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 $\mu g/m^3$, with a mean concentration of 0.04 $\mu g/m^3$ reported for urban/suburban air samples collected

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 μg/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 μg/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 μg/L in surface water or groundwater and <300 μg/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

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-methyl-naphthalene, 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

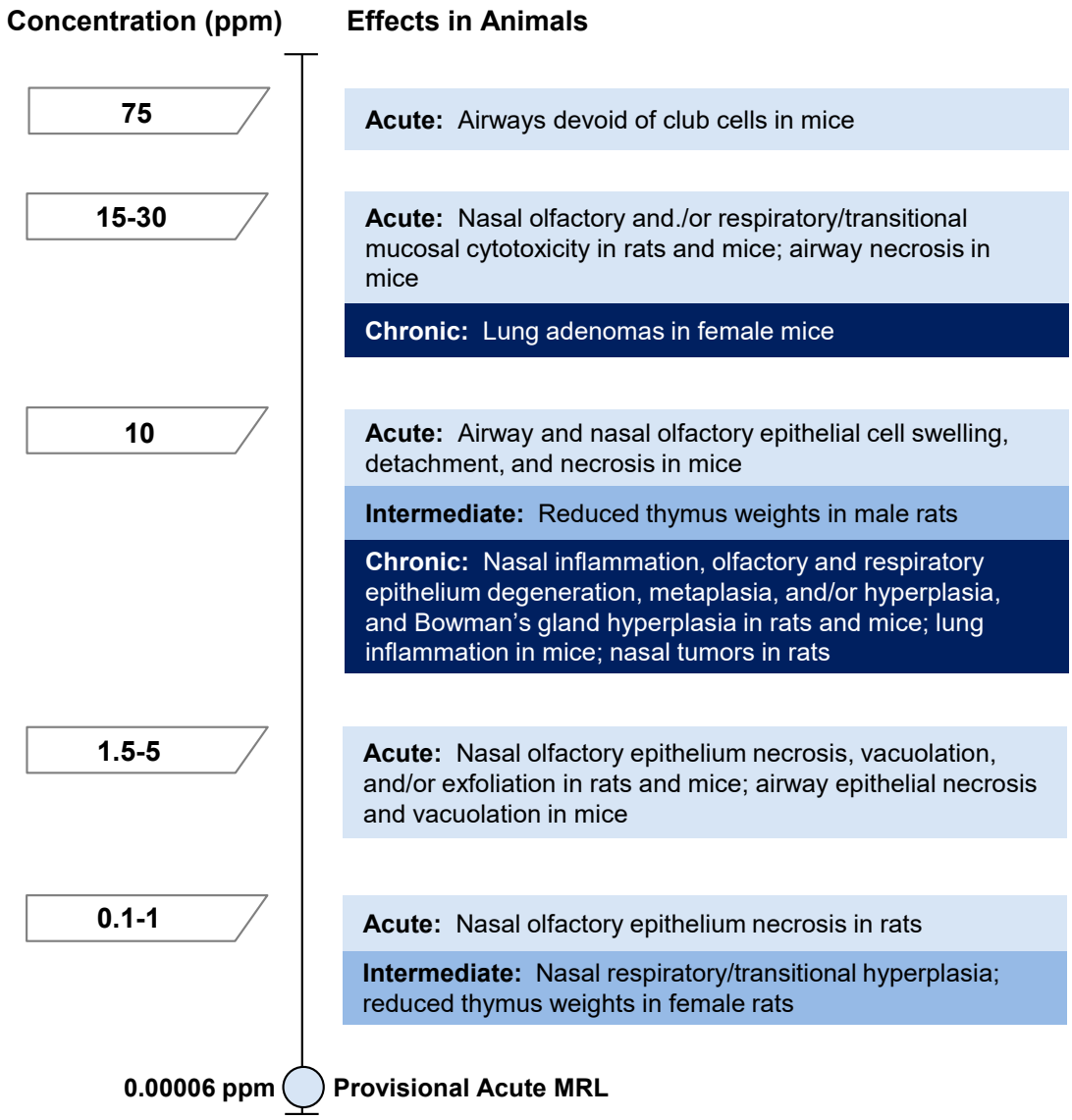


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Naphthalene

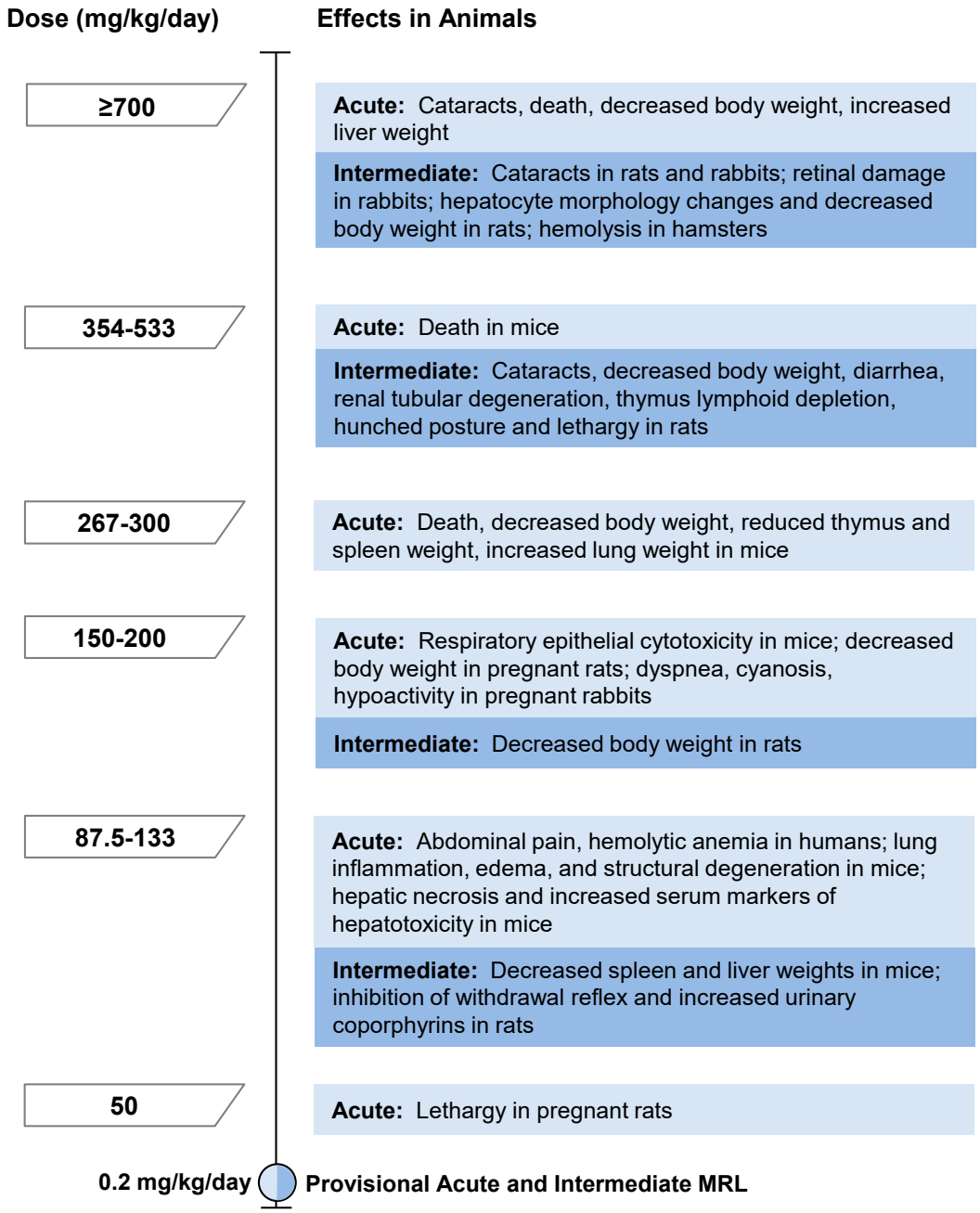


Figure 1-3. Health Effects Found in Animals Following Inhalation Exposure to 1-Methylnaphthalene

