2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE IN THE UNITED STATES

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. Naphthalene is also produced commercially from either coal tar or petroleum. In 2000, estimates of commercial production of naphthalene in Japan, Western Europe, and the United States were 179, 205, and 107 thousand tonnes. Commercially-produced naphthalene is predominately used in the production of phthalic anhydride, which is used as an intermediate for polyvinyl chloride plasticizers such as di(2-ethylhexyl) phthalate. In 1999, this use of naphthalene accounted for 73 and 60% of commercial demand for naphthalene in Japan and the United States, respectively. 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.

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, its use as an intermediate in the production of plasticizers, resins, and insecticides, and its use in a variety of consumer products such as moth repellants. In 2002, environmental releases of naphthalene reported under the EPA Toxics Release Inventory (TRI) program were about 2.07 million pounds in air emissions, 0.03 million pounds in surface water discharges, 0.23 million pounds in underground injection discharges, and 0.37 million pounds in releases to land. These figures reflect estimates that most naphthalene entering the environment is discharged to the air, with the largest releases associated with the combustion of plant material and fossil fuels and volatilization from naphthalene-containing consumer products.

Monitoring studies of outdoor ambient air levels of naphthalene have reported concentrations in the range of about 0.4–170 μg/m^3, with a median naphthalene concentration of 0.94 μg/m^3 (0.0002 ppm) reported for urban/suburban air samples collected from 11 U.S. cities. The highest outdoor air concentrations have been found in the immediate vicinity of certain industrial sources and hazardous waste sites. For example, average concentrations of naphthalene in ambient air at five hazardous waste sites and one landfill in New Jersey ranged from 0.42 to 4.6 μg/m^3 (0.00008–0.0009 ppm). In indoor air, emissions

from cooking, tobacco smoking, or moth repellants are expected to be the predominant sources of naphthalene. Indoor air concentrations of naphthalene in homes with smoking residents and homes without smoking residents were reported to be 2.2 μg/m^3 (0.0004 ppm) and 1.0 μg/m^3 (0.0002 ppm), respectively. A study of indoor and outdoor air in 24 low-income homes in North Carolina found naphthalene levels ranging from 0.33–9.7 μg/m^3 and 0.57–1.82 μg/m^3 respectively. Methylnaphthalenes have also been detected in ambient outdoor and indoor air. For example, average concentrations of 1-methylnaphthalene and 2-methylnaphthalene in ambient outdoor air samples were reported to be 0.51 and 0.065 μg/m^3, respectively, whereas 2-methylnaphthalene in indoor air samples showed an average concentration of 1.5 μg/m^3 (0.0003 ppm). Based on a median concentration of 0.95 μg/m^3 (0.0002 ppm) naphthalene in urban and suburban air samples and an inhalation rate of 20 m^3/day, the average daily intake of naphthalene from ambient air is estimated at 19 μg/day, or 0.3 μg/kg/day assuming 70-kg body weight.

Levels of naphthalene (and methylnaphthalenes), when detected in water, sediments, and soil tend to be low: usually <10 μg/L in surface water or groundwater, <500 μg/kg in sediments, and 0–3 μg/kg in untreated agricultural soils. However, in the immediate vicinity of point sources of release, such as chemical waste sites, concentrations can be higher. For example, concentrations of 6.1 and 2.9 mg/kg were reported for naphthalene and methylnaphthalene, respectively, in soil samples contaminated with coal tar.

