Naphthalene (CASRN 91-20-3)

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Reference Dose for Chronic Oral Exposure (RfD) go

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe* PDF format (116 Pages, 786 Kbytes). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

Links to specific pages in the toxicological review are available throughout this summary. To utilize this feature, your Web browser and Adobe program must be configured properly so the PDF displays within the browser window. If your browser and Adobe program need configuration, please go to the IRIS Help page for instructions.

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Naphthalene; CASRN 91-20-3 (09/17/1998)

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 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 12/01/1990

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	09/17/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

A. Reference Dose for Chronic Oral Exposure (RfD)

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

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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.

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__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased mean terminal body weight in males	NOAEL: 100 mg/kg-day; 71 mg/kg-day (adjusted)	3000	1	2E-2 mg/kg-day
Subchronic oral rat study BCL, 1980a	LOAEL: 200 mg/kg-day; 142 mg/kg-day (adjusted)			

*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 (CAS 904), 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 3000 (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.

= 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 3000 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.

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

__I.A.5. Confidence in the Oral RfD

Study -- High
Database -- 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 her 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.

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

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

Source Document -- U.S. EPA, 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 in an appendix to the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

Other EPA Documentation -- U.S. EPA, 1980, 1986, 1987a, 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@epa.gov (Internet address).

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_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/m^3. 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.

B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Nasal effects: hyperplasia and metaplasia in respiratory and olfactory epithelium,	NOAEL: None	3000	1	3E-3 mg/m^3

respectively LOAEL (HEC) 9.3 mg/m^3

Chronic mouse inhalation study

NTP, 1992a

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*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). (1992a) 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, 1992a). 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	Respiratory lesion		
		Hyperplasia, nasal respiratory	Metaplasia, nasal

(ppm)	Inflammation, lung	epithelium	olfactory epithelium
0/male male	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, 1992a.

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)

e 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 × 6h/24h × 5d/7d = mg/m^3 × 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.

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.

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 rats: 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 and 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 < 1/2 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 (1992a) study were therefore selected as the critical effects for the purpose of RfC derivation.

Adkins et al. (1986) exposed female A/J mice (30 g each) 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 is 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.

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

I.B.5. Confidence in the Inhalation RfC

Study -- Medium
Database -- Low to Medium
RfC -- Low to 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section

6 (PDF).

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

Source Document -- U.S. EPA, 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 in an appendix to the Toxicological Review of Naphthalene in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

Other EPA Documentation -- U.S. EPA, 1980, 1986, 1997a, 1988

Agency Consensus Date - 7/1/98

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 (Internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

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

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 from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m^3 air breathed. The unit form in which risk is presented is a concentration of the chemical in drinking water or air associated with lifetime risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's subsequent Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) also utilize those Guidelines where indicated. Users are referred to Section I of this IRIS file for information on long-term effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

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

Using criteria of the 1986 Guidelines for Carcinogen Risk Assessment, naphthalene is classified in Group C, a possible human carcinogen. This is based on the inadequate data of carcinogenicity in humans exposed to naphthalene via the oral and inhalation routes, and the limited evidence of carcinogenicity in animals via the inhalation route.

Using the 1996 Proposed Guidelines for Carcinogen Risk Assessment, the human carcinogenic potential of naphthalene via the oral or inhalation routes "cannot be determined" at this time based on human and animal data; however, there is suggestive evidence (observation of benign respiratory tumors and one carcinoma in female mice only exposed to naphthalene by inhalation [NTP, 1992a]). Additional support includes increase in respiratory tumors associated with exposure to 1-methylnaphthalene.

At the present time the mechanism whereby naphthalene produces benign respiratory tract tumors are not fully

understood, but are hypothesized to involve oxygenated reactive metabolites produced via the cytochrome P-450 monooxygenase system. However, based on the many negative results obtained in genotoxicty tests, a genotoxic mechanism appears unlikely.

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

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

__II.A.2. Human Carcinogenicity Data

Available data are inadequate to establish a causal relationship between exposure to naphthalene and cancer in humans. Adequately scaled epidemiological studies designed to examine a possible association between naphthalene exposure and cancer were not located. Consequently, no data are available to evaluate the carcinogenic potential in exposed human populations.

