurements of naphthalene were measured for workers over the course of a 4–5.5-hour shift. The measurement for workers with direct naphthalene exposure by mixing or sieving was  $8.0\pm 3.0 \text{ mg}/\text{m}^3$ , and the measurement for workers with direct naphthalene exposure by pressing or moulding was  $4.9\pm 3.7 \text{ mg}/\text{m}^3$  (Weiss et al. 2020). Bystander exposure from post-pressing or finishing was  $0.6\pm 0.2 \text{ mg}/\text{m}^3$  naphthalene. Naphthalene was still detected during shifts of spatially separated workers who were finishing or packing, or working in an office, at  $0.2\pm 0.1 \text{ mg}/\text{m}^3$  (Weiss et al. 2020). In coke plants in Poland between 2005 and 2010, naphthalene was measured by personal air

## 5. POTENTIAL FOR HUMAN EXPOSURE

monitoring at medians of 86.0  $\mu\text{g}/\text{m}^3$  for coke-oven workers, 175.5  $\mu\text{g}/\text{m}^3$  for coke byproduct workers, and 73.5  $\mu\text{g}/\text{m}^3$  for total area workers (Bieniek and Łusiak 2012). In 2003, personal air monitoring of road construction workers in the Milan and Lodi provinces of Italy was conducted during the first part of the work shift (about 4 hours). Naphthalene exposure for asphalt workers was reported to be 426  $\text{ng}/\text{m}^3$ , and exposure for road construction workers was reported to be 371  $\text{ng}/\text{m}^3$  (Buratti et al. 2007).

McCormick et al. (2022) evaluated exposure to PAHs including naphthalene in a group of 21 workers using refined coal tar sealant to seal asphalt. The exposure measures included area and personal air samples, wipe samples of the hand and neck, and analysis of pre- and post-shift urine samples for urinary metabolites. The median personal air concentration was 61.81  $\mu\text{g}/\text{m}^3$ , the median post-shift hand wipe exposure was 0.28  $\mu\text{g}/\text{cm}^2$ , and the median post-shift neck wipe exposure was 1.10  $\mu\text{g}/\text{sample}$  (McCormick et al. 2022). The median post-shift urinary 1- and 2-naphthol concentrations were 14.75 and 18.27  $\mu\text{g}/\text{g}$  creatinine (McCormick et al. 2022). A 1980 National Institute for Occupational Safety and Health (NIOSH 1980) survey of worker exposures to PAHs at a petroleum refinery in Tulsa, Oklahoma reported average air concentrations of naphthalene as high as 10.18  $\mu\text{g}/\text{m}^3$  in an area sample and 19.27  $\mu\text{g}/\text{m}^3$  for a personal sample, measured over a day shift. For the methylnaphthalenes, 16.4 and 17.56  $\mu\text{g}/\text{m}^3$  were the maximum average area concentrations reported for 1-methylnaphthalene and 2-methylnaphthalene, respectively, and the highest average concentrations in personal samples over a shift detected were 17.81 and 31.9  $\mu\text{g}/\text{m}^3$  for 1-methylnaphthalene and 2-methylnaphthalene, respectively. The workers at greatest risk of exposure included mining machine operators, aircraft engine mechanics, and miscellaneous machine operators.

Recent estimates of the number of workers exposed to naphthalene during its manufacture and subsequent use are 250–500 in the United Kingdom and 1,500–2,000 in the European Union (EU). These estimates do not include operators handling creosote treated lumber or brush applicators, or users of tar paints/membranes (EU 2003).

## CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, and 6-3. The purpose of this figure is to illustrate the information concerning the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

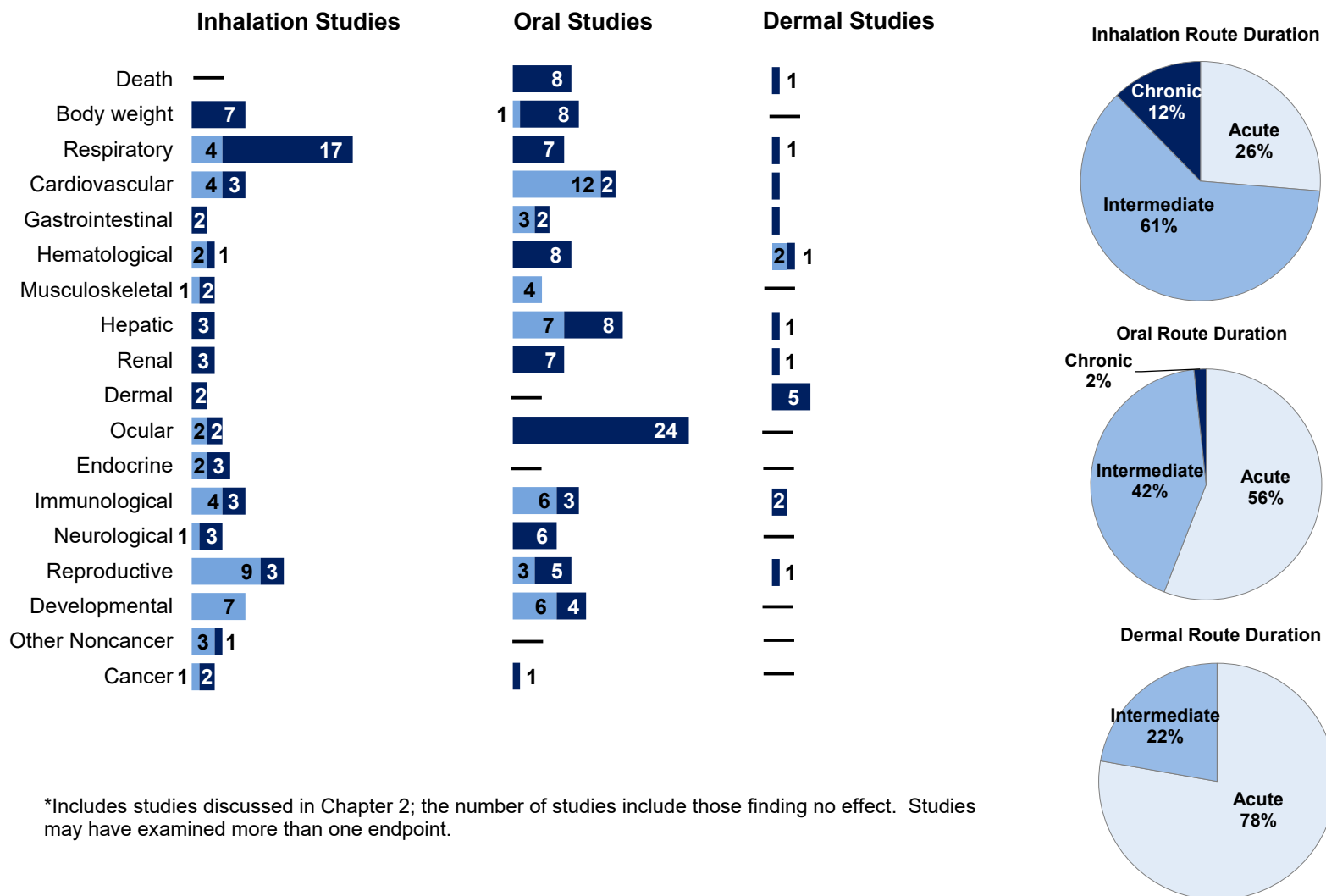
### 6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, and 6-3 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

