June 2004

This IRIS Summary is an external review draft of the reassessment of the inhalation carcinogenicity of naphthalene. Changes from the current IRIS Summary (1998) are indicated by highlighting.

Please review the highlighted sections.

0436
Naphthalene; CASRN 91-20-3

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 Naphthalene

File First On-Line 12/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	On-line	09/17/1998
Inhalation RfC Assessment (I.B.)	On-line	09/17/1998
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)

Naphthalene
CASRN – 91-20-3
Last Revised -- 09/18/1998

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
Decreased mean terminal body weight in males Subchronic oral rat study BCL, 1980a	NOAEL: 100 mg/kg-day; 71 mg/kg-day (adjusted) LOAEL: 200 mg/kg-day; 142 mg/kg-day (adjusted)	3,000	1	2E-2 mg/kg-day

*Conversion Factors and Assumptions -- MW = 128.19. Duration adjustment (5/7) of the doses (100, 200 mg/kg-day) arrived at a critical NOAEL/LOAEL pair of 71 and 143 mg/kg-day for decreased mean terminal body weight in male rats.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Battelle's Columbus Laboratories (BCL). (1980a) Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle Laboratories under NTP Subcontract No. 76-34-106002.

Naphthalene (> 99% pure) in corn oil was administered by gavage to groups of 10 male and 10 female Fischer 344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg (duration-adjusted 0, 17.9, 35.7, 71.4, 142.9, and 285.7 mg/kg-day), 5 days/week for 13 weeks (BCL, 1980a). Measured parameters included food consumption and body weight weekly, twice-daily observation for clinical signs of toxicity, hematological parameters for blood collected at termination (hemoglobin, hematocrit, total and differential white blood cell count, red blood cell count, mean cell volume, mean cell hemoglobin concentration), necropsy of all rats in the study, and complete histopathological examination of 27 organs and tissues (including the eyes, lungs, stomach, liver, kidney, reproductive organs, thymus, and kidney) from all control and 400-mg/kg rats. Male kidneys and female thymuses from the 200-mg/kg group were also examined histopathologically (according to the histopathology tables; however, the report text states that the 100-mg/kg group was examined). Organ weight data were not reported.

At the highest dose level, two males died during the last week of treatment, and rats of both sexes displayed diarrhea, lethargy, hunched posture, and rough coats at intermittent intervals throughout the study (BCL, 1980a). Food consumption was not affected by exposure, but mean decreases in terminal body weight greater than 10% compared with control values were found in several groups of exposed rats (over the 13-week period); namely, 23% depression in females at 400 mg/kg and a 29% and 12% depression in males at 400 and 200 mg/kg-day, respectively. Differences between mean values of hematological parameters in exposed groups

and control groups were < 10% of control values, except for a 94% increase in numbers of mature neutrophils and a 25.1% decrease in numbers of lymphocytes in male 400-mg/kg rats and a 37.2% increase in mature neutrophils in 400-mg/kg females. Histological examinations revealed low incidences of lesions in exposed male kidneys and exposed female thymuses; no lesions were observed in respective control kidneys or thymuses. Lesions such as focal cortical lymphocytic infiltration or focal tubular regeneration were observed in kidneys of 2/10 male rats exposed to 200 mg/kg naphthalene, and diffuse renal tubular degeneration occurred in 1/10 male rats exposed to 400 mg/kg naphthalene. Other lesions include lymphoid depletion of the thymus, which occurred in 2/10 females exposed to 400 mg/kg naphthalene, but not in any other females. No other tissue lesions were detected. Decreased body weight was the most sensitive effect noted in this study and was identified as the most appropriate critical effect for the purposes of RfD derivation. Mean terminal body weight decreases greater than 10% compared with control values were found in male rats following a 90-day gavage exposure to 200 mg/kg-day (LOAEL). The NOAEL for a > 10% decrease in body weight in this study was 100 mg/kg-day (71 mg/kg-day duration-adjusted).

Shopp, GM; White, KL, Jr.; Holsapple, MP; et al. (1984) Naphthalene toxicity in CD-1 mice: general toxicology and immunotoxicology. Fundam Appl Toxicol 4(3 pt 1):406-419.

Groups of male and female albino CD-1 mice (approximately 6 weeks old at the start) were administered gavage doses of 0, 5.3, 53, or 133 mg/kg naphthalene (99.3% pure) in corn oil for 90 consecutive days (Shopp et al., 1984). A naive control group and the 5.3- and 53-mg/kg dose groups each contained 76 male mice and 40 female mice. The vehicle control group contained 112 male mice and 76 female mice. The high-dose group contained 96 male mice and 60 female mice. Significant chemical-related decreases in terminal body weights or survival were not observed in either sex. No significant alterations in absolute or relative organ weights occurred in exposed male mice. Significant decreases in absolute weights of brain, liver, and spleen and relative weight of spleen occurred in high-dose females; however, organ-to-body weight ratios were significantly different only for the spleen. Histopathological examination of organs was not conducted, but the authors noted that cataracts were not formed in exposed mice (methods used to assess the presence of cataracts were not specified). Examination of hematological parameters (including numbers of leukocytes, erythrocytes, and platelets and determination of hematocrit and hemoglobin) at termination revealed only slight, but statistically significant, increases in hemoglobin in high-dose females only; however, the hematological data were not shown in the report. Chemical analysis of serum showed statistically significant decreased blood urea nitrogen in all exposed female groups, and increased serum globulin and protein in the two highest female dose groups. In the same study, no exposure-related responses were found in a battery of immunological assays (humoral immune response, lymphocyte responsiveness, delayed-type hypersensitivity response, popliteal lymph node response, and bone marrow function); immunotoxic responses were observed in positive controls given intraperitoneal injections of 50 mg/kg cyclophosphamide on days 87, 88, 89, and 90. The study identified a LOAEL of 133 mg/kg-day and a NOAEL of 53 mg/kg-day with significant decreases in absolute weight of brain, liver, and spleen and relative weight of spleen in high-dose females. Therefore, the LOAEL of 133 mg/kg-day is based on the observed organ effects, especially the decrease in the relative weight of the spleen along with the suggestive evidence for effects on hepatic enzyme function. The toxicological significance of the statistically significant alterations in hematological and serum chemical parameters is not clear.

The use of the BCL (1980a) study in deriving the RfD was based on the following reasons:

The verification of the chemical dose, animal maintenance, and study design (10 rats/sex/dose group for 5 dose groups and 1 control group) are consistent with GLP guidelines submitted for 90-day studies, unlike the Shopp et al. (1984) study, in which the numbers of animals actually evaluated compared to those exposed for most endpoints (organ weights, clinical chemistry, and immunological testing) were small.