__II.A.3. Animal Carcinogenicity Data

Inhalation: In an NTP (1992a) 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. Mice were housed five to a cage. There were 150 mice housed in each of 4 inhalation chambers: 2 chambers were used for the high-exposure level. A comprehensive histological examination was performed on all control and high-dose mice and on low-dose mice that died or were sacrificed before 21 months of exposure. After 21 months of exposure, only the nasal cavity and lung were examined in the low-dose group. In each chamber, 5 animals per sex were designated for the 2-year studies; 5 animals per sex were designated for hematological evaluations at 14 days and 3, 6, 12, and 18 mo. However, because of high mortality in the male control group (see next paragraph), only the 14-day hematological evaluation was conducted. The other surviving interim mice were incorporated into the 2-year study.

Statistically significant decreases in survival were observed in the control male mice compared with the exposed groups. Exposed male mice were observed to hide in corners of the cages during exposure and were less inclined to fight. Survival percentages at the end of the study were 37% (26/70), 75% (52/69), and 89% (118/133) for the 0, 10, and 30 ppm male groups, respectively. Survival percentages did not include mice sacrificed at 14 days, mice that died before the study, or mice that were accidentally killed, or mice that were lost during the study. Survival at 2 years in the control female mice (86%; 59/69) was comparable to survival in the exposed groups; survival percentages were 88% (57/65) and 76% (102/135) for low- and high-dose females. Body weights were not affected by exposure for either sex.

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): chronic inflammation of the lung (0/70, 21/69, and 56/135 for males; 3/69, [illegible]/135 for females); chronic inflammation (0/70, 67/69, and 133/135 for males and 1/69, 65/65, and [illegible] for females); metaplasia of the olfactory epithelium (0/70, 66/69, and 134/135 for males; 0/69, 65/65, and [illegible] 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).

The 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 39/4[illegible] (8.[illegible]%, 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, 1[illegible]/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 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, 1992a). 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 expansive nodular masses consisting of cords of well-differentiated epithelial cells," whereas the carcinomas were "composed of ribbons and/or coalescing sheets of smaller, more anaplastic, cells which sometimes extend 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 (0/65 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, 1992a).

Adkins et al. (1986) exposed groups of 30 female A/J strain mice (6 to 8 weeks old) to 0, 10, or 30 ppm naphthalene (98%-99% pure) vapors, 6 hr/day, 5 days/week for 6 mo. After the 6-mo exposure period, excised lungs were examined for tumors. Tumors were examined histologically. The authors did not describe any noncancer histopathological effects that their examination may have revealed. Survival was not different between the exposed and control groups. Lung tumors were found in all 20 positive control mice given single intraperitoneal injections of 1 g urethane/kg; the mean number of tumors per mouse in the positive control was 28.9. Increased numbers of lung tumors were found in the naphthalene-exposed groups compared with the control group, but the differences were not statistically significant (6, 10, and 11 for the 0, 10, and 30 ppm groups). Tumors were described as alveolar adenomas consisting of "large cuboidal or columnar pithelial cells supported by a sparse fibroblastic stroma and arranged in well-defined acinar structures with papillary formations." No carcinomas were found. Naphthalene exposure did not significantly increase the percentage of animals with tumors (21%, 29%, and 30% for 0, 10, and 30 ppm mice, respectively). Statistically significant increases in the number of adenomas per tumor-bearing lung were observed in the exposed mice, but there was no increase in response with increasing dose. Mean numbers of tumors per tumor-bearing lung (sd noted in parentheses) were: 1.00 (0.00), 1.25 (0.07), and 1.25 (0.[illegible]) for 0, 10, and 30 ppm mice, respectively. Applicability of this study to the assessment of risk from lifetime exposure is limited due to the less-than-lifetime exposure and observation periods, and the limited tissue examination examining only the lung. Nevertheless, the finding that only 6 months of exposure caused statistically significant increased numbers of lung tumors per tumor-bearing lung in the exposed groups, coupled with the results of the NTP (1992a) mouse bioassay, provides further suggestive evidence that naphthalene has a tumorigenic response in the mouse lung.

Oral: Schmahl (1955) reported that naphthalene [illegible] 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 when compared with published data for naphthalene, suggesting high purity. The daily dose was reported to be 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 [illegible] 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, 1987b, 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 [illegible] histological examinations were restricted to the statement that no toxic effects were seen, including [illegible] 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 [illegible] 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.

