NAPHTHALENE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
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CRITERION DOCUMENT

C23639

NAPHTHALENE

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for napthalene can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for naphthalene can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of naphthalene ingested through water and through contaminated aquatic organisms, the ambient water criterion is determined to be 143 µg/l.

NAPHTHALENE

Introduction

Naphthalene is the most abundant single constituent of coal tar (Schmeltz, et al. 1977). In 1974, 1.8×10^5 metric tons of naphthalene were produced from coal tar, and 1.1×10^5 metric tons were produced from petroleum (Brown, et al. 1975; U.S. EPA, 1976). This compound is used as an intermediate in the production of dye compounds and the formulation of solvents, lubricants, and motor fuels. One of the principal uses of naphthalene as a feedstock in the United States is for the synthesis of phthalic anhydride. It has also been used directly as a moth repellant and insecticide as well as an antihelminthic, vermicide, and an intestinal antiseptic.

Napthalene is a bicyclic aromatic hydrocarbon with the chemical formula $C_{10}H_8$ and a molecular weight of 128.16. Pure naphthalene forms a white crystalline solid at room temperature whereas the crude or technical grades may range in color from brown to tan. Naphthalene vapor and dust can form explosive mixtures with air (Windholz, 1976).

Pure naphthalene melts at 80.2°C; the less pure forms of the compound will melt at temperatures ranging from 74 to 80°C. The boiling point of naphthalene is 217.96° at atmospheric pressure (Manufacturing Chemists Assoc. 1956). At 15.5°C, the density is 1.145 (Manufacturing Chemists Assoc. 1956) and at 100°C the density is 0.9625 (Marti, 1930; Weast, 1975). At 19.8°C the vapor pressure of solid naphthalene is 0.0492 mm Hg (Gil'denblat, et al. 1960).

The solubility of naphthalene in water has been reported to range between 30,000 µg/l (Mitchell, 1926) and 40,000 µg/l (Josephy and Radt, 1948) at 25°C. The solubility of naphthalene in seawater will vary according to the degree of chlorosity; in seawater of average composition the solubility of naphthalene is approximately 33,000 µg/l (Gordon and Thorne, 1967). Naphthalene has also been reported to be soluble in organic solvents (Spector, 1956).

Naphthalene can oxidize in the presence of light and air, and it was determined that 50 percent of the theoretical CO_2 was liberated after 14 days (Ludzack and Ettinger, 1963). The process involves initial conversion to naphthaquinone with subsequent rupture of one of the aromatic rings and the release of CO_2 (Kirk and Othmer, 1967). However, this oxidation process occurs only at elevated temperatures (Josephy and Radt, 1948).

When combined with alcohol and ozone, cyclic alkoxy-hydroxyperoxides are formed. In an acidic medium, these peroxides will be converted to methyl phthalaldehydate; in a basic medium, they are converted to phthalaldehydic acid (Bailey, et al. 1964). When combined with metal nitrate within a temperature range of 55°C to 180°C, naphthalene can be nitrated at the alpha position (Alama and Okon, 1964). In the presence of oxygen, K_2SO_4, a vanadium oxide catalyst, and SiO_4, naphthalene can be converted to phthalic anhydride (Morotskii and Kharlampovich, 1968).

Microorganisms can degrade naphthalene to 1,2-dihydro-1,2,-dihydroxynaphthalene and ultimately to carbon dioxide

and water. Studies have indicated a degredation rate under laboratory conditions of up to 3.3 ug/l (Lee and Anderson, 1977).

Naphthalene has been shown to be toxic to microorganisms and has been reported to reduce photosynthetic rates in algae. It has also been reported to be acutely toxic to various invertebrate and vertebrate species of aquatic organisms. In laboratory mammals and humans, naphthalene has been linked to blood disorders and is suspected of traversing the placental membrane in humans following naphthalene ingestion by the mother.