The decrease in mean terminal body weight in the BCL (1980a) study was not a result of decreased food consumption and was accompanied by clinical signs (diarrhea, lethargy, and rough coats) consistent with sick animals.

Decreases in mean terminal body weight of at least 10% were observed in females and males in the case of the BCL (1980a) study, unlike the Shopp et al. (1984) study, in which no significant changes in body weight were reported at any dose level.

The statistically significant alterations ($p < 0.05$) observed in the absolute (brain, liver, and spleen) and relative weight (spleen) of some organs in the absence of any decrease in body weight (Shopp et al., 1984) is not consistent with the absence of lesions and the lack of significant alterations in the clinical chemistry data, hematology, mixed-function oxidase activity, or the immunotoxicity assays for either sex.

Although the gross and histopathological examination was limited to the control and high-dose group in the BCL (1980a) study, renal lesions of low incidence were observed in the kidneys (focal cortical lymphocytic infiltration, focal and diffuse tubular regeneration) and thymus (lymphoid depletion) in males and females, respectively, at 100 mg/kg (71 mg/kg-day), unlike the Shopp et al. (1984) study, in which gross necropsy (no histopathological examination of tissues) on a randomly selected number of animals revealed no lesions.

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3000.

The duration-adjusted NOAEL for terminal body weight decrease (> 10% of control) in male rats from the BCL (1980a) 90-day gavage study, 71 mg/kg-day, was divided by an uncertainty factor of 3,000 (10 to extrapolate from rats to humans, 10 to protect sensitive humans, 10 to extrapolate from subchronic to chronic exposure, and 3 for database deficiencies including the lack of chronic oral exposure studies and 2-generation reproductive toxicity studies) to arrive at a chronic RfD for naphthalene of 2E-2 mg/kg-day.

MF = 1.

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

In deriving the RfD additional studies were evaluated for a variety of critical effects. Nervous system depression in pregnant rats (NTP, 1991) occurring at a lower dose (50 mg/kg-

day), was judged to be nonadverse, because the effect was considered to be transient in nature. Data from studies of mice exposed acutely to injections of naphthalene, or 1- or 2-methylnaphthalene (Buckpitt and Franklin, 1989), or chronically to 1- or 2-methylnaphthalene in the diet (Murata et al., 1993, 1997) provide suggestive evidence that chronic oral exposure to naphthalene at low doses may produce lung injury. However, deriving an RfD for naphthalene based on the methylnaphthalene data was judged to be too uncertain, because of metabolic differences between naphthalene and methylnaphthalenes and the absence of lung injury in subchronic oral studies in rats (BCL, 1980a) and mice with naphthalene (BCL, 1980b; Shopp et al., 1984).

A benchmark dose (BMD) approach to modeling the male rat body weight data fits mathematical models for a continuous variable to the data using maximum likelihood methods (see Appendix B to the Toxicological Review of Naphthalene, "Benchmark Dose Calculations"). In this approach, maximum likelihood estimates (MLEs) of dose (with no duration adjustment) associated with a 10% decrease in mean body weight compared with nonexposure conditions were 171 and 172 mg/kg-day using a polynomial and power model, respectively; respective 95% confidence lower limits on these doses, taken as BMDs, were 130 and 135 mg/kg-day. Assuming that either of these BMDs are surrogates for NOAELs, as suggested by the analysis of developmental toxicity data by Allen et al. (1994a,b) and Kavlock et al. (1995), making duration adjustments (BMD × 5/7) and applying the same 3,000 uncertainty factor used for the NOAEL/LOAEL approach arrives at a prospective RfD for naphthalene, 3E-2 mg/kg-day, that is comparable to the RfD derived with the NOAEL/LOAEL approach.

Benchmark dose approaches to deriving a chronic RfD for naphthalene were also examined using data for maternal body weight decreases in the NTP (1991) rat developmental toxicity study and data for lung proteinosis in mice exposed for 81 weeks to 1-methylnaphthalene in the diet (Murata et al., 1993). Decreased maternal body weight was not selected as the basis of chronic RfD derivation because the pregnant rats were exposed for only a small percentage of their lives. As discussed earlier, deriving the naphthalene RfD based on 1-methylnaphthalene data was judged to be too uncertain because of metabolic differences between naphthalene and methylnaphthalenes and the absence of lung injury in rats and mice orally exposed to naphthalene for subchronic periods.

The benchmark methodology for naphthalene is contained within an appendix of the Toxicological Review for the readers' information, however it was decided to use the LOAEL/NOAEL approach rather than the benchmark approach in the derivation of the RfD/RfC.

I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- High
Data Base -- Low
RfD -- Low

The principal study was given a high confidence rating because adequate numbers of animals were included and experimental protocols were adequately designed, conducted, and reported. Confidence in the database was rated low because of the lack of adequate chronic oral

data for naphthalene; the lack of any dose-response data for naphthalene-induced hemolytic anemia, probably one of the most well-known health hazards to humans exposed to naphthalene; and the lack of two-generation reproductive toxicity studies. Humans exposed via inhalation, combined inhalation and dermal exposure, and combined inhalation and oral exposure have developed hemolytic anemia. Hemolytic anemia is characterized by findings of lowered hemoglobin, hematocrit, and erythrocyte values, elevated reticulocyte counts, Heinz bodies, elevated serum bilirubin, and fragmentation of erythrocytes. In severe cases, the hemolytic anemia was accompanied by jaundice, high serum levels of bilirubin, cyanosis, and kernicterus with pronounced neurological signs. Neither oral nor inhalation exposure levels were available in human studies reporting anemia (Melzer-Lange and Walsh-Kelly, 1989; Owa, 1989; Owa et al., 1993). Infants deficient in G6PDH are thought to be especially sensitive to naphthalene-induced hemolytic anemia. Resulting confidence in the RfD is low. A quantitative comparison of the acute dog study (7 days at 262 mg/kg-day; free-standing LOAEL of 262 mg/kg-day based hemolytic anemia) with the RfD (chronic oral rat study based on decrease in mean terminal body weight) to determine whether the RfD is protective of hemolytic anemia in humans is not possible since adequate dose-response data in a subchronic or chronic dog study are lacking. Therefore, because of the absence of an appropriate animal model one cannot extrapolate either qualitatively or quantitatively to humans with respects to hemolytic anemia.

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 1998

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 the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998).

