2-Methylnaphthalene; CASRN 91-57-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 2-METHYLNAPHTHALENE

File First On-Line 12/22/2003

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	12/22/2003
Inhalation RfC (I.B.)	qualitative discussion	12/22/2003
Carcinogenicity Assessment (II.)	yes	12/22/2003

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 2-Methylnaphthalene
CASRN — 91-57-6
Last Revised — 12/22/2003

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Pulmonary alveolar proteinosis **B6C3F1 male and female mice 81-week dietary study** **Murata et al. (1997)**	BMD_{05}: 4.7 mg/kg-day $BMDL_{05}$: 3.5 mg/kg-day	1000	1	4E-3 mg/kg-day

* Conversion Factors and Assumptions: Incidence data for pulmonary alveolar proteinosis in control and exposed male and female mice were analyzed by benchmark dose modeling. The lower 95% confidence interval on the benchmark dose associated with a 5% extra risk (BMD_{05}) for pulmonary alveolar proteinosis in male and female mice was the point of departure for the RfD.

I.A.2. Principal and Supporting Studies (Oral RfD)

Murata, Y; Denda, A; Maruyama, H; Nakae, D; Tsutsumi, M; Tsujiuchi, T; Konishi, Y (1997) Short communication. Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol. 36:90 93.

Murata et al. (1997) fed B6C3F1 mice (50/sex/group) diets containing 0, 0.075, or 0.15% 2-methylnaphthalene for 81 weeks. The 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. Mice were monitored daily for clinical signs of toxicity. For the first 16 weeks, food consumption and body weight were measured weekly and every other week thereafter. Blood was collected at sacrifice for leukocyte classification and comprehensive biochemical analyses. Organ weights were measured for the brain, heart, kidney, liver, individual lobes of the lung, pancreas, salivary glands, spleen, and testis. Histopathology was performed for these tissues and the adrenals, bone (sternal, vertebral, and rib), eye, harderian glands, mammary gland, ovary, seminal vesicle, skeletal muscle, skin, small and large intestine, spinal cord, stomach, trachea, uterus,

and vagina. Pulmonary function was not measured. Quantitative differences between groups were statistically analyzed using Fisher's exact test and analysis of variance (ANOVA) with a multiple comparison post-test by Dunnett ($p <= 0.05$% was used as the threshold for statistical significance).

The toxicities of 2-methylnaphthalene and 1-methylnaphthalene (CASRN 90 12 0) were evaluated simultaneously under the same experimental conditions and protocols, including the use of a shared control group (Murata et al., 1993, 1997). The 1- and 2-methylnaphthalene dose groups, as well as the controls, were housed in the same room. Results of these studies were reported separately (Murata et al., 1993, 1997). Some quantitative details regarding the control animals and descriptions of methodology and histology were provided in the earlier paper (Murata et al., 1993) evaluating 1-methylnaphthalene toxicity, but were omitted from the later paper (Murata et al., 1997) evaluating the toxicity of 2-methylnaphthalene.

Survival and food consumption were not affected by exposure to 2-methylnaphthalene at 0.075 or 0.15% for 81 weeks (Murata et al., 1997). Body weight data were presented graphically as mean growth curves for males and females in the control and exposed groups. Group means and standard deviations were not presented. The study specified that the reduction in final mean body weight was statistically significant for the high-dose male group. The mean final body weights for the male and female high-dose groups were reported to be reduced by 7.5 and 4.5%, respectively, when compared with controls. The decrease was not considered to be biologically significant for this assessment.

As shown in Table I.A.2.1, dietary exposure to 2-methylnaphthalene was associated with an increased incidence of pulmonary alveolar proteinosis that was statistically significant in both sexes at both exposure levels when compared with controls (Murata et al., 1997). Both male and female exposed groups showed statistically significant ($p<0.05$) trends for an increased incidence of pulmonary alveolar proteinosis with increasing dose using Cochran-Armitage trend tests (U.S. EPA, 2003). Pulmonary alveolar proteinosis was characterized by the authors as being similar to the lesions described previously in their laboratory (Murata et al., 1993, 1997). According to the Murata et al. (1993) report, pulmonary alveolar proteinosis was characterized by an accumulation of phospholipids in the alveolar lumens and, upon gross inspection, white protuberant nodules approximately 1-5 mm in diameter. Histologically, there was visible filling of alveolar lumens with cholesterol crystals, foamy cells, and an amorphous acidophilic material. No prominent fibrosis, edema, alveolitis, or lipidosis were seen in alveolar walls or in epithelial cells. No evidence of bronchiolar Clara cell necrosis or sloughing was reported in the Murata et al., (1997) study nor was there histopathological evidence of non-neoplastic effects in any other tissue.