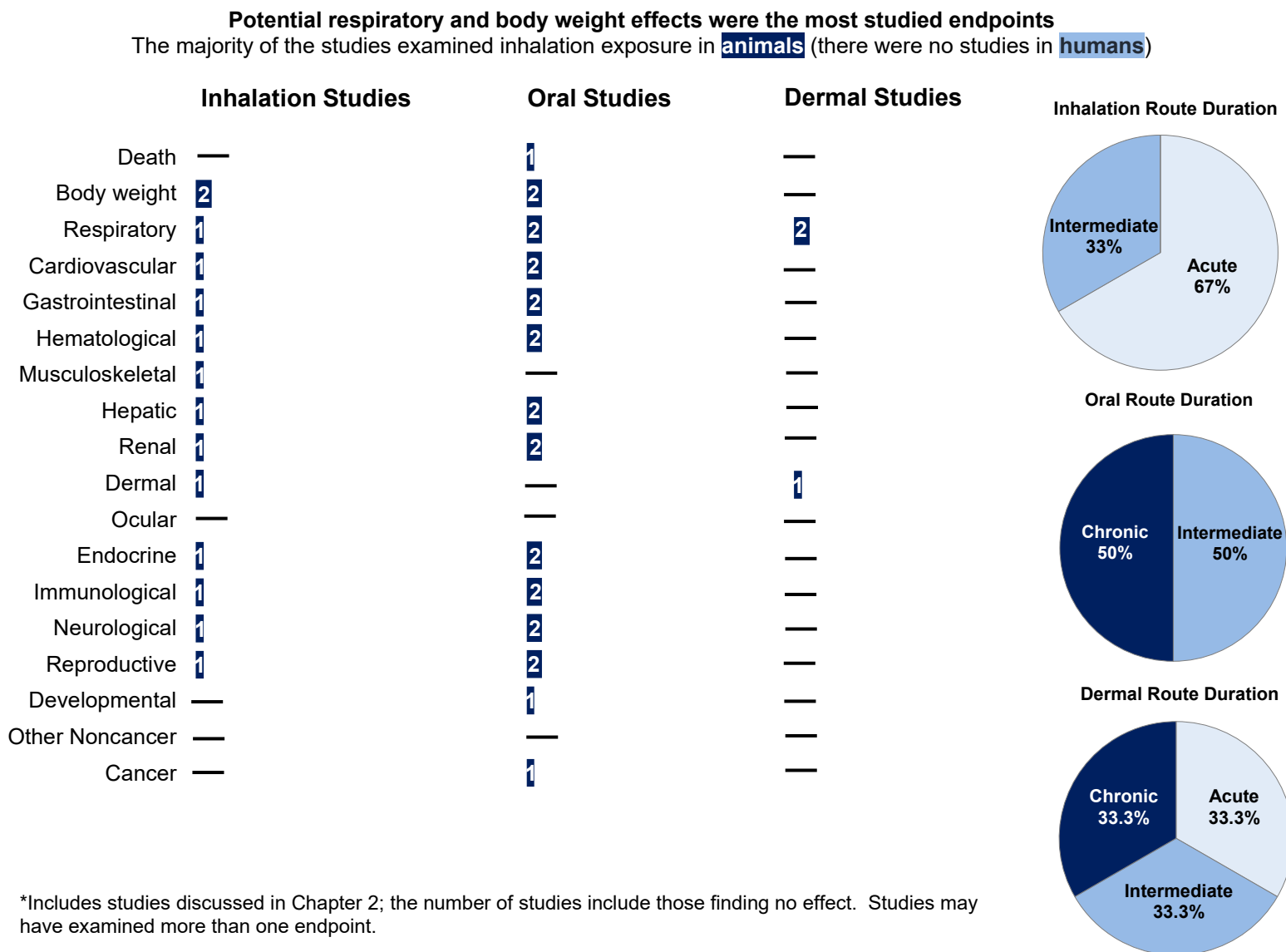
## 6. ADEQUACY OF THE DATABASE

**Figure 6-1. Summary of Existing Health Effects Studies on Naphthalene by Route and Endpoint\***

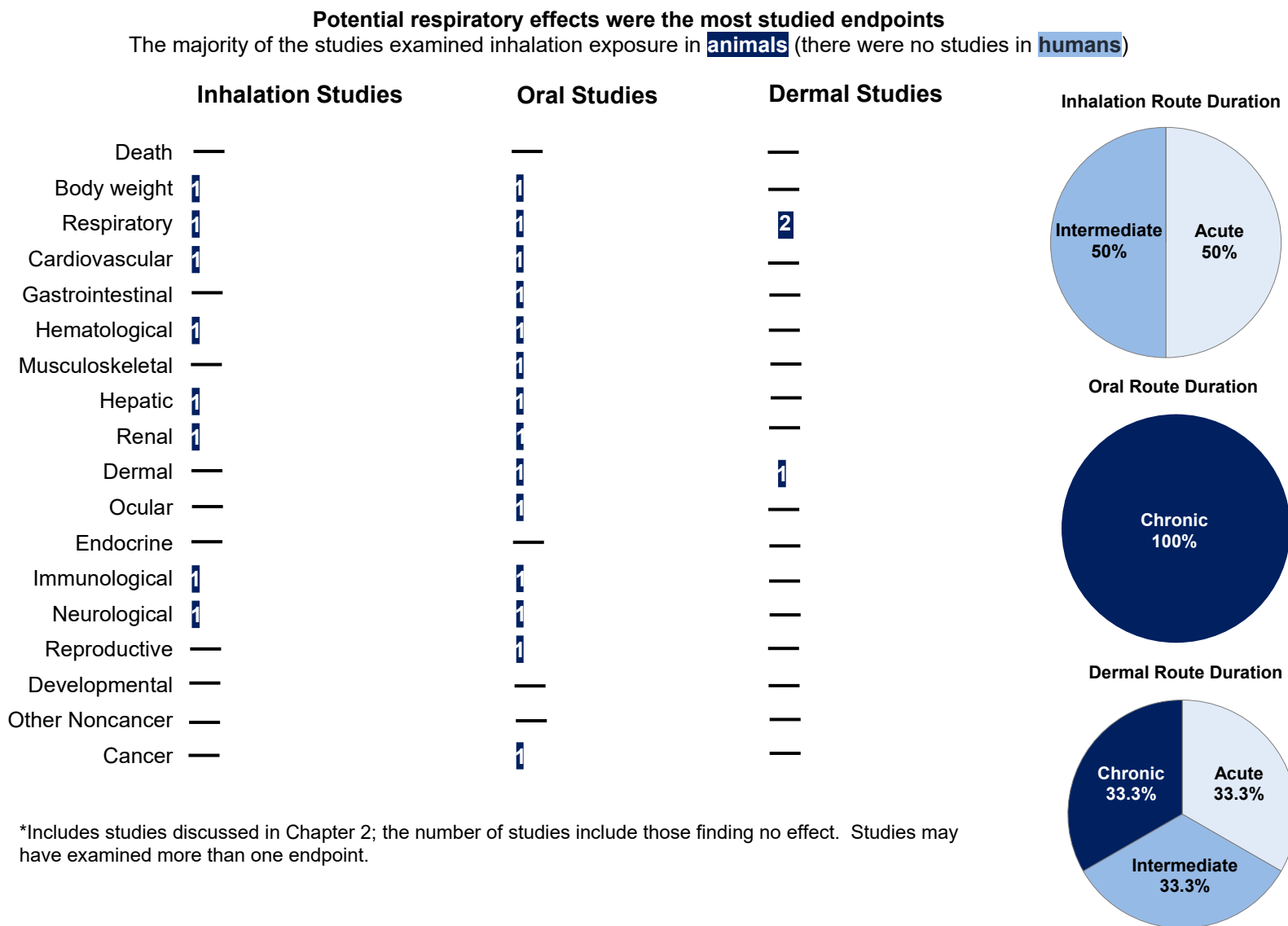
Potential respiratory and ocular effects were the most studied endpoints  
 The majority of the studies examined oral exposure in **animals** (versus **humans**)



## 6. ADEQUACY OF THE DATABASE

**Figure 6-2. Summary of Existing Health Effects Studies on 1-Methylnaphthalene by Route and Endpoint\***

## 6. ADEQUACY OF THE DATABASE

**Figure 6-3. Summary of Existing Health Effects Studies on 2-Methylnaphthalene by Route and Endpoint\***

\*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Studies may have examined more than one endpoint.

## 6. ADEQUACY OF THE DATABASE

**Acute-Duration MRLs.**

***Naphthalene.*** Provisional acute-duration inhalation and oral MRLs were derived for naphthalene.

***1-Methylnaphthalene.*** The inhalation and oral toxicity databases are inadequate to derive provisional acute-duration inhalation and oral MRLs for 1-methylnaphthalene. Comprehensive acute-duration inhalation and oral studies could provide data needed to develop these MRLs.

***2-Methylnaphthalene.*** The inhalation and oral toxicity databases are inadequate to derive provisional acute-duration inhalation and oral MRLs for 2-methylnaphthalene. Comprehensive acute-duration inhalation and oral studies could provide data needed to develop these MRLs.

**Intermediate-Duration MRLs.**

***Naphthalene.*** A provisional intermediate-duration oral MRL was derived for naphthalene. The database of intermediate-duration studies of inhaled naphthalene was not considered adequate for derivation of an MRL, because the one available study (Dodd et al. 2012) identified a NOAEL in F344 rats at the same concentration as the LOAEL for nasal lesions in an acute-duration exposure in Sprague-Dawley rats (Dodd et al. 2010). An intermediate-duration study employing lower exposure concentrations and using Sprague-Dawley rats would serve to determine whether this strain is truly more sensitive than F344 rats and may identify a POD for MRL derivation.

***1-Methylnaphthalene.*** Provisional intermediate-duration inhalation and oral MRLs were derived for 1-methylnaphthalene.

***2-Methylnaphthalene.*** A provisional intermediate-duration inhalation MRLs was derived for 2-methylnaphthalene. The database of intermediate-duration oral toxicity studies was not considered adequate to derive a provisional intermediate-duration oral MRL for 2-methylnaphthalene. The only intermediate-duration oral study of 2-methylnaphthalene was a range-finding study (described by Murata et al. 1997) with limited reporting of experimental details and results.

## 6. ADEQUACY OF THE DATABASE

**Chronic-Duration MRLs.**

***Naphthalene.*** Chronic-duration toxicity studies of oral exposure to naphthalene were not located; thus, a chronic study of oral exposure is needed to derive an MRL. The database of chronic-duration studies of inhaled naphthalene was not considered adequate for derivation of an MRL, because the available studies (Abdo et al. 2001; NTP 1992a, 2000) identified LOAELs at higher concentrations than the LOAEL for nasal lesions in an acute-duration study in Sprague-Dawley rats exposed by inhalation (Dodd et al. 2010). A chronic-duration inhalation study employing lower exposure concentrations may identify a POD for MRL derivation.

***1-Methylnaphthalene.*** A provisional chronic-duration oral MRLs was derived for 1-methylnaphthalene. No chronic-duration studies of inhaled 1-methylnaphthalene were located, precluding derivation of a provisional chronic-duration inhalation MRL. A comprehensive chronic-duration inhalation toxicity study could provide data needed to develop an MRL.

***2-Methylnaphthalene.*** A provisional chronic-duration oral MRLs was derived for 2-methylnaphthalene. No chronic-duration studies of inhaled 2-methylnaphthalene were located, precluding derivation of a provisional chronic-duration inhalation MRL. A comprehensive chronic-duration inhalation toxicity study could provide data needed to develop an MRL.

**Health Effects.**

***Reproductive.*** One- or two-generation reproductive toxicity studies evaluating reproductive performance variables in male and female animals exposed to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are not available. Results from such studies may help to better determine the potential reproductive toxicity of naphthalene.

***Developmental.*** No developmental toxicity studies involving inhalation or dermal exposure to naphthalene are available. Although naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958), oral-exposure developmental toxicity studies in animals do not provide evidence that naphthalene was fetotoxic or impaired fetal development, even at maternally toxic dose levels as high as 450 mg/kg/day (NTP 1991; Plasterer et al. 1985; Texaco 1986). Additional developmental toxicity studies in animals with inhalation or dermal exposure would determine if naphthalene exposure by these routes represents a greater developmental hazard than oral exposure.



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There were no developmental effects in the offspring of Sprague-Dawley rats administered 1-methylnaphthalene at doses up to 250 mg/kg/day for 42 days (NITE 2009). No other studies are available on the developmental toxicity of 1- or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure.

**Immunotoxicity.** There have been no comprehensive studies of the immunotoxicity of naphthalene in humans exposed by the inhalation, oral, or dermal routes. The animal oral exposure data indicate that naphthalene did not affect humoral or cell-mediated immunity in mice (Shopp et al. 1984). Minor effects on the thymus and spleen were noted in mice and rats (NTP 1980b; Shopp et al. 1984), but in no case were animals of both sexes affected. Because there are few data pertaining to the immunotoxicity of naphthalene, a battery of *in vitro/in vivo* screening assays of immune function may be useful to determine whether more detailed and longer-term studies are needed.

No studies are available on the immunotoxicity of 1- or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure. As with naphthalene, a battery of *in vitro/in vivo* screening assays of immune function may be useful to determine whether more detailed and longer-term studies are needed.

**Neurotoxicity.** The direct effects of naphthalene on the central nervous system have not been investigated in either humans or animals. Persistent clinical signs of toxicity (lethargy and prone position) were seen in pregnant rats given naphthalene by gavage during gestation (NTP 1991), and transient clinical signs were seen in rats and mice exposed orally for 13 weeks (NTP 1980a, 1980b). In rabbits, hypoactivity and dyspnea were also noted at 200 mg/kg/day (Texaco 1985d, 1986). Additional studies involving batteries of neurological endpoints following oral and/or inhalation exposure are needed to better determine the potential neurotoxicity of naphthalene.

No human studies on the neurotoxicity of 1- or 2-methylnaphthalene following inhalation, oral, or dermal exposure were located. An acute animal study found decreased pain sensitivity following exposure to 1- and 2-methylnaphthalene, but no effects on rotarod performance (Korsak et al. 1998). The biological significance of these findings is uncertain. A combined repeated-dose, reproduction and developmental toxicity study that included a FOB examination as well as

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detailed open field observations found no neurotoxic effects in animals administered up to 250 mg/kg/day 1-methylnaphthalene for approximately 42 days (throughout mating and breeding) (NITE 2009). Additional intermediate- and chronic-duration inhalation and acute- and chronic-duration oral studies for 1-methylnaphthalene, and oral studies of all durations for 2-methylnaphthalene involving batteries of neurological endpoints may help to better determine the potential neurotoxicity of the methylnaphthalenes.

**Respiratory.** The respiratory effects of naphthalene have been extensively studied. However, available intermediate- and chronic-duration inhalation studies (Abdo et al. 2001; Dodd et al. 2012; NTP 1992a, 2000) did not use the most sensitive rat strain (Sprague-Dawley) and did not use low enough exposure concentrations to identify NOAELs for respiratory effects. Additional studies using lower concentrations might enable the development of a chronic-duration inhalation MRL.

No studies on the respiratory effects of 1- or 2-methylnaphthalene in humans following inhalation, oral, or dermal exposure were located. Limited animal studies provide evidence for respiratory effects after exposure to 1- and 2-methylnaphthalene. Studies on the respiratory effects from 2-methylnaphthalene inhalation of any duration are needed. Studies on respiratory effects of 1- and 2-methylnaphthalene oral exposure include chronic-duration studies by Murata et al. (1993, 1997). Oral studies of acute and intermediate durations are needed.

**Hepatic.** The liver does not appear to be a sensitive target of naphthalene exposure. Liver effects of 1- and 2-methylnaphthalene are well-studied.

