

## 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.

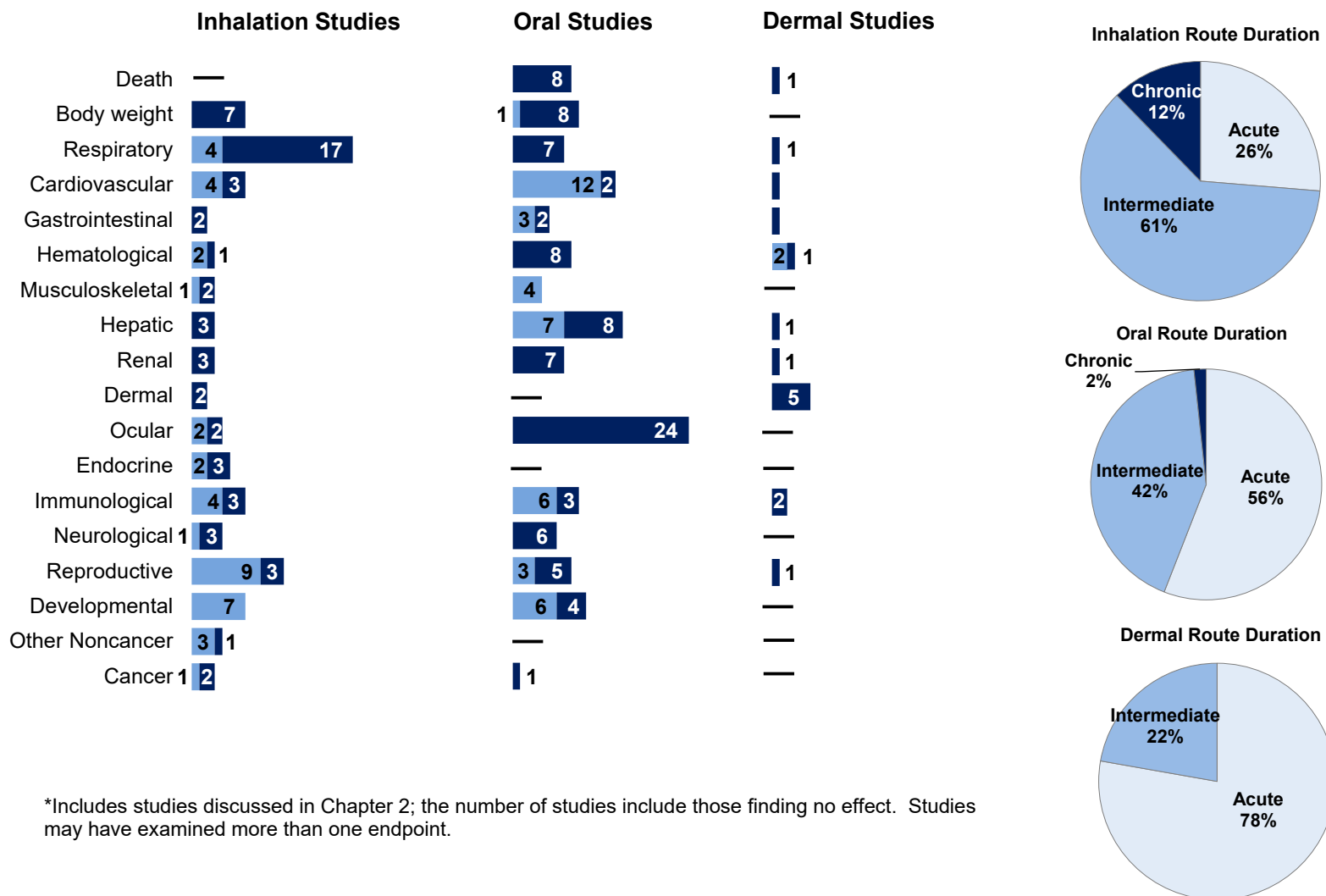
### 6.2 IDENTIFICATION OF DATA NEEDS

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.