Table I.A.2.1. Incidence of pulmonary alveolar proteinosis in B6C3F1 mice fed 2-methylnaphthalene for 81 weeks

	Female			Male		
Dose (% diet) Dose (mg/kg-day)	0 0	0.075 50.3	0.15 107.6	0 0	0.075 54.3	0.15 113.8
Pulmonary alveolar proteinosis	5/50	27/49*	22/48*	4/49	21/49*	23/49*

* Statistically significant by Fisher's exact test as reported by Murata et al (1997).
Source: Adapted from Murata et al., 1997.

The authors also reported other statistically significant differences between control and exposure groups, but no data were provided regarding their magnitude or the exposure levels at which they occurred. Serum neutral fat levels were elevated in exposed males and females, and relative and absolute brain and kidney weights were increased among exposed males. In exposed females, differential counts of stab (young) and segmented (adult) neutrophils were significantly decreased while lymphocyte counts were increased when compared to controls (Murata et al., 1997). The biological significance of these differences is unclear, due to the lack of reported data (response magnitude and exposure level). Evidence of exposure-related neoplastic lesions was restricted to statistically significant increases in lung adenomas or total lung tumors (adenomas or carcinomas) in male mice in the 0.075% group, but not in the 0.15% male group or in either exposed group of female mice (see IRIS Summary Section II).

The RfD was derived by benchmark dose analysis of the incidence data for pulmonary alveolar proteinosis in B6C3F1 male and female mice exposed to 2-methylnaphthalene in the diet for 81 weeks (Murata et al., 1997). The incidences for pulmonary alveolar proteinosis for males and females at each exposure level were not statistically significantly different from each other, according to Fisher's exact test ($p <= 0.05$). Because neither sex was clearly more sensitive, the incidence data for males, females, and both males and females combined were fit to all dichotomous variable models available in the BMDS Version 1.3.2 software. The best fit was obtained using data for the combined male and female control and low dose groups. The practice of excluding the high dose group from modeling is justified by several considerations (U.S.EPA, 2000d). First, without a mechanistic understanding of how pulmonary alveolar proteinosis results from exposure to 2-methylnaphthalene, data from exposures much higher than that associated with the benchmark response do not provide very much information about the shape of the response in the region of the benchmark response. Also, the lack of fit for the

full data set appears to be due to the characteristics of the high dose groups, where the response plateaus (U.S. EPA, 2003). Although dropping the high dose groups ignores some of the data and decreases the degrees of freedom for modeling, it is a reasonable approach because the focus of BMD analysis is on the low dose and response region (U.S.EPA, 2000). The BMDS quantal-linear model provides a model closest to a straight line, which is all that can be justified for modeling essentially two data points, the combined control groups and the similar male and female low dose groups.

A benchmark response level of 5% extra risk of the critical effect, pulmonary alveolar proteinosis, was selected for this assessment. This effect is similar to a disorder of unknown etiology that has been identified in humans. If this disorder were to occur in humans following exposure to 2-methylnaphthalene, it is anticipated that children may be more susceptible especially since children affected with the disorder often experience more severe symptoms than adults. Thus, a 5% extra risk of pulmonary alveolar proteinosis was judged to be an appropriate level of extra risk for this critical effect. The BMD_{05} from the quantal-linear model was 4.7 mg/kg-day for pulmonary alveolar proteinosis in male and female mice exposed to 2-methylnaphthalene in the diet for 81 weeks (Murata et al, 1997). The lower 95% confidence limit on the BMD_{05} (i.e., $BMDL_{05}$) was 3.5 mg/kg-day.

A limitation of the principal study (Murata et al., 1997) was the occurrence of pulmonary alveolar proteinosis in control mice (9/99; see Table I.A.2.1.). The authors noted that pulmonary alveolar proteinosis had never been observed previously by them in more than 5,000 B6C3F1 control mice, and speculated that the background incidence may have been elevated by inhalation exposure to volatilized test chemicals. The principal study (Murata et al., 1997) described here was conducted simultaneously with a study evaluating 0.075 and 0.15% 1-methylnaphthalene in the diet (Murata et al., 1993). Potential confounding from possible inhalation exposure of controls to volatilized 2-methylnaphthalene and 1-methylnaphthalene adds some uncertainty to the dose-response relationship between oral exposure to 2-methylnaphthalene and pulmonary alveolar proteinosis described by the results from this study.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 1000. A total uncertainty factor of 1000 was applied to the $BMDL_{05}$ of 3.5 mg/kg-day: 10 for extrapolation for interspecies differences (UF_A: animal to human); 10 for consideration of intraspecies variation (UF_H: human variability); and 10 for deficiencies in the database (UF_D).