**Hematological.** Hematological changes are not a sensitive effect of exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene in laboratory rodents. Hemolytic effects of naphthalene exposure in humans, particularly those with G6PDH deficiency, are well-known. The mechanism(s) underlying differences in species susceptibility to hemolytic effects of naphthalene has not been established. Research on the mechanism(s) for this difference could be beneficial, especially if it provides a basis for predicting the potential for hematological effects of methylnaphthalenes in humans.

**Epidemiology and Human Dosimetry Studies.** A small number of reports have equivocally suggested that workers exposed to naphthalene for long periods of time may have an elevated risk of

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cataract development (Ghetti and Mariani 1956; Lezenius 1902). This information, coupled with the cataractogenic effects of naphthalene in orally exposed rats (Kojima 1992; Xu et al. 1992b; Yamauchi et al. 1986) and rabbits (Rossa and Pau 1988; Srivastava and Nath 1969; van Heyningen and Pirie 1967) in acute- and intermediate-duration studies, suggests that studies of occupationally-exposed workers would help to determine naphthalene's potential to produce ocular toxicity in humans. Currently, no cohort mortality or morbidity studies or case-control studies examining possible associations between naphthalene exposure and increased risk of cancer are available. If human populations that are specifically and repeatedly exposed to naphthalene can be identified, epidemiological studies of these populations may help to better assess the potential carcinogenicity of naphthalene.

No epidemiological or human dosimetry studies on the effects of 1- or 2-methylnaphthalene were located. Exposure to these compounds, particularly through dermal contact or inhalation, can occur in workplaces where the compounds are produced or used. Populations living near hazardous waste sites can potentially be exposed by the oral, inhalation, and dermal routes. If an appropriate population can be identified, it may be helpful to conduct epidemiological studies to determine if there are toxic effects (particularly on the lungs) resulting from exposure to methylnaphthalenes.

**Biomarkers of Exposure and Effect.** There are methods to determine the presence of naphthalene in adipose tissue. Metabolites of naphthalene, such as naphthols and naphthoquinones, have been measured in urine. 1-Naphthol is present in the urine of workers occupationally exposed to naphthalene. Maximum 1-naphthol levels occurred immediately after the end of the work period and in some cases had returned to baseline levels 8 hours later (Bieniek 1994). Techniques have been developed to measure cysteinyl adducts formed from reactions of hemoglobin and albumin with reactive metabolites of naphthalene (Troester et al. 2002; Waidyanatha et al. 2002). The adducts are expected to be useful in estimating internal doses of these metabolites, and with further development, they may become useful biomarkers of exposure.

There are no known specific biomarkers of effects for naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. Hemolytic anemia has been frequently associated with human exposure to naphthalene, but may also be the result of exposure to other chemicals. Pulmonary alveolar proteinosis in mice has been associated with chronic oral exposure to 1- and 2-methylnaphthalene. The condition has been described in humans but has not been associated with human exposure to 1- or 2-methylnaphthalene. These effects (hemolytic anemia or pulmonary alveolar proteinosis) are not specific biomarkers of effect for naphthalene or methylnaphthalenes. Identification of specific biomarkers of effect such as particular

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protein adducts in naphthalene-affected target tissues in animals may be useful to test whether similar biomarkers of effect may exist in naphthalene-exposed human populations.

**Absorption, Distribution, Metabolism, and Excretion.** There are hybrid computational fluid dynamics-PBPK models that predict nasal tissue concentrations of naphthalene metabolites in rats and humans exposed by inhalation (Campbell et al. 2014; Kapraun et al. 2020). The calibration of the Kapraun et al. (2020) model was limited to observations of blood naphthalene levels following dermal exposures to JP-8. While the calibrated model performed well for predicting observed blood naphthalene levels, the predicted blood naphthalene levels were relatively insensitive to nasal cavity parameter values and highly sensitive to dermal and systemic parameters. Therefore, the model could perform well for predicting blood naphthalene following dermal exposures but perform poorly at predicting nasal cavity doses following inhalation. Additional research to directly evaluate the Campbell et al. (2014) or Kapraun et al. (2020) models for predicting nasal cavity doses in human would provide confidence in the model and enable its application to MRL derivation.

Adequate information is available on the absorption, distribution, and excretion of 1- and 2-methylnaphthalene. Data on the metabolism of 1-methylnaphthalene are limited to an *in vitro* study of human and rat liver microsomes. However, the metabolism of the related compound 2-methylnaphthalene is well-studied and is expected to be similar to that of 1-methylnaphthalene based on structural similarity and similar metabolism *in vitro*.

**Comparative Toxicokinetics.** The comparative toxicokinetics of naphthalene in rodent and primate nasal and lung tissues has been well studied. Limited information is available on the comparative toxicokinetics of 1-methylnaphthalene. Studies identifying metabolites in rodents and urinary metabolites in occupationally-exposed humans would be useful.

**Children's Susceptibility.** Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in the Developmental Toxicity subsection above.

Cases of naphthalene-induced hemolytic anemia in children have been frequently reported (Owa 1989; Owa et al. 1993; Santucci and Shah 2000; Valaes et al. 1963). Newborns and infants are thought to be more susceptible than older people because hepatic enzymes involved in conjugation and excretion of naphthalene metabolites are not well developed after birth, and children with genetically determined

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G6PD deficiency are thought to be especially susceptible to chemically induced hemolytic anemia (EPA 1987). There are no studies that have specifically examined the influence of age on naphthalene toxicokinetic capabilities in humans. Although the availability of such studies may increase the understanding of the specific physiological basis for the apparent susceptibility of newborns, they are unlikely to be conducted. Experiments examining the most sensitive targets in animals (see below) are likely surrogates.

Neonatal mice (7 days old) appear to be more susceptible than adult mice to lung injury induced by acute i.p. injection of naphthalene (Fanucchi et al. 1997). The mechanistic basis of this difference is currently unknown, but does not appear to be explained by differences in CYP catalytic capabilities to produce epoxide metabolites, since CYP activities were 2.5 times lower in neonates than in adults. Downstream metabolic capabilities, however, were not examined in this study. Comparison of neonatal and adult tissues in these metabolic steps may help to explain this apparent susceptibility of neonatal mice. Based on findings that *in utero* exposure to other CYP-bioactivated chemicals caused club cell tumors in adult offspring, Fanucchi et al. (1997) postulated that naphthalene exposure during the neonatal period may lead to loss of regulatory mechanisms resulting in club cell proliferation and tumor formation in adult animals. Direct evidence for naphthalene in support of this hypothesis, however, is not available. Additional research may help to determine whether or not *in utero* or neonatal naphthalene exposure will cause increased incidence of lung tumors in adult mice.

**Physical and Chemical Properties.** The physical and chemical properties of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene that are required to evaluate its behavior in the environment have been determined (see Table 4-2).

**Production, Import/Export, Use, Release, and Disposal.** Naphthalene producers, production locations and volumes, uses, and releases are well documented (EPA 2022a; TRI21 2023). Disposal practices are reported generally, and naphthalene-specific recommendations were not located. Disposal of naphthalene-containing wastes are regulated by EPA, and major spills or accidental releases must be reported to EPA. Data regarding production volume of 1- or 2-methylnaphthalene were well documented (EPA 2022a); however, no data were located on releases, and disposal practices. This information would be helpful to predict the potential for human exposure to these chemicals.

**Environmental Fate.** Existing information indicates that most naphthalene and methylnaphthalene is released to the atmosphere and undergoes rapid reaction with hydroxyl and nitrate (Atkinson et al. 1987;

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Phousongphouang and Arey 2002). Available data indicate that volatilization and biodegradation are important removal processes from water and soil (EPA 1982; Howard 1989; Tabak et al. 1981; Wakeham et al. 1983). Additional studies on the rates of volatilization, degradation, and transport in groundwater would be helpful in assessing potential human exposure in the vicinity of industrial sources and chemical waste sites. Data describing the volatilization, biodegradation, and transport of 1- and 2-methylnaphthalene would be useful in predicting the potential for human exposure.

**Bioavailability from Environmental Media.** No studies were located on the bioavailability of naphthalene in various environmental media. Available toxicity data indicate that naphthalene present in contaminated air and ingested in drinking water or soil is probably absorbed. Confirmatory, quantitative data would be useful. Data on infants indicate that toxicologically significant amounts of naphthalene may be absorbed dermally from residues left on stored clothing, especially under circumstances where baby oil was used on the infants' skin (Schafer 1951). Quantitative studies of the dermal absorption of naphthalene from water and soil would be useful in determining potential exposure for populations living near hazardous waste sites.

No data were located pertaining to the bioavailability of 1- or 2-methylnaphthalene in environmental media. Studies in laboratory animals to assess the absorption of this compound via the oral, inhalation, and dermal routes would be useful before bioavailability from each medium can be reasonably estimated.

**Food Chain Bioaccumulation.** Naphthalene is often readily degraded in the environment and is easily metabolized by a wide variety of organisms. Studies indicate that although naphthalene may bioconcentrate to some degree for brief periods, it will not significantly bioaccumulate in organisms due to metabolism, and thus, is unlikely to biomagnify through the food chain (Howard 1989; Thomann 1989). Naphthalene has been found to be present in fish and shellfish (Bender and Huggett 1989; Miles and Roster 1999; Neff and Burns 1996; WQP 2023; Zitko et al. 1998). It has also been located in the flesh of fresh fruits and vegetables (Gomez et al. 1993; Kipopoulou et al. 1999; Seitz et al. 1999). Other food monitoring data were from products bought outside of the United States. Because cooking and processing methods, packaging, and production site can impact naphthalene levels in food, additional data on naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene concentrations in foods and processed foods commercially available would be useful to assess the extent of human exposure via the food chain.

**Exposure Levels in Environmental Media.** Reliable monitoring data for the levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in contaminated media at hazardous waste sites are

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needed so that the information obtained on levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in the environment can be used in combination with the known body burden of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

The concentrations of naphthalene in the air, water, and soil have been documented. In addition, indoor air levels have been measured (Chuang et al. 1991; Jia and Batterman 2011; Wheeler et al. 2014; Wilson et al. 1989). Additional information regarding exposure levels of 1- and 2-methylnaphthalene in environmental media would be useful for deriving exposure estimates for the general population.

**Exposure Levels in Humans.** NHANES biomonitoring data from 2015 to 2016 in the U.S. population and the U.S. smoking adult population were available for two urinary metabolites of naphthalene, 1-hydroxynaphthalene and 2-hydroxynaphthalene. Urinary metabolites are sensitive to recent exposures, and 1-hydroxynaphthalene is also a metabolite of carbaryl and may not be a specific indicator of naphthalene exposure. Other biomonitoring studies that reflect long-term exposure and measure naphthalene and methylnaphthalenes directly would be useful. A national survey of adipose tissue samples indicates that about 40% of the study subjects had measurable levels of naphthalene (EPA 1986b). More recent monitoring data of blood (Hao et al. 2020) and breastmilk (Wheeler et al. 2014) had small sample sizes. More large-scale biomonitoring data would be useful to see how body burdens of naphthalene have changed compared to the NHATS study, and how common detections in blood and breastmilk are. Further, data on the effect of cigarette filters on naphthalene uptake by the adipose tissues would be useful.

No data on exposure levels in humans were located for 1- or 2-methylnaphthalene. This information would be useful to determine whether any significant exposure to these chemicals occurs.

This information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** No monitoring studies have been performed to investigate the exposure to, and the body burden of, naphthalene in children. No studies are available on the dermal absorption of naphthalene in infants and toddlers due to activities such as crawling, which will result in contact with the floor (carpet) and soil or from exposure to clothes stored with mothballs. Since naphthalene is likely to be adsorbed to these materials, more information would allow the estimation of a child's exposure to naphthalene to be more rigorously determined. Naphthalene has been detected in house dust (Chuang et

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al. 1995). No studies on amounts of naphthalene present in foods eaten by children are available. Such studies may help to identify childhood-specific means of decreasing exposure to naphthalene.