Other Routes of Administration: Schmähl (1955) [illegible] that naphthalene repeatedly administered by subcutaneous or intraperitoneal injection did not [illegible] tumors in rats (in-house strains BDI and BDIII). Groups of 10 rats were given either subcutaneous or intraperitoneal weekly injections of naphthalene in oil (20 mg/rat per injection) starting at 100 days of age [illegible] for 40 weeks (the total doses were 820 mg/rat). Rats were maintained until spontaneous death occurred; [illegible] were reported to be 700 or 900 days for rats with subcutaneous or intraperitoneal doses, respectively. Autopsies were performed on dead animals, and organs which appeared unusual were examined histologically (the report did not specify which organs were examined, if any). The author reported that no toxic effects were found with parenteral administration of naphthalene. No tumors developed in either group. The [illegible] information on control rats was restricted to the

statement that lifespan for exposed rats was similar [illegible] for control rats (700 days with subcutaneous doses and 900 days with intraperitoneal doses).

and et al. (1964) implanted naphthalene into the [illegible] of stock Chester Beatty mice and examined them after 30 weeks in an effort to determine the suitability [illegible] naphthalene as a potential vehicle for carcinogenicity testing. The original number of mice implanted with [illegible] alone was not reported, but 23 mice were reported to have survived 30 weeks. One mouse developed a bladder carcinoma (1/23; 4%); no adenomas or papillomas were found. Tumor incidence was as low as when [illegible] was used (2-4%), and lower than with the implantation of cholesterol (12%). There are limitations [illegible] this study that make it an inadequate lifetime cancer bioassay including the short exposure and observation [illegible] and the lack of untreated controls.

Coal tar-derived naphthalene that contained approximately [illegible] unidentified impurities was tested for carcinogenicity by Knake (1956). White rats (40, [illegible] were given seven subcutaneous injections of 0 or 500 mg/kg naphthalene in sesame oil at 2-week [illegible] over an approximate 3.5-month period. Thirty-four of 38 naphthalene rats and 32/38 control rats survived the injection period. Survival was somewhat reduced in the naphthalene-exposed rats compared to [illegible] vehicle-control rats during the following 18-month period. Survival incidences at 6, 11, and 17 months [illegible] injection period were 21/34, 6/34, and 0/34 for the naphthalene-exposed rats and 17/32, 12/32, and [illegible] control rats. Lymphosarcomas were found in 5/34 (14.7%) exposed rats during the 18-month observation [illegible] one exposed rat showed a mammary fibrosarcoma. Vehicle controls showed a 6% [illegible] of tumors (one with lymphosarcoma and one with mammary fibrosarcoma). Mice (25, inbred [illegible] painted with 0.5% naphthalene in benzene 5 days/week for life; 21 control mice were painted with benzene alone. Four treated mice developed lymphomatic leukemia, three had lung adenomas, [illegible] lymphosarcoma, and one had a non-specified tumor (9/25 with tumors). In the benzene controls, one had [illegible] sarcoma, one had lung adenoma, and one had a non-specified tumor (3/21 with tumors). These studies are [illegible] for the assessment of carcinogenicity due to the presence of unknown impurities that may have [illegible] properties. Moreover, the vehicle (benzene) in the mouse study has been shown to cause leukemia in [illegible] and rodents, and the site of injection in the rat study was painted, prior to injection, with carbolfuchsin, [illegible] carcinogen.

La Voie et al. (1988) gave intraperitoneal naphthalene [illegible] dimethylsulfoxide) of 0.25, 0.50, and 1.0 [illegible]e to male and female newborn CD-1 mice [illegible] 15 of life (total dose = 1.75 µmole naphthalene). The report did not specify the purity [illegible] naphthalene tested. Forty-nine pups were treated with naphthalene and 46 control pups were treated with [illegible] alone. Mice were maintained (10 mice/cage) until moribund or until 52 weeks when [illegible] were killed. All gross lesions as well as liver sections from all mice were examined histologically. [illegible] statistically significant increased incidence of liver tumors (adenomas or hepatomas) was found in the [illegible] Reported incidences for the number of mice with liver tumors were (denominators are for the [illegible] that lived at least 6 months): 0/16 and 2/31 for exposed females and males, and 0/21 and 4/21 [illegible] control females and males. This assay is inadequate to assess the carcinogenicity of lifetime [illegible] naphthalene because the exposure period (2 weeks) and observation period (52 weeks) were significantly [illegible] than the lifetime for mice (approximately 2 years), and complete histological examinations were [illegible] conducted.