Naphthalene has a varied environmental distribution and has been detected in ambient water (up to 2.0 µg/l), sewage plant effluents (up to 22 µg/l), and drinking water supplies (up to 1.4 µg/l) (U.S. EPA, 1971-1977). Recent studies have determined that naphthalene will accumulate in sediments by more than 100 times the concentration in the overlying water (Cox, et al. 1975; Lee and Anderson, 1977).

Naphthalene has been shown to bioconcentrate in both invertebrate and vertebrate species of aquatic organisms. It has also been suggested that much of the naphthalene taken up by aquatic organisms returns to the ecosystem in fecal matter without being metabolized. In addition, *in vitro* studies have identified three naphthalene metabolites derived from rat liver microsome preparations; these probably resulted from hydroxylation and conjugation with water-soluble moieties.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

A limited variety of aquatic species has been exposed to naphthalene and all tests were under static procedures with unmeasured test concentrations. Fifty percent effect levels are in the range of 5,600 to 82,000 µg/l. One embryo-larval test with the fathead minnow demonstrated no adverse effects at the highest test concentration of 440 µg/l.

Acute Toxicity

The adjusted 96-hour LC50 value for the mosquitofish (Wallen, et al. 1957) is 82,000 µg/l (Table 1) and after division by the species sensitivity factor (3.9) results in a Final Fish Acute Value of 21,000 µg/l.

Daphnia magna appears to be more sensitive with an adjusted 48-hour EC50 of 7,260 µg/l (Table 2). Based on this single datum,

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

the Final Invertebrate Acute Value for naphthalene is 350 µg/l. Since this concentration is lower than the equivalent value for fish, 350 µg/l is also the Final Acute Value.

Chronic Toxicity

Exposure concentrations as high as 440 µg/l (Table 3) caused no adverse effects on survival or growth during an embryo-larval test with the fathead minnow (U.S. EPA, 1978). This datum results in a Final Fish Chronic Value that is greater than 33 µg/l. No chronic data for invertebrate species are available.

Plant Effects

A 50 percent reduction in the number of cells of the alga, Chlorella vulgaris, occurred at a concentration of 33,000 µg/l (Table 4). This concentration is the Final Plant Value.

Residues

No measured steady-state bioconcentration factor (BCF) is available for naphthalene. A BCF can be estimated using the octanol-water partition coefficient of 2,300. This coefficient is used to derive an estimated BCF of 210 for aquatic organisms that contain about 8 percent lipids. If it is known that the diet of the wildlife of concern contains a significantly different lipid content, an appropriate adjustment in the estimated BCF should be made.

Miscellaneous

Soto, et al. (1975a) observed the death of 61 percent of the cells of the alga, Chlamydomonas angulosa, at a concentration of 34,400 µg/l (Table 5). There was a 50 percent mortality of coho salmon after an exposure of less than six hours to 5,600 µg/l (Holland, et al. 1960).

CRITERION FORMULATION

Freshwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 21,000 µg/l

Final Invertebrate Acute Value = 350 µg/l

Final Acute Value = 350 µg/l

Final Fish Chronic Value = greater than 33 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 33,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 33 µg/l

0.44 x Final Acute Value = 150 µg/l

No freshwater criterion can be derived for napthalene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Freshwater fish acute values for naphthalene (Wallen, et al. 1957)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mosquitofish, *Gambusia affinis*	S	U	96	150,000	82,000

* S = static

** U = unmeasured

Geometric mean of adjusted values = 82,000 µg/l; $\frac{82,000}{3.9}$ = 21,000 µg/l

Table 2. Freshwater invertebrate acute values for naphthalene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Cladoceran, *Daphnia magna*	S	U	48	8,570	7,260

* S = static

** U = unmeasured

Geometric mean of adjusted values = 7,260 µg/l; $\frac{7,260}{21}$ = 350 µg/l

Table 3. Freshwater fish chronic values for naphthalene (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, *Pimephales promelas*	E-L	>440	>220