A 10-fold UF was used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). No information was available regarding the toxicity of

2-methylnaphthalene in humans exposed orally. No information was available to assess toxicokinetic differences between animals and humans.

A 10-fold UF was used to account for variation in sensitivity among members of the human population (i.e., interindividual variability).

A 10-fold UF was used to account for uncertainty associated with deficiencies in the database. One chronic duration oral toxicity study in one animal species (mice) is available (Murata et al., 1997). The database lacks adequate studies of oral developmental toxicity, reproductive toxicity, and neurotoxicity. The database also lacks a 2-generation reproductive toxicity study.

An UF was not needed to account for subchronic to chronic extrapolation because a chronic study (81 weeks) was used to derive the RfD.

An UF for LOAEL-to-NOAEL extrapolation was not considered as such, since benchmark dose modeling was used to determine the point of departure. While the 5% extra response level used to derive the RfD is not a no-response level, some consideration of what level of extra risk of pulmonary alveolar proteinosis constitutes a minimal health risk is appropriate.

MF = 1.

I.A.4. Additional Studies/Comments (Oral RfD)

The database for the oral toxicity of 2-methylnaphthalene is restricted to the principal study (Murata et al., 1997) and two prechronic toxicity studies (Fitzhugh and Buschke, 1949; Murata et al., 1997). Fitzhugh and Buschke (1949) did not observe cataract formation in rats fed 2-methylnaphthalene (approximately 40 mg/kg-day) for at least 2 months, and did not investigate any other endpoints. Murata et al. (1997) conducted a range-finding study in which groups of B6C3F1 mice (10/sex/group) were fed diets containing 2-methylnaphthalene for 13 weeks delivering approximate average daily doses of 0, 31, 92, 276, 827, or 2,500 mg/kg-day. No histopathological effects were observed in tissues and organs of male or female mice exposed to 827 or 2,500 mg/kg-day (tissues from mice in lower dose groups were not examined histologically). Decreased body weights, compared with control values, were observed at the three highest dose levels in both males and females, and were attributed to food refusal (Murata et al., 1997). The absence of pulmonary alveolar proteinosis in the prechronically exposed mice, which were exposed to much higher doses than those experienced by mice with pulmonary alveolar proteinosis in the principal study, suggests that the development of pulmonary alveolar proteinosis from oral exposure to 2-methylnaphthalene may require exposures at chronic durations.

Additional supporting data have been derived from dermal studies using a methylnaphthalene mixture (CASRN 1321 94 4) of 2-methylnaphthalene and 1-methylnaphthalene in an approximate 2:1 ratio in mice. Murata et al. (1992) exposed female B6C3F1 mice (15/group) to 0 or 119 mg/kg of a methylnaphthalene mixture by applying an acetone solution containing 1.2% methylnaphthalene to their backs twice weekly for 30 weeks. Lung surfaces grossly contained multiple grayish white nodules. Histologically, the alveoli appeared to be filled with cholesterol crystals, an amorphous eosinophilic material, and many mononucleated giant cells with foamy cytoplasm. The alveolar spaces in areas where proteinosis was present were also filled with free myelinoid structures. The authors stated that most myelinoid structures appeared to originate from hyperplastic and hypertrophic type II pneumocyte meocrine secretion. The enlarged mononucleated giant cells contained similar myelinoid structures to those seen in the alveolar space, along with lipid droplets. The myelinoid structures consisted of concentrically arranged and multilayered membranes interspersed with amorphous materials. Various numbers and sizes of needle-like crystals were also seen in the mononucleated giant cells' cytoplasm. Alveolar walls were thickened but there was no prominent fibrosis. Partial thickening was due to hyperplasia and hypertrophy of type II pneumocytes or focal hyperplasia of cells resembling type I pneumocytes in appearance. Ultrastructural analyses verified these observations, and detected numerous necrotic cells in areas of proteinosis. Murata et al. (1992) concluded that the mononucleated giant cells were type II pneumocytes overfilled with myelinoid structures, rather than macrophages that might have engulfed lamellar bodies, and that some of these cells ruptured into the alveolar lumens. The authors reported that a higher dermal dose (238 mg/kg, twice weekly) than that used in the present study induced a 100% incidence of pulmonary alveolar proteinosis in a shorter period of time (20 weeks), but noted that this was unpublished data (Murata et al., 1992). Murata et al. (1992) stated that the pulmonary alveolar proteinosis observed in mice exposed to a methylnaphthalene mixture via the dermal route in the current study had been demonstrated previously by their laboratory (Emi and Konishi, 1985).