__II.A.4. Supporting Data for Carcinogenicity

The genotoxic potential of naphthalene has been [illegible] many test systems. Most studies provided negative results. Naphthalene was not mutagenic in [illegible] *Salmonella typhimurium* assays in the presence or absence of liver metabolic preparations (Eiss et al., 1958; [illegible] 1985; Florin et al., 1980; Godek et al., 1985; McCann et al., 1975; Nakamura et al., 1987; Narbonne [illegible] 1992; NTP, 1992a; Sakai et al., 1985). Naphthalene did not damage DNA (as assayed [illegible] the SOS-repair system) in *E. coli* PQ37 (Mersch-Sundermann et al., 1993).

NTP (1992a) found that naphthalene induced [illegible] in cultured Chinese hamster ovary cells, sister chromatid exchanges within a concentration range of 27 to 9[illegible] in the presence or absence of metabolic activation, and chromosomal aberrations within a range of 50 to 5[illegible] only in the presence of metabolic activation.

Naphthalene was mutagenic in the marine bacterium [illegible] *fischeri* (Arfsten et al., 1994) and in the *Drosophila melanogaster* wing somatic mutation and [illegible] test (Delgado-Rodriguez et al., 1995). [illegible] of mouse embryos in medium containing [illegible] naphthalene produced a 10-fold increase in chromosomal damage compared to untreated controls. [illegible] response to naphthalene was amplified by the inclusion of a hepatic metabolic activation system [illegible] (Goliahon et al., 1990).

Incubation of human peripheral lymphocytes in [illegible] containing naphthalene and a human liver metabolic

activation system did not produce increased frequencies of chromatid exchanges compared with controls (Tingle et al., 1993; Wilson et al., 1995). Naphthalene did not induce unscheduled DNA synthesis in cultured rat hepatocytes (Barfknecht et al., 1985) or increase frequencies of micronuclei in bone marrow cells of mice following intraperitoneal injection of single 250-mg/kg doses (Sorg et al., 1985). Single oral doses of naphthalene as high as 500 mg/kg did not increase frequencies of micronucleated erythrocytes in exposed mice compared with untreated control mice (Hartwig et al., 1994). Naphthalene did not induce in vitro transformations of Fischer rat embryo cells (Freeman et al., 1973) or Swiss mouse embryo cells (Rhim et al., 1974). Sina et al. (1983) reported that naphthalene did induce single-strand DNA breaks in cultured rat hepatocytes as detected by alkaline dilution.

Naphthalene metabolites 1-naphthol and 2-naphthol were not mutagenic in *S. typhimurium*, with or without metabolic activation (Florin et al., 1980; McCann et al., 1975; Narbonne et al., 1987). Another proposed naphthalene metabolite, naphthoquinone, was not mutagenic in several strains of *S. typhimurium* with or without metabolic activation (Sakai et al., 1985), but Gorny et al. (1994) reported that naphthalene-1,2-dione was mutagenic in strains of *S. typhimurium* with metabolic activation. The naphthalene metabolite, 1-naphthol, failed to produce positive results in several other genotoxicity assays including tests for sex- linked recessive lethal mutations in *Drosophila melanogaster* (Gocke et al., 1981), mutations in mouse L5178Y cells (Amacher and Turner, 1982), unscheduled DNA synthesis in cultured rat hepatocytes (Probst and Hill, 1980), and induction of micronuclei in bone marrow cells of mice (Gocke et al., 1981) and rats (Hossack and Richardson, 1977) after acute in vivo exposure.

Tsuda et al. (1980) found no evidence for neoplastic transformation of liver cells in a group of 10 young adult F344 rats (sex not specified) treated with single gavage doses of 100 mg/kg naphthalene in corn oil compared with a group of 10 vehicle control rats. Rats were given single doses of naphthalene or vehicle following partial hepatectomy, but before dietary treatment with a cell proliferation agent (2-acetylaminofluorene) and a necrotizing agent (carbon tetrachloride). Gamma-glutamyl transpeptidase foci (observed following the dietary treatments of exposed and control rats) were used as an indicator of neoplastic transformation. In contrast to naphthalene, a single gavage dose of 200 mg/kg benzo[a]pyrene induced significant increases in the number, area, and size of gamma-glutamyl transpeptidase foci.

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

An oral slope factor for naphthalene was not derived because of a lack of chronic oral naphthalene studies.