Other EPA Documentation -- U.S. EPA, 1980, 1986, 1987, 1988

Agency Consensus Date – 07/01/98

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@epamail.epa.gov (email address).

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

Naphthalene
CASRN -- 91-20-3
Last Revised -- 09/17/1998

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are 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.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
Nasal effects: hyperplasia and metaplasia in respiratory and olfactory epithelium, respectively Chronic mouse inhalation study NTP, 1992	NOAEL: None mg/m^3 LOAEL(HEC): 9.3 mg/m^3	3000	1	3E-3

*Conversion Factors and Assumptions -- Following the Category 3 guidance (U.S. EPA, 1994), experimental exposure concentrations of 0, 10, and 30 ppm were converted to 0, 52, and 157 mg/m^3, respectively; adjusted to a continuous exposure basis in mg/m^3 (6/24 hr × 5/7 days) equals mg/m^3 × 0.1786: 0, 9.3, and 28 mg/m^3. Because the blood:gas (air) coefficients for naphthalene were not available, the default ratio of 1 was used and the values for the LOAEL(HEC) were 0, 9.3, and 28 mg/m^3. Scenario -- The LOAEL human equivalent concentration (HEC) was calculated for an extrarespiratory effect for a category 3 gas. Since the b:a lambda for humans (h) is unknown, a default value of 1.0 is used for this ratio. LOAEL(HEC) × [b:a lambda(animal)/b:a lambda(human)] = 9.3 mg/m^3.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

National Toxicology Program (NTP). (1992) Toxicology and carcinogenesis studies of naphthalene in B6C3F1 mice (inhalation studies). Technical Report Series No. 410. NIH Publication No. 92-3141.

B6C3F1 mice (75/sex/group) were exposed to naphthalene (scintillation grade, > 99% pure) at target concentrations of 0, 10, and 30 ppm (0, 52, 157 mg/m^3) for 6 hr/day, 5 days/week, for 103 weeks (NTP, 1992). The duration-adjusted levels were 0, 9.3, and 28 mg/m^3, respectively. Additional groups of 75 male and 75 female replacement animals were exposed to 30 ppm to ensure that a sufficient number of mice lived to study termination. Naphthalene vapor was generated by direct sublimation and monitored by a software feedback arrangement. Average weekly concentrations were within 20% of target concentrations, except one week when the mean concentration in the low-concentration chamber was 5.5 ppm. Supplemental hematology studies were scheduled with 25 animals/sex/group, but only the first sacrifice (at 14 days) was conducted because of high mortality in the male control group from fighting. Serial slit-lamp biomicroscopy and indirect ophthalmoscopic examinations were conducted on 5 animals/sex/group at 6-mo intervals. Gross necropsies were conducted on all animals. Complete histopathologic examinations of major tissues were conducted on all animals, except that the only tissues examined from low-concentration animals dying or killed after 21 mo of exposure were the lungs and nasal cavities.

Survival of the male controls was significantly lower than in the exposed males. Reduced survival was related to wound trauma and lesions from increased fighting in this group. Similar effects were not seen in the exposed males, because they tended to huddle in cage corners during exposure periods and so fought less. There was no significant difference in survival between the treatment and control females. There were no treatment-related ocular lesions in the selected mice that underwent ophthalmologic examinations at 6-mo intervals. There were no biologically significant changes in hematology parameters at day 14 of the study. Final mean body weights of the treated animals were within 10% of the corresponding controls.

Inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium were noted in the noses of virtually all exposed mice of both sexes, but in only one control female mouse. These effects were slightly more severe in the high-concentration group. See Table 1 for incidence data. The lesions were focal or multifocal, occurred mainly in the posterior nasal cavity, and were minimal to mild in severity. Inflammatory lesions included substantia propria edema, congestion, mixed inflammatory cell infiltrates, necrotic debris, and intraluminal serous to fibrinopurulent exudate. Respiratory epithelial hyperplasia resulted in a thickened, folded, irregular mucosal surface. Olfactory epithelial metaplasia often involved ciliated columnar or pseudocolumnar respiratory-like epithelial cells replacing the usual olfactory cell layer. The lesions were collectively considered features of a generalized inflammatory and regenerative process.

Table 1. Incidence of nonneoplastic respiratory lesions in B6C3F1 mice exposed by inhalation to naphthalene, 6 hr/day, 5 days/week for 2 years

Exposure level/sex (ppm)	Respiratory lesion		
	Inflammation, lung	Hyperplasia, nasal respiratory epithelium	Metaplasia, nasal olfactory epithelium
0/male 0/female	0/70 3/69	0/70 0/69	0/70 0/69
10/male 10/female	21/69 13/65	66/69 65/65	66/69 65/65
30/male 30/female	56/135 52/135	134/135 135/135	134/135 135/135

Source: NTP, 1992.

Minimal to mild lung lesions, including infiltration of histiocytes or lymphocytes, inflammation, hyperplasia of the alveolar epithelium, and bronchial submucosal gland distension, were observed in both controls and treated mice. The incidence and severity were generally higher in the treated groups of both sexes, but there was no clear concentration-response relationship.

Females in the high-exposure group had elevated incidences of alveolar/bronchiolar adenomas and carcinomas (combined incidence 22%, compared with 7% in the control group and 3% in the low-exposure group). The incidence was also above that of historical controls and was considered compound-related. The incidences of alveolar/bronchiolar adenomas and carcinomas in treated males were marginally increased (10%, 25%, and 23%, in the control, low-concentration, and high-concentration groups, respectively). However, because the increase was not statistically significant and was within the range of historical controls, it was not considered exposure related. Instead, it was attributed to the longer life span of the treated animals. Nasal adenomas occurred in the anterior nasal cavities of two females in the low-concentration group. They were not considered compound related because the increase was not concentration related or statistically significant. Therefore, the nasal lesions discussed above should not be considered preneoplastic.

Calculation of the Human Equivalent Concentration (HEC)

Dose conversion: Because of its low water solubility and low reactivity, naphthalene-related effects on the nasal epithelium are expected to result following absorption of naphthalene and metabolism to reactive oxygenated metabolites, rather than being a result of direct contact. This hypothesis is supported by data on naphthalene metabolism indicating that toxic effects on the respiratory tract are due to a naphthalene metabolite that may be formed either in the liver or in the respiratory tract. For example, necrosis of bronchial epithelial (Clara) cells in mice (O'Brien et al., 1985, 1989; Tong et al., 1981) and necrosis of olfactory epithelium in mice, rats,

and hamsters (Plopper et al., 1992) occur following intraperitoneal injection of naphthalene. The nasal effects from inhalation exposure to naphthalene were considered to be extra-respiratory effects of a category 3 gas, as defined in the U.S. EPA guidance for deriving RfCs (U.S. EPA, 1994). Following this guidance, experimental exposure concentrations were adjusted to a mg/m^3 basis (0, 52, and 157 mg/m^3), adjusted to a continuous exposure basis ($mg/m^3 \times 6h/24h \times 5d/7d = mg/m^3 \times 0.1786$: 0, 9.3, and 28 mg/m^3), and converted to human equivalent concentrations (HECs) by multiplying the adjusted concentrations by the ratio of mouse:human blood/gas partition coefficients. Because the blood/gas coefficients for naphthalene were not available, the default ratio of 1 was used.