2.2 SUMMARY OF HEALTH EFFECTS

Reports that establish associations between naphthalene exposure and health effects in humans are restricted to numerous reports of hemolytic anemia or cataracts following acute exposure or occupational exposure to naphthalene, either by ingestion or by inhalation of naphthalene vapors, but these reports have not identified exposure levels associated with these effects. A relationship appears to exist between an inherited deficiency in the enzyme, glucose 6-phosphate dehydrogenase (G6PD), and susceptibility to naphthalene-induced hemolysis. Newborn infants also appear to be susceptible to naphthalene-induced hemolysis presumably due to a decreased ability to conjugate and excrete naphthalene metabolites. The only studies of cancer in humans exposed to naphthalene are two case series reports of cancer; one report of four laryngeal cancer cases (all of whom were smokers) among workers in a naphthalene purification plant in East Germany, and another report of 23 cases of colorectal carcinoma admitted to a hospital in Nigeria. NTP, EPA, and IARC concur that these studies provide inadequate evidence of naphthalene

carcinogenicity in humans. No cohort mortality or morbidity studies or case-control studies examining possible associations between naphthalene exposure and increased risk of cancer (or other health effects) are available.

Epidemiology studies, case reports, or controlled-exposure studies examining the potential health effects of human exposure to 1-methylnaphthalene or 2-methylnaphthalene by any route of exposure are not available.

Results from animal studies exposed to naphthalene by oral administration, by inhalation exposure, or by parenteral administration identify several health effects of potential concern for humans, including maternal toxicity during pregnancy with acute oral exposure, decreased body weight (without lesions developing in any tissues or organs) with intermediate oral exposure, and increased incidence of nonneoplastic and neoplastic lesions in the nose (in rats and mice) and the lung (in mice only) with chronic inhalation exposure.

Hemolytic and Ocular Effects of Naphthalene in Animals. Rats and mice do not appear to be susceptible to the hemolytic effects of naphthalene as hematological end points have not been affected in acute or intermediate duration oral studies or in acute 14-day inhalation studies. There is one report of hemolytic anemia in a few dogs orally exposed to naphthalene, but the data are inadequate to describe dose-response relationships that can be reliably extrapolated to human exposure scenarios. Naphthalene-induced cataracts or lens opacities are well studied in rats and rabbits and appear to occur at acute- or intermediate-duration oral exposure levels >500 mg/kg/day. Naphthalene-induced cataracts were not found with intermediate-duration (i.e., 13 weeks) oral exposure at lower dose levels up to 200 mg/kg/day in mice or 400 mg/kg/day in rats.

Maternal and Developmental Toxicity of Naphthalene in Animals. Acute oral exposure of pregnant rats to naphthalene doses of 150 or 450 mg/kg/day (but not 50 mg/kg/day) during gestation has produced maternal toxicity including clinical signs (lethargy and prone position) and severe decreases in body weight gain, but clear effects on the developing fetus have not been found at maternal oral doses as high as 450 mg/kg/day in rats, 300 mg/kg/day in mice, or 120 or 400 mg/kg/day in rabbits. Reduced numbers of mouse pups per litter were observed when naphthalene (300 mg/kg/day) in corn oil was orally administered to pregnant mice; however, no fetotoxic effects were seen when pregnant rabbits were orally administered naphthalene at even higher doses (400 mg/kg/day) but delivered in methylcellulose rather than in an oil vehicle. It is unclear if these differences are due to species differences in sensitivity or to

the vehicle used to deliver naphthalene. The finding of maternal toxicity in orally exposed pregnant rats serves as the basis of the acute oral MRL for naphthalene (see Section 2.3). Dermal or inhalation developmental toxicity studies in animals are not available.