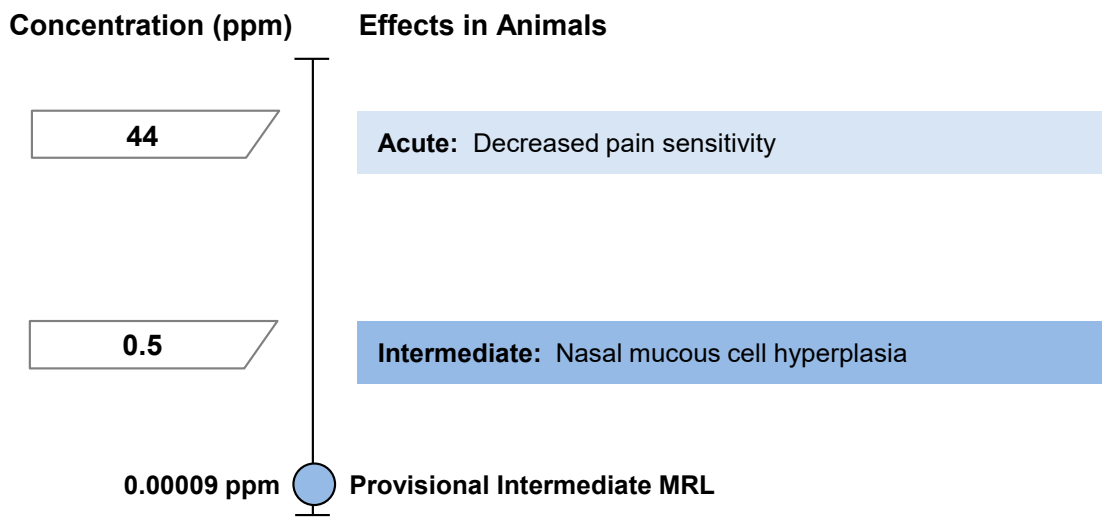


Figure 1-4. Health Effects Found in Animals Following Oral Exposure to 1-Methylnaphthalene

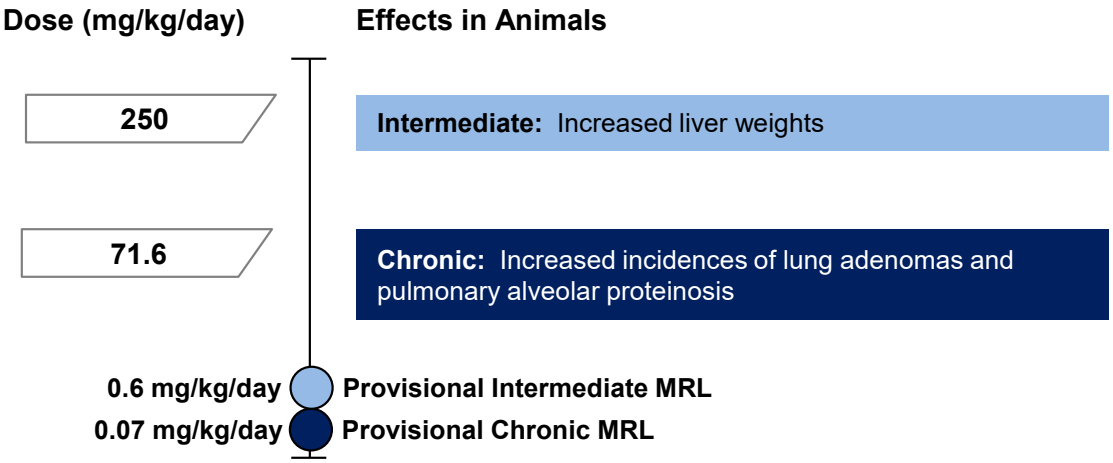


Figure 1-5. Health Effects Found in Animals Following Inhalation Exposure to 2-Methylnaphthalene