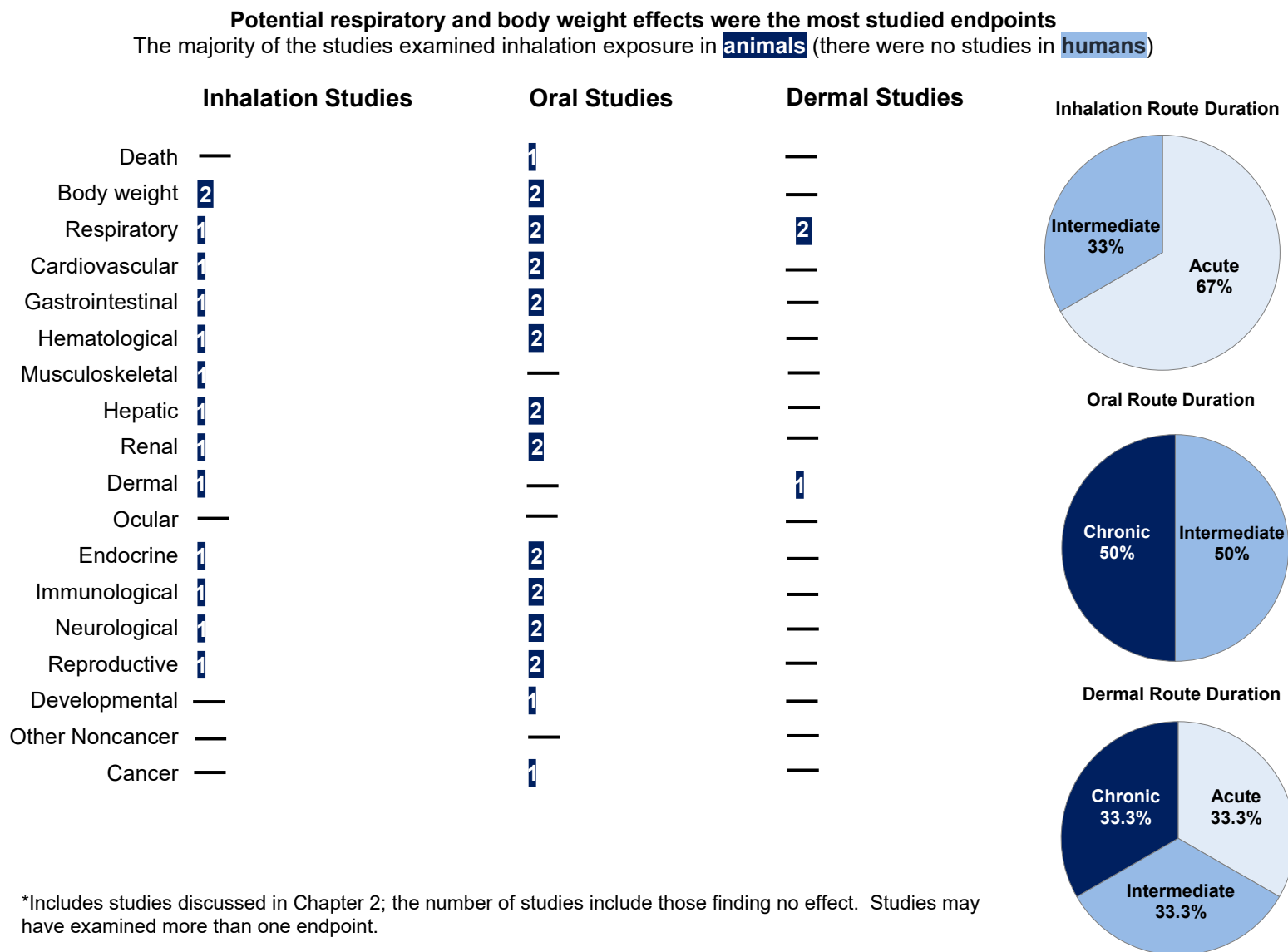
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**Figure 6-1. Summary of Existing Health Effects Studies on Naphthalene by Route and Endpoint\***