* E-L = embryo-larva

Geometric mean of chronic values = >220 µg/l; $\frac{>220}{6.7}$ = >33 µg/l

Lowest chronic value = >220 µg/l

Table 4. Freshwater plant effects for naphthalene (Kauss & Hutchinson, 1975)

Organism	Effect	Concentration (ug/l)
Alga, *Chlorella vulgaris*	EC50 48-hr cell numbers	33,000

Final plant value = 33,000 µg/l

Table 5. Other freshwater data for naphthalene

Organism	Test Duration	Effect	Result (ug/l)	Reference
Alga, *Chlamydomonas angulosa*	24 hrs	Death of 61% of cells	34,400	Soto, et al. 1975a
Alga, *Chlamydomonas angulosa*	24 hrs	Loss of photosynthetic capacity	10% saturation	Soto, et al. 1975b
Coho salmon, *Oncorhynchus kisutch*	<6 hrs	50% mortality	5,600	Holland, et al. 1960

SALTWATER ORGANISMS

Introduction

As with freshwater organisms, the data base for napthalene and saltwater organisms is limited to a few species for which static test procedures were used with measured concentrations. A variety of adverse effects were observed at concentrations of 1,000 to 2,600 µg/l.

Acute Toxicity

The adjusted 96-hour LC50 value for the sheepshead minnow was 1,125 µg/l (Anderson, et al. 1974) and this result provides a Final Fish Acute Value of 300 µg/l (Table 6).

Anderson, et al. (1974) also exposed grass and brown shrimp for 24 hours to napthalene and these data provide adjusted LC50 values of 744 and 715 µg/l, respectively (Table 7). Tatem (1976) tested the grass shrimp (Palaemonetes pugio) and this result leads to an adjusted LC50 of 2,585 µg/l. The geometric mean of these data is 996 µg/l and after division by the sensitivity factor (49), a Final Invertebrate Acute Value of 20 µg/l is derived. This also becomes the Final Acute Value since 20 µg/l is lower than the Final Fish Acute Value of 300 µg/l.

Chronic Toxicity

No data are available on the chronic effects of naphthalene on saltwater organisms.

Residues

There is only one test result (Harris, et al. 1977b) that determined an apparent equilibrium bioconcentration factor (BCF) for napthalene. After nine days, the BCF for a copepod was 5,000 (Table 8). Data for other species for exposures of one hour to one day are listed in Table 9. These BCF's range from 32 to 77 and indicate that equilibrium does not occur rapidly when those results are compared to the BCF of 5,000 after nine days.

Miscellaneous

Berdugo, (1977) exposed the copepod (Eurytemora affinis) to a concentration of 1,000 µg/l and observed effects on egg production and ingestion rate.

CRITERION FORMULATION

Saltwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 300 µg/l

Final Invertebrate Acute Value = 20 µg/l

Final Acute Value = 20 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 8.8 µg/l

No saltwater criterion can be derived for napthalene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 6. Marine fish acute values for naphthalene (Anderson, et al. 1974)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Sheepshead minnow, Cyprinodon variegatus	S	M	24	2,400	1,125

* S = static

**M = measured.

Geometric mean of adjusted values = 1,125 µg/l, $\frac{1,125}{3.7}$ = 300 µg/l

Table 7. Marine invertebrate acute values for naphthalene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Grass shrimp, Palaemonetes pugio	S	M	24	2,600	744	Anderson, et al. 1974
Grass shrimp, Palaemonetes pugio	S	M	96	2,350	2,585	Tatem, 1976
Brown shrimp, Penaeus aztecus	S	M	24	2,500	715	Anderson, et al. 1974

* S = static
** M = measured
Geometric mean of adjusted values = 996 ug/l ; $\frac{996}{49}$ = 20 µg/l

Table 8. Marine residues for napthalene (Harris, et al. 1977b)

Organism	Bioconcentration Factor *	Time (days)
Copepod, *Eurytemora affinis*	5,000	9

* Dry weight to wet weight conversions.

