DRAFT IRIS SUMMARY

Substance code
2-Methylnaphthalene; CASRN 91-57-6; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR 2-Methylnaphthalene

File First On-Line 00/00/00

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	00/00/0000
Inhalation RfC Assessment (I.B.)	inadequate data	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_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 – 00/00/0000

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	NOAEL: Not identified	1000	1	9E-3 mg/kg-day
	LOAEL: 54.3 mg/kg-day			
Male B6C3F1 mice 81-week dietary study Murata et al. (1997)	LED_{10}: 9.1 mg/kg-day			

*Conversion Factors and Assumptions – Incidence data for pulmonary alveolar proteinosis in control and exposed male mice were analyzed by benchmark dose modeling. The lower 95% confidence interval on the benchmark dose associated with a 10% extra risk (ED_{10}) for pulmonary alveolar proteinosis in male 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% of 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, then 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. 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; $p \leq 0.05\%$ 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 using a shared control group (Murata et al., 1993, 1997). The 2-methylnaphthalene and 1-methylnaphthalene

The toxicities of 2-methylnaphthalene and 1-methylnaphthalene (CASRN 90-12-0) were evaluated simultaneously under the same experimental conditions and protocols using a shared control group (Murata et al., 1993, 1997). The 2-methylnaphthalene and 1-methylnaphthalene dose groups, as well as the controls, were housed in the same room. The results of these simultaneous 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 report 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, compared with controls. Because the magnitudes were less than 10% compared with controls, the decreased body weight was not considered a biologically significant effect.

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 compared with controls (Murata et al., 1997). Both male and female exposed groups showed statistically significant ($p<0.05$) trends for increased incidence of pulmonary alveolar proteinosis with increasing dose (Cochran-Armitage trend tests, U.S. EPA, 2003). Pulmonary alveolar proteinosis was previously described (Murata et al., 1993) as grossly visible white protuberant nodules approximately 1–5 mm in diameter with histologically 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 observed (Murata et al., 1997). No histopathological evidence of non-neoplastic effects was reported for any other tissue.

Table I.A.2.1. Incidence of Pulmonary Alveolar Proteinosis in B6C3F1 Mice Fed 2-Methylnaphthalene for 81 Weeks (from Murata et al., 1997)

	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*	22/49*	4/49	21/49*	23/49*

* Statistically significant by Fisher's exact test as reported by 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 and segmented form neutrophils were significantly decreased, and lymphocyte counts were increased compared to controls (Murata et al., 1997). The biological significance of these differences is unclear, due to the lack of reported data (response magnitude, 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).

Currently there is no health assessment for 2-methylnaphthalene on the IRIS database. Thus, this is the first derivation of an RfD for inclusion in the IRIS health assessment of this chemical. The RfD was derived by benchmark dose analysis of the incidence data for pulmonary alveolar proteinosis in B6C3F1 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 ($p \leq 0.05$). 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 software. A benchmark response level of 10% extra risk of pulmonary alveolar proteinosis was selected for this assessment. Pulmonary alveolar proteinosis produces mild symptoms, and is a treatable condition in adult humans (U.S. EPA, 2003). It is not considered a frank effect following exposure to 2-methylnaphthalene, nor is there any indication that it is a precursor of more severe adverse effects. Thus, a 10% extra risk of pulmonary alveolar proteinosis was judged to be an acceptable level of extra risk for this critical effect. From this model, the ED_{10} was 14 mg/kg-day for pulmonary alveolar proteinosis in male mice exposed to 2-methylnaphthalene in the diet for 81 weeks (Murata et al, 1997). The lower 95% confidence limit on the ED_{10} (i.e., LED_{10}) was 9.1 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 seen previously by them in more than 5000 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 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 this effect level: 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. In the absence of data to the contrary, the pulmonary alveolar proteinosis observed in mice is assumed to be relevant to humans.

A 10-fold UF was used to account for variation in sensitivity among members of the human population (i.e., interindividual variability). This UF was not reduced, due to a lack of human oral exposure data.