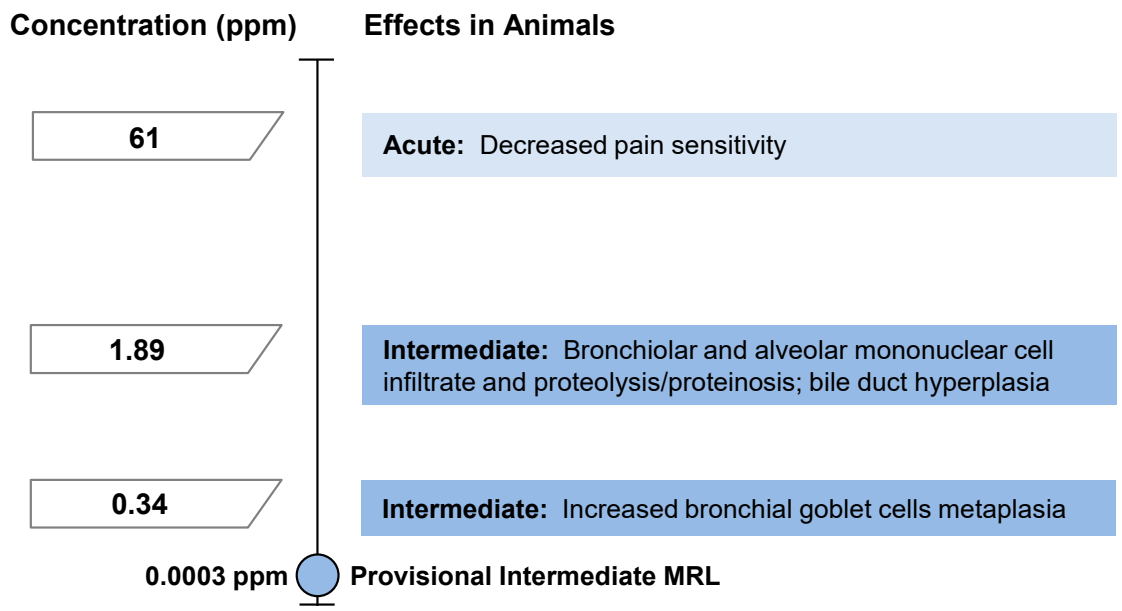
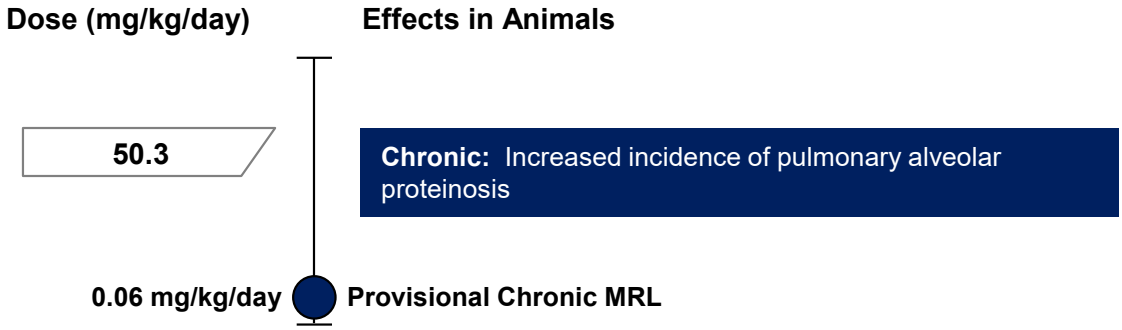


Figure 1-6. Health Effects Found in Animals Following Oral Exposure to 2-Methylnaphthalene



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.

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,

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 ≥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.

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 (≥0.52 ppm) (Kim et al. 2020). Intermediate-duration exposure of rats to 2-methylnaphthalene concentrations ≥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-methyl-naphthalene in animals provide limited evidence for the carcinogenicity of these chemicals. In the

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.

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.