Table 9. Other marine data for napthalene

Organism	Test Duration	Effect	Result (ug/l)	Reference
Copepod, *Eurytemora affinis*	0.16 days	Reduction in ingestion rate of 10% (P = 0.05)	1,000	Berdugo, 1977
Copepod, *Eurytemora affinis*	1 day	Reduction in egg production by 83% (P = 0.05)	1,000	Berdugo, 1977
Copepod, *Calanus helgolandicus*	1 day	Bioconcentration factor = 50	-	Harris, et al. 1977b
Copepod, *Calanus helgolandicus*	1 day	Bioconcentration factor = 60	-	Harris, et al. 1977a
Blue mussel, *Mytilus edulis*	4 hrs	Bioconcentration factor = 44	-	Lee, et al. 1972b
Sand goby, *Gillichtus mirabilis*	1 hr	Bioconcentration factor = 63	-	Lee, et al. 1972a
Sculpin, *Oligocottus maculosus*	3 hrs	Bioconcentration factor = 32	-	Lee, et al. 1972a
Sand dab, *Citharichtys stigmaeus*	1 hr	Bioconcentration factor = 77	-	Lee, et al. 1972a

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

Naphthalene, $C_{10}H_8$, is an aromatic hydrocarbon with two orthocondensed benzene rings. In 1965, 74.4 percent of the napthalene produced in this country was used for the manufacture of phthalic anhydride which, in turn, was used in the manufacture of alkyd and polyester resins, dyes, pigments, pharmaceuticals and insecticides: 12.2 percent was used in the manufacture of insecticides such as 1-naphthyl-N-methylcarbamate (carbaryl); 11 percent was used for the production of 2-naphthol (used as a dyestuff, pigment and pharmaceutical intermediate) and mothballs. The remainder was used in the manufacture of alkyl-naphthalenesulfonates (used in the manufacture of detergents and textile wetting agents), alkylnaphthalenes (used in making textile spinning lubricants), chlorinated naphthalenes and tetra and decahydro naphthalenes (used in solvent mixtures). In 1965, the total U.S. production of naphthalene was 373,000 metric tons while in 1976 production of petroleum derived naphthalene was 48,720 metric tons.

In 1973, 91 percent of the production was from petroleum while the remainder originated from coal tar distillates. In 1974, 35 percent was from petroleum while 58 percent was from coal tar distallates originating from the high temperature coking of bituminous coal (Brown, et al. 1975; U.S. EPA, 1976). This coal tar naphthalene in its crude state contains impurities such as alkylnaphthalenes,

alkylcoumarones and thianaphthene. This latter impurity has been hypothesized as being the active ingredient in moth balls (Thiessen, 1967).

Pure naphthalene melts at 80.29°C. and boils at 217.955°C. It has a high vapor pressure (0.054 mmHg at 20°C.) and high water solubility (19,000 µg/l at 0°C and 30,000 µg/l at 100°C.) compared to other polynuclear aromatic hydrocarbons.

Ingestion from Food and Water

The two major sources of naphthalene in the aquatic environment are from industrial effluents and from oil spills. Industrial effluents have been found to have up to 32,000 µg/l naphthalene. The final effluents of sewage treatment plants receiving discharges from these facilities have been noted to have up to 22 ug/l naphthalene. Natural waters have been noted to have up to 2.0 ug/l of naphthalene while drinking water supplies have been found to have up to 1.4 µg/l naphthalene (U.S.EPA, Region IV, unpublished data).

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor, (BCF) is available for naphthalene, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about eight percent lipids from the octanol-water partition coefficient (P). Based on an octanol-water partition coefficient of 2,300, the steady-state bioconcentration factor for naphthalene is estimated to be 210. An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for napthalene and the edible portion of all aquatic orgnisms consumed by Americans is calculated to be 210 x 0.2875 = 60.