A 10-fold UF was used to account for uncertainty associated with deficiencies in the data base. One chronic duration oral toxicity study in one animal species (mice) is available (Murata et al., 1997). The data base lacks adequate studies of oral developmental toxicity, reproductive toxicity, and neurotoxicity. The data base 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. The 10% increased response level used to derive the RfD is not a no-response level, however, so some consideration of what level of extra risk of pulmonary alveolar proteinosis constitutes a minimal health risk is appropriate. EPA is developing guidance on the application of effect level extrapolation factors as uncertainty factors to extrapolate to risks below the effect level at the point of departure. Since pulmonary alveolar proteinosis is a treatable disorder, with mild symptoms, it is considered to be of limited severity. Further, it is not thought to be a precursor to a more severe adverse noncancer or cancer effect. Pending final guidance on this issue, it was determined that an effect level extrapolation factor was not necessary for the derivation of the RfD for 2-methylnaphthalene from the LED_{10}.

MF = 1. None.

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

The data base 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) 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 2500 mg/kg-day. No histopathological effects were observed in tissues and organs of male or female mice exposed to 827 or 2500 mg/kg-day (tissues from mice in lower dose groups were not examined histologically). Decreased body weights, compared with control values, were seen 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 requires chronic duration.

Additional supporting data come from dermal studies with 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 (equivalent to 0 or 34 mg/kg-day) by applying an acetone solution containing a 1.2% mixture of methylnaphthalenes to their backs twice a week for 30 weeks. Lung tissue samples were analyzed using light and electron microscopy. Exposure to a methylnaphthalene mixture resulted in a 14% reduction in final body weight that was not statistically significantly different from control values. No adverse pulmonary effects were seen in control mice. All mice exposed to the methylnaphthalene mixture (15/15) exhibited pulmonary alveolar proteinosis. This condition appeared grossly as multiple grayish white nodules. Histologically, the alveoli appeared filled with many mononucleated giant cells (balloon cells), cholesterol crystals, and an amorphous eosinophilic myeloid material. The mononucleated giant cells exhibited foamy cytoplasm, which frequently contained lipid droplets and myeloid structures, and some were enlarged. Alveolar walls were thickened due to hyperplasia and hypertrophy of Type II pneumocytes and focal hyperplasia of Type I pneumocytes. Focal interstitial fibrosis was seen only in restricted areas. Focal interstitial accumulation of plasma cells was also observed. Ultrastructural analyses verified these observations, and detected numerous necrotic cells in areas of proteinosis. The authors 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. A higher dermal dose of 238 mg/kg twice weekly (68 mg/kg-day) was reported to have induced a 100% incidence of the same type of pulmonary alveolar proteinosis in a shorter period, 20 weeks (Murata et al., 1992).

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 (equivalent to 0, 8.49 or 33.94 mg/kg-day). 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 incidence at 38 weeks was attributed to lipid pneumonia. Lipid pneumonia was observed (in animals

that died) as early as 10 weeks. The final incidences for 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 indicate that type II pneumocytes may be the specific cellular target of 2-methylnaphthalene (Murata et al., 1992). From these observations, Murata et al. (1992) hypothesized that, in response to 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 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. Studies designed to test this hypothesis, however, have not been conducted.

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 adaptive changes in Clara cells (Lakritz et al., 1996).

In humans, pulmonary alveolar proteinosis is a rare condition that has been associated with decreased pulmonary function, 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.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study – Medium
Data Base – 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 only medium because there was potential confounding from possible inhalation exposure of controls to 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 data base 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. There are no toxicity studies in which animals were exposed to 2-methylnaphthalene by inhalation for extended periods of time (see Section I.B.). No assays of developmental toxicity, reproductive toxicity or neurotoxicity following oral or inhalation exposure to 2-methylnaphthalene are available. Confidence in the oral RfD is low, principally due to the low confidence in the data base.