### 6.3 ONGOING STUDIES

There are several ongoing studies evaluating the mechanisms of naphthalene toxicity to the lung (Table 6-1).

**Table 6-1. Ongoing Studies on Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

Investigator	Affiliation	Research description	Sponsor
Begley, Thomas	State University of New York at Albany	Role of tRNA epitranscriptome in response to naphthalene in environmental tobacco smoke	NIEHS
Ding, Xinxin	University of Arizona	Metabolic mechanisms of naphthalene lung toxicity	NIEHS
Hannon, Sarrah	University of Arizona	DNA adducts induced by naphthalene in mouse and in human firefighters	NIEHS
Que, Jianwen	Columbia University Health Sciences	Mechanisms of airway regeneration after naphthalene injury	NHLBI
Wong, Irene Gar-Ling	Harvard Medical School	Mechanisms of airway regeneration after naphthalene injury	NHLBI

DNA = deoxyribonucleic acid; NIEHS = National Institute of Environmental Health Sciences; NHLBI = National Heart, Lung, and Blood Institute; tRNA = transfer ribonucleic acid

Source: RePORTER 2023



## CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

**Table 7-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

Agency	Description	Information	Reference
<b>Air</b>			
EPA	RfC Naphthalene	$3 \times 10^{-3}$ mg/m <sup>3</sup> (0.0006 ppm)	<a href="#">IRIS 1998</a>
WHO	Indoor air quality guidelines Naphthalene	0.01 mg/m <sup>3</sup> (0.002 ppm) annual average	<a href="#">WHO 2010</a>
<b>Water &amp; Food</b>			
EPA	Drinking water standards and health advisories Naphthalene		<a href="#">EPA 2018a</a>
	1-Day health advisory (10-kg child)	0.5 mg/L	
	10-Day health advisory (10-kg child)	0.5 mg/L	
	DWEL	0.7 mg/L	
	Lifetime health advisory	0.1 mg/L	
	10 <sup>-4</sup> Cancer risk	No data	
	National primary drinking water regulations	Not listed	<a href="#">EPA 2009b</a>
	Chronic RfD (IRIS)		
	Naphthalene	$2 \times 10^{-2}$ mg/kg/day	<a href="#">IRIS 1998</a>
	2-Methylnaphthalene	$4 \times 10^{-3}$ mg/kg/day	<a href="#">IRIS 2003</a>
	Provisional peer reviewed toxicity values		
	2-Methylnaphthalene		
	Subchronic provisional RfD	$4 \times 10^{-3}$ mg/kg/day	<a href="#">EPA 2007b</a>

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**Table 7-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

Agency	Description	Information	Reference
	Human health risk assessment in support of registration review (OPP)		
	Naphthalene		<a href="#">EPA 2018b</a>
	Chronic RfD	0.1 mg/kg/day	
	Acute RfD	0.4 mg/kg/day	
WHO	Drinking water quality guidelines	No data	<a href="#">WHO 2017</a>
FDA	Substances added to food <sup>a</sup>		
	1-Methylnaphthalene	FEMA GRAS	<a href="#">FDA 2022b</a>
<b>Cancer</b>			
HHS	Carcinogenicity classification		
	Naphthalene	Reasonably anticipated to be a human carcinogen	<a href="#">NTP 2021</a>
EPA	Carcinogenicity classification		
	Naphthalene	Group C <sup>b</sup>	<a href="#">IRIS 1998</a>
	Provisional peer reviewed toxicity values		
	1-Methylnaphthalene		
	Provisional oral slope factor	2.9x10 <sup>-2</sup> mg/kg/day	<a href="#">EPA 2008</a>
IARC	Carcinogenicity classification		
	Naphthalene	Group 2B <sup>c</sup>	<a href="#">IARC 2002</a>
<b>Occupational</b>			
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		
	Naphthalene	10 ppm (50 mg/m <sup>3</sup> )	OSHA <a href="#">2020a</a> , <a href="#">2020b</a> , <a href="#">2020c</a>
NIOSH	REL and IDLH		
	Naphthalene		
	REL TWA (up to 10-hour TWA)	10 ppm (50 mg/m <sup>3</sup> )	<a href="#">NIOSH 2019</a>
	REL ST (15-minute TWA)	15 ppm (75 mg/m <sup>3</sup> )	
	IDLH	250 ppm	<a href="#">NIOSH 1994</a>
<b>Emergency Criteria</b>			
EPA	AEGLs-air	No data	<a href="#">EPA 2018c</a>
DOE	PACs-air		<a href="#">DOE 2018a</a>
	Naphthalene		
	PAC-1 <sup>d</sup>	15 ppm	
	PAC-2 <sup>d</sup>	83 ppm	
	PAC-3 <sup>d</sup>	500 ppm	
	1-Methylnaphthalene		
	PAC-1 <sup>d</sup>	20 mg/m <sup>3</sup>	
	PAC-2 <sup>d</sup>	61 mg/m <sup>3</sup>	
	PAC-3 <sup>d</sup>	360 mg/m <sup>3</sup>	

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**Table 7-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene**

Agency	Description	Information	Reference
	2-Methylnaphthalene		
	PAC-1 <sup>d</sup>	9 mg/m <sup>3</sup>	
	PAC-2 <sup>d</sup>	54 mg/m <sup>3</sup>	
	PAC-3 <sup>d</sup>	320 mg/m <sup>3</sup>	

<sup>a</sup>The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS."

<sup>b</sup>Group C: possible human carcinogen.

<sup>c</sup>Group 2B: possibly carcinogenic to humans.

<sup>d</sup>Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FAO = Food and Agriculture Organization; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OPP = Office of Pesticide Programs; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RFC = inhalation reference concentration; RfD = oral reference dose; ST = short-term; TWA = time-weighted average; WHO = World Health Organization

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## APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

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

## APPENDIX A

## MINIMAL RISK LEVEL (MRL) WORKSHEET

**Chemical Name:** Naphthalene  
**CAS Numbers:** 91-20-3  
**Date:** May 2024  
**Profile Status:** Draft for Public Comment  
**Route:** Inhalation  
**Duration:** Acute  
**Provisional MRL:**  $6 \times 10^{-5}$  ppm ( $3 \times 10^{-4}$  mg/m<sup>3</sup>)  
**Critical Effect:** Nasal olfactory epithelial necrosis  
**References:** Dodd et al. 2010  
**Point of Departure:** BMCL<sub>HEC</sub> of 0.0017 ppm  
**Uncertainty Factor:** 30  
**LSE Graph Key:** 4  
**Species:** Rat

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

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

**Table A-1. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Inhalation Exposure to Naphthalene<sup>a</sup>**

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

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**Table A-1. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Inhalation Exposure to Naphthalene<sup>a</sup>**

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

<sup>a</sup>Green shading shows principal study for MRL derivation.

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

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

**Summary of the Principal Study:**

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

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

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

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

Source: Dodd et al. 2010

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

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

Model	BMC <sub>10</sub> <sup>a</sup> (ppm)	BMCL <sub>10</sub> <sup>a</sup> (ppm)	p-Value <sup>b</sup>	AIC	Scaled residuals <sup>c</sup>	
					Dose below BMC	Dose above BMC
Dichotomous Hill	0.062	0.017	0.87	51.00	-0.10	0.27
Gamma <sup>d</sup>	0.064	0.037	0.99	46.85	-0.24	0.31
<b>Log-Logistic<sup>e,f</sup></b>	<b>0.062</b>	<b>0.017</b>	<b>0.96</b>	<b>49.00</b>	<b>-0.10</b>	<b>0.27</b>
Multistage Degree 5 <sup>g</sup>	0.064	0.037	0.97	48.85	-0.24	0.31



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

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

<sup>a</sup>BMC and BMCLs values for models that do not provide adequate fit or yield BMCLs more than 10-fold lower than the lowest nonzero exposure concentration are not included in this table.

<sup>b</sup>Values <0.1 fail to meet conventional  $\chi^2$  goodness-of-fit criteria.

<sup>c</sup>Scaled residuals at doses immediately below and above the BMC.

<sup>d</sup>Power restricted to  $\geq 1$ .

<sup>e</sup>Slope restricted to  $\geq 1$ .

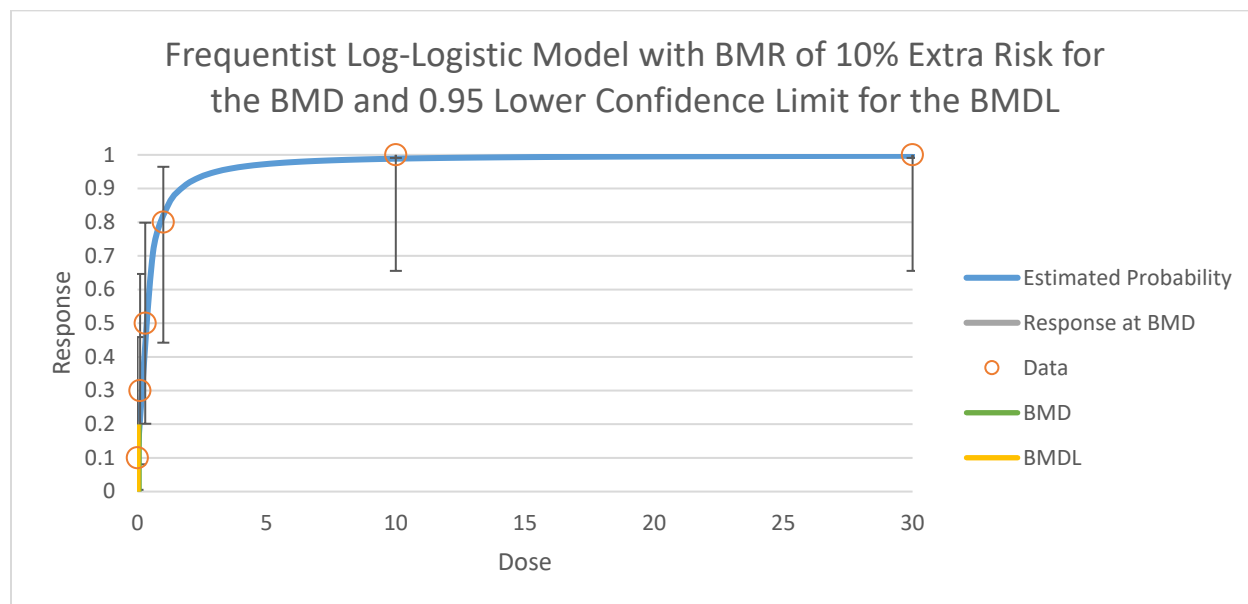
<sup>f</sup>All models provided an adequate fit to the data. BMCLs were not sufficiently close (differed by >3-fold). Therefore, the model with the lowest BMCL was selected (Log-Logistic).

<sup>g</sup>Betas restricted to  $\geq 0$ .

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

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



### Calculations

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

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

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

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

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

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where:

$V_{Ea}$  = ventilation rate for male and female Sprague-Dawley rats = 0.413 L/minute (EPA 2012)

$SA_a$  = surface area of the extrathoracic region in rats = 15 cm<sup>2</sup> (EPA 1994)

$V_{Eh}$  = ventilation rate for humans = 13.8 L/minute (EPA 1994)

$SA_h$  = surface area of the extrathoracic region in humans = 200 cm<sup>2</sup> (EPA 1994)

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

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

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

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

This results in the following MRL:

$$MRL = \frac{BMCL_{HEC}}{UFs} = \frac{0.0017 \text{ ppm}}{30} \approx 0.00006 \text{ ppm } (6 \times 10^{-5} \text{ ppm})$$

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

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

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

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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

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

## APPENDIX A

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

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

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

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

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

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

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

**Table A-5. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Oral Exposure to Naphthalene<sup>a</sup>**

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



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**Table A-5. Summary of Lowest NOAEL and LOAEL Values for Sensitive Targets of Acute Oral Exposure to Naphthalene<sup>a</sup>**

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

<sup>a</sup>Green shading shows principal study for MRL derivation.

