Interim Ground Water Criterion

for

1-Methylnaphthalene

Prepared by

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Introduction

The New Jersey Department of Environmental Protection's Site Remediation Program (NJDEP-SRP) requested that the NJDEP's Office of Science (OS) develop an interim health-based ground water criterion for 1-methylnaphthalene (1-MN) to assist in its site remediation work. OS conducted an online search of the published literature using the PubMed.gov database of the U.S. National Library of Medicine of the National Institutes of Health, and the Hazardous Substances Data Bank of the Toxicology Data Network of the US National Library of Medicine. Additional searches of the scientific literature were conducted through the Information Resource Center (IRC) of the New Jersey State Library. The IRC also conducted searches of the non-peer-reviewed literature including submissions to the USEPA under TSCA reporting requirements. In addition, published ATSDR and USEPA documents (see below) were also located and reviewed.

Summary

1-methylnaphthalene (1-MN) has the CASRN designation, 90-12-0. It is also known as alpha-methylnaphthalene. 1-MN is a liquid under normal environmental conditions and is moderately soluble in water. 1-MN can be considered to have limited volatility.

Its chief industrial use is as an intermediate in the production of phthalate anhydrides, themselves, an intermediate in production of a large number of products. Most of the 1-MN entering the environment originates from incidental releases, mainly from combustion sources.

There do not appear to be any standards for exposure or occurrence specific to 1-MN (ATSDR, 2005; HSDB, 2013). The USEPA (2008) has derived an informal chronic screening value Reference Dose of 7×10^{-3} mg/kg/day (7 µg/kg/day). In the same document, the USEPA described the data on carcinogenicity of 1-MN as "Suggestive Evidence of Carcinogenicity," and derived a cancer potency of 2.9×10^{-2} $(mg/kg/day)^{-1}$ based on the chronic ingestion study of Murata et al. (1993). As discussed below, we do not believe that this study is capable of supporting the derivation of either a Reference Dose or a cancer slope factor.

There do not appear to be any pharmacokinetic data specific to 1-MN. Inferences from the closely related compound, 2-methylnaphthalene (2-MN) suggest that 1-MN has a short half-life in the human body, that it is metabolized, in part through epoxidation of one of its benzene rings, producing a potentially reactive epoxide intermediate, and that it is largely excreted in the urine following metabolism.

Based on very limited data for 1-MN, itself, and from data on 2-MN, it appears that the primary target of acute oral exposure to 1-MN is likely to be the ciliated and non-cilated (Clara) epithelial cells of the small airways.

Limited toxicity data for 1-MN (Murata et al., 1993; Emi and Konichi, 1985) supported by limited observation on 2-MN (Murata et al., 1997) indicate that chronic and subchronic oral exposure to 1-MN can result in alveolar proteinosis, an otherwise rare condition. In addition, subchronic data (Jin et al, 2012) also indicates that 1-MN, in a similar dose range can cause a range of effects on hematological, organ weight and liver pathology parameters.

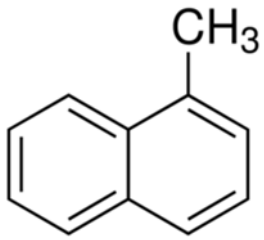
1-MN is judged to present "Suggestive Evidence of Carcinogenicity." This is supported by limited evidence suggesting a genotoxic potential. Evidence for mutagenicity appears to be limited to high doses that are, themselves, toxic.

A Reference Dose is derived based on the subchronic study of Jin et al. (2012). However, the cumulative uncertainty in this Reference Dose (as indicated by the cumulative uncertainty factor adjustment of 300,000) is considered to be incompatible with application of this Reference Dose. Therefore, we recommend the use of the NJDEP interim generic ground water criterion of 5 µg/L for chemicals with some evidence of carcinogenicity for which a cancer slope factor cannot be derived.

Identity

Figure 1 presents the chemical structure of 1-methylnaphthalene.

Figure 1.



1-methylnaphthalene has the CASRN designation, 90-12-0. It is also known as alpha-methylnaphthalene.

Physical and Chemical Properties

1-methylnaphthalene (1-MN) (MW = 142.20) is a liquid under normal environmental conditions, with a melting point of -22 ºC and a boiling point of 244.6 ºC. It is moderately soluble in water at 25.8 mg/L and is soluble in benzene, ethanol, and ether. Its octanol-water partition coefficient (K_{OW}) is 3.87. Given its moderately large lipophilicity, it can be expected to be readily absorbed across cell membranes (ATSDR, 2005). Its vapor pressure at 25 ºC is 0.067 mm Hg (HSDB, 2013). By comparison, the vapor pressure of benzene at the same temperature is 94.8 mm Hg. Thus, 1-MN can be considered to have limited volatility.

Although chemically similar with an identical molecular weight, the melting point of 2-MN, 34.6 ºC, is much higher than that of 1-MN, -22 ºC (HSDB, 2013). However, the water solubility, organic solvent solubility and K_{OW} of 2-MN are quite similar to those of 1-MN (ATSDR, 2005). Thus, given the paucity of 1-MN-specific data, data generated for 2-MN may provide insight into

the potential human health risk from 1-MN. Given the symmetry of naphthalene, 1-MN and 2-MN are the only possible forms of a single methyl group addition to naphthalene.

Background – production, use, occurrence

In 1996, the US produced 238,000,000 pounds of 1-MN. Its chief industrial use is as an intermediate in the production of phthalate anhydrides, themselves, an intermediate in production of a large number of products. Most of the 1-MN entering the environment originates from incidental releases, mainly from combustion sources. Based on its physical-chemical properties, ATSDR predicts that 1-MN is slightly mobile-to-immobile in the soil column (ATSDR, 2005). While 1-MN is expected to have a small volatilization potential from moist soil, it is not expected to volatilize from dry soil given its Henry's law partition coefficients. 1-MN is expected to be subject to digestion by microorganisms in soil (HSDB, 2013).