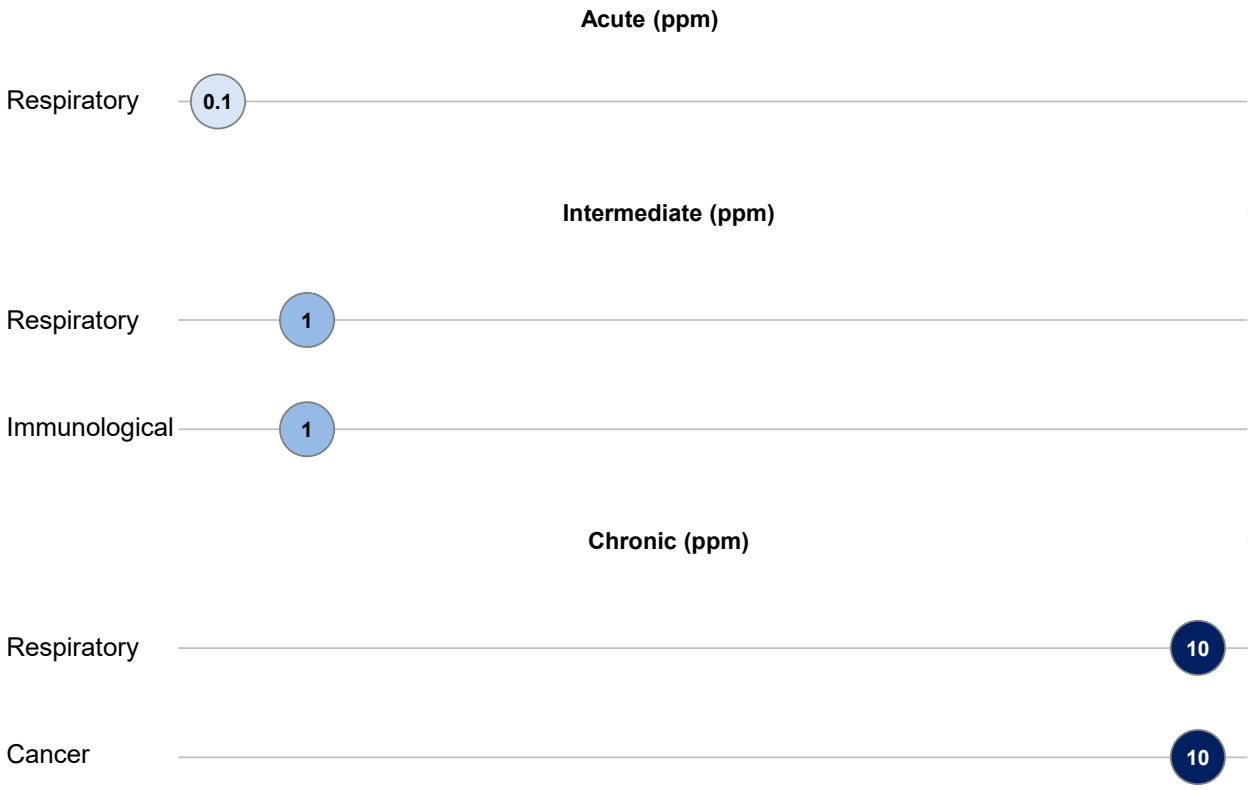
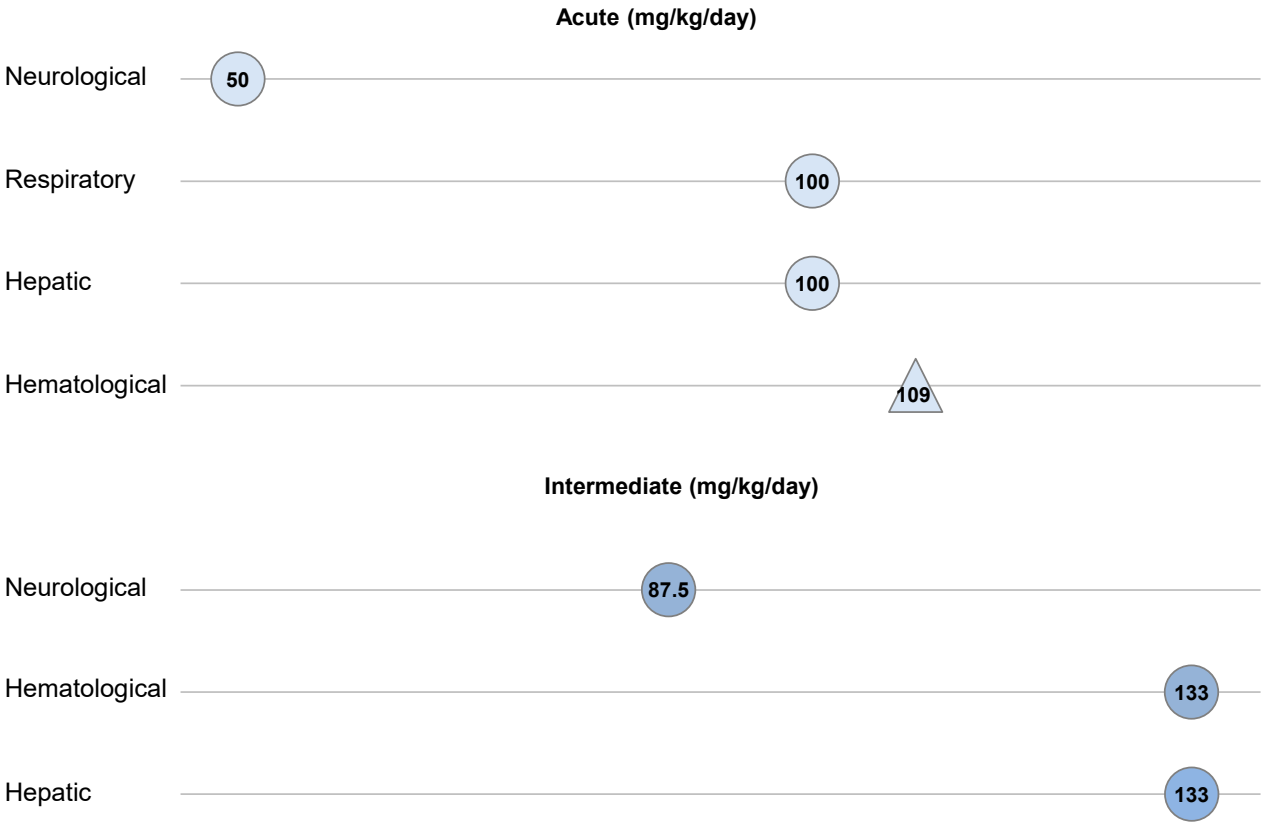