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

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

**Summary of the Principal Study:**

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

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

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

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

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

### ***Calculations***

***Adjustment for Intermittent Exposure:*** Not applicable.

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

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

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$$\begin{aligned}\text{MRL} &= \text{LOAEL} \div \text{UF} \\ &= 50 \text{ mg/kg/day} \div (10 \times 10 \times 3) = 0.16 \text{ mg/kg/day, rounded to } 0.2 \text{ mg/kg/day}\end{aligned}$$

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

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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



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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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## MINIMAL RISK LEVEL (MRL) WORKSHEET

**Chemical Name:** 1-Methylnaphthalene  
**CAS Numbers:** 90-12-0  
**Date:** May 2024  
**Profile Status:** Draft for Public Comment  
**Route:** Inhalation  
**Duration:** Intermediate  
**Provisional MRL:**  $9 \times 10^{-5}$  ppm ( $5 \times 10^{-4}$  mg/m<sup>3</sup>)  
**Critical Effect:** Nasal mucous cell hyperplasia  
**Reference:** Kim et al. 2020  
**Point of Departure:** BMCL of 0.06 ppm  
(BMCL<sub>HEC</sub> of 0.0027 ppm)  
**Uncertainty Factor:** 30  
**LSE Graph Key:** 4  
**Species:** Rat

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

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

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

**Summary of the Principal Study:**

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

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

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

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

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

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

**Bold** indicates dataset selected for benchmark dose modeling.

Source: Kim et al. 2020

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

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

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

Model	BMC <sub>10</sub> <sup>a</sup> (ppm)	BMCL <sub>10</sub> <sup>a</sup> (ppm)	p-Value <sup>b</sup>	AIC	Scaled residuals <sup>c</sup>	
					Dose below BMC	Dose above BMC
<b>Dichotomous Hill<sup>d</sup></b>	<b>0.35</b>	<b>0.06</b>	<b>0.9993</b>	<b>17.46</b>	<b>-0.0004</b>	<b>-0.0005</b>
Gamma <sup>e</sup>			1.0000	17.46	-0.0007	-0.0007
Log-Logistic <sup>f</sup>	0.35	0.06	0.9993	17.46	-0.0004	-0.0004
Multistage Degree 3 <sup>g</sup>			0.9969	19.46	-0.0004	-0.0004
Multistage Degree 2 <sup>g</sup>			1.0000	17.46	-0.0004	-0.0004
Multistage Degree 1 <sup>g</sup>			0.9825	15.74	-0.0004	-0.0004
Weibull <sup>e</sup>			0.9967	17.47	-0.0004	-0.0004
Logistic	0.27	0.15	0.7612	17.41	-0.9332	0.5430
Log-Probit			1.0000	17.46	-0.0004	-4.5x10 <sup>-10</sup>
Probit	0.46	0.30	0.2916	21.68	-1.5295	0.83

<sup>a</sup>BMC and BMCLs values for models that do not provide adequate fit or yield BMCLs more than 10-fold lower than the lowest nonzero exposure concentration are not included in this table.

<sup>b</sup>Values <0.1 fail to meet conventional  $\chi^2$  goodness-of-fit criteria.

<sup>c</sup>Scaled residuals at doses immediately below and above the BMC.

<sup>d</sup>All models provided an adequate fit to the data. BMCLs were not sufficiently close (differed by >3-fold). Therefore, the model with the lowest BMCL was selected (Dichotomous Hill).

<sup>e</sup>Power restricted to  $\geq 1$ .

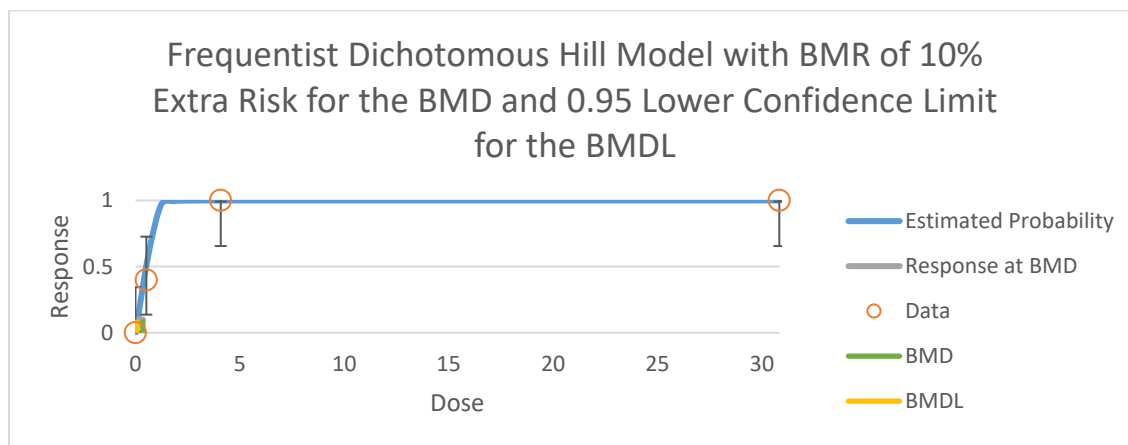
<sup>f</sup>Slope restricted to  $\geq 1$ .

<sup>g</sup>Betas restricted to  $\geq 0$ .

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

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



### Calculations

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

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

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

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

where:

$V_{Ea}$  = ventilation rate for male F344 rats = 0.254 L/minute (EPA 2012)

$SA_a$  = surface area of the extrathoracic region in rats = 15 cm<sup>2</sup> (EPA 1994)

$V_{Eh}$  = ventilation rate for humans = 13.8 L/minute (EPA 1994)

$SA_h$  = surface area of the extrathoracic region in humans = 200 cm<sup>2</sup> (EPA 1994)

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

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

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

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

$$MRL = BMCL_{HEC} \div UFs$$

$$MRL = 0.0027 \text{ ppm} \div (3 \times 10) = 0.00009 \text{ ppm} (9 \times 10^{-5} \text{ ppm})$$

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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



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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

**Summary of the Principal Study:**

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

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

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

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

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

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

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

**Bold** indicates datasets selected for benchmark dose modeling.

Source: NITE 2009

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

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

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

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

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

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

Model	BMD <sub>1SD</sub> <sup>a</sup> (mg/kg/day)	BMDL <sub>1SD</sub> <sup>a</sup> (mg/kg/day)	p-Value <sup>b</sup>	AIC	Scaled residuals <sup>c</sup>	
					Dose below BMD	Dose above BMD
Linear	75.67	51.57	0.29	4.05	-0.9530	0.3615

<sup>a</sup>BMD and BMDL values for models that do not provide adequate fit or yield BMDs more than 10-fold lower than the lowest nonzero dose are not included in this table.

<sup>b</sup>Values <0.1 fail to meet conventional  $\chi^2$  goodness-of-fit criteria.

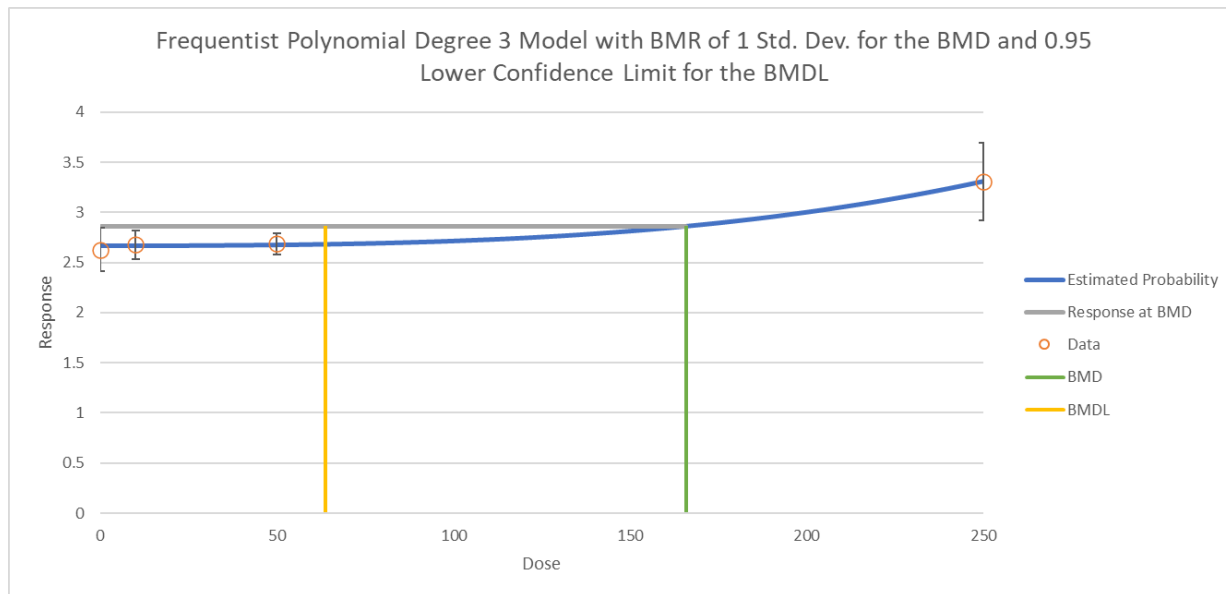
<sup>c</sup>Scaled residuals at doses immediately below and above the BMD.

<sup>d</sup>Restricted model.

<sup>e</sup>Recommended model (lowest AIC). The constant variance model did not provide an adequate fit to the data (Test 2; p-value < 0.1); however, the nonconstant variance model did provide an adequate fit. With the nonconstant variance model applied, all models except for the Exponential 5 and Hill models, provided adequate fit to the means. Of these models, the BMDs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Polynomial 3-degree model).

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

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



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

Model	BMD <sub>1SD</sub> <sup>a</sup> (mg/kg/day)	BMDL <sub>1SD</sub> <sup>a</sup> (mg/kg/day)	p-Value <sup>b</sup>	AIC	Scaled residuals <sup>c</sup>	
					Dose below BMD	Dose above BMD
Exponential (model 2) <sup>d</sup>	152.66	124.78	0.45	9.18	-0.51	0.16
Exponential (model 3) <sup>d</sup>	235.64	109.65	0.68	9.74	0.14	-2.6x10 <sup>-5</sup>
Exponential (model 4) <sup>d</sup>	150.40	92.52	0.19	11.28	-0.54	0.19
Exponential (model 5) <sup>d</sup>			NA	11.74	0.14	0.0008
Hill <sup>d</sup>			NA	11.74	0.14	-0.001
<b>Polynomial (3-degree)<sup>d,e</sup></b>	<b>212.35</b>	<b>108.64</b>	<b>0.98</b>	<b>5.78</b>	<b>0.11</b>	<b>-0.001</b>
Polynomial (2-degree) <sup>d</sup>	194.57	105.04	0.84	7.93	0.00	0.007
Power <sup>d</sup>	245.04	107.35	0.68	9.74	0.14	-0.002
Linear	150.34	92.29	0.43	9.27	-0.54	0.18

<sup>a</sup>BMD and BMDL values for models that do not provide adequate fit or yield BMDLs more than 10-fold lower than the lowest nonzero dose are not included in this table.