1-MN has been reported in ambient air at a concentration of 0.51 $\mu g/m^3$, however this may reflect areas with known sources. 1-MN has been found in groundwater at a concentration of 0.02–12 mg/L at the site of a former oil gasification works, and in urban snowpack in MI at a concentration of <0.05–0.177 µg/L.

Existing standards and guidelines

There do not appear to be any standards for exposure or occurrence specific to 1-MN (ATSDR, 2005; HSDB, 2013). The USEPA has published a Provisional Peer-Reviewed Toxicity Value (PPRTV) document for 1-MN (USEPA, 2008). In its review of the available data in that document, the USEPA judged that there were insufficient data to derive a provisional Reference Dose. They did, however, derive an informal chronic screening value Reference Dose of (7×10^{-3} mg/kg/day (7 µg/kg/day) based on data presented in Murata et al. (1993) (see below). In the same document, the USEPA described the data on carcinogenicity of 1-MN as "Suggestive Evidence of Carcinogenicity," and derived a cancer potency of 2.9×10^{-2} $(mg/kg/day)^{-1}$. As discussed below, based on methodological problems with the Murata et al. (1993) study, we do not believe that study is capable of supporting the derivation of either a Reference Dose or a

cancer slope factor. It should be noted that the USEPA PPRTV document pre-dates the publication of the Jin et al. (2012) study from which a Reference Dose can be calculated.

Pharmacokinetics and Metabolism

There do not appear to be any pharmacokinetic data available that are specific to the absorption, distribution or elimination 1-MN. Reports (see below) of adverse toxic effects following ingestion of 1-MN imply that it has a toxicologically significant absorption after oral exposure. Teshima et al. (1983) gave male guinea pigs an oral dose of 10 mg/kg ^{3}H-2-MN. The label reached its maximum level in blood and gallbladder at 3 hr post-dosing and in all other organs (including lung) at 6 hr post-dosing. Levels declined to ≤10% of their maximum value at 48 hr. Concentrations by organ at 6 hr were in the order of: gallbladder>kidney>liver>>lung>blood. The concentration in the blood at 6 hr was 0.26 that in the liver. Based on the decline in concentration at 3, 6, 24 and 48 hr post-dosing, the authors calculated the half-life in blood as 10.4 hr based on an assumed first order rate. The decline in the other tissues was found to be biphasic. At 24 hr, 84% of the recovered label was found in urine and 10% in the feces.

Griffin et al. (1982) found that following single intraperitoneal injection of 2-MN at 200 or 400 mg/kg to male mice (age unspecified), the half-life for elimination from blood of radioactivity originating as ^{14}C-2-MN was approximately 3 hr. The highest level of accumulation was in the fat (Griffin et al., 1982). The level of irreversible binding to the cellular macromolecular protein fraction in various organs reached a maximum at approximately 8 hr post dosing and remained elevated at 24 hr. Macromolecular protein binding was examined in the liver, kidney and lung with the highest levels in liver and kidney and lowest in lung. However, there was no evidence of liver or kidney toxicity in this study. Thus, notwithstanding the toxicity of 2-MN (and 1-MN) in the lungs (see below), there does not appear to be significant retention in the lungs.

Swiercz et al. (2010) exposed male Wistar rats (3-4 mos old) to 2-MN by inhalation to 200 or 400 mg/m^3. Kinetics of elimination from blood after a 6 hr exposure to 200 mg/m^3 were biphasic with a rapid component with a half-life of 0.52 hr and a slower component with a half-

life of 4.96 hr. After repeated exposures (5 days for 6 hr/day) to 200 mg/m^3, the half-lives of the two components were similar to those found for the single exposure – 1.00 hr and 5.18 hr respectively. With exposure to 400 mg/m^3, the half-lives of the two kinetic components were disproportionally larger. The half-life estimates for elimination of 2-MN from blood in this study are about half those reported by Teshima et al. (1983). However, given that the Teshima et al. measurements are in guinea pigs as opposed to rats and that Teshima et al. exposed the guinea pigs to 2-MN by ingestion whereas the route of exposure in this study was inhalation, the half-lives in blood from the two studies are in reasonably close agreement in indicating little retention of 2-MN. This is likely to be the case for 1-MN, but no firm conclusions can be drawn in the absence of chemical-specific data.

There do not appear to be any data specific to the metabolism of 1-MN. ATSDR (2005) has summarized studies of the metabolism of 2-MN. This scheme is presented in Figure 2. This scheme has two major bifurcations: one involving the oxidation of the methyl group, leading ultimately to 2-napthuric acid; and the other proceeding through the epoxidation of one or the other of the benzene rings followed by opening of the epoxide, resulting in substitution with or without production of the dihydrodiol. In rats and mice, the majority of 2-MN is metabolized initially to the 2-hydroxymethylnaphthalene. Consequently, 2-napthuric acid is the major urinary product of 2-MN exposure. Metabolism through ring epoxidation appears to account for all or most of the metabolism that does not proceed through oxidation of the methyl group (ATSDR, 2005). Thus, the potential exists for reactions of cellular and extra-cellular components with the reactive epoxide. At least some of the metabolic products of the ring epoxidation pathways are conjugated with glutathione. Depletion of glutathione appears to lead to toxicity via this pathway in one strain of mouse, but not in another (ATSDR, 2005). This may be more of an issue for high dose acute exposures than for lower-dose chronic exposures. Since neither the oxidation of the methyl group, nor the epoxidation of the benzene rings appears to involve processes that have an obvious requirement for a specific orientation of the position of the methyl group, it is likely that same pathways described for 2-MN function in the metabolism of 1-MN.