Dose-response modeling: Whereas the data from the NTP (1992a) study show nasal effects to be the most sensitive effects from chronic inhalation exposure to naphthalene, they provide no indication of the shape of the dose-response curve because the incidence of nasal lesions at the lowest exposure level was 100% in females and nearly 100% in males (see Table 1). In this case, application of a BMD approach, in which quantal mathematical models are fit to the incidence data for nasal effects, does not sensibly assist in extrapolating to a NOAEL, and a NOAEL/LOAEL approach was taken for deriving an RfC for naphthalene.

I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 3000.

The adjusted LOAEL(HEC) of 9.3 mg/m^3 for nasal effects (hyperplasia in respiratory epithelium and metaplasia in olfactory epithelium) was divided by an uncertainty factor of 3000 (10 to extrapolate from mice to humans, 10 to protect sensitive humans, 10 to extrapolate from a LOAEL to a NOAEL, and 3 for database deficiencies including the lack of a 2-generation reproductive toxicity study and chronic inhalation data for other animal species) to arrive at a chronic RfC for naphthalene of 3E-3 mg/m^3.

MF = 1.

I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

SUPPORTING STUDIES

Human experience with acute accidental exposures to naphthalene identifies the development of hemolytic anemia and cataracts as health hazards of concern. However, information is not available regarding dose-response relationships for these effects in humans with acute, subchronic, or chronic exposure by any route. Animal inhalation studies are restricted to three studies of mice: a 2-year study (NTP, 1992), a 6-mo study (Adkins et al., 1986), and a 4-hr study (Buckpitt, 1982). Results from the chronic study, supported by the subchronic and acute studies, identify nasal and pulmonary injuries as critical effects from chronic inhalation exposure to naphthalene; effects in other organs or tissues were not found. Incidence data for male and female mice with hyperplasia of the nasal respiratory epithelium, metaplasia of the nasal olfactory epithelium, and chronic pulmonary inflammation clearly show that the nose is more sensitive than the lung to chronic inhalation exposure to naphthalene. At both exposure levels (10 and 30 ppm, 6 hr/day, 5 days/week), > 95% of mice of either sex

showed nasal lesions, whereas pulmonary lesions were found in < 1/3 and < ½ of mice exposed at 10 and 30 ppm, respectively (Table 1). Nasal lesions in the respiratory and olfactory epithelium in mice found in the NTP (1992) study were therefore selected as the critical effects for the purpose of RfC derivation.

Adkins et al. (1986) exposed female A/J mice (30/group) to 0, 10, or 30 ppm (0, 52, or 157 mg/m^3) naphthalene for 6 hr/day, 5 days/week for 6 mo, and counted the number of adenomas in each lung. The duration-adjusted concentrations were 0, 9.2, and 28 mg/m^3, respectively. Exposure to naphthalene caused increases in the total number of adenomas and the percentage of animals with adenomas, but the differences were not significant. The number of tumors per tumor-bearing mouse lung was significantly increased at both exposure levels.

Buckpitt (1982) subjected groups of five male mice (Swiss Webster) plus control group to 1-hr exposures to naphthalene concentrations of 0, 52.4, 95.8, 204, or 380 mg/m^3. Adverse effects were seen only at the highest concentration, and included swelling of cells and sloughing into the airway lumen of cells from either the major and/or terminal airways. The effects were milder in the presence of cytochrome P450 inhibitor and stronger in the presence of a glutathione depletor, suggesting that cytotoxicity is due to a naphthalene metabolite produced by P450 and that glutathione plays a protective role. Naphthalene reduced glutathione levels in the lung, liver, and kidney, but the concentration-response curve was flat.

Following a single 4-hr exposure of five male and five female Wistar Albino rats to 77.7 ppm (407 mg/m^3), closed eyes, lacrimation, and mouth breathing were observed (Bushy Run Research Center, 1986). No signs of toxicity were observed postexposure or during the 14-day observation period, and gross necropsy revealed no exposure-related lesions.

I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- Low to Medium
RfC – Medium

The principal study was given medium confidence because adequate numbers of animals were used, and the severity of nasal effects increased at the higher exposure concentration. However, the study produced high mortality, < 40% survival in the male control group due to wound trauma and secondary lesions resulting from increased fighting). Also, hematological evaluation was not conducted beyond 14 days. The database was given a low-to-medium confidence rating because there are no chronic or subchronic inhalation studies in other animal species, and there are no reproductive or developmental studies for inhalation exposure. In the absence of human or primate toxicity data, the assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans; however, it cannot be said with certainty that this RfC for naphthalene based on nasal effects will be protective for hemolytic anemia and cataracts, the more well-known human effects from naphthalene exposure. Medium confidence in the RfC follows.

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- U.S. EPA, 1998

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 the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998).

Other EPA Documentation -- U.S. EPA, 1980, 1986, 1987, 1988
Agency Consensus Date – 07/01//98

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 @epamail.epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Naphthalene
CASRN -- 91-20-3
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 *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), naphthalene is likely to be carcinogenic to humans by the inhalation route of exposure based on: (1) increased incidences of rare nasal tumors including olfactory epithelial neuroblastomas in female rats and respiratory epithelial adenomas in male rats exposed to naphthalene vapor concentrations of 10, 30, or 60 ppm for 2 years (Abdo et al., 2001; NTP, 2000); (2) increased incidences of alveolar/bronchiolar adenomas or carcinomas in female (but not male) B6C3F1 mice exposed to 30 ppm naphthalene for 2 years (NTP, 1992); and (3) increased numbers of tumors in tumor-bearing A/J strain mice exposed to 10 or 30 ppm for 6 months (Adkins et al., 1986). Evidence from human studies is limited to a few case series reports of laryngeal cancer in naphthalene purification workers and colorectal cancer in several patients who reported taking an indigenous medication containing naphthalene. Refer to Sections 4.1.4 and 4.2.2 of the Toxicological Review (U.S. EPA, 2004) for more information on available human and animal studies.