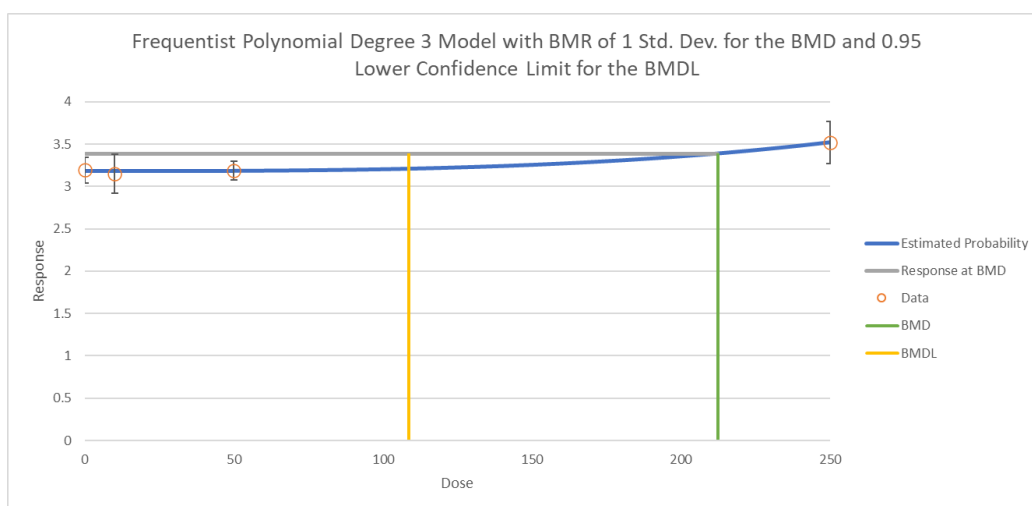
<sup>b</sup>Values <0.1 fail to meet conventional  $\chi^2$  goodness-of-fit criteria.

<sup>c</sup>Scaled residuals at doses immediately below and above the BMD.

<sup>d</sup>Restricted model.

<sup>e</sup>Recommended model (lowest AIC). The constant variance model did not provide an adequate fit to the data (Test 2; p-value < 0.1); however, the nonconstant variance model did provide an adequate fit. With the nonconstant variance model applied, all models except for the Exponential 5 and Hill models, provided adequate fit to the means. Of these models, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Polynomial 3-degree model).

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

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

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**Calculations**

**Adjustment for Intermittent Exposure:** Not applicable.

**Uncertainty Factor:** The BMDL<sub>1SD</sub> of 64 mg/kg/day was divided by a composite UF of 100:

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

This results in the following MRL:

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

**Summary of the Principal Study:**

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

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

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

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

**Table A-11. Incidences<sup>a</sup> of Pulmonary Alveolar Proteinosis in Mice Exposed to 1-Methylnaphthalene in the Diet for 81 Weeks**

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

<sup>a</sup>Number affected/number examined (percent).

Source: Murata et al. 1993

**Selection of the Point of Departure for the MRL:** The lowest exposure level (71.6 mg/kg/day) was a LOAEL for increased incidence of pulmonary alveolar proteinosis in male and female mice. The incidences of this lesion in male and female mice (see Table A-11) were subjected to BMD modeling to determine a POD for the provisional chronic-duration oral MRL. The data were fit to all available dichotomous models in EPA's BMDS (version 3.2.0.1) using BMRs of 10% and 5% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMD (BMDL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. None of the models provided adequate fit for either the male or female data. Therefore, the LOAEL of 71.6 mg/kg/day was selected as the POD for the derivation of the provisional chronic-duration oral MRL.

**Calculations:** Not applicable

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

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

This results in the following MRL:

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

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



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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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## MINIMAL RISK LEVEL (MRL) WORKSHEET

**Chemical Name:** 2-Methylnaphthalene  
**CAS Numbers:** 91-57-6  
**Date:** May 2024  
**Profile Status:** Draft for Public Comment  
**Route:** Inhalation  
**Duration:** Intermediate  
**Provisional MRL:**  $3 \times 10^{-4}$  ppm (0.002 mg/m<sup>3</sup>)  
**Critical Effect:** Bronchial goblet cell metaplasia  
**Reference:** Świercz et al. (2011)  
**Point of Departure:** LOAEL<sub>HEC</sub> of 0.081 ppm  
**Uncertainty Factor:** 300  
**LSE Graph Key:** 5  
**Species:** Rat

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

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

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

**Summary of the Principal Study:**

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

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

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

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

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

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

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

Source: Świercz et al. 2011

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

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

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

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

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

where:

$[V_E]_a$  = minute volume for rats = 0.141 L/min

$SA_{TB,a}$  = TB surface area for rats = 22.5 cm<sup>2</sup>

$e^{-(SA_{et}/V_E)_a}$  = Fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in rats = 0.899

$[V_E]_h$  = minute volume for humans = 13.8 L/min

$SA_{TB,h}$  = TB surface area for humans = 3200 cm<sup>2</sup>

$e^{-(SA_{et}/V_E)_h}$  = Fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in humans = 0.986

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

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

**Uncertainty Factor:** The LOAEL<sub>HEC</sub> is divided by a total uncertainty factor of 300:

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

$$\begin{aligned} \text{MRL} &= \text{LOAEL}_{HEC} \div \text{uncertainty factors} \\ &= 0.081 \text{ ppm} \div (3 \times 10 \times 10) \approx 0.0003 \text{ ppm} (3 \times 10^{-4} \text{ ppm}) \end{aligned}$$

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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



## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

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

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

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

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

**Summary of the Principal Study:**

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

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

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

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

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

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

**Table A-13. Incidences<sup>a</sup> of Pulmonary Alveolar Proteinosis in B6C3F1 Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks**

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

<sup>a</sup>Incidence reported as number affected/number examined.

<sup>b</sup>Statistically significantly different from control at  $p < 0.05$  as reported by study authors.

Source: Murata et al. 1997

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

Adequate model fit was judged by four criteria: goodness-of-fit statistics ( $p$ -value  $> 0.1$ ), visual inspection of the dose-response curve, a 95% confidence limit on the BMD (BMDL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within  $\pm 2$  units at the data point (except the control) closest to the predefined BMR. Among the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was  $> 3$ -fold; otherwise, the BMDL from the model with the lowest AIC was chosen.

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

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

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

Model	BMD <sub>05</sub> <sup>a</sup> (mg/kg/day)	BMDL <sub>05</sub> <sup>a</sup> (mg/kg/day)	p-Value <sup>b</sup>	AIC	Scaled residuals <sup>c</sup>	
					Dose below BMD	Dose above BMD
Dichotomous Hill			NA	168.38	-5.9x10 <sup>-5</sup>	0.00
Gamma <sup>d</sup>	8.76	6.40	0.11	168.93	-0.30	1.29
Log-Logistic <sup>e</sup>			0.23	167.81	-0.13	0.90
Multistage Degree 2 <sup>f</sup>	8.76	6.40	0.11	168.93	-0.30	1.29
<b>Multistage Degree 1<sup>f,g</sup></b>	<b>8.76</b>	<b>6.40</b>	<b>0.11</b>	<b>168.93</b>	<b>-0.30</b>	<b>1.29</b>
Weibull <sup>d</sup>	8.76	6.40	0.11	168.93	-0.30	1.29
Logistic			0.01	172.84	-1.33	1.98
Log-Probit			NA	168.38	8.95x10 <sup>-7</sup>	1.69x10 <sup>-6</sup>
Probit			0.01	172.40	-1.20	1.95

<sup>a</sup>BMD and BMDLs values for models that do not provide adequate fit or yield BMDLs more than 10-fold lower than the lowest nonzero dose are not included in this table.

<sup>b</sup>Values <0.1 fail to meet conventional  $\chi^2$  goodness-of-fit criteria.

<sup>c</sup>Scaled residuals at doses immediately below and above the BMC.

<sup>d</sup>Power restricted to  $\geq 1$ .

<sup>e</sup>Slope restricted to  $\geq 1$ .

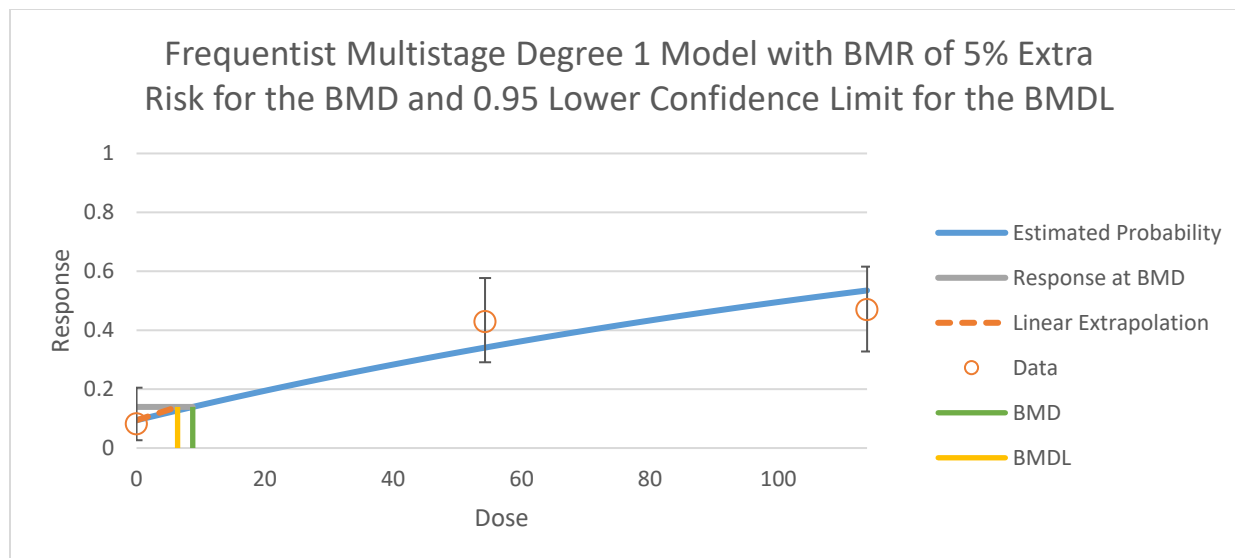
<sup>f</sup>Betas restricted to  $\geq 0$ .

<sup>g</sup>The Gamma, Log-Logistic, Multistage 1- and 2-degree, and Weibull models provided adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold). The log-logistic model had the lowest AIC; however, at a BMR of 5%, the BMDL for this model was 10 times lower than the lowest non-zero dose. The Gamma, Weibull, and Multistage 2- and 1-degree models converged on the same model; the 1-degree Multistage model was selected as the most parsimonious choice.

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

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



### Calculations

**Adjustment for Intermittent Exposure:** Not applicable

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

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

$$\begin{aligned} \text{MRL} &= \text{BMDL}_{05} \div \text{UF} \\ &= 6.4 \text{ mg/kg/day} \div (100) \approx 0.06 \text{ mg/kg/day} \end{aligned}$$

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

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

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

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

### B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are presented in Table B-1.

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

#### Health Effects

##### Species

Human

Laboratory mammals

##### Route of exposure

Inhalation

Oral

Dermal (or ocular)

Parenteral (these studies will be considered supporting data)

##### Health outcome

Death

Systemic effects

Body weight effects

Respiratory effects

Cardiovascular effects

Gastrointestinal effects

Hematological effects

Musculoskeletal effects

Hepatic effects

Renal effects

Dermal effects

Ocular effects

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


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

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**B.1.1 Literature Search**

The current literature search was intended to update the 2005 toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene; thus, the literature search was restricted to studies published between January 2003 and April 2022. The following main databases were searched in April 2022:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were identified by searching international and U.S. agency websites and documents.