Emi and Konishi (1985) painted the shaved backs of female B6C3F1 mice with 0, 29.7, or 118.8 mg/kg of a methylnaphthalene mixture in acetone twice weekly for 61 weeks. The control through high-dose groups contained 4, 11, and 32 mice, respectively. At sacrifice, animals were necropsied, and histology was performed on the skin and principal organs. Although survival information was not provided, a reported peak in mortality at 38 weeks was attributed to lipid pneumonia. Lipid pneumonia was observed in animals that died as early as 10 weeks. The final incidence of this effect were 0/4, 3/11, and 31/32 for the control, low-, and high-dose groups, respectively. Lipid pneumonia was characterized grossly by multiple delocalized white spots and soft clearly demarcated nodules. The predominant histological feature was hypertrophy and hyperplasia of type II pneumocytes in the lung. Additional observations included slight alveolar wall thickening, multinucleated giant cell reaction, and the presence in the alveolar lumens of foamy cells and cholesterol crystals. Evidence of focal

alveolar dilation and emphysema were also observed, but were considered compensatory reactions.

The mechanisms by which 2-methylnaphthalene may cause pulmonary alveolar proteinosis are poorly understood (U.S. EPA, 2003), but light and electron microscopic observations of lung tissues from mice repeatedly exposed to dermal doses of methylnaphthalene mixtures (containing 1- and 2-methylnaphthalene in a 2:1 ratio) indicate that type II pneumocytes may be the specific cellular target of mixtures containing 2-methylnaphthalene (Murata et al., 1992). From these observations, Murata et al. (1992) hypothesized that, in response to a mixture containing 2-methylnaphthalene, type II pneumocytes produce increased amounts of lamellar bodies due to hyperplasia and hypertrophy, and eventually transform into mononucleated giant cells. The rupture of mononucleated giant cells is hypothesized to lead to the accumulation of the myelinoid structures in the alveolar lumen.

It is unknown whether 2-methylnaphthalene or its metabolites are responsible for the development of pulmonary alveolar proteinosis. Given the enrichment of type II pneumocytes in cytochrome P450 (CYP) enzymes (Castranova et al., 1988) and the involvement of these enzymes in metabolizing 2-methylnaphthalene (U.S. EPA, 2003), it is plausible that metabolites may play a role in the pathogenesis of pulmonary alveolar proteinosis.

Acute intraperitoneal injection studies in mice support the conclusion that the lung is a sensitive target organ for 2-methylnaphthalene (Buckpitt et al., 1986; Griffin et al., 1981, 1982, 1983; Honda et al., 1990; Rasmussen et al., 1986), but the site of adverse affects in the lungs associated with acute exposure (Clara cells in the bronchiolar lining) is different from the site (type II pneumocytes in alveoli) associated with chronic oral exposure. The absence of bronchiolar lesions in mice exposed chronically to 2-methylnaphthalene (Murata et al., 1993, 1997) may be related to changes in the resistance of Clara cells to 2-methylnaphthalene induced toxicity (Lakritz et al., 1996).

In humans, pulmonary alveolar proteinosis is a rare condition that has been associated with decreased pulmonary function. It is characterized by decreased functional lung volume, reduced diffusing capacity, and symptoms such as dyspnea and cough. It has not been associated with airflow obstruction (Lee et al., 1997; Mazzone et al., 2001; Wang et al., 1997). Although cases of pulmonary alveolar proteinosis in humans have not been directly associated with exposure to 2-methylnaphthalene, the observations of 2-methylnaphthalene-induced pulmonary alveolar proteinosis in mice are assumed to be relevant to humans.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The principal study for the RfD (Murata et al., 1997) examined a comprehensive number of endpoints, including extensive histopathology, and tested two dietary dose levels using sufficient numbers (50/sex/group) of B6C3F1 mice. Confidence in the study is medium because there was potential confounding from possible inhalation exposure of controls to volatilized 2-methylnaphthalene and 1-methylnaphthalene. This adds some uncertainty to the dose-response relationship between oral exposure to 2-methylnaphthalene and pulmonary alveolar proteinosis described by the results. Confidence in the oral toxicity database is low. No epidemiology studies or case reports were located which examined the potential effects of human exposure to 2-methylnaphthalene. Only mice have been examined in adequate animal studies on toxicity from repeated exposure to 2-methylnaphthalene. No assays of developmental toxicity, reproductive toxicity, or neurotoxicity following oral exposure to 2-methylnaphthalene are available. Confidence in the oral RfD is low, principally due to the low confidence in the database.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA (2003).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments isincluded as an appendix to the Toxicological Review of 2-Methylnaphthalene (U.S. EPA, 2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***