Figure 1-8. Summary of Sensitive Targets of Naphthalene – Oral

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.

Table 1-1. Provisional Minimal Risk Levels (MRLs) for Naphthalene[a]

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

[a]See Appendix A for additional information.
[b]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.
[c]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-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.

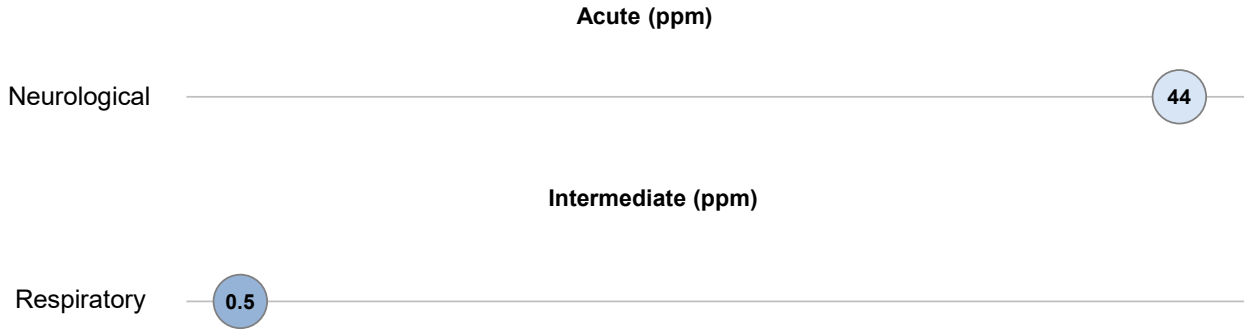
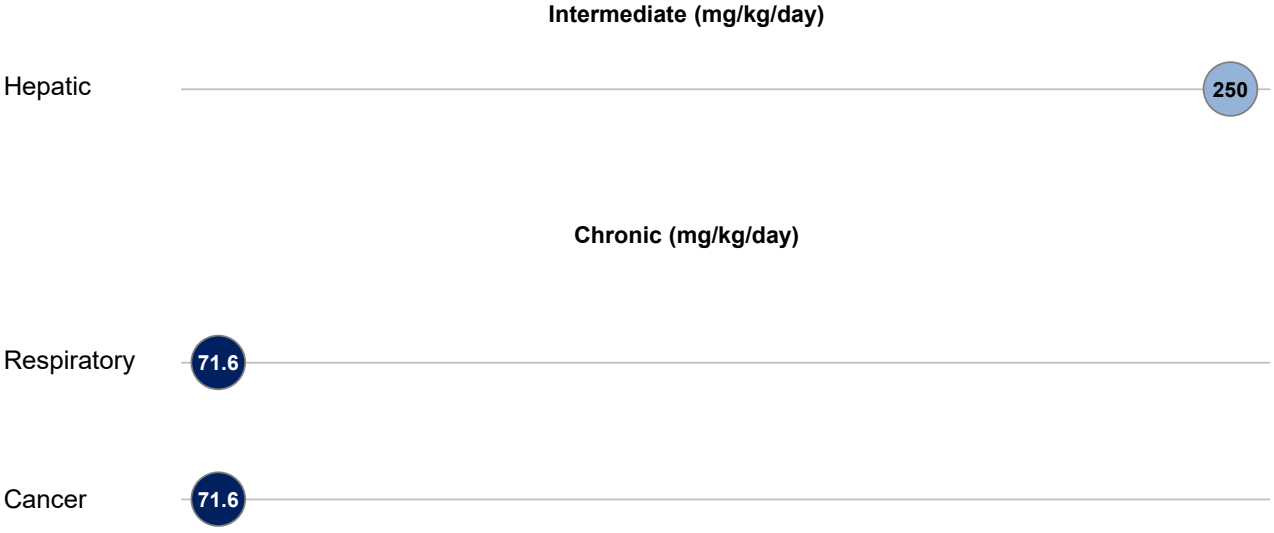