Inhalation

Unusual exposure to naphthalene can occur to cigarette smokers, naphthalene being identified as one of the polynuclear aromatic hydrocarbons found in cigarette smoke conden-

sate (Akin, et al. 1976). Under industrial conditions individuals can be exposed to levels of naphthalene up to 1.1 x 10^6 $\mu g/m^3$ (210 ppm) as vapor and up to 4.4 $\mu g/m^3$ as particulates (Table 1). Potential exposure categories in this group are outlined in Table 2. Ambient air levels of naphthalene are negligible (Table 1), but the number of measurements have been limited.

Dermal

Data on dermal exposure to naphthalene are very sparse. See the "Effects" section for discussion of effects from possible dermal exposure.

PHARMACOKINETICS

Absorption, Distribution and Excretion

Little detailed information is available on the absorption, distribution or excretion of naphthalene in man or animals. Adequate amounts of naphthalene can be absorbed when ingested as a solid to cause toxicity in man (Chusid and Fried, 1955; Zuelzer and Apt, 1949; Nash, 1903; Gross, et al. 1958; Haggerty, 1956). When taken as a solid, fragments of naphthalene can appear in the stool (MacGregor, 1954). The toxicity appears to be increased if taken dissolved in oil (Solomon, 1957). The oral toxicity of a metabolite of naphthalene, 1,4-naphtoquinone, is increased at least fivefold when administered, dissolved in oil, to rabbits as compared to an aqueous solution (Talakin, 1966). Sanborn and Malins (1977) found a marked decrease in absorption of naphthalene if bound to protein in shrimp. The authors give this as evidence that naphthalene would be less likely

TABLE 1

Air Levels of Naphthalene

Area Investigated	Air Level ($\mu g/m^3$)		Reference
	Vapor	Particulate	
Industrial:			
Naphthalene melt present	1600 - 1.1×10^6	---	Robbins, 1951
Coke Oven	11.35 - 1120	0-4.40	Bjørseth, et al. 1978a
Aluminum Reduction Plant	.72 - 311.3	.090-4.00	Bjørseth, et al. 1978b
Ambient:			
Providence, R.I.	.0001	.00025	Krstulovic, et al. 1977
Kingston, R.I.	.00003	.00003	Krstulovic, et al. 1977
Narragansett Bay, R.I.	.00005	.000003	Krstulovic, et al. 1977

TABLE 2

Workers with Potential Naphthalene Exposure

(Tabershaw, et al. 1977)

Beta naphthol makers

Celluloid makers

Coal tar workers

Dye chemical makers

Fungicide makers

Hydronaphthalene makers

Lampblack makers

Moth repellant workers

Phthalic anhydride makers

Smokeless powder makers

Tannery workers

Textile chemical workers

Aluminum reduction plant workers

to be absorbed when exposure was from food than when from water.

When dissolved in a nonpolar solvent, absorption of naphthalene by skin application caused less experimental toxicity than when taken orally (Gaines, 1969). Dawson, et al. (1958), however, found that two infants exposed to naphthalene treated clothes developed toxic effects after their skin was covered with baby oil. These authors suggest that skin absorption might be significant under these circumstances.

Enough absorption can occur by inhalation of naphthalene vapor to cause significant toxicity. Valaes, et al. (1963) found toxicity in newborn infants when the only exposure was to naphthalene vapor from clothes or blankets treated with naphthalene stored in the infants' rooms or in an adjacent hall. One of these infants died.

Naphthalene distributes widely after absorption. Lawler, et al. (1978) found that in mallards given naphthalene in oil over a period of two weeks, naphthalene could be identified in all tissues examined. Its relative distribution was as follows: skin >liver >brain = blood >muscle >heart. Naphthalene has not been identified in urine after absorption. With sufficient absorption of naphthalene to result in toxicity to an 18 month old infant, Mackell, et al. (1951) noted metabolites of naphthalene in the urine that were still identifiable two weeks after exposure but which had disappeared 18 days after exposure.