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

An inhalation unit risk estimate for naphthalene was not derived because of the weakness of the evidence (observations of predominant benign respiratory tumors at high dose only) that naphthalene may be carcinogenic in humans.

_II.D. EPA Documentation, Review, and Consensus (Carcinogenicity Assessment)

_II.D.1. EPA Documentation

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 [illegible] of these comments is included in an appendix to the Toxicological Review of Naphthalene in support [illegible] Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). *To [illegible] appendix, exit to the toxicological review, [illegible]endix A, Summary of and Response to External Peer Review Comments (PDF).*

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

Agency Consensus Date - 07/01/1998

__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@[illegible] (internet address).

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

_VI. Bibliography

Naphthalene
CASRN -- 91-20-3
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_VI.A. Oral RfD References

Allen, BC; Kavlock, RJ; Kimmel, CA; et al. (1994) [illegible] response assessments for developmental toxicity: II. Comparison of generic benchmark dose estimates [illegible] Fundam Appl Toxicol 23:487-495.

Allen, BC; Kavlock, RJ; Kimmel, CA; et al. (1994) [illegible] response assessments for developmental toxicity: III. Statistical models. Fundam Appl Toxicol 23[illegible]

Battelle's Columbus Laboratories (BCL). (1980a) [illegible] subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle [illegible] under NTP Subcontract No. 76-34-106002. Available from the Center for Environmental Research Information, (202)566-1676.

Battelle's Columbus Laboratories (BCL). (1980b) [illegible] subchronic toxicity study: Naphthalene (C52904), B6C3F1 mice. Prepared by Battelle [illegible] under NTP Subcontract No. 76-34-106002.

Buckpitt, AR; Franklin, RB. (1989) Relationship [illegible] and 2-methylnaphthalene metabolism to pulmonary bronchiolar epithelial cell necrosis. Pharm [illegible] 393-410.

Kavlock, RJ; Allen, BC; Faustman, EM; et al. (1995) [illegible] response assessments for developmental toxicity: IV. Benchmark doses for fetal weight changes. Fundam [illegible] Toxicol 26:211-222.

Melzer-Lange, M; Walsh-Kelly, C. (1989) Naphthalene [illegible] and hemolysis in a black female toddler deficient in glucose-6-phosphate dehydrogenase. Pediatr [illegible] 84:24-26.

Murata, T; Denda, A; Maruyama, H; et al. (1993) [illegible] and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice. Fundam Appl [illegible] 44-51.

Murata, Y; Denda, A; Maruyama, H; et al. (1997) [illegible] and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. Fundam Appl [illegible] 96-93.

National Toxicology Program (NTP). (1991) Final [illegible] developmental toxicity of naphthalene (CAS no. 91-20-3) in Sprague Dawley (CD) rats. #[illegible] Technical Report (NTIS/PB92-135623).

[illegible], JA. (1989) Relationship between exposure [illegible] agents, glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Nigeria. Acta [illegible]

78(6):848-852.

Owa, JA; Izedonmwen, OE; Ogundaini, AO; et al. [illegible] quantitative analysis of 1-naphthol in urine of neonates exposed to mothballs: the value in infants [illegible] defined anaemia. Afr J Med Sci 22:71-76.

Shopp, GM; White, KL, Jr.; Holsapple, MP; et al. [illegible] naphthalene toxicity in CD-1 mice: general toxicology and immunotoxicology. Fundam Appl [illegible] 1):406-419.

U.S. Environmental Protection Agency (U.S. EPA). [illegible] ambient water quality criteria for naphthalene. Prepared by the Office of Health and Environmental [illegible] Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards, Washington, DC. EPA/440/5-80-059. NTIS PB81-117707.

U.S. EPA. (1986) Health and environmental effects [illegible] naphthalene. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, [illegible] EPA/600 X-86/241. NTIS/PB88-24238.

U.S. EPA. (1987a) Summary review of health effects associated with naphthalene: health issue assessment. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-87/055F.

U.S. EPA. (1988) Health effects assessment for naphthalene. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH 45268. EPA/60[illegible] NTIS/PB90-142464.

U.S. EPA. (1998) Toxicological review for naphthalene. [illegible] available online at http://www.epa.gov/iris.