The previous IRIS assessment classified naphthalene as a possible human carcinogen (Group C; inadequate human and limited animal data) via the oral and inhalation routes using criteria of the Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1986). In addition, using the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), it was stated that the human carcinogenic potential via the oral and inhalation routes cannot be determined based on human and animal data; however, there was suggestive evidence of potential human carcinogenicity based on increased lung tumor incidence in one animal species and one sex at the high dose only. Additional support included increased respiratory tumors associated with 1-methylnaphthalene. The current reassessment of inhalation carcinogenicity supersedes the previous assessment.

The International Agency for Research on Cancer has classified naphthalene as a 2B carcinogen (possibly carcinogenic to humans) based on inhalation data in animals (IARC, 2002). The National Toxicology Program is in the process of reevaluating the carcinogenicity of naphthalene for the upcoming 11th Report on Carcinogens (http://ntp-server.niehs.nih.gov/).

The mode of action by which naphthalene affects mouse lung epithelial tissue and mouse and rat nasal tissue may involve the metabolic intermediates, naphthalene-1,2-oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone, which may damage tissue macromolecules either directly by their inherent electrophilicity or by the generation of reactive oxygen species (Buckpitt et al., 1992, 1995, 2002; D'Arcy Doherty et al., 1985; Flowers et al., 1997; Greene et al., 2000; Tao et al., 1991a, b; Xu et al., 1992; Zheng et al., 1997). However, identification which metabolites are responsible for naphthalene toxicity and carcinogenicity is unknown. Tissue sites of nonneoplastic cellular damage (bronchoalveolar region in mice and nasal tissues in rats and mice) show some correlation with tissue sites of carcinogenicity (lung tumors in mice, but not rats, and nasal tumors in rats, but not mice), suggesting that naphthalene metabolites may act by nongenotoxic modes involving sustained cellular proliferation following cellular damage. This hypothesis is supported by negative results for naphthalene in numerous short-term genotoxicity assays. However, an understanding of the mode of action is inadequate for determining why

rats, but not mice, develop tumors originating in nasal tissues even though both species show nonneoplastic lesions in nasal epithelial tissues following inhalation exposure to naphthalene. Other events preceding tumor formation have not been identified. A possible genotoxic mode of carcinogenic action cannot be discounted as there are some data indicating genotoxicity of 1,2-naphthoquinone.

II.A.2. HUMAN CARCINOGENICITY DATA

As discussed in Section 4.1.4 of the Toxicological Review (U.S. EPA, 2004), the only available studies of cancer in humans exposed to naphthalene are a few case series reports of cancer: one report of four laryngeal cancer cases (all of whom were smokers) among workers in a naphthalene purification plant in East Germany (Kup, 1978; Wolf, 1976, 1978), and a report of 23 patients with colorectal carcinoma admitted to a hospital in Nigeria, half of whom recalled taking sometime during their life a local medication, *Kafura*, which contains naphthalene (Ajao et al., 1988). No cohort mortality, morbidity studies or case-control studies examining possible associations between naphthalene exposure and increased risk of cancer (or other health effects) are available.

II.A.3. ANIMAL CARCINOGENICITY DATA

The NTP mouse (NTP, 1992) and rat (Abdo, 2001; NTP, 2000) inhalation studies are adequately designed to examine the carcinogenicity of lifetime naphthalene exposure. The studies involved exposure to 0, 10, or 30 ppm naphthalene for mice and 0, 10, 30, or 60 ppm for rats (6 hours/day, 5 days/week for 104-105 weeks). The studies provide evidence of naphthalene carcinogenicity in male and female rats (increased incidences of olfactory epithelial neuroblastomas and respiratory epithelial adenomas) and female mice (increased incidences of alveolar/bronchiolar adenomas and carcinomas). These results provide adequate evidence of carcinogenicity in two animal species exposed by inhalation to naphthalene vapors.

Inhalation: In a 2-year inhalation bioassay, groups of 49 male and 49 female F344/N rats were exposed to naphthalene at concentrations of 0, 10, 30, or 60 ppm for 6 hours/day, 5 days/week for 105 weeks (Abdo et al. 2001; NTP, 2000).

Increased incidences of nonneoplastic and neoplastic lesions of the nose occurred in exposed rats of both sexes (see Table 2). Nonneoplastic nasal lesions included 1) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium and 2) hyperplasia, metaplasia, or degeneration of the respiratory epithelium or glands. Mean severity scores on a 4-point scale from minimal (1) to marked (4) generally increased with increasing exposure level (Table 2). Nasal lesions showing the greatest severity scores were olfactory epithelial atrophy (e.g., mean scores were 0, 2.1, 2.8, and 3.5 for control through 60-ppm males, respectively) and Bowman's gland hyperplasia (mean scores were 1.0, 2.2, 2.9, and 3.5 for males, respectively). Neoplastic lesions associated with naphthalene exposure in rats were olfactory epithelial neuroblastomas and respiratory epithelial adenomas. Olfactory epithelial neuroblastomas and respiratory epithelial adenomas are rare tumors in rats and in humans.

Increased incidences of neoplastic lesions were restricted to the nose in exposed rats compared with controls. Findings for naphthalene-induced nonneoplastic lesions at sites other

than the nose were restricted to scattered observations for alveolar epithelial hyperplasia and chronic inflammation of the lung. Incidences of alveolar epithelial hyperplasia were significantly increased in 10- and 30-ppm female rats compared with controls, but not in 60-ppm female rats or in any of the exposed male rat groups. Incidences of alveolar epithelial hyperplasia in females in the control through 60-ppm groups were 4/49, 11/49, 11/49, and 9/49, respectively. Chronic pulmonary inflammation, described as minimal inflammatory foci often found in chamber control rats, was significantly increased in male rats exposed to 10 or 60 ppm, but not in males exposed to 30 ppm (male incidences were 2/49, 13/49, 6/48, and 15/49, respectively), or in any of the exposed female groups. These observations do not provide clear evidence of a relationship between pulmonary nonneoplastic lesions and naphthalene exposure in this study.