There do not appear to be any data on the routes of elimination of 1-MN from the body. In guinea pigs about 80% of an oral dose of 2-MN, is excreted in the urine, the remainder appears to be accounted for by fecal elimination (ATSDR, 2005).

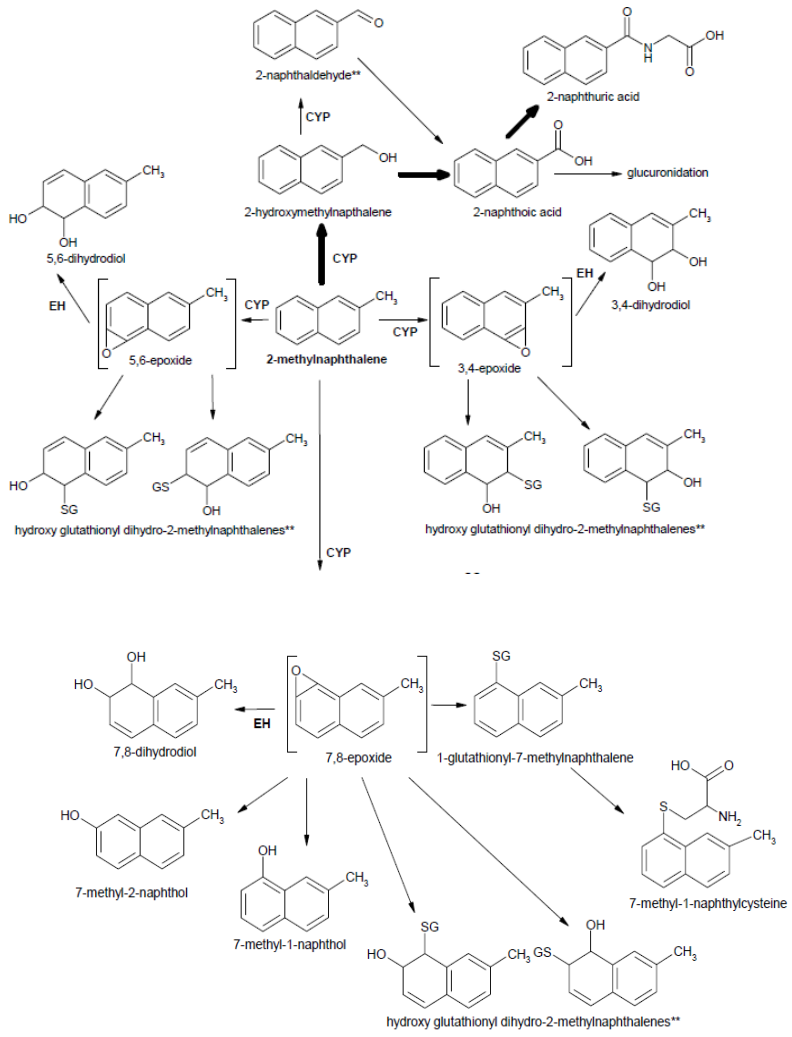


Figure 2. Proposed scheme for the metabolism of 2-methylnaphthalene (ATSDR, 2005).

Acute and Sub-Acute Toxicity

There are limited data on the effects of acute exposure to 1-MN. Rasmussen et al. (1986) administered single intraperitoneal injections of 1-MN (or naphthalene, or 2-MN) to 8-10 week-old male mice. Doses were 0.5, 1.0, 2.0 or 3.0 mmol/kg (71, 142, 284, 427 mg/kg) in peanut oil.

By optical microscopy, there was no alteration of squamous alveolar epithelial cells or granular pneumocytes. However, there was a dose-related alteration in Clara cells and ciliated cells in terminal bronchioles with 1-MN being the least toxic of the three related compounds with observation over 24 hr-14 days. In Clara cells, cell flattening and cytoplasmic vacuolization were observed at the lowest dose (0.07 μg/kg). With increased doses, increased vacuolization, hydration and desquamation were observed. In ciliated cells, the low-dose effect was cell flattening, with cell sloughing at the highest dose. There were "minimal" optical microscopy liver changes with 1-MN (or naphthalene or 2-MN). No kidney effects were observed by optical microscopy. Electron microscopy observations are reported only for the lower respiratory tract. There was little or no observable damage to alveolar cells. Ciliated (bronchiole) cells were affected only moderately and at high doses. However, consistent with the light microscope observations, Clara cells were affected at the lowest dose (0.07 μg/kg) including reduction in microvilli and "dramatic" reduction in smooth endoplasmic reticulum (SER).

Dinsdale et al. (1987) injected female Wistar rats intraperitoneally with 1 nmol/kg (0.1 μg/kg) of 1-MN. Respiratory tissue was examined microscopically at 24 hr post-injection. In contrast to the findings of lower respiratory toxicity by Rasmussen et al. (1986), there were no observed lung lesions from 1-MN (or 2-MN) injection.

In a non-published (and non-peer-reviewed) sub-acute study reported to the USEPA (Dupont Corp., 1951), six rats (sex not specified) each received 10 treatments of 1,500 mg/kg/day of "alpha-methylnaphthalene" (a synonym of 1-MN) over 2 weeks. The exposure method was not specified, although based on the description, exposure was presumably by gavage.

The report noted weight loss (not quantified), ill appearance, and "bad tempers." All animals survived to the end of treatment. The rats regained the lost weight and were reported to be in "good condition" 14 days after end of treatment. No gross or microscopic pathological abnormalities were noted (it is unclear what organs were examined or whether alveolar proteinosis would have been detected).