Agency Consensus Date — 12/11/2003

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 2-Methylnaphthalene
CASRN — 91-57-6
Last Revised — 12/22/2003

An RfC cannot be calculated for 2-methylnaphthalene due to inadequate data. No epidemiology studies or case reports were located which examined the potential effects of human inhalation exposure to 2-methylnaphthalene. No chronic or prechronic toxicity studies were identified in which animals were exposed to 2-methylnaphthalene by inhalation.

I.B.1. Inhalation RfC Summary

Not applicable.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Not applicable.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

Not applicable.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2003

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments isincluded as an appendix to the Toxicological Review of 2-Methylnaphthalene (U.S. EPA, 2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***

Agency Consensus Date — 12/11/2003

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2-Methylnaphthalene
CASRN — 91-57-6
Last Revised — 12/22/2003

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999 Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July. Risk Assessment Forum. http://www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm). The quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper bound estimate of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per (mg/kg)/day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per µg/L drinking water or per µg/cu.m air breathed. The third form in which risk is presented is the 95% lower bound on the estimated concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under EPA's Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), the data regarding the carcinogenicity of 2-methylnaphthalene in mice and the lack of human carcinogenicity data are *inadequate to assess human carcinogenic potential*. Animal cancer data are limited to one 81-week dietary study in mice exposed to 2-methylnaphthalene in the diet. Statistically significant increases in the incidence of lung adenomas and total lung tumors (adenomas and carcinomas combined) for the low-dose male group (54.3 mg/kg-day) were observed when compared to controls. However, no evidence of carcinogenicity was observed in male mice exposed to the high dose (113.8 mg/kg-day), or in female mice exposed to 50.3 or 107.6 mg/kg-day 2-methylnaphthalene. Lack of an apparent dose-response relationship makes the data unsuitable for a quantitative assessment of carcinogenic potential. Mice dermally exposed biweekly to 2-methylnaphthalene (equivalent to 32 µg/kg-day) plus benzo[a]pyrene (BaP) for 78 weeks had no increased incidence of skin tumors, compared to mice receiving BaP alone (Schmeltz et al., 1978). The incidence of non-skin tumors were not reported. The study is of limited toxicological value since 2-methylnaphthalene was not tested alone. In addition, short-term genotoxicity tests with 2-methylnaphthalene provide no consistent evidence of mutagenic activity in bacteria or clastogenic activity in human lymphocytes *in vitro* (Florin et al., 1980; Hermann, 1981; Kulka et al., 1988).

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited evidence.

The Murata et al. (1997) study that was used to derive the RfD for 2-methylnaphthalene (see Section I.A.2) evaluated the chemical's carcinogenicity. Statistically significant increased incidences of lung adenomas or total lung tumors (adenomas or adenocarcinomas) were found in the 0.075% male mouse group, but not in the 0.15% male mouse group or in either of the

female exposed groups (Table II.A.3.1.). No evidence of a trend of increasing tumor incidence with increasing dose was observed in males or females (U.S. EPA, 2003). No statistically significant elevations in incidences of tumors in other tissues or organs were seen in any exposure group, when compared with controls.

Table II.A.3.1. Lung tumor incidence in B6C3F1 mice fed 2-methylnaphthalene for 81 weeks

	Female			Male		
Dose (% diet)	0	0.075	0.15	0	0.075	0.15
Dose (mg/kg-day)	0	50.3	107.6	0	54.3	113.8
Lung adenoma	4/50	4/49	5/48	2/49	9/49*	5/49
Lung adenocarcinoma	1/50	0/49	1/48	0/49	1/49	1/49
Total lung tumors	5/50	4/49	6/48	2/49	10/49*	6/49

* Statistically significant by Fisher's exact test ($p<0.05$).
Source: Adapted from Murata et al., 1997.