Page [illegible]

_VI.B. Inhalation RfC References

ACGIH. (1986) Documentation of the threshold limit values and biological exposure indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Adkins, B, Jr.; Van Stee, EW; Simmons, JE; et al. [illegible] genic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 17(2-3):3[illegible]

Buckpitt, AR. (1982) Comparative biochemistry and [illegible] lung. Part II: naphthalene lung toxicity. Prepared for Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH. AFAMRL-TR-82-52. p. 25-30.

Bushy Run Research Center. (1986) Naphthalene [illegible] inhalation toxicity study. TSCATS/303984, EPA/OTS Doc no. 86-870000558.

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

O'Brien, KAF; Smith, LL; Cohen, GM. (1985) Differential [illegible] naphthalene-induced toxicity in the mouse and rat. Chem Biol Interact 55(1-2):109-122

O'Brien, KAF; Suverkropp, C; Kanekal, S; et al. (1989) [illegible] tolerance to multiple doses of the pulmonary toxicant,

naphthalene. Toxicol Appl Pharmacol 99(3):[illegible]

Plopper, CG; Suverkropp, C; Morin, D; et al. (1[illegible]) [illegible] of cytochrome P-450 activity to Clara cell toxicity. I. Histopathologic comparison of the [illegible] of mice, rats and hamsters after parenteral administration of naphthalene. J Pharmacol Exp [illegible] 83-363

Tong, SS; Hirokata, Y; Trush, MA; et al. (1981) [illegible] and inhibition of pulmonary mixed-function oxidase activity by naphthalene. Biochem [illegible] Commun 100(3):944-950.

U.S. Environmental Protection Agency (U.S. EPA) [illegible] ambient water quality criteria for naphthalene. Prepared by the Office of Health and Environmental [illegible] Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards, Washington, DC. EPA/440/5-80-059. NTIS PB81-117707.

U.S. EPA. (1986) Health and environmental effects profile for naphthalene. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/X-86/241. NTIS/PB88-24238.

U.S. EPA. (1987a) Summary review of health effects associated with naphthalene: health issue assessment. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-87/055F.

U.S. EPA. (1988) Health effects assessment for naphthalene. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH 45268. EPA/600/8-[illegible]/[illegible]94. NTIS/PB90-142464.

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC. EPA/600/8-90/066F.

U.S. EPA. (1998) Toxicological review for naphthalene. [illegible] available online at http://www.epa.gov/iris.

Ba[illegible]

_VI.C. Carcinogenicity Assessment References

Adkins, B; Van Stee, EW; Simmons, JE; et al. (1986) [illegible] response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 17:311-322.

Amacher, DE; Turner, GN. (1982) Mutagenic evaluation of carcinogens and non-carcinogens in the L5178Y/TK assay utilizing postmitochondrial fractions [illegible] from normal rat liver. Mutat Res 97:49-65.

Arfsten, DP; Davenport, R; Schaeffer DJ. (1994) Reversion of bioluminescent bacteria (Mutatox™) to their luminescent state upon exposure to organic compounds, [illegible] ions, and metal salts. Biomed Environ Sci 7:144-149.

Barfknecht, TR; Naismith, RW; Matthews RJ. (1985) [illegible] primary culture/DNA repair test. PH 311-TX-008-85. 5601-56-1 (unpublished material). [illegible] Research International, Inc., Waverly, PA. Submitted to Texaco, Inc., Beacon, NY. Submitted [illegible] by Texaco, Inc. Office of Toxic Substances Microfiche No. 0TS0513638.

Bos, RP; Theuws, JL; Jongeneelen, FJ; et al. (1[illegible]) [illegible] of bi-, tri- and tetracyclic aromatic hydrocarbons in the taped-plate assay and in the co[illegible] Salmonella mutagenicity assay. Mutat Res 204:2033-206.

Boyland, E; Busby, ER; Dukes, CE; et al. (1964) Further experiments on implantation of materials into the urinary bladder of mice. Br J Cancer 18:575-581.

Buckpitt, AR. (1982) Comparative biochemistry and [illegible] Part II: naphthalene lung toxicity. Prepared for Air Force Aerospace Medical Research Laboratory, [illegible] Patterson Air Force Base, OH. AFAMRL-TR-82-52. p. 25-30.

Connor, TH; Theiss, JC; Hanna, HA; et al. (1985) [illegible] of organic chemicals frequently found in the air of mobile homes. Toxicol Lett 25:33-40.