For 2-MN, at much larger acute doses, intraperitoneal administration of ≥200 mg/kg to mice resulted in nearly complete sloughing off of the inner lining cells of bronchioles (Clara cells) at

24 hr. With increased acute doses, this effect was found higher up the respiratory tract (Griffin et al., 1981; 1982). Although binding of 2-MN radiolabel in the cellular macromolecular portion was highest in the liver, no liver toxicity was noted in this dose range.

Overall, based on very limited data for 1-MN, itself, and from data on 2-MN, it appears that the primary target of acute exposure to 1-MN is likely to be the ciliated and non-ciliated (Clara) epithelial cells of the small airways.

Chronic/Subchronic Toxicity including Carcinogenicity and Neurobehavioral Effects

Jin et al. (2012) conducted a sub-chronic dietary exposure study of 1-MN using B6C3F1gpt delta mice, a transgenic strain incorporating bacterial genes incorporated in multiple phage λ DNA copies intended largely for mutagenesis testing (see below). Ten mice of each sex and dose group were exposed starting at 6 wks of age to 0, 0.075% or 0.15% 1-MN in their diet for 13 wks. In the portion of this study that was not designed to test for mutagenicity, mice were evaluated for hematology, serum biochemistry, organ weights, and histopathology. The doses experienced by the mice were estimated from the mass of food consumed and the body weight. For males, Jin et al. reported doses of 0.12 mg/kg/day and 0.22 mg/kg/day for the low and high doses respectively. For females, they reported doses of 0.17 and 0.28 mg/kg/day for the low and high doses respectively. However, based on the data provided by Jin et al. (2012) on food consumption and body weight, the units of the reported dose estimates are incorrect. As given, these values correspond to the dose in **g**/kg/day rather than **mg**/kg/day. In units of mg/kg/day, the correct high and low doses for males are 120 and 220 mg/kg/day, respectively, and the correct doses for females for high and low doses are 170 and 280 mg/kg/day, respectively.

There was no significant change in body weight. Food intake was decreased as a function of dose at various times points, but this did not appear to be related to changes in body weight.

There was a significant decrease in band-form neutrophils in males at low dose, and an increase in segmented neutrophils at high dose. In females, there was a significant increase in basophils at both doses. In males, there was a significant decrease in phospholipids, BUN and creatinine – all at the high dose only, and a decrease in serum Ca at both doses. In addition, there was a significant increase in ALT and AST at the high dose only. In females, there was a significant decrease in phospholipids and total cholesterol and serum Cl only at the high dose. The effects

on serum biochemistry between males and females differ except with respect to serum phospholipids.

In males, there was a significant absolute and relative decrease in spleen and heart weight at both doses, and a significant relative decrease in spleen weight at both doses and in heart at the high dose. In females, there was a significant absolute decrease in liver weight and an increase in thymus weight at the high dose only (and no differences in relative weights). The authors attribute thymus weight gain to a single mouse with a lymphoma. Overall, there was a lack of consistency in organ weight changes between males and females.

Organ-specific histopathology showed a dose-related incidence of hepatic single cell necrosis in males, with an incidence of 0/10, 3/10, 5/10 for controls, low, and high doses respectively. The incidence was statistically significant only in the high dose group. No similar pathology was observed in females. Histopathology was also conducted on lung tissue (as well as tissue of other organs). However, from the limited description provided in this paper, it is not clear which specific lung tissue was examined and whether alveolar proteinosis or Clara cell toxicity would have been detected.

Murata et al. (1993) exposed male and female mice (50 per sex and dose) for 81 wk to 0, 0.075, or 0.15% 1-MN in the diet starting at 6 wk of age**.** Based on food intake and body weights averaged over the entire exposure period and across sexes, the corresponding doses were 73.4 and 142.0 mg/kg/day.

There were no significant differences in body weight, food intake, or survival based on dose. There was a significant increase in absolute and relative brain weight at both doses in males only, a significant decreased absolute and relative heart weight in males at both doses, and a significant decrease in absolute (but not relative) heart weight at both doses in females.

Alveolar proteinosis was prominently observed. This condition is characterized by amorphous, acidophilic material accumulated in alveolar lumens, foamy cells, and cholesterol crystals. There was a background incidence of alveolar proteinosis in controls, but the increase at both doses was significant and dramatic for both sexes: Females – controls = 5/50(10%); low dose = 23/50 (46%); high dose = 17/49 (35%); Males – controls = 4/49 (8.2%); low dose = 23/50 (46%); high dose = 19/50 (38%).

There was a significant increase in monocytes as a percent of leukocytes in peripheral blood at both doses in males (controls = 0.17%; low dose = 0.81%; high dose = 1.18%) and at high dose in females (controls = 0.42%; low dose = 0.91%; high dose = 1.10%). In females only, there was a significant increase in lymphocytes as a percent of leukocytes at high dose (controls = 82.3%; low dose = 81.4%; high dose = 86.7%), but a significant decrease at both doses in males (controls = 85.6%; low dose = 75.5%; high dose = 81.3%). In females only, there was a significant increase in hemoglobin (Hb) concentration and mean corpuscular Hb concentration at both doses. In males, there was a decrease in hematocrit and mean corpuscular volume at the low dose only. The effect of 1-MN exposure on the hematological parameters is not consistent across sexes and, overall, the toxicological significance of hematological parameters is not clear.

In serum, neutral fat concentration was significantly increased in females at the low and high doses, and in males at the low dose only.