Body Weight Effects of Naphthalene in Animals. Comprehensive intermediate-duration (13 weeks) oral toxicity studies found no evidence for naphthalene-induced lesions in any tissue or organs in male or female Fischer 344 rats exposed to doses as high as 400 mg/kg/day or in male or female B6C3F1 mice exposed to doses as high as 200 mg/kg/day. The only biologically significant effects found in these studies were decreases in rat terminal body weights compared with controls at dose levels of 200 mg/kg/day (12% decrease in male rats) and 400 mg/kg/day (28 and 23% decreases in male and female rats, respectively). No effect on food consumption was observed in exposed rats. Exposed male mice had higher body weights than controls, and exposed female mice had lower body weights than controls, but mean body weights were not decreased by more than 5%. In another intermediate-duration oral study with CD-1 mice that focused on a battery of immunologic tests (but did not include comprehensive histopathologic examination of tissues), no biologically significant effects were found except for decreases in weights of several organs (brain, liver, and spleen) in mice exposed to 133 mg/kg/day, but not to 53 or 5.3 mg/kg/day. The lack of naphthalene-induced lesions in these organs in the NTP studies suggests that the brain, liver, and spleen are not sensitive targets of naphthalene following intermediate oral exposure. Body weight changes in rats were the most sensitive, biologically relevant effects observed in the available toxicity studies in animals orally exposed for intermediate durations. These effects were considered in deriving the intermediate-duration oral MRL for naphthalene (see Section 2.3). Chronic-duration oral toxicity studies with naphthalene in animals are not available.

Cancer and Respiratory Effects of Naphthalene in Animals. Chronic inhalation studies found increased incidences of nonneoplastic and neoplastic lesions in the nose of rats, nonneoplastic lesions in the nose of mice, and neoplastic and nonneoplastic lesions in the lungs of mice. In mice of both sexes, chronic inhalation of 10 or 30 ppm naphthalene induced inflammation of the nose and lung, metaplasia of the olfactory epithelium, and hyperplasia of the nasal respiratory epithelium. 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 nonneoplastic and neoplastic lesions only in the nasal cavity. Nonneoplastic nasal lesions included (1) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium and (2) hyperplasia, metaplasia or degeneration of the respiratory epithelium or

glands. Neoplastic lesions associated with naphthalene exposure in rats were olfactory epithelial neuroblastoma (a rare malignant tumor) and respiratory epithelial adenoma. The chronic inhalation MRL for naphthalene is based on the LOAEL of 10 ppm for nonneoplastic lesions in the olfactory epithelium and respiratory epithelium of the nose of rats (see Section 2.3).

The mechanisms by which naphthalene causes nonneoplastic or 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(see Sections 3.4.3. and 3.5).

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 study) and that differences in rates and stereoselectivity of naphthalene metabolism to epoxide intermediates may be involved in this species difference. 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. Some evidence has been reported that rates and stereoselectivity of naphthalene metabolism in primate lung tissue may be more like rats than mice. 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. 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. To date, mechanistic understanding of species differences in naphthalene bioactivation in the lung is too incomplete to definitively rule out the possible human relevance of naphthalene-induced lung lesions in mice (see Section 3.5).

In contrast, 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 chronic 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. CYP monooxygenases, which might be involved in naphthalene metabolism and bioactivation, have been demonstrated to exist in nasal respiratory epithelial and olfactory epithelial tissue from rodents and humans. Studies designed to specifically characterize

metabolism of naphthalene in nasal tissue, however, have not been conducted, with the exception of a single study, which examined *in vitro* rates of metabolism of naphthalene to naphthalene oxides in postmitochondrial supernatants from mouse, rat, and hamster olfactory tissue. Metabolic rates (units of nmol/min/mg protein) showed the following order: mouse (87.1) > rat (43.5) > hamster (3.9). This order did not correspond with species differences in sensitivity to single intraperitoneal injections of naphthalene in a companion study. The lowest dose levels producing substantial necrosis and exfoliation in olfactory epithelium were 200 mg/kg in rats and 400 mg/kg in mice and hamsters. To date, mechanistic understanding of species differences in naphthalene bioactivation in the respiratory tissues is too incomplete to definitively rule out the possible human relevance of naphthalene-induced nasal lesions in rodents (nonneoplastic lesions in rats and mice and neoplastic lesions in rats; see Section 3.5).