Delgado-Rodriguez, A; Ortiz-Marttelo, R; Graf, U; et al. (1991) Genotoxic activity of environmentally important polycyclic aromatic hydrocarbons and their [illegible] derivatives in the wing spot test of *Drosophila melanogaster*. Mutat Res 341:235-247.

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

Flowers-Geary, L; Bleczinski, W; Harvey, RG; et al. (1984) Cytotoxicity and mutagenicity of polycyclic aromatic hydrocarbons (PAH) o-quinones produced by [illegible] diol dehydrogenase. Proc Ann Meet Am Assoc Cancer Res 35:A965.

Freeman, AE; Weisburger, EK; Weisburger, JH; et al. (1973) Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. J Natl Cancer Inst 51:799-808.

Gocke, E; King, M-T; Eckhardt, K; et al. (1981) Mutagenicity of cosmetics ingredients licensed by the European communities. Mutat Res 90:91-109.

Godek, EG; Naismith, RW; Matthews, RJ. (1985) Ames Salmonella/microsome plate test (EPA/OECD) (unpublished material). Pharmakon Research International, Inc, Waverly, PA. Submitted to Texaco, Inc, Beacon, NY. Submitted to U.S. EPA by Texaco Inc. Office of Toxic Substances Microfiche No. OTS0513637.

Allahon, LS; Iyer, P; Martin, JF; et al. (1990) Chromosomal damage to preimplantation embryos in vitro by naphthalene. Toxicologist 10:274.

Harper, BL; Ramanujam, VMS; Gad-El-Karim, MV; et al. (1984) The influence of simple aromatics on benzene clastogenicity. Mutat Res 128:105-114.

Hossack, DJN; Richardson, JC. (1977) Examination of the potential mutagenicity of hair dye constituents using the micronucleus test. Experientia 33:377-378.

Ijiri, I; Shimosato, K; Ohmae, M; et al. (1987) A case report of death from naphthalene poisoning. Jpn J Legal Med 41(1):52-55.

Knake, E. (1956) Weak tumor producing effect of [illegible] and benzene. Virchows Arch Pathol Anat Physiol 329:141-176. (Ger.)

La Voie, EJ; Dolan, S; Little, P; et al. (1988) Carcinogenicity of quinoline, 4- and 8-methylquinoline and benzoquinolines in newborn mice and rats. Food Chem Toxicol 26:625-629.

McCann, J; Choi, E; Yamasaki, E; et al. (1975) Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals. Proc Natl Acad Sci 72:5135-5139.

Mersch-Sundermann, V; Mochayedi, S; Kevekordes, S; et al. (1993) The genotoxicity of unsubstituted and nitrated polycyclic aromatic hydrocarbons. Anticancer Res 13:2037-2044.

Murata, T; Denda, A; Maruyama, H; et al. (1995) Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol 121:44-51.

Murata, Y; Denda, A; Maruyama, H; et al. (1997) Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. 36:90-93 (1997).

Nakamura, S; Oda, Y; Shimada, T; et al. (1987) SO[illegible] activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK 1002: [illegible] 251 chemicals. Mutat Res 192:239-246.

[illegible]onne, JF; Cassand, P; Alzieu, P; et al. (1987) Su[illegible] activity relationships of the N-methylcarbamate series in *Salmonella typhimurium*. Mutat Res 19[illegible]

National Toxicology Program (NTP). (1992a) Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F1 Mice. [illegible] Studies). DHHS, PHS, NIH, Rockville, MD.

Probst, GS; Hill, LE. (1980) Chemically-induced DN[illegible] synthesis in primary rat hepatocytes: A correlation with bacterial mutagenicity. Ann NY Acad [illegible] 405-406.

Rhim, JS; Parks, DK; Weisburger, EK. (1974) Evalu[illegible] *in vitro* assay system for carcinogens based on prior infection of rodent cells with nontransforming [illegible] virus. J Natl Cancer Inst 52:1167-1173.

Sakai, M; Yoshida, D; Mizusdki, S. (1985) Mu[illegible] polycyclic aromatic hydrocarbons and quinones on *Salmonella typhimurium* TA97. Mutat Res 156:61-[illegible]

Schmähl, D. (1955) Examination of the carcinogen[illegible] naphthalene and anthracene in rats. Z Krebsforsch 60:697-710.

Sina, JF; Bean, CL; Dysart, GR; et al. (1983) Evalu[illegible] unscheduled DNA elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat [illegible] 367-391.