___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 is included as an appendix to U.S. EPA (2003).

Other EPA Documentation -- _____

Agency Consensus Date -- __/__/__ *[note: leave this BLANK until consensus is reached*]

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name – 2-Methylnaphthalene
CASRN – 91-57-6
Last Revised – 00/00/0000

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 toxicity studies were identified in which animals were exposed to 2-methylnaphthalene for an extended period of time. Lorber et al. (1972) investigated hematoxicity endpoints in intact and splenectomized dogs exposed to mists of 2-methylnaphthalene (at uncertain concentrations) for 41-50 minutes for 4 consecutive days. No clear evidence of hematoxicity was observed. Korsak et al. (1998) exposed male Wistar rats (10-20 rats/group) to 2-methylnaphthalene (0, 229, 352, or 525 mg/m^3) for 4 hours to evaluate neurotoxicity, and male Balb/C mice (8-10/group) to 2-methylnaphthalene (0, 28, 58, 125, or 349 mg/m^3) for 6 minutes to evaluate sensory/respiratory irritation via inhalation. In rats, none of the concentrations tested affected a neuromuscular test (rotarod performance), but the two highest doses decreased pain sensitivity (measured by latency of paw-lick response in response to a heated surface). In mice, rapid, but reversible, decreases in respiratory rate were seen, with the response magnitude increasing with increasing exposure concentration.

No chronic or prechronic studies were identified that exposed animals by inhalation to 2-methylnaphthalene.

A route-to-route extrapolation is not appropriate. No toxicokinetic models are available for 2-methylnaphthalene, and there is evidence to suggest that its potency to induce pulmonary alveolar proteinosis in mice may vary across routes of exposure; specifically that dermal exposure to a methylnaphthalene mixture containing 2-methylnaphthalene may be more potent than oral exposure to 2-methylnaphthalene (U.S. EPA, 2003).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – 2-Methylnaphthalene
CASRN – 91-57-6
Last Revised – 00/00/0000

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/ncea/raf/cancer.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 the 1999 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. Incidences for lung adenomas and total lung tumors (adenomas and carcinomas combined) for the low-dose male group (54.3 mg/kg-day) were statistically significantly elevated compared to controls. However, no evidence of carcinogenicity was seen in male mice exposed to the high dose (113.8 mg/kg-day), or in female mice exposed to either dose. Lack of an apparent dose-response relationship makes these data unsuitable for quantitative assessment of carcinogenic potential. Mice dermally exposed biweekly to 2-methyl-naphthalene (equivalent to 32 μg/kg/day) plus BaP for 78 weeks had no increased incidence of skin tumors, compared to mice receiving BaP alone (Schmeltz et al., 1978). The incidences of non-skin tumors were not reported. This 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 of clastogenic activity in human lymphocytes *in vitro* (Florin et al., 1980; Hermann, 1981; Kulka et al., 1988).

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Limited evidence.

The Murata et al. (1997) study used to derive the RfD for 2-methylnaphthalene and described in Section I.A.2 evaluated the carcinogenicity of 2-methylnaphthalene. Statistically significantly 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 seen for 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, compared with control incidences.

Table II.A.3.1. Lung Tumor Incidence in B6C3F1 Mice Fed 2-Methylnaphthalene for 81 Weeks (from Murata et al., 1997)

	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 ($p<0.05$).

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Supporting evidence for the carcinogenicity of 2-methylnaphthalene is restricted to evidence from a cancer study which 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. This 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: CASRN 1321-94-4) 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 incidences 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 seen 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, and considered the chromatid breaks to be minor because no damage was seen 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 inhibition of intracellular communication could be an epigenetic mechanism of tumor promotion by preventing intercellular transport of regulatory molecules. The relevance of this finding to human health is unclear.

Differences in metabolism between2-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) has 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; NTP 2000; Van Winkle et al., 1999). The metabolic formation of ring epoxides is a relatively minor pathway for 2-methylnaphthalene, whereas it is the principal pathway for naphthalene (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. However, no studies providing evidence for this common pathway of metabolism were found.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not applicable.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

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 is included as an appendix to _____.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__ *[note: Leave BLANK until consensus is reached]*

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name – 2-Methylnaphthalene
CASRN -- 91-57-6
Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

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_VII. REVISION HISTORY

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

Date	Section	Description
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[note: chemical managers must fill in this section]

_VIII. SYNONYMS

Substance Name 2-Methylnaphthalene
CASRN -- 91-57- 6
Last Revised -- 00/000000

β-methylnaphthalene