There was a significant increase in lung tumors in males only (controls = 2/49 (4.1%); low dose = 13/50 (26%); high dose = 15/50 (30%). The increase was due mostly to (benign) adenomas with 3/50 (malignant) adenocarcinomas at high dose. In general, there was a single tumor observed per mouse. There was no significant increase in lung tumors in females with no suggestion of trend (controls = 5/50 (10%); low dose = 2/50 (4%); high dose = 5/49 (10.2%).

It is interesting to note that in contrast with the toxicity observed with acute exposure to 1-MN at higher doses (or 2-MN), the respiratory toxicity observed by Murata et al. (1993) with chronic exposure did not include effects on the ciliated or unciliated (Clara) epithelial cells of the lower bronchiole. Conversely, alveolar proteinosis, observed in this study, was not observed in studies with acute exposure.

Murata et al. (1997) found both alveolar proteinosis in males and females and, to a lesser extent, evidence of lung tumors in males in a parallel study of 2-MN.

In its consideration of a Provisional Peer Reviewed Toxicity Value (PPRTV) for 1-Methylnaphthalene, the USEPA (2008) critiqued the Murata et al. (1993) study. (It should be noted that the USEPA PPRTV document contains an incorrect attribution of dates, confusing the 1993 Murata et al. study of 1-MN, with the 1997 Murata et al. study of 2-MN). The USEPA

noted that in both the Murata et al. (1993) 1-MN study and its parallel and simultaneously conducted chronic ingestion study of 2-MN (Murata et al., 1997), there was an incidence of alveolar proteinosis in both male and female control mice. Murata et al. (1997) noted that historically, in 5,000 histopathological analyses in the same strain of mouse, all housed in the same room, no background incidence of this condition was noted. Since the 1-MN study and the 2-MN study were conducted simultaneously, Murata et al. hypothesize that the background incidence of alveolar proteinosis arose from off-gassing of the chemicals from the food of the dosed animals. If this were the case, not only would the control mice have been exposed, but the dosed mice would also have received a significant inhalation exposure to 1-MN (and presumably, 2-MN). Thus, the total dose based on ingestion alone would have been underestimated due to the contribution from inhalation. At the same time, however, the ingestion dose would have been overestimated due to loss of 1-MN from feed due to volatilization. Furthermore, it seems possible that if there was exposure resulting from volatilization of 1-MN and 2-MN from food, there could have been cross exposure of the mice to both 1-MN and 2-MN. However, from the standpoint of hazard identification, the overall lower tumor and non-tumor toxicity of 2-MN suggests that the qualitative effects observed in the (primarily) 1-MN exposed mice arose largely from 1-MN exposure rather than from the potential exposure to 2-MN. While the relatively low vapor pressure of 1-MN raises some doubt as to the extent to which volatilization could account for significant exposure throughout the animal storage facility, no other explanation is available to account for the highly unusual background incidence of alveolar proteinosis. Thus, while the qualitative findings of this study appear to be valid, the quantitative (i.e., dose-response) data are of uncertain utility.

Emi and Konishi (1985) briefly describe a chronic skin painting study in which "methylnaphthalene" (presumably mixed 1, and 2-MN isomers) dissolved in acetone was applied to the skin of female mice at 29.7 or 118.8 mg/kg twice per week for 61 wks. The study was terminated apparently in response to increasing mortality among the mice.

Emi and Konishi reported the development of endogenous lipid pneumonia characterized as foamy cells, cholesterol crystals in alveoli, "multinucleated giant cell reaction," hypertrophy of type II pneumocytes with increase in number, and focal alveolar dilation. The incidence of this effect was: controls - 0/4; low dose – 3/11; high dose – 31/32. This pathology appears to be the same as that described in Murata et al. (1993) as alveolar proteinosis.

Reproductive and Developmental Toxicity

No reports of reproductive or developmental toxicity testing on 1-MN or 2-MN were located.

Genotoxicity/Mutagenicity

Kaden et al. (1979) tested the mutagenicity of 1-MN relative to benzo-a-pyrene (BAP) in the *S. Typhimurium* TM677 tester strain with Arochlor-induced rat liver S9 fraction. Based on the dose-revertant slope, 1-MN was mutagenic with 1% of BAP potency. Mutagenicity occurred in a dose range (3.5-6 mM) that reduced bacterial survival.

Florin et al. (1980) tested 1-MN (and 2-MN) in Ames Salmonella strains TA 98, 100, 1535, 1537 with and without Arochlor-induced and 3-methylcholanthrene induced S9, at concentration of 0.03, 0.3 and 3 μmol/plate. There was no significant increase in number of revertants in any of the strains with or without metabolic activation (S9 addition). Doses >3 μmol/plate were toxic. Note that these concentrations were about three orders of magnitude lower than those observed by Kaden et al. (1979) to be slightly mutagenic (and toxic).

Jin et al. (2012), in the study described previously in the context of its investigation of sub-chronic toxicity, exposed B6C3F1gpt delta mice, 10 of each sex and dose group, to 0, 0.075% or 0.15% 1-MN in diet for 13 wks. This is a transgenic mouse strain containing multiple copies of a phage λ that incorporates genes that function in the bacterial metabolism of bactericidal elements in the plating agar. When those genes are in their wild-type form, the bacteria metabolize the bactericidal elements in the agar resulting in bacterial toxicity and plaques do not appear on the agar. However, if these genes are mutated to an inactive form, the bacteria are able to grow on the agar and form plaques. At sacrifice, DNA was extracted from mouse lung tissue and the phage portion of the DNA containing the bactericidal metabolizing genes was used to transfect *E. coli*. *E. coli* plaques resulting from mutation of the bactericide metabolizing genes while in the mice were counted to give the mutation frequency. No significant increase in mutation frequency as a function of 1-MN dose to the mice was observed in either sex. PCNA (proliferating cell nuclear antigen), a gene that is a measure of DNA replication was also monitored immunohistologically in the mice. No differences in immunologically based levels of

PCNA were seen. It should be noted that the PCNA assay was apparently conducted only in lung tissue. Thus, this assay did not provide any indication of a proliferative effect of 1-MN that could have indirectly resulted in an increased mutation rate or clonal expansion of mutated loci.