It is unknown whether the naphthalene-induced neoplastic lesions found in mice (lung adenomas) and rats (nose respiratory epithelial adenomas and olfactory epithelial neuroblastomas) 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 (see Section 3.3), and the general sites of neoplastic lesions, the nose in rats and the lungs in mice, show some correspondence (but not complete) with the general sites of nonneoplastic lesions. However, 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:

(1) the possible significance of the few positive genotoxicity results that have been obtained, including: reverse mutations in *Salmonella typhimurium* by 1,2-naphthoquinone; *in vitro* formation of N-7 guanine adducts of DNA by 1,2-naphtoquinone; reverse mutations for luminescence in the marine bacteria, *Vibrio fischeri*, by naphthalene; induction of sister chromatid exchanges in Chinese hamster ovary cells by naphthalene and in human mononuclear leukocytes by 1,2- or 1,4-naphthoquinone; induction of chromosomal aberrations in Chinese hamster ovaries and preimplantation mouse embryos by naphthalene; induction of somatic mutations and recombination in *Drosophila melanogaster* by naphthalene; and weak (about 2-fold) induction of micronuclei in red blood cells from *Pleurodeles waltl* larvae by naphthalene.

(2) the lack of a mechanistic explanation of why nearly all rats and mice develop nasal nonneoplastic lesions following chronic exposure to naphthalene at concentrations ≥10 ppm, but only some rats develop nasal tumors;

(3) 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 exposure to 10 or 30 ppm, but only female mice showed statistically significant increased incidence of lung tumors;

(4) the lack of *in vivo* genotoxicity assays involving target tissues of naphthalene carcinogenicity (nose and lung); and

(5) the lack of information on the possible threshold exposure levels for nonneoplastic nasal lesions in rats and mice at air concentrations <10 ppm.

The National Toxicology Program *11th Report on Carcinogens* includes naphthalene in its list of chemicals *reasonably anticipated to be human carcinogen*.

International Agency for Research on Cancer 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 considered the findings for nasal tumors in male and female rats and lung tumors in female mice in the NTP 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. In the EPA (1998c) *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 1986e 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. Currently, the EPA Integrated Risk Information System (IRIS) Office is reassessing the inhalation carcinogenicity of naphthalene.

Cancer and Respiratory Effects of 1- and 2-Methylaphthalene in Animals. Increased incidences of pulmonary alveolar proteinosis have been observed in mice of both sexes exposed to 1-methyl-

naphthalene in the diet for 81 weeks at approximate dose levels of 72–75 and 140–144 mg/kg/day and 2-methylnaphthalene in the diet at doses of 50–54 and 108–114 mg/kg/day. Histologic examination of major tissues and organs in these studies showed no other exposure-related nonneoplastic or neoplastic lesions at other sites (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 incidence of pulmonary alveolar proteinosis. The chronic studies with mice exposed to 1- or 2-methylnaphthalene in the diet provide the basis for the chronic oral minimal risk levels (MRLs) for these substances (see Section 2.3).

Pulmonary alveolar proteinosis is characterized by an accumulation in the alveolar lumen of foamy cells, cholesterol crystals, and proteinaceous materials rich in lipids. The condition is rare in humans and has not been associated with human exposure to 2-methylnaphthalene or 1-methylnaphthalene. Human subjects with this condition can display pulmonary function deficits. The absence of pulmonary alveolar proteinosis in a 13-week range-finding study that exposed B6C3F1 mice to dietary doses as high as 2,500 mg/kg/day suggests that the development of this lesion requires chronic-duration exposure.

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. 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. 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 methyl-naphthalenes themselves or their metabolites are responsible for the development of pulmonary alveolar proteinosis.

The chronic dietary studies with 1- or 2-methylnaphthalene 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. 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. The available data on the methylnaphthalenes appear inadequate to determine their carcinogenicity potential in

humans, given the lack of any human studies on the potential carcinogenicity of the methylnaphthalenes and the limited evidence of carcinogenicity in animals.

The NTP *11th Report on Carcinogens* does not include 1-methylnaphthalene 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 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.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

- An MRL of 0.0007 ppm was derived for chronic inhalation exposure to naphthalene.