Metabolism

The metabolism of naphthalene has been extensively studied in mammals. Naphthalene is first metabolized by hepatic mixed function oxidases to the epoxide, naphthalene-1,2-oxide (Figure 1). This epoxide has the distinction of being the first arene oxide metabolite to have been isolated (Jerina, et al. 1970). Epoxide formation is an obligatory step. The epoxide can be enzymatically converted into the dihydrodiol, 1,2-dihydroxy-1,2-dihydronaphthalene or conjugated with glutathione. The dihydrodiol can then be conjugated to form a polar compound with glucuronic acid or sulfate or be further dehydrogenated to form the highly reactive 1,2-dihydroxynaphthalene. This too can be enzymatically conjugated to sulfate or glucuronic acid or spontaneously oxidized to form another highly reactive compound, 1,2-naphthoquinone.

The epoxide can also be converted spontaneously to 1-naphthol or 2-naphthol by a keto tautomer intermediate (Boyd, et al. 1972). 1-naphthol is the predominant spontaneous decomposition product of the epoxide, being a more stable resonant structure than 2-naphthol (Jerina, et al. 1970). 1-naphthol is excreted unchanged as well as conjugated with glucuronic acid or sulfate prior to excretion. The finding of 1,4-naphthoquinone in the urine of a child poisoned with naphthalene (Mackell, et al. 1951) suggests that 1-naphthol can also be further oxidized in mammals (Cerniglia and Gibson, 1977).

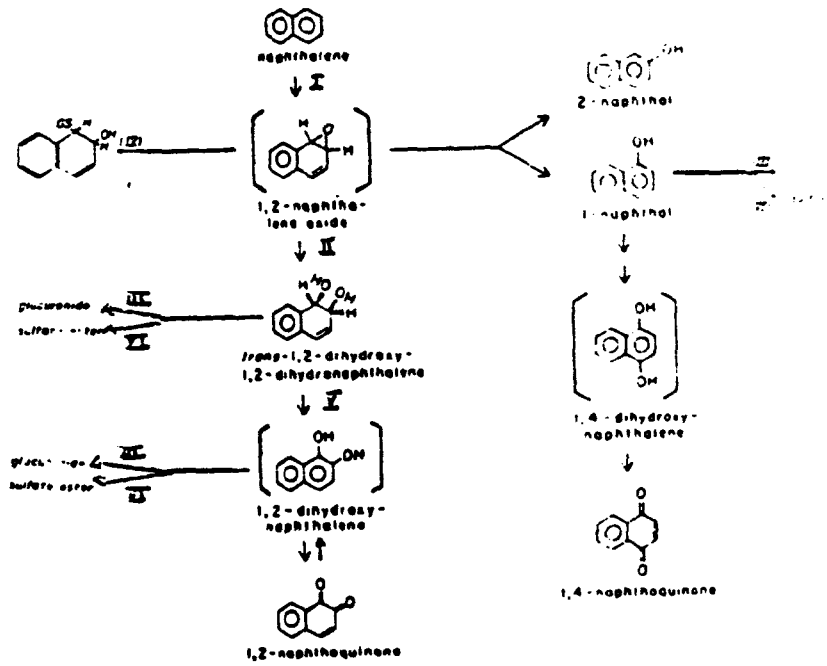

Figure 1: Pathways for the Metabolism of Naphthalene (adapted from Bock, et al. 1976).

Enzymes: I- monooxygenase

II- epoxide hydrase

III- UDP-gluconyltransferase

IV- glutathione-S-transferase

V- dihydrodiol dehydrogenase

VI- sulfotransferase

A number of other metabolites have been found in liver cells, liver microsomal preparations or bile as noted in Table 3. The glutathione conjugate can be progressively broken down to a cysteinylglycine compound and then a cysteine conjugate prior to acetylation to the mercapturic acid, N acetyl-S-(1,2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine either in the liver or kidney (Booth, et al. 1960). A number of these metabolites have been identified in the urine of mammals (Table 4). The presence of 1-naphthyl mercapturic acid may be explained by a spontaneous dehydrogenation of the mercapturic acid of the dihydrodiol in acid urine (Jerina, et al. 1968).