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

**Table B-2. Database Query Strings**

Database	search date	Query string
<b>PubMed</b>		
04/2022		<p>((((91-20-3[rn] OR 90-12-0[rn] OR 91-57-6[rn]) OR ("1-METHYL-NAPHTHALENE"[tw] OR "1-Methylnaphtalene"[tw] OR "1-Methylnaphthalene"[tw] OR "1-Methylnaphthalin"[tw] OR "alpha-Methylnaphthalene"[tw] OR "Mechinafu H"[tw] OR "METHYL NAPHTHALENE"[tw] OR "Methylnaphthalene"[tw] OR "Methylnaphthalene, 1-"[tw] OR "Methynaph H"[tw] OR "Naphthalene, 1-methyl-"[tw] OR "Naphthalene, alpha-methyl-"[tw] OR "α-Methylnaphthalene"[tw] OR "2-Methylnaphtalene"[tw] OR "2-Methylnaphthalene"[tw] OR "2-Methylnaphthalin"[tw] OR "2-Methylnaphthalene"[tw] OR "beta-Methylnaphthalene"[tw] OR "Methylnaphthalene, 2-"[tw] OR "Naphthalene, 2-methyl-"[tw] OR "Naphthalene, beta-methyl-"[tw] OR "β-Methylnaphthalene"[tw])) OR (((("Albocarbon"[tiab] OR "Camphor tar"[tiab] OR "Dezodorator"[tiab] OR "Mighty 150"[tiab] OR "Mighty RD1"[tiab] OR "Moth balls"[tiab] OR "Moth flakes"[tiab] OR "Mothballs"[tiab] OR "Naphtalene"[tiab] OR "Naphtalinum"[tiab] OR "Naphthalene"[tiab] OR "Naphthalin"[tiab] OR "Naphthaline"[tiab] OR "Naphthalinum"[tiab] OR "Naphthene"[tiab] OR "Naphthalene"[tiab] OR "Tar camphor"[tiab] OR "White tar"[tiab])) AND (((("Naphthalenes/toxicity"[mh] OR "Naphthalenes/adverse effects"[mh] OR "Naphthalenes/poisoning"[mh] OR "Naphthalenes/pharmacokinetics"[mh]) OR ("Naphthalenes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Naphthalenes"[mh] AND toxicokinetics[mh:noexp]) OR ("Naphthalenes/blood"[mh] OR "Naphthalenes/cerebrospinal fluid"[mh] OR "Naphthalenes/urine"[mh]) OR ("Naphthalenes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Naphthalenes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR</p>

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**Table B-2. Database Query Strings**

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



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**Table B-2. Database Query Strings**

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

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**Table B-2. Database Query Strings**

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

## APPENDIX B

**Table B-2. Database Query Strings**

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

## APPENDIX B

### Table B-2. Database Query Strings

Database  
search date Query string

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L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPB OR  
EPIDEMIOLOGY/ST,CT,  
IT)  
L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR  
LC(W)50)  
L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT  
L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)  
L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)  
L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS  
OR  
DIETARY OR DRINKING(W)WATER?)  
L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR  
PERMISSIBLE))  
  
L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)  
L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM?  
OR  
OVUM?)  
L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)  
L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR  
TERATOGEN?)  
L17 QUE (SPERM OR SPERMATOC? OR SPERMATOG? OR SPERMATID? OR  
SPERMATID? OR  
SPERMATOC? OR SPERMATOC? OR SPERMATOC?)  
L18 QUE (SPERMATOC? OR SPERMATOC? OR SPERMATOC? OR  
SPERMATOC? OR  
SPERMATOC? OR SPERMATOC? OR SPERMATOC?)  
L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR  
DEVELOPMENTAL?)  
L20 QUE (ENDOCRIN? AND DISRUPT?)  
L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR  
INFANT?)  
L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)  
L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)  
L24 QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER?  
OR  
NEOPLAS?)  
L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR  
CARCINOM?)  
L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR  
GENETIC(W)TOXIC?)  
L27 QUE (NEPHROTOX? OR HEPATOTOX?)  
L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)  
L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)  
L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR  
L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR  
L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29  
L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR  
MURIDAE

## APPENDIX B

**Table B-2. Database Query Strings**

Database search date	Query string
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
L32	QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L33	QUE L30 OR L31 OR L32
L34	QUE (NONHUMAN MAMMALS)/ORGN
L35	QUE L33 OR L34
L36	QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL?
OR	
	PRIMATES OR PRIMATE?)
L37	QUE L35 OR L36
	-----
L38	9198 SEA L4 AND L37
L39	614 SEA L38 AND MEDLINE/FS
L40	8584 SEA L38 NOT MEDLINE/FS
L41	8313 DUP REM L39 L40 (885 DUPLICATES REMOVED)
	FILE 'TOXCENTER' ENTERED AT 11:22:56 ON 04 MAY 2022
	CHARGED TO COST=EH038.15.05.LB.04
L1	1062 SEA FILE=TOXCENTER 1321-94-4
L2	1044 SEA FILE=TOXCENTER L1 NOT TSCATS/FS
L3	894 SEA FILE=TOXCENTER L2 NOT PATENT/DT
L4	444 SEA FILE=TOXCENTER L3 AND PY>2002
	ACTIVATE TOXQUERY/Q
	-----
L5	QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
L6	QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,
	IT)
L7	QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
L8	QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
L9	QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
L10	QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
L11	QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS
OR	
	DIETARY OR DRINKING(W)WATER?)
L12	QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
L13	QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
L14	QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM?
OR	
	OVUM?)
L15	QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
L16	QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

## APPENDIX B

**Table B-2. Database Query Strings**

Database search date	Query string
L17	QUE (SPERM OR SPERMATOC? OR SPERMATOG? OR SPERMATOI? OR SPERMATOL? OR SPERMATOT? OR SPERMATOX? OR SPERMATOC? OR SPERMATOG?)
L18	QUE (SPERMATOC? OR SPERMATOG? OR SPERMATOI? OR SPERMATOL? OR SPERMATOT? OR SPERMATOX? OR SPERMATOC? OR SPERMATOG?)
L19	QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
L20	QUE (ENDOCRIN? AND DISRUPT?)
L21	QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
L22	QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
L23	QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
L24	QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER? OR NEOPLAS?)
L25	QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
L26	QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
L27	QUE (NEPHROTOX? OR HEPATOTOX?)
L28	QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
L29	QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
L30	QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
L31	QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
L32	QUE (MARMOSSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L33	QUE L30 OR L31 OR L32
L34	QUE (NONHUMAN MAMMALS)/ORGN
L35	QUE L33 OR L34
L36	QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
L37	QUE L35 OR L36
L38	158 SEA FILE=TOXCENTER L4 AND L37
L39	0 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
L40	154 DUP REM L38 (4 DUPLICATES REMOVED)

## APPENDIX B

**Table B-3. Strategies to Augment the Literature Search**

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



## APPENDIX B

The 2022 results were:

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

### B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

***Title and Abstract Screen.*** Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

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

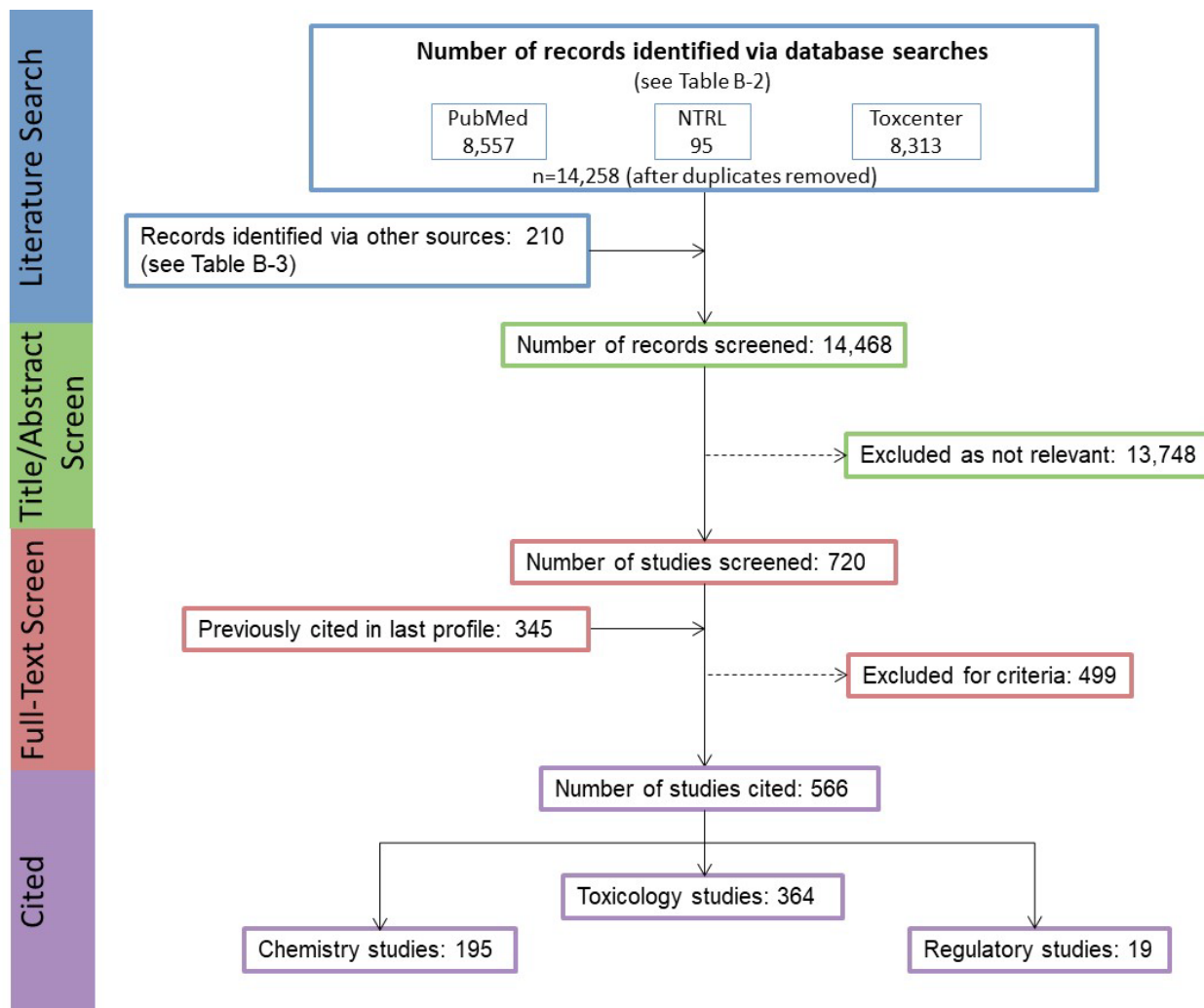
***Full Text Screen.*** The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

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

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



## APPENDIX B

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

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

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

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

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

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

### **C.1 PROBLEM FORMULATION**

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

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

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

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

## C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

### C.2.1 Literature Search

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

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

## APPENDIX C

**C.2.2 Literature Screening**

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

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

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

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

**C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES**

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

**Table C-2. Data Extracted From Individual Studies**

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

**Table C-2. Data Extracted From Individual Studies**

---

Outcome summary (one entry for each examined outcome)

No-observed-adverse-effect level (NOAEL) value

Lowest-observed-adverse-effect level (LOAEL) value

Effect observed at the LOAEL value

---

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

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

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

## APPENDIX C

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort		3			2					2	1	2	1	3	1	2	
		3			2					2	0	2	1	3	0	2	
Case control														1			1
														1			1
Population		1	3			1					1	2		5	6	1	
		1	2			1					0	2		5	5	1	
Case series			1														
			1														
Oral studies																	
Cohort																	
Case control																	
Population				1													
				1													
Case series	1			11	3		4	7					6		3	6	
	1			11	3		4	7					6		3	6	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series							2										
							2										
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological <sup>a</sup>	Neurological <sup>a</sup>	Reproductive <sup>a</sup>	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	4 0	14 13			1 0					1 1							
Intermediate-duration	1 0	1 1	1 1				1 0	1 0			1 0	1 1	1 0	1 0			
Chronic-duration	2 0	2 2	2 0	2 0		2 0	2 0	2 0	2 0	1 0	2 0	2 0	2 0	2 0		1 0	2 2
Oral studies																	
Acute-duration	2 2	4 4			3 2		3 2	2 0		2 1		1 1	2 1	3 1	4 2		
Intermediate-duration	6 3	3 0	2 0	2 1	5 2		5 2	5 2		21 18		2 1	4 2	2 0			
Chronic-duration										1							1 0
Dermal studies																	
Acute-duration									4 2			1 0					
Intermediate-duration		1 0	1 0	1 0	1 0		1 0	1 0	1 1			1 0		1 1			
Chronic-duration																	
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

<sup>a</sup>Number of studies examining endpoint includes studies evaluating histopathology, but not evaluating function.