Table 2. Incidences of nonneoplastic‡ and neoplastic lesions of the nose in male and female F344/N rats exposed to naphthalene 6 hours/day, 5 days/week for up to 105 weeks (Abdo et al., 2001; NTP, 2000)

Lesion	Concentration (ppm)							
	0		10		30		60	
	M	F	M	F	M	F	M	F
NONCANCER LESIONS								
olfactory epithelium								
hyperplasia, atypical	0/49	0/49	48/49* (2.1)	48/49* (2.0)	45/48* (2.5)	48/49* (2.4)	46/48* (3.0)	43/49* (2.9)
atrophy	3/49	0/49	49/49* (2.1)	49/49* (1.9)	48/48* (2.8)	49/49* (2.7)	47/48* (3.5)	47/49* (3.2)
chronic inflammation	0/49	0/49	49/49* (2.0)	47/49* (1.9)	48/48* (2.2)	47/49* (2.6)	48/48* (3.0)	45/49* (3.4)
hyaline degeneration	3/49 (1.3)	13/49 (1.1)	46/49* (1.7)	46/49* (1.8)	40/48* (1.7)	49/49* (2.1)	38/48* (1.5)	45/49* (2.1)
respiratory epithelium								
hyperplasia	3/49 (1.0)	0/49	21/49* (2.2)	18/49* (1.6)	29/48* (2.0)	22/49* (1.9)	29/48* (2.2)	23/49* (1.7)
squamous metaplasia	0/49	0/49	15/49* (2.1)	21/49* (1.6)	23/48* (2.0)	17/49* (1.5)	18/48* (1.8)	15/49* (1.8)
hyaline degeneration	0/49	8/49 (1.0)	20/49* (1.2)	33/49* (1.2)	19/48* (1.4)	34/49* (1.4)	19/48* (1.2)	28/49* (1.2)
goblet cell hyperplasia	0/49	0/49	25/49* (1.3)	16/49* (1.0)	29/48* (1.2)	29/49* (1.2)	26/48* (1.2)	20/49* (1.0)
gland hyperplasia	1/49 (1.0)	0/49	49/49* (2.2)	48/49* (1.9)	48/48* (2.9)	48/49* (3.1)	48/48* (3.5)	42/49* (3.3)
gland squamous metaplasia	0/49	0/49	3/49 (3.0)	2/49 (2.0)	14/48* (2.1)	20/49* (2.5)	26/48* (2.5)	20/49* (2.8)
NEOPLASMS								
respiratory epithelial adenoma	0/49†	0/49	6/49*	0/49	8/48*	4/49	15/48*	2/49
olfactory epithelial neuroblastoma	0/49†	0/49†	0/49	2/49	4/48	3/49	3/48	12/49*

‡ Mean severity scores for rats with a specific lesion are noted in parentheses: 1=minimal; 2=mild; 3=moderate; 4=marked
* Significantly ($p<0.05$) different from control value by the Poly-3 test, which adjusts for intercurrent mortality
† Significant ($p<0.05$) trend by the Poly-3 test

In another NTP (1992) cancer bioassay, groups of male and female B6C3F1 mice were exposed (whole-body) to naphthalene (> 99% pure) vapors at concentrations of 0 (75 mice/sex), 10 (75 mice/sex), or 30 ppm (150 mice/sex) 6 hr/day, 5 days/week for 2 years.

Statistically significant increases in incidences of nonneoplastic lesions were found in the lung and nose of males and females at both exposure levels. Observed nonneoplastic effects included the following (with respective incidences listed in the order of control, low-, and high-exposure groups, respectively): chronic inflammation of the lung (0/70, 21/69, and 56/135 for males; 3/69, 13/65, and 52/135 for females); chronic inflammation (0/70, 67/69, and 133/135 for males and 1/69, 65/65, and 135/135 for females); metaplasia of the olfactory epithelium (0/70, 66/69, and 134/135 for males; 0/69, 65/65, and 135/135 for females); and hyperplasia of the respiratory epithelium in the nose (0/70, 66/69, and 134/135 for males; 0/69, 65/65, and 135/135 for females).

Lung inflammation in the exposed mice was described as consisting of focal intra-alveolar mixed inflammatory cell exudates and interstitial fibrosis that in more advanced lesions consisted primarily of large foamy macrophages, sometimes accompanied by multinucleated giant cells. Foci of alveolar epithelial hyperplasia were noted to occur generally in regions distant to inflammation.

A statistically significant increase in the incidence of alveolar/bronchiolar adenomas was observed in the 30 ppm group of females (28/135), but not in the 10 ppm group (2/65), relative to the control female group (5/69). Among females, an additional mouse in the 30-ppm group displayed an alveolar/bronchiolar carcinoma. The historical combined incidence of alveolar/bronchiolar adenomas and carcinomas in control B6C3F1 female mice from NTP inhalation studies was cited as 39/466 (8.4%, range 0-12%). The authors commented that alveolar/bronchiolar adenomas and carcinomas constitute a morphologic continuum. The incidences of male mice with alveolar/bronchiolar adenomas were 7/70, 15/69, and 27/135 for the control, 10 ppm, and 30 ppm groups, respectively; for combined adenomas and carcinomas of the alveolar/bronchiolar region, the respective incidences were 7/70, 17/69, and 31/135. A statistical analysis that adjusted for intercurrent mortality (logistics regression analysis) determined that the tumor incidences for control and exposed groups of male mice were not significantly different (NTP, 1992). Historical incidence for combined alveolar/bronchiolar adenomas and carcinomas in control male B6C3F1 mice from NTP inhalation studies was cited as 94/478 (19.7%, range 10%-30%). The adenomas were described as locally compressive nodular masses consisting of cords of well-differentiated epithelial cells, whereas the carcinoma was composed of ribbons and/or coalescing sheets of smaller, more anaplastic, cells which sometimes extended into adjacent parenchyma.

Hemangiosarcomas occurred at various sites within the vascular endothelium in five high-dose female mice (5/135), but not within the other groups of female mice (0/69 and 0/65 for control and 10 ppm females, respectively). The high-dose female incidence (3.7%) was not significantly different from the concurrent control incidence and was within the range of historical control incidences from NTP inhalation studies (range: 0-8%; overall incidence: 17/467 or 3.6%). No significantly elevated incidences of tumors were found at other tissue sites in exposed male or female mice (NTP, 1992). Refer to Section 4.2.2 of the Toxicological Review (U.S. EPA, 2004) for more detailed study descriptions.