Kulka et al. (1988) tested 1-MN and 2-MN in a primary human lymphocyte culture. 1-MN was tested at 0, 1.0 and 2.0 mM without S9 activation, and at 0, 0.25, 0.5, 1.0 and 2.0 mM with Clophen A-50-induced rat liver S9 for 66 hrs. Cell proliferation was inhibited at concentrations >2.0 mM. For 1-MN, there was no significant induction of chromosome abnormalities at any dose. For 2-MN, chromosome abnormalities were seen only at 4.0 mM (the highest dose not affecting cell proliferation). SCE (sister chromatid exchange) was significantly increased at all concentrations for 1-MN and 2-MN, but only with S9 incubation.

Based on this limited evidence, it appears that 1-MN has mutagenic potential only at high concentrations and that mutagenicity at high concentrations may be secondary to toxicity. There is limited evidence from Kulka et al. (1988) that 1-MN may have genotoxic potential as reflected in SCE. However, additional evidence would be required to draw a reasonably firm conclusion that this compound is genotoxic.

Development of Toxicity Factor:

Choice of appropriate carcinogenicity descriptor based on weight of evidence

There is only a single study (Murata et al., 1993) that provides data on the possible carcinogenicity of 1-MN. In that study, there was a statistically significant, monotonic dose-dependent increase in benign plus malignant lung tumors in male mice, but not in females. This observation is qualitatively consistent with a carcinogenic potential. However, as noted above, there is evidence that the control mice in this study received an exposure to 1-MN, apparently from volatilization of the 1-MN in the feed of the dosed mice that were housed in the same room. This makes estimation of the received dose in both controls and dosed mice uncertain. Thus, the data from this study cannot be used for quantitative dose-response modeling. The observation of an increased incidence of lung tumors in this study is consistent with the observation from the same study that the lung was the primary target of non-cancer toxicity (i.e., alveolar proteinosis).

The observation of a possible carcinogenic potential for 1-MN receives some support from the related study of 2-MN of Murata et al. (1997). In that study, there was a statistically significant increase in lung tumors in male mice at the low dose, but not at the high dose. There was no increase in tumors at either dose in female mice. However, the mice in that study were housed with the mice used in the 1-MN study of Murata et al. (1993) and the received dose in Murata et al. (1997) is, likewise, undeterminable.

The evidence for a carcinogenic potential of 1-MN is supported somewhat by limited evidence that 1-MN has a mutagenic potential, but this appears to be a high-dose phenomenon that may be secondary to cytotoxicity (Kaden et al., 1979). A possible carcinogenic potential also receives limited support from evidence of a genotoxic potential based on SCE (Kulka et al., 1988).

Based on the foregoing information, the most appropriate designation of the carcinogenic potential of 1-MN under the USEPA's Guidelines for Carcinogen Risk Assessment (USEPA, 2005) is "suggestive evidence of carcinogenic potential." Based on the same rationale, under the older 1986 USEPA Guidelines for Carcinogen Risk Assessment (USEPA, 1986), the appropriate classification of carcinogenic potential is Group C – Possible Human Carcinogen. However, the quality of the database underlying these categorizations is low. Although there is a statistically significant dose-response relationship for tumor production in male mice at both doses in Murata et al. (1993), methodological problems with the conduct of this study make these results difficult to interpret. There is only weak support from other studies for the carcinogenic potential of 1-MN.

Choice of most appropriate study /Choice of most appropriate endpoint

There are two studies that provide evidence of non-carcinogenic adverse effects from exposure to 1-MN, the 81-week study of Murata et al. (1993) and the 13-week study of Jin et al. (2012). Murata et al. (1993) found a statistically significant elevation in alveolar proteinosis in both male and female mice. Alveolar proteinosis appears to be a rare condition that is fairly specific to 1-MN and to a lesser extent 2-MN. However, given this, the occurrence of alveolar proteinosis in the control mice in this study, as discussed above, strongly suggests a cross-exposure of the controls as well as reduction in the calculated dose in the dosed animals. This makes the Murata et al. (1993) study unusable for the development of a toxicity factor. The finding of a dose-response relationship between 1-MN and aveolar proteinosis is supported by the skin painting

study of Emi and Konishi (1985). In that study methylnaphthalene, presumably a mixture of 1 and 2-MN applied in a similar dose range to that in Jin et al. (2012) for 61 wks also produced alveolar proteinosis. However, the lack of clarity as to the applied chemical(s) and the uncertain internal dose resulting from the skin painting do not allow the Emi and Konishi (1985) study to be used as a primary basis for determining a Reference Dose. Jin et al (2012) observed a range of adverse effects at the same nominal 1-MN low and high concentrations. The statistically significant increased adverse effects relative to controls occurred at both feed concentrations of 1-MN. Jin et al. (2012) estimated the 1-MN dose based on body weight and the mass of food consumed (g food/mouse/day). Based on the corrected calculation of dose described above, the low and high doses for males are reported as 120 and 220 mg/kg/day respectively, and the low doses for females are 170 and 280 mg/kg/day, respectively. There are several effects in that study that were identified at the low 1-MN feed concentration. These include changes in hematological and serum parameters, changes in organ weights and liver cytotoxicity.