The MRL was derived from two chronic inhalation toxicity and carcinogenicity studies with mice (NTP 1992a) and rats (Abdo et al. 2001; NTP 2000). In one study, groups of 75 B6C3F1 mice of each sex were exposed by inhalation at concentrations of 0, 10, or 30 ppm, 6 hours/day, 5 days/week for 104 weeks. In the other study, groups of 49 male and 49 female F344/N rats were exposed to naphthalene at concentrations of 0, 10, 30, or 60 ppm, 6 hours/day, 5 days/week for 105 weeks. The lowest exposure level in both studies, 10 ppm, was a lowest-observed-adverse-effect level (LOAEL) in both sexes of both species for nonneoplastic lesions in nasal olfactory epithelium (metaplasia in mice, and hyperplasia, atrophy, and chronic inflammation in rats) and respiratory epithelium (hyperplasia in mice, and hyperplasia, metaplasia, hyaline degeneration, or gland hyperplasia in rats). At 10 ppm, nearly all of the animals showed nasal lesions. Exposed rats also showed increased incidences of nasal tumors (respiratory epithelial adenomas and olfactory epithelial neuroblastomas), but mice did not develop nose tumors. Exposed mice also showed an increased incidence of chronic lung inflammation at both exposure levels and an increased incidence of lung tumors in females exposed to 30 ppm. Lung lesions did not occur in exposed rats.

Following EPA (1994b) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, equations for a category 1 gas producing nasal effects were used to derive human equivalent concentrations of 0.2 ppm based on the rat data and 0.3 ppm based on the mouse data (see Appendix B). Using public health protection reasoning, the $LOAEL_{HEC}$ based on the rat data, 0.2 ppm, was selected as the point of departure for the chronic inhalation MRL, which was divided by a total uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustment, and 10 for human variability) to derive the MRL of 0.0007 ppm ($3x10^{-3}$ mg/m^3).

No appropriate data were located on effects of acute- and intermediate-duration inhalation exposure in humans or animals that could be used to derive acute and intermediate MRLs for inhalation exposure to naphthalene.

No appropriate data were located for deriving inhalation MRLs for 1-methylnaphthalene or 2-methyl-naphthalene.

Oral MRLs

- An MRL of 0.6 mg/kg/day was derived for acute oral exposure to naphthalene.

A rat developmental toxicity study involving exposure of Sprague-Dawley rats to gavage doses of 50, 150, or 450 mg/kg/day naphthalene on gestation days 6-15 was selected as the basis of the acute oral MRL (NTP 1991a). The only maternal or fetal effects observed at the lowest dose level were slow respiration, lethargy, or prone body posture in most dams following dose administration on the first and second day of dosing. These effects did not occur on subsequent days of dosing at this dose level. Because of the transient nature of these observations and the lack of any other effect, 50 mg/kg/day was judged to be a minimal lowest-observed-adverse-effect level (LOAEL) for clinical signs of toxicity. At 150 and 450 mg/kg/day, clinical signs of toxicity were more persistent and were accompanied with severe decreases in body weight gain during the exposure period (31 and 53%, respectively, compared with controls). No exposure-related fetal effects were found in any of the exposure groups compared with the controls in this study.

The MRL was calculated from the minimal LOAEL of 50 mg/kg/day using an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability) to derive the MRL of 0.6 mg/kg/day (see Appendix A). An uncertainty factor of 3 was used for human variability because the critical effect is based on effects in a sensitive animal subpopulation. Pregnant rats appear to be more sensitive for the effects observed (clinical signs of toxicity in response to gavage exposure and decreased body weight gain) than nonpregnant rats. In 13-week gavage studies with nonpregnant rats (NTP 1980b), similar persistent clinical signs were not observed following administration of doses as high as 200 mg/kg/day, but were observed at 400 mg/kg/day. In nonpregnant rats exposed for 13 weeks, significant body weight decreases occurred at 200 mg/kg/day throughout exposure, but not at 100 mg/kg/day (NTP 1980b) or in nonpregnant mice exposed for 13 weeks to 133 mg/kg/day (Shopp et al. 1984) or 200 mg/kg/day (NTP 1980a). Mice in the NTP (1980a) study showed transient signs of toxicity (lethargy, rough hair coats, and decreased food consumption), but these only occurred between weeks 3 and 5 in the 200-mg/kg/day group.