Figure 1-10. Summary of Sensitive Targets of 1-Methylnaphthalene – Oral

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.



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

Table 1-2. Provisional Minimal Risk Levels (MRLs) for 1-Methylnaphthalene[a]

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

[a]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

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.

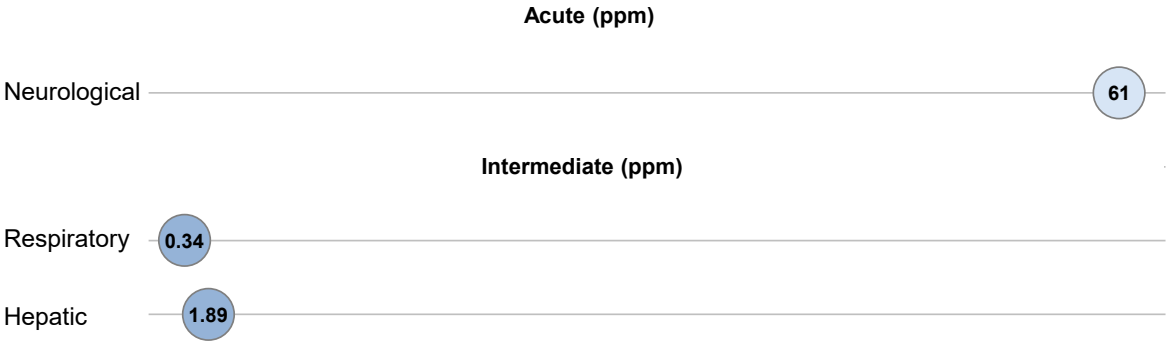
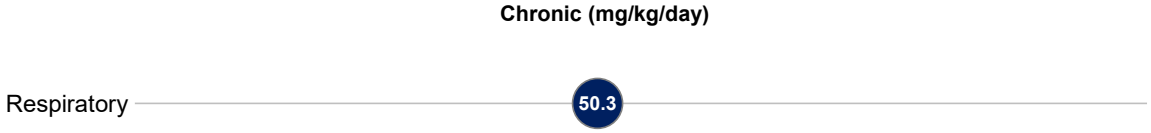


Figure 1-12. Summary of Sensitive Targets of 2-Methylnaphthalene – Oral

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.

Table 1-3. Provisional Minimal Risk Levels (MRLs) for 2-Methylnaphthalene[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	**$3x10^{-4}$ ppm** ($0.002\ mg/m^3$)	Bronchial goblet cell metaplasia	$LOAEL_{HEC}$	0.081 ppm	UF: 300	Świercz et al. 2011
	Chronic	None	–	–	–	–	–
Oral	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	**0.06 mg/kg/day**	Pulmonary alveolar proteinosis	$BMDL_{05}$	6.4 mg/kg/day	UF: 100	Murata et al. 1997

[a]See Appendix A for additional information.

$BMCL_{05}$ = 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