Development of a Reference Dose

The adverse effects discussed above were found in both males and females at the lower of the two 1- MN concentrations in the feed. However, the low feed concentration of 1-MN resulted in a lower dose in males (120 mg/kg/day) than in females (170 mg/kg/day). Therefore, the low dose experienced by the males in the Jin et al. (2012) is the appropriate basis for consideration of the development of a Reference Dose. The low dose in this study is a LOAEL for the several adverse effects detailed above. With only two exposure levels and a control group, benchmark dose modeling does not appear appropriate and the LOAEL estimated by Jin et al. is used as the basis for the Reference Dose.

Following USEPA risk assessment policy as applied in its IRIS database, the human equivalent dose (HED) is estimated based on the assumption of an interspecies conversion of (body-weight)$^{3/4}$ (Fed. Reg., 2011; USEPA, 2013). The human equivalent dose is calculated as follows:

$LOAEL_{mouse}$ = 120 mg/kg/day
Mean mouse body weight from Jin et al. (2012) = 0.03 kg
Mouse intake (mass) of 1-MN/day at the LOAEL dose = 120 mg/kg/day x 0.03 kg = 3.6 mg/day
Default human body weight = 70 kg
$body\text{-}weight_{human}$ /$body\text{-}weight_{mouse}$ = 70 kg/0.03 kg = 2333

$(2333)^{3/4} = 336$
Human equivalent intake = 336 x 3.6 mg/day = 1210 mg/day
Human equivalent dose = 1210 mg/day/70 kg = 17.29 mg/kg/day

The interspecies conversion of dose based on (body-weight)$^{3/4}$ addresses those general metabolic and physiological factors that govern kinetic processes of absorption, distribution, metabolism and excretion. As such, this interspecies scaling is assumed to address those differences between humans and mice based on toxicokinetics that would otherwise result in uncertainty in interspecies extrapolation. Species-specific differences in cellular and molecular events leading to toxicity (i.e., toxicodynamic factors) are not assumed to be addressed by this interspecies scaling procedure (USEPA, 2013).

The following uncertainty factors are applied to the human equivalent dose corresponding to the mouse LOAEL from Jin et al. (2012) to derive the Reference Dose:

$UF_{interspecies}$ – (uncertainty in interspecies differences in toxicodynamic factors-only in the estimation of the equivalent human LOAEL from the mouse LOAEL, see above) – 3.

UF_{NOAEL} - (uncertainty in the estimation of a NOAEL from a LOAEL) – 10.

$UF_{subchronic}$ - (uncertainty in the estimation of a chronic NOAEL from a (13 wk) subchronic NOAEL) – 10.

$UF_{sensitive}$ - (uncertainty in the difference between the average population NOAEL and the sensitive population NOAEL) – 10.

$UF_{database}$ - (uncertainty due to insufficiencies in the database – in this case, lack of reproductive, developmental, or neurobehavioral studies) – 10.

The Reference Dose is then calculated as:
Human equivalent dose/ $UF_{total} = UF_1 \times UF_2 \ldots =$
17 mg/kg/day/ (3 x 10 x 10 x 10 x 10) = 5.7×10^{-4} mg/kg/day = 0.6 µg/kg/day.

The NJDEP policy for addressing chemicals that are characterized as "suggestive evidence of carcinogenicity"/Group-C is to apply an additional factor of 10 to the Reference Dose, to address the uncertainty regarding carcinogenicity when the derivation of a cancer slope factor is not supported by the data. Following this approach, the Reference $Dose_{Group\text{-}C}$ would be calculated as (0.6 µg/kg/day)/10 = 0.06 µg/kg/day.

However, this procedure results in an overall uncertainty adjustment factor of 300,000. This is judged to be an unsupportable degree of uncertainty upon which to derive a meaningful risk-based value. This is consistent with USEPA policy that does not support the derivation of an Reference Dose when the overall uncertainty factor is equal to or greater than 10,000. Therefore, the NJDEP interim generic ground water criterion of 5 µg/L for chemicals with some evidence of carcinogenicity, but for which a cancer slope factor cannot be derived, is recommended for 1-MN.

Discussion of uncertainties and confidence in the derivation

There is only a single study of chronic exposure to 1-MN (Murata et al., 1993) and that study is not useable for quantitative dose-response analysis due to uncertainties relating to possible cross exposure of dose groups as well as a possible cross exposure between 1-MN and 2-MN and a possible related, but unknown, reduction in the intended feed concentration of 1-MN. This study is useful for hazard identification and provides some evidence of a potential for 1-MN to produce lung tumors as well as strong evidence for alveolar proteinosis, a clear, non-cancer endpoint. Additional evidence for alveolar proteinosis is provided by the skin painting study of Emi and Konichi (1985). There is only one oral subchronic study of 1-MN toxicity (Jin et al., 2012). That study does not suffer from significant structural flaws, but it incorporates only two dose levels, and the lower of these corresponds to a LOAEL. This study is, in theory, useful for the derivation of a Reference Dose. However, despite employing the same strain of mouse and closely similar doses to those in the chronic study, this study did not detect lung pathology. While the duration of exposure may not have been sufficient to detect 1-MN mediated lung tumors, it is unclear to what extent the histopathological examination of the lungs in this study was sufficiently specific to detect alveolar proteinosis. Thus, it is not known to what extent the LOAEL from Jin et al. (2012) is inclusive of the toxicity observed by Murata et al. (1993). A

significant area of uncertainty in this assessment is the lack of reproductive, developmental, or neurobehavioral toxicity studies.