Sorg, RM; Naismith, RW; Matthews, RJ. (1985) Ma[illegible] test (MNT) OECD (unpublished material). Pharmakon Research International Inc., Waverly PA. [illegible] to U.S. EPA by Texaco, Inc. Office of Toxic Substances Microfiche No. OTS0513639.

T[illegible]le, MD; Pirmohamed, M; Templeton, E; et al. [illegible] investigation of the formation of cytotoxic, [illegible]toxic, protein-reactive and stable metabolites from [illegible]alene by human liver microsomes. Biochem Pharmacol 46:1529-1538.

Tsuda, H; Lee, G; Farber, E. (1980) Induction of resistant hepatocytes as a new principle for a possible short-term in vivo test for carcinogens. Cancer Res 40:1357-[illegible]

U.S. EPA. (1987b) Recommendations for and documentation of biological values for use in risk assessment. Environmental Criteria and Assessment Office. Office of Health and Environmental Assessment, Cincinnati, OH. EPA/600/6-87-008.

U.S. EPA. (1996, April 23) Proposed guidelines for carcinogen risk assessment. Federal Register 61 (79):17960-18011.

U.S. EPA. (1998) Toxicological review for naphthalene. [illegible] available online at http://www.epa.gov/iris.

Wilson, AS; Tingle, MD; Kelly, MD; et al. (1995) [illegible] of the generation of genotoxic and cytotoxic metabolites of benzo[a]pyrene, aflatoxin B, naphthalene [illegible] using human liver microsomes and human lymphocytes. Human Exp Toxicol 14:507-5[illegible]

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_VII. Revision History

[illegible]thalene
CASRN -- 91-20-3
Last Revised -- 09/17/1998

Date	Section	Description

12/01/1990	II.	Carcinogen assessment [illegible]
12/01/1990	VI.	Bibliography on-line
[illegible]/01/1992	IV.	Regulatory Action [illegible] on-line
[illegible]/01/1992	II.	Classification noted [illegible] cancer change
09/01/1992	II.D.2	Work group review [illegible]
11/01/1993	I.A.	Work group review [illegible]
09/01/1994	I.A.	Work group review [illegible]
05/01/1995	II.	Pending change [illegible]
05/01/1995	II.D.2.	Work group review [illegible]
07/01/1995	II.	Pending change [illegible] see new note
08/01/1995	I.A., II., II.D.2	EPA's RfD/RfC and RAGS workgroups were discontinued in [illegible]. Chemical substance reviews that were not completed by September 1995 were taken off the IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in Sep[illegible]
08/01/1995	II.	Note revised
08/01/1995	II.A.3.	Paragraph [illegible]
04/01/1997	III., IV., V.	Drinking water [illegible] EPA Regulatory Action [illegible] Supplementary Data were removed from [illegible] before April 1997. IRIS users [illegible] to the appropriate EPA Program Offices for this information.
09/17/1998	I., II., VI.	Revised RfD, RfC [illegible] toxicity assessments
01/09/2002	II.	This chemical is [illegible] under the IRIS Program.

Ba[illegible]

_VIII. Synonyms

Naphthalene
CASRN -- 91-20-3
Last Revised -- 12/01/1990

91-20-3
Naphthalene
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
NAPTHALENE, molten
NCI-C52904
NSC 37565
RCRA WASTE NUMBER U165
TAR CAMPHOR
UN 1334

UN 2304
WHITE TAR

e: ATOXICOLOGICAL REVIEW is available f[illegible] electrical in Adobe* PDF format (116 Pages, 786 Kbytes). Similar documents can be found in the List [illegible] IRIS Toxicological Reviews.

[redacted]* Some of the documents pr[illegible] Adobe Acrobat PDF (Portable Document Format) files. They can be viewed, and printed, with [illegible] an Adobe Acrobat Reader. The Adobe Acrobat's Reader is available, free, for Windows (N[illegible]), OS/2, Unix, and Mac OS operating systems. Click this button to download the latest vers[illegible] Adobe Acrobat. The readers are available directly from Adobe. Exit EPA

Users with disabilities may be using screen readers t[illegible] compatible with viewing PDFs. A plug-in is available that will enable screen readers to view the[illegible] information and to acquire the plug-in, please go to access.adobe.com. Exit EPA

Ba[illegible]

This page we[illegible] on Tuesday, January 13, 2004

View the graphical version [illegible] at: http://www.epa.gov/iris/subst/0436.htm