- The acute-duration oral MRL of 0.6 mg/kg/day is adopted as the intermediate-duration oral MRL for naphthalene.

There are three intermediate-duration oral toxicity studies in laboratory animals that were considered for deriving the intermediate-duration oral MRL for naphthalene. A 13-week comprehensive oral toxicity study in Fischer 344 rats found no adverse exposure-related effects other than decreased body weight (NTP 1980b). This study identified 100 mg/kg/day as a no-observed-adverse-effect level (NOAEL) and 200 mg/kg/day as a LOAEL for decreased body weight in male and female rats. Another 13-week

comprehensive oral toxicity study in B6C3F1 mice found no adverse effects in mice exposed to doses as high as 200 mg/kg/day (NTP 1980a). Another 90-day gavage study in CD-1 mice focused on immune system variables and other toxicity variables (e.g., body weight, organ weight, haematological parameters) and identified 133 mg/kg/day as a LOAEL and 53 mg/kg/day as a NOAEL for weight decreases in several organs (brain, liver, and spleen), but found no biologically significant exposure-related changes in other end points evaluated (Shopp et al. 1984). This study, however, did not include histopathological examination of tissues.

The findings from the three intermediate-duration oral toxicity studies do not collectively identify a clear, biologically significant target of toxicity other than body weight changes in rats (see Appendix A for comprehensive descriptions of the design and results of these studies). Consideration was given to basing the MRL on the NOAEL of 53 mg/kg/day and LOAEL of 133 mg/kg/day for decreases in absolute weight of brain, liver, and spleen, and in relative weight of spleen, in female mice (Shopp et al. 1984). However, the biological significance of these effects is uncertain because (1) the effects were only observed in females, and (2) histological effects in the affected organs were not observed in the other 13-week oral studies with rats and mice.

As discussed in Appendix A, a potential intermediate-duration MRL of 0.7 mg/kg/day was derived based on the duration-adjusted NOAEL of 71 mg/kg/day for decreased body weight in male and female rats exposed by gavage to naphthalene 5 days/week for 13 weeks (NTP 1980b) and a total uncertainty factor of 100 (10 for extrapolating from rats to humans and 10 for human variability). Because the value of 0.7 mg/kg/day is slightly larger than the acute-duration oral MRL of 0.6 mg/kg/day, the acute MRL is expected to be protective for intermediate-duration exposure scenarios and was adopted as the intermediate-duration oral MRL.

No appropriate studies were located for deriving an MRL for chronic oral exposure to naphthalene. One chronic study was located that examined the toxicity of naphthalene in rats (Schmahl 1955). No treatment-related effects were reported at a dose level of 41 mg/kg/day for 700 days. The study was not suitable as the basis for deriving a chronic MRL because only one dose level was evaluated, histopathological examination was limited, and dosing was not precisely controlled.

- An MRL of 0.07 mg/kg/day was derived for chronic oral exposure to 1-methylnaphthalene.

The MRL for 1-methylnaphthalene was derived from an 81-week study in groups of 50 male and 50 female mice using diets containing 0, 71.6 (males), 75.1 (females), 140.2 (males), or 143.7 (females) mg/kg/day (Murata et al. 1993). Food intake, clinical signs, and body weight were determined throughout the study. At the end of 81 weeks, peripheral blood samples were collected and the animals were sacrificed. Organ weights were determined and the tissues examined histologically; tumors were identified and characterized. Hematological parameters and biochemical indices were evaluated in the blood samples.