II.A.4. Supporting Data for Carcinogenicity

Supporting evidence for the carcinogenicity of 2-methylnaphthalene is restricted to evidence from a cancer study that did not find an increased incidence of skin tumors in ICR/Ha Sprague-Dawley mice (30/group) dermally exposed three times weekly to 0 or 25 µg 2-methylnaphthalene (equivalent to 32 µg/kg-day) plus 300 ng benzo[a]pyrene for 78 weeks, compared to mice receiving BaP alone (Schmeltz et al., 1978). The incidences of non-skin tumors were not reported. The study is of limited toxicological value since 2-methylnaphthalene was not tested alone.

No evidence of lung tumors was reported in studies involving exposure of B6C3F1 mice to a methylnaphthalene mixture (a 2:1 mixture of 2-methylnaphthalene and 1-methylnaphthalene) at doses of 0 or 119 mg/kg twice weekly for 30 weeks (Murata et al., 1992), or 0, 29.7, or 118.8 mg/kg twice weekly for 61 weeks (Emi and Konishi, 1985); however, the less-than-lifetime duration of these studies limits their usefulness as cancer bioassays.

No mutagenicity was observed in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 treated with 2-methylnaphthalene (Florin et al., 1980; Hermann, 1981) or a

methylnaphthalene mixture (Kopper Co. Inc., 1982), with or without metabolic activation by S9 hepatic microsomal fractions. *In vitro* exposure of human lymphocytes to 2-methylnaphthalene with metabolic activation by S9 produced statistically significant increases in the incidence of sister chromatid exchanges (up to 22%) at all concentrations tested (0.25 to 4 mM) and of chromatid breaks (6.5-fold) only at the highest concentration tested (4 mM) (Kulka et al., 1988). No differences were observed following exposure without metabolic activation. The authors considered the sister chromatid response to be negative because the magnitude of the response was less than a 2-fold increase. They also considered the chromatid breaks to be minor because no damage was observed at lower concentrations (up to 2 mM). In these studies, S9 hepatic microsomal fractions were prepared from male Sprague-Dawley, Fischer 344, or Wistar rats induced with either Aroclor 1254 or 3-methylcholanthrene.

In vitro assays in WB F344 rat liver epithelial cells found that 2-methylnaphthalene, as well as naphthalene and 1-methylnaphthalene, inhibited gap junctional intercellular communication (Weis et al., 1998). The authors suggested that the inhibition could be an epigenetic mechanism of tumor promotion by preventing intercellular transport of regulatory molecules.

Differences in metabolism between 2-methylnaphthalene and naphthalene or other methylnaphthalene isomers preclude the use of evidence for carcinogenicity of these structurally similar chemicals as supporting evidence for 2-methylnaphthalene carcinogenicity. Naphthalene toxicity and carcinogenicity have been hypothesized to be due to, at least in part, metabolism via CYP-mediated ring epoxidation to reactive metabolites such as the 1,2-epoxide or 1,2-quinone derivatives (Cho et al., 1995; Greene et al., 2000; Lakritz et al., 1996; NTP, 1992, 2000; Van Winkle et al., 1999). The metabolic formation of ring epoxides is a relatively minor pathway for 2-methylnaphthalene (NTP 2000; U.S. EPA, 2003). No studies evaluating the metabolism of 1-methylnaphthalene in humans or animals are available. Metabolism of this chemical may follow a similar pathway as that described here for 2-methylnaphthalene (i.e., side chain oxidation) since these chemicals are structurally related to each other.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

II.B.1. Summary of Risk Estimates

Not applicable.

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable.

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Documents -- U.S. EPA (2003).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments isincluded as an appendix to the Toxicological Review of 2-Methylnaphthalene (U.S. EPA, 2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 12/11/2003

II.D.3. EPA Contacts (Carcinogenicity Assessment

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 2-Methylnaphthalene
CASRN — 91-57-6

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VI.B. Inhalation RfC References

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VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — 2-Methylnaphthalene
CASRN — 91-57-6

Date	Section	Description
12/22/2003	All	First IRIS RfD, cancer assessment, RfC discussion

VIII. Synonyms

Substance Name — 2-Methylnaphthalene
CASRN — 91-57-6
Last Revised — 12/22/2003

- 91-57-6
- Beta-methylnaphthalene
- methyl naphthalene
- methylnaftalen