Oral: Schmahl (1955) reported that naphthalene administered in food did not cause cancer in a group of 28 rats (in-house strains BDI and BDII). Naphthalene (purchased from Merck Co. and described as "Naphthalene puriss. cryst. alcoh. depur. [54935]") was dissolved in oil and given 6 times/week in food. The absorption spectrum of the test material displayed no atypical peaks compared with published data for naphthalene, suggesting high purity. The daily dose was reported to vary between 10 and 20 mg, but further details regarding dose variation were not provided. After reaching a total dose of 10 g/rat (food intake and body weights were not reported), treatment was stopped on the 700th experimental day, and animals were observed until spontaneous death, between 700 and 800 days of age. Assuming an average daily dose of 15 mg/rat and a body weight of 0.36 kg (U.S. EPA, 1987, reference body weight for male Fischer 344 rats), an estimated average daily dose of 42 mg/kg is calculated. Autopsies were performed on dead animals, and organs that appeared unusual were examined histologically (the report did not specify which organs were histologically examined). The number of rats in the control group was not reported; survival for control and exposed rats was reported to be similar. Reported results from the autopsy and histological examinations were restricted to the statement that no toxic effects were seen, including eye damage and tumors. Inadequacies in experimental design (e.g., only one dose level was administered, the histopathological examination was not complete, hematological endpoints were not evaluated, and some rats lived as long as 300 days beyond exposure before being examined) and inadequacies in reporting of experimental details and results limit the conclusions that can be drawn from this study regarding either the carcinogenicity or noncarcinogenic toxicity of naphthalene. This study is considered inadequate as a cancer bioassay because of reporting and design inadequacies and the likelihood that the maximum tolerated dose may not have been approached.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Weight of evidence evaluation: Genotoxicity of naphthalene

Results from genotoxicity testing for naphthalene are mostly negative. Most results in bacterial mutation assays for naphthalene or its metabolites were negative, with the exception of two positive results. 1,2-Naphthoquinone induced reverse mutations in *S. typhimurium* without metabolic activation (Flowers-Geary et al., 1996), and naphthalene induced reverse mutations in *Vibrio fischeri* in the presence of rat liver metabolic activation (Arfsten et al., 1994). *In vitro* genotoxicity assays with eukaryotic cells are limited and show positive or negative results in different assays. However, these *in vitro* tests include observations that naphthalene metabolites generated from rat liver microsomes induced chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (NTP, 1992), and that 1,2- and 1,4-naphthoquinone induced sister chromatid exchanges in human leukocytes (Wilson et al., 1996). The potential genotoxicity of 1,2-naphthoquinone is supported by *in vitro* findings that 1,2-naphthoquinone formed N7 adducts with deoxyguanosine (McCoull et al., 1999) and caused DNA strand scission in the presence of NADPH and copper via reactive oxygen species (Flowers et al., 1997). Yu et al. (2002) showed that 1,2-naphthoquinone was capable of inactivating the p53 tumor suppressor gene in a yeast reporter system in the presence of copper and a reducing agent. Limited *in vivo* genotoxicity assays with naphthalene provide both negative or positive results for naphthalene genotoxicity (including a report that naphthalene induced wing spot mutations in *Drosophila melanogaster*). See Section 4.4.4 of the Toxicological Review (U.S. EPA, 2004) for a more detailed description of the genotoxicity data.

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

There are no human data and inadequate laboratory animal data to determine the carcinogenicity of naphthalene by the oral route of exposure. Thus, no oral slope factor was derived.

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

Note: EPA recognizes that the derivation of the human equivalent concentration differs in the proposed inhalation cancer assessment and the existing RfC assessment. EPA may revisit the RfC assessment in the future.

II.C. 1. SUMMARY OF RISK ESTIMATES

II.C.1.1. Inhalation Unit Risk, 95% upper bound – 0.1 per mg/m^3 (1x10^{-4} per µg/m^3)
central tendency estimate – 0.09 per mg/m^3 (9x10^{-5} per µg/m^3)

II.C.1.2. Extrapolation Method - An inhalation unit risk of 0.1 per mg/m^3, based on time-to-tumor modeling and a summed risk for respiratory epithelial adenomas and olfactory epithelial neuroblastomas in male rats, was chosen as the best estimate of human risk. This value is approximately 35% higher than the summed unit risk resulting from the quantal dose-response modeling of the same data.

Air Concentrations at Specified Risk Levels:

Risk Level	95% lower bound on Concentration estimate
1 in 10,000 (1x10^{-4})	1 µg/m^3
1 in 100,000 (1x10^{-5})	0.1 µg/m^3
1 in 1,000,000 (1x10^{-6})	0.01 µg/m^3

II.C. 2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type – summed nasal tumors (respiratory epithelial adenomas and olfactory epithelial neuroblastomas) in male rats
Test Species – F344/N rats
Route – Inhalation
References – Abdo et al., 2001; NTP, 2000

II.C. 3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

As discussed in Section 4.6 of the Toxicological Review (U.S. EPA, 2004), naphthalene is likely to be carcinogenic to humans by the inhalation route of exposure based on increased incidences of rare nasal tumors (olfactory epithelial neuroblastomas and respiratory epithelial adenomas) in rats exposed to naphthalene vapor concentrations of 10, 30, or 60 ppm for 2 years (Abdo, 2001; NTP, 2000), increased incidences of alveolar/bronchiolar adenomas or carcinomas in female mice exposed to 30 ppm for 2 years (NTP, 1992), and increased numbers of tumors in tumor-bearing A/J strain mice exposed to 10 or 30 ppm for 6 months (Adkins et al., 1986). Evidence from human studies is inadequate to determine naphthalene carcinogenicity.

Characteristics of the dose-response relationships for the male and female rat respiratory epithelial adenomas and male and female nasal olfactory neuroblastomas were assessed by a quantal analysis and through time-to-tumor analyses. The latter analyses were conducted in order to adjust for competing mortality and differing time courses of tumor incidence with increasing dose. The quantal analysis is discussed in Section 5.3.2 of the Toxicological Review (U.S. EPA, 2004) and will not be discussed further here. In addition, quantal analysis of the alveolar/bronchiolar adenomas and carcinomas in female mice (NTP, 1992) was performed.

As discussed in Sections 3.3 and 4.6.3 of the Toxicological Review (U.S. EPA, 2004), respiratory effects are likely due to reactive naphthalene metabolites formed either within the affected tissue or as a result of systemic metabolism. In the absence of appropriate naphthalene-specific PBPK models for humans and rats, default dosimetric equations (U.S. EPA, 1994) for a category 1 gas was considered for converting rat exposure levels to human equivalent concentrations due to direct respiratory effects.