Male and female mice in both exposure groups showed increased incidences of pulmonary alveolar proteinosis. In males, there was also a significant increase in pulmonary adenomas. The alveolar nodules were filled with an amorphous acidophilic material, cholesterol crystals, and foamy cells. They were not accompanied by inflammation, edema, or fibrosis. The LOAEL of 71.6 mg/kg/day for pulmonary alveolar proteinosis in female mice was used for the derivation of the MRL (see Appendix A), employing an uncertainty factor of 1,000 (10 for using a LOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

- An MRL of 0.04 mg/kg/day was derived for chronic oral exposure to 2-methylnaphthalene.

The chronic MRL is based on a study in which groups of 50 male and 50 female B6C3F1 mice were exposed to dietary levels of 0, 0.075, or 0.15% 2-methylnaphthalene (Murata et al. 1997). Average intakes were reported as 0, 54.3, or 113.8 mg/kg/day for males and 0, 50.3, or 107.6 mg/kg/day for females. Survival and food consumption were not affected by exposure. Mean final body weights were decreased by 7.5 and 4.5% in high-dose males and females, respectively; these changes are not considered to be biologically significant. Histopathology only found exposure-related changes in the lung. Tissues examined were brain, heart, kidney, liver, lung, pancreas, salivary glands, spleen, testis, adrenals, bone, eye, Harderian glands, mammary gland, ovary, seminal vesicle, skeletal muscle, skin, small and large intestine, spinal cord, stomach, trachea, uterus, and vagina. No evidence of bronchiolar Clara cell necrosis or sloughing was found. Females showed statistically significantly decreased differential counts of stab and segmented form neutrophils and increased lymphocytes compared to controls, but the biological significance of these changes is not clear due to a lack of reporting of the data (i.e., the report did not specify the response magnitudes or the dose levels at which they occurred). Incidences for mice with pulmonary alveolar proteinosis were (control through high-dose groups): 5/50, 27/49, and 22/49 for females, and 4/49, 21/49, and 23/49 for males. Incidences for mice with lung adenomas were: 4/50, 4/49, and 5/48 in females, and 2/49, 9/49, and 5/49 in males. Only the lung adenoma incidence in the male

54.3-mg/kg/day groups was significantly different from the control incidence. Combined incidences for lung adenomas or adenocarcinomas were: 5/50, 4/49, and 6/48 for females, and 2/49, 10/49, and 6/49 for males.

Support for pulmonary alveolar proteinosis as the critical effect for the chronic oral MRL for 2-methylnaphthalene comes from chronic duration studies with the isomer, 1-methylnaphthalene, and methylnaphthalene (a mixture of 1- and 2-methylnaphthalene). Increased incidence of pulmonary alveolar proteinosis was reported in B6C3F1 mice exposed to 1-methylnaphthalene in the diet for 81 weeks at dose levels as low as 71.6 mg/kg/day (Murata et al. 1993), and in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (a mixture of 1- and 2-methylnaphthalene) (Emi and Konishi 1985; Murata et al. 1992).

The lower 95% confidence limit on a benchmark dose associated with 5% extra risk for pulmonary alveolar proteinosis in male mice (4 mg/kg/day) was selected as the point of departure for deriving the chronic-duration oral MRL for 2-methylnaphthalene (see Appendix A). A benchmark response of 5% extra risk was selected over a default value of 10% extra risk in order to provide protection for children who may develop pulmonary alveolar proteinosis. This selection is supported by reports that children with pulmonary alveolar proteinosis (albeit of unknown etiology) experience more severe symptoms of respiratory dysfunction than do adults (EPA 2003r; Mazzone et al. 2001). The point of departure was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive the chronic oral MRL of 0.04 mg/kg/day for 2-methylnaphthalene.

No appropriate studies were located for deriving acute or intermediate-duration oral MRLs for 1-methylnaphthalene or 2-methylnaphthalene.