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

### C.5.1 Risk of Bias Assessment—Naphthalene

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

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

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

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

#### **Selection bias**

Were the comparison groups appropriate?

#### **Confounding bias**

Did the study design or analysis account for important confounding and modifying variables?

#### **Attrition/exclusion bias**

Were outcome data complete without attrition or exclusion from analysis?

#### **Detection bias**

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

#### **Selective reporting bias**

Were all measured outcomes reported?

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

#### **Selection bias**

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

#### **Performance bias**

Were the research personnel and human subjects blinded to the study group during the study?

#### **Attrition/exclusion bias**

Were outcome data complete without attrition or exclusion from analysis?

#### **Detection bias**

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?



**Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies****Selective reporting bias**


---

Were all measured outcomes reported?

---

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

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

---

**Performance bias**

Were experimental conditions identical across study groups?

Were the research personnel blinded to the study group during the study?

---

**Attrition/exclusion bias**

Were outcome data complete without attrition or exclusion from analysis?

---

**Detection bias**

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

---

**Selective reporting bias**

Were all measured outcomes reported?

---

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

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

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

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

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

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

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

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

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

\*Key question used to assign risk of bias tier

## APPENDIX C

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

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

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

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

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

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

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

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

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

\*Key question used to assign risk of bias tier

## APPENDIX C

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

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

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

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

### C.6.1 Initial Confidence Rating—Naphthalene

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

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

## APPENDIX C

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**C.6.2 Adjustment of the Confidence Rating—Naphthalene**

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

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

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

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- No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier
- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direction of the effect
- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies— inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

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

- No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect
- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is  $\geq 10$  for tests of ratio measures (e.g., odds ratios) and  $\geq 100$  for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions
- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

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

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias
- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies
- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect
- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

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

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

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

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

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

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

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

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

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

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



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

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

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

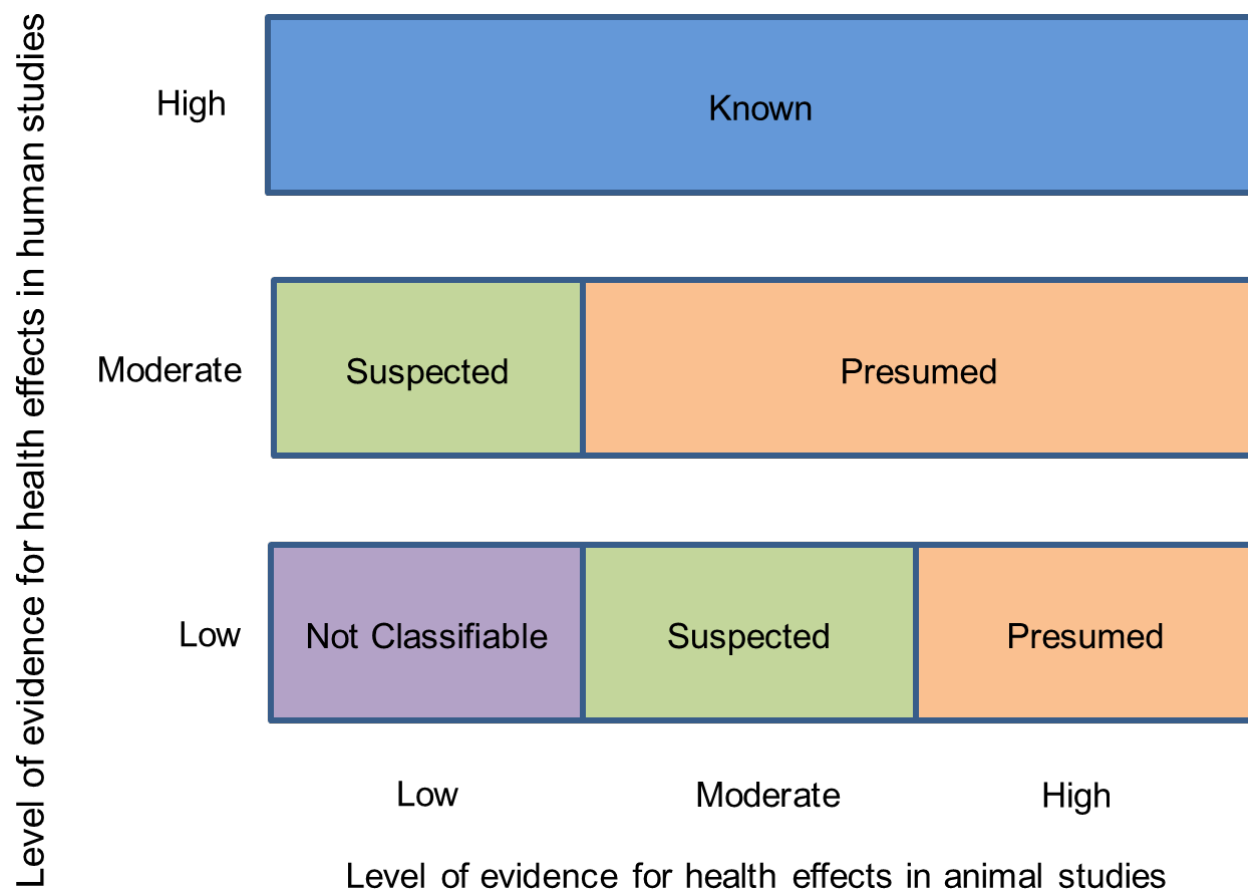
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

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

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**Figure C-1. Hazard Identification Scheme**

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

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

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

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

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

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**Presumed Health Effects**

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

**Suspected Health Effects**

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

**Not Classifiable**

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

**Table C-19. Hazard Identification Conclusions for Naphthalene**

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

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

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

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

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological <sup>a</sup>	Neurological <sup>a</sup>	Reproductive <sup>a</sup>	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	1 0												1 1				
Intermediate-duration	1 0	1 1	1 0	1 0	1 0	1 0	1 0	1 0	1 0		1 0	1 0		1 0			
Chronic-duration																	
Oral studies																	
Acute-duration																	
Intermediate-duration	1 0	1 0	1 0	1 0	1 0		1 1	1 1			1 0	1 0	1 0	1 0	1 0		
Chronic-duration	1 0	1 1	1 0	1 0	1 0		1 0	1 0			1 0	1 0	1 0	1 0			1 1
Dermal studies																	
Acute-duration									1 1								
Intermediate-duration		1 1															
Chronic-duration		1 1															
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

<sup>a</sup>Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

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**C.10 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—  
1-METHYLNAPHTHALENE****C.10.1 Risk of Bias Assessment—1-Methylnaphthalene**

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

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

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

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

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

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

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

\*Key question used to assign risk of bias tier



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

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

### C.11.1 Initial Confidence Rating—1-Methylnaphthalene

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### Presumed Health Effects

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

#### Suspected Health Effects

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

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

Outcome	Hazard identification
Respiratory	Presumed health effect
Hepatic	Suspected health effect

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

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

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological <sup>a</sup>	Neurological <sup>a</sup>	Reproductive <sup>a</sup>	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration													1				
Intermediate-duration	1 0	1 1	1 0		1 0		1 1	1 0				1 0	1				
Chronic-duration																	
Oral studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration	1 0	1 1	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0		1 0	1 0	1 0			1 1
Dermal studies																	
Acute-duration									1 1								
Intermediate-duration		1 1															
Chronic-duration		1 1															
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

<sup>a</sup>Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

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**C.15 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—  
2-METHYLNAPHTHALENE****C.15.1 Risk of Bias Assessment—2-Methylnaphthalene**

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

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

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

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

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

\*Key question used to assign risk of bias tier



## APPENDIX C

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

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

### C.16.1 Initial Confidence Rating—2-Methylnaphthalene

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Presumed Health Effects**

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

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

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

Outcome	Hazard identification
Respiratory	Presumed health effect
Hepatic	Presumed health effect

## APPENDIX D. USER'S GUIDE

### Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

### Minimal Risk Levels (MRLs)

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

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

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

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

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

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

## Chapter 2. Health Effects

### Tables and Figures for Levels of Significant Exposure (LSE)

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

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

#### TABLE LEGEND

##### See Sample LSE Table (page D-5)

- (1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.
- (2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).
- (4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to "Chemical X" via feed for 2 years. For a

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

- (6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).
- (7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.
- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.
- (10) Reference. The complete reference citation is provided in Chapter 8 of the profile.
- (11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

**FIGURE LEGEND**

**See Sample LSE Figure (page D-6)**

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

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

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- (13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.
- (14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).
- (16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.
- (17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.



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Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral												
	4		5		6		7		8		9	
	Species		Exposure		Parameters		Endpoint		NOAEL		Less serious	
	Figure (strain)		parameters		monitored				(mg/kg/day)		LOAEL	
	key <sup>a</sup> No./group										LOAEL	
											(mg/kg/day)	
											(mg/kg/day)	
											(mg/kg/day)	

<sup>a</sup>The number corresponds to entries in Figure 2-x.

<sup>b</sup>Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the BMDL<sub>05</sub> of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

<sup>c</sup>Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the BMDL<sub>10</sub> of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).



## APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

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### *Primary Chapters/Sections of Interest*

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

**Chapter 2: Health Effects:** Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

**NOTE:** Not all health effects reported in this section are necessarily observed in the clinical setting.

### **Pediatrics:**

<b>Section 3.2</b>	<b>Children and Other Populations that are Unusually Susceptible</b>
<b>Section 3.3</b>	<b>Biomarkers of Exposure and Effect</b>

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### *ATSDR Information Center*

**Phone:** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

**Internet:** <http://www.atsdr.cdc.gov>

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

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

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

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

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## APPENDIX E

***Other Agencies and Organizations***

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

*The National Institute for Occupational Safety and Health (NIOSH)* conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/niosh/>.

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

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***Clinical Resources (Publicly Available Information)***

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

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

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

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

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

## APPENDIX F. GLOSSARY

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

**Acute Exposure**—Exposure to a chemical for a duration of  $\leq 14$  days, as specified in the Toxicological Profiles.

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

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

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

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

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

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

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

**Carcinogen**—A chemical capable of inducing cancer.

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

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

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

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**Ceiling Value**—A concentration that must not be exceeded.

**Chronic Exposure**—Exposure to a chemical for  $\geq 365$  days, as specified in the Toxicological Profiles.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(LO)</sub> (LD<sub>LO</sub>)**—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

**Minimal LOAEL**—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) exposure limit. The REL may be a time-weighted average (TWA) concentration for up to an 8 or 10-hour workday during a 40-hour workweek. The REL may also be a short-term exposure limit (denoted ST), typically a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q <sub>1</sub> <sup>*</sup>	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result