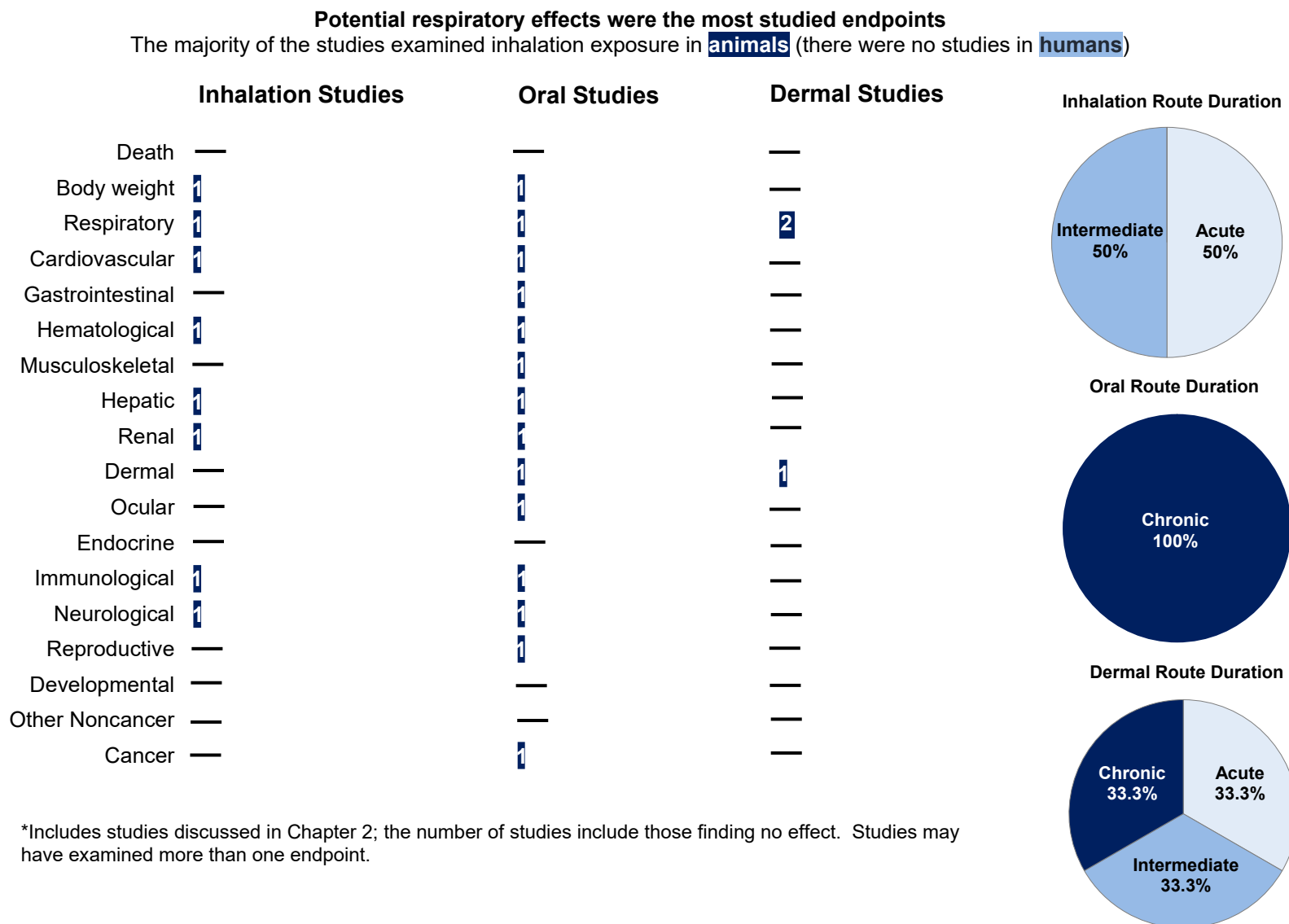
Potential respiratory and ocular effects were the most studied endpoints  
 The majority of the studies examined oral exposure in **animals** (versus **humans**)



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

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**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.

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**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.

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**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