It should be noted that in its Provisional Peer Reviewed Toxicity Value (PPRTV) document for 1-MN (USEPA, 2008), the USEPA found that methodological problems and deficiencies with the Murata et al. (1993) study precluded its use in the derivation of a Reference Dose for 1-MN. The USEPA, therefore, declined to derive a Reference Dose. We concur with this assessment as it applies to Murata et al. (1993). However, the PPRTV document predates the Jin et al. (2012) study.

The absence of useable quantitative chronic dose-response data and the lack of reproductive/developmental/neurobehavioral toxicity data, in combination with the generic uncertainties inherent in utilizing animal data for the derivation of a Reference Dose, result in an overall uncertainty factor adjustment that is excessive and incompatible with the derivation of a meaningful Reference Dose. Therefore, the NJDEP interim generic ground water criterion of 5 µg/L for chemicals with some evidence of carcinogenicity, but for which data are not available to develop a specific ground water criterion, is recommended for 1-MN. Overall, the confidence in the resulting criterion is low.

References

ATSDR (Agency for Toxic Substances Disease Registry) (2005). Toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, accessed at: http://www.atsdr.cdc.gov/ToxProfiles/tp67.pdf , 1/25/13.

Buckpitt A, Plopper C, Silverkopp C, O'Brien K, Morin D. (1988). Tolerance to multiple doses of the pulmonary brochiolar cytotoxicant naphthalene. FASER J 2:2936.

Buckpitt AR, Franklin RB. Relationship of naphthalene and 2-methylnaphthalene metabolism to pulmonary bronchiolar epithelial cell necrosis. Pharmacol Ther. 1989;41(1-2):393-410 (Review)

Dinsdale D, Verschoyle RD. 1987. Pulmonary toxicity of naphthalene derivatives in the rat. Arch Toxicol (Suppl 11): 288-291.

Dupont Corp. (1951). Preliminary Toxicity Investigation of 2-Tertiarybutyl Anthraquinone, alphamethyl Naphthalene, Diisobutyl Carbinol, Organic Working Solution. USEPA TSCA submission 8EHQ-1192-13158.

Emi Y, Konishi Y. 1985. Endogenous lipid pneumonia in B6C3F1 mice. In: Jones TC, Mohr U, Hunt RD, eds. Respiratory system: Monographs on pathology of laboratory animals. New York: Springer-Verlag, 166-168.

Fed. Reg. (U.S. Federal Register) (2011). Notice of Availability; Recommended Use of Body Weight[bds3][bdsol][bds4] as the Default Method in Derivation of the Oral Reference Dose. Environmental Protection Agency [EPA/100/R-11/001; FRL-9270-7], Volume 76, Number 38 (Friday, February 25, 2011)], accessed at: http://www.gpo.gov/fdsys/pkg/FR-2011-02-25/html/2011-4250.htm, 2/12/13.

Florin I, Rutberg L, Curvall M, Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 18:219-232.

Griffin KA, Johnson CB, Breger RK, Franklin RB. Effects of inducers and inhibitors of cytochrome P-450-linked monooxygenases on the toxicity, in vitro metabolism and in vivo irreversible binding of 2-methylnaphthalene in mice. J Pharmacol Exp Ther. 1982 Jun;221(3):517-24.

HSDB (Hazardous Substances Database) (2013). 1-Methylnaphthalene, accessed at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~oqUuHI:1, 2/20/13.

HSDB (Hazrdous Substances Database) (2013). 1-Methylnaphthalene, accessed at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~IBDani:1:cpp , 1/25/13.

Jin M, Kijima A, Suzuki Y, Hibi D, Ishii Y, Nohmi T, Nishikawa A, Ogawa K, Umemura T. In vivo genotoxicity of 1-methylnaphthalene from comprehensive toxicity studies with B6C3F1 gpt delta mice. J Toxicol Sci. 2012;37(4):711-21.

Kaden DA, Hites RA, Thilly WG. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium Cancer Res. 1979 Oct;39(10):4152-9.

Kulka U, Schmid E, Huber R, Bauchinger M (1988). Analysis of the cytogenetic effect in human lymphocytes induced by metabolically activated 1- and 2-methylnaphthalene. Mutat Res 208:155-158.

Murata Y, Denda A, Maruyama H, Konishi Y. Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice.Fundam Appl Toxicol. 1993 Jul;21(1):44-51.

Murata Y, Denda A, Maruyama H, Nakae D, Tsutsumi M, Tsujiuchi T, Konishi Y. 1997. Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol. 1997 Mar;36(1):90-3.

Rasmussen RE, Do DH, Kim TS, Dearden LC. Comparative cytotoxicity of naphthalene and its monomethyl- and mononitro-derivatives in the mouse lung. J Appl Toxicol. 1986 Feb;6(1):13-20.

Swiercz R, Wąsowicz W, Majcherek W. The toxicokinetics of 2-methylnaphtalene in rats. Int J Occup Med Environ Health. 2010;23(4):385-9.

Teshima R, Nagamatsu K, Ikebuchi H, et al. 1983. *In vivo* and *in vitro* metabolism of 2-methyl-naphthalene in the guinea pig. Drug Metab Dispos 11(2):152-157.

USEPA (1986). EPA/630/R-00/004, accessed at: http://www.epa.gov/raf/publications/pdfs/CA%20GUIDELINES_1986.PDF, 2/11/2013.

USEPA (2005). Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001F, accessed at: http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF, 2/11/2013.

USEPA (2008). Provisional Peer Reviewed Toxicity Values for 1-Methylnaphthalene. Superfund Health Risk Technical Support Center, National Center for Environmental Assessment.

USEPA (2011). Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose, EPA/100/R11/0001 Final, accessed at: http://www2.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf. 6/19/15.