The general model used for the time-to-tumor (or time-to-response) analyses is the multistage-Weibull model, which has the form

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)*(t - t_0)^z]$$

where P(d,t) represents the probability of a tumor (or other response) by age t (in bioassay weeks) for dose d (i.e., human equivalent exposure), and parameters $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for i = 0, 1, ..., k, where k = the number of dose groups - 1. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death (see below). The analyses were conducted using the computer software TOX_RISK version 5.2 (K.S. Crump Group, 2000-2001), which is based on Weibull models drawn from Krewski et al. (1983). Parameters are estimated using the method of maximum likelihood. Note that it was not necessary to adjust the administered dose for lifetime exposure prior to modeling, because the software program characterizes the tumor incidence over time from which it provides an extrapolation to lifetime exposure. The times of observation of the tumors for time-to-tumor modeling are presented in Appendix C of the Toxicological Review (U.S. EPA, 2004).

The tumor types were categorized by tumor context as either fatal or incidental tumors, in order to adjust appropriately for competing risks. Incidental tumors are those tumors thought not to have caused the death of an animal, while fatal tumors are thought to have resulted in animal death. The neuroblastomas were treated as fatal tumors unless observed at the terminal sacrifice, in which case they were considered incidental. The parameter t_0 was set equal to 0, as there were insufficient data to reliably estimate t_0. The work of Portier et al. (1986) in analyzing tumor types in NTP historical controls lends support to these tumor context assumptions.

Specific n-stage Weibull models were selected for the individual tumor types for each sex based on the values of the log-likelihoods according to the strategy used by EPA (U.S. EPA, 2002). If twice the difference in log-likelihoods was less than a chi-square with degrees of freedom equal to the difference in the number of stages included in the models being compared, the models were considered comparable and the most parsimonious model (i.e., the lowest-stage model) was selected.

The maximum likelihood estimates of the benchmark doses (BMCs) and 95% lower bounds (BMCLs) for 10% extra risk for each tumor are provided in Section 5.3 of the Toxicological Review, consistent with the BMDS Technical Guidance (U.S.EPA, 2000) and the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S.EPA, 1999). In general, site- and sex-specific $BMCL_{10}$s using the time-to-tumor approach were approximately 20% higher than those calculated using the quantal approach.

Reliance on single tumor sites may underestimate the carcinogenic potential of naphthalene by the inhalation route (see Section 5.3.2.1 of the Toxicological Review (U.S. EPA, 2004)). Thus, time-to-tumor modeling was applied to calculate the summed risk for multiple tumor types in rats. Accordingly, a statistically appropriate upper bound risk was estimated using the following steps. Summing the cancer risks in this manner, after the dose-response for each tumor site has been evaluated, is superior to EPA's previous practice of carrying out one dose-response analysis of tumor-bearing animals. The primary reason is that the biological relevance of the multistage model is maximized, by allowing different multistage models to be fit to qualitatively different tumor types which might not be expected to develop through exactly the same modes of action. The time courses of the tumor types evaluated here did vary, for example. Note that the neuroblastomas tended to occur earlier than the adenomas, suggesting that the adenomas are not precursors to the neuroblastomas, and mostly occur independently of the neuroblastomas; only one high dose female and mid-dose male were observed with both tumors.

For the male rats, the summed unit risk was 1.5×10^{-2} per ppm, and the summed central tendency risk was 1.1×10^{-2} per ppm. In terms of human equivalent exposures in mg/m^3, the summed risks were 12.1×10^{-2} per mg/m^3 (upper bound) and 8.9×10^{-2} per mg/m^3 (central tendency). Both estimates were approximately 35% higher than the summed risks resulting from the quantal dose-response modeling. Results for female rats were proportionately similar, and are not presented.

An inhalation unit risk of 0.1 per mg/m^3, based on time-to-tumor modeling and a summed risk for respiratory epithelial adenomas and olfactory epithelial neuroblastomas in male rats, was chosen as the best estimate of human risk. For a discussion of the rationale for linear low-dose extrapolation see Section 5.3.3 of the Toxicological Review (U.S. EPA, 2004).

II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

Current mechanistic understanding of the mode by which naphthalene induces nasal tumors in rats and lung tumors in mice is inadequate. Likewise, understanding of the mode of naphthalene carcinogenic action is inadequate to confidently rule out a possible genotoxic mode of action involving metabolites. The current inhalation unit risk estimates are based on assumptions that humans will respond like rats to inhaled doses of naphthalene and that default dosimetric equations for a category 1 gas predict deposited doses of naphthalene to nasal tissues in humans. Additional research examining 1,2-naphthoquinone and 1,2-epoxide formation from naphthalene exposure may help to decrease uncertainty about naphthalene's mode of carcinogenic action. Development of rodent and human PBPK models that predict deposited doses of naphthalene or pertinent naphthalene metabolite(s) in nasal tissue may help to decrease uncertainty associated with extrapolating cancer risks from animals to humans.

II.C. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 2004

This assessment is undergoing peer review by external scientists. Comments of the reviewers will be evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments will be included in an appendix to the *revised* Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 2004).

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

Agency Completion Date – --/--/--

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 @epamail.epa.gov (email address).

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IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Naphthalene
CASRN – 91-20-3
Last Revised -- 00/00/0000

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VII. REVISION HISTORY

Naphthalene
CASRN – 91-20-3

Date	Section	Description
12/01/90	II.	Carcinogen assessment on-line
12/01/90	VI.	Bibliography on-line
01/01/92	IV	Regulatory Action section on-line
09/01/92	II.	Classification noted as pending change
09/01/92	II.D.2.	Work group review date added
11/01/93	I.A.	Work group review date added
09/01/94	I.A.	Work group review date added
05/01/95	II.	Pending change note replaced
05/01/95	II.D.2.	Work group review date added
07/01/95	II.	Pending change note replaced; see new note

08/01/95	I.A.,II,II.D.2	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
08/01/95	II.	Note revised
08/01/95	II.A.3.	Paragraph 1 revised
04/01/97	III,IV,V	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
09/17/98	I,II,VI	Revised RfD, RfC, carcinogenicity assessments
00/00/0000	II,VI.C	Inhalation carcinogenicity assessment revised

VIII. SYNONYMS

Naphthalene
CASRN -- 91-20-3
Last Revised – 12/01/90

Albocarbon
Caswell No. 587
Dezodorator
EPA Pesticide Chemical Code 055801
HSDB 184
MOTH BALLS
MOTH FLAKES
Naftalen [Polish]
Naftaleno [Spanish]
Naphtalene [French]
Naphthalene
Naphthalin
Naphthaline
Naphthene
NAPHTHALENE, molten
NCI-C52904
NSC 37565
RCRA WASTE NUMBER U165
TAR CAMPHOR
UN 1334
UN 2304
WHITE TAR