Naphthalene metabolites undergo further conversions in the eye. The eye contains beta glucuronidase and sulfatase which can hydrolyze the glucuronide and sulfate esters of the dihydrodiol (Van Heyningen and Pirie, 1967). Catechol reductase is also present in the eye. This enzyme can oxidize the dihydrodiol to 1,2-dihydroxynaphthalene which in turn can be spontaneously oxidized to 1,2-naphthaquinone with the concomitant release of hydrogen peroxide. 1,2-naphthaquinone can then oxidize ascorbic acid, which is found in high concentration in the eye, to dihydroascorbic acid with the release of more hydrogen peroxide. Dihydroascorbic acid can then be broken down to oxalate or diffuse into the lens where it is reconverted to ascorbic acid with the associated nonenzymatic oxidation of reduced glutathione (Van Heyningen, 1970). As 1,2-naphthaquinone is reduced by the reaction with ascorbic acid to 1,2-dihydroxynaphthalene, it oxidizes NADPH. The dihydroxide will rapidly reduce

TABLE 3

Naphthalene Metabolites: Liver/Bile

Metabolite	Found in: Rabbit	Rat	Fish
1-naphthol	2	3,4	5
2-naphthol	2	3	
1-naphthyl glucosiduronic acid		3,4	5
1-naphthyl mercapturic acid		3	5
1,2-dihydro-1,2-dihydroxy napthalene	2	3,4	5
1,2-dihyro-2-hydroxy-1-naphthyl-glucosiduronic acid		3,4	5
1,2-dihydro-1-hydroxy-2-naphthyl-glucosiduronic acid		3	
S-(1,2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine		3	
N-acetyl-S-(1,2-dihydro-2-hydroxy-1-naphthyl)-1-cysteine		3	
1,2-dihydroxy naphthalene		4	
1,2-naphthoquinone		4	
Naphthalene-1,2-oxide	2		
S-(1,2-dihydro-2-hydroxy-1-naphthyl)-glutathione	2	1,3	
S-(1,2-dihydro-2-hydroxy-1-naphthul)-L-cysteinyl glycine		3	
(1,2-dihydro-2-hydroxy-1-naphthyl)-sulfate		4	
2-hydroxy-1-naphthyl-glucosiduronic acid		3	

References: 1-Booth, et al. 1960 4-Bock, et al. 1976

TABLE 4

Naphthalene Metabolites: Kidney/Urine

Metabolite	Found in: Rabbit	Guinea Pig	Mice	Rat	Man
1-naphthol	1,2	7	7	7	9
2-naphthol	1	7	7	7	9
1-naphthyl sulfate	1,7	7	7	7	
1-naphthyl glucosiduronic acid	1				
S-(1-naphthyl)-L-cysteine				3	
1-naphthyl mercapturic acid	1				
1,2-dihydro-1,2-dihydroxy naphthalene	1,5,7	7	7	4,5,7	
1,2-dihydro-2-hydroxy-1-naphthyl-glucosiduronic acid	1,2,6,7			7	
1,2-dihydro-1-hydroxy-2-naphthyl-glucosiduronic acid	2				
S-(1,2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine				3	
N-acetyl-S-(1,2-dihydro-2-hydroxy-1-napthyl)-L-cysteine	1	1	1	1,3	
2-hydroxy-1-naphthyl sulfate	1				
1-hydroxy-2-naphthyl sulfate	2				
1,2-dihydroxynapthalene		7			
1,2-naphthoquinone					9
1,4-naphthoquinone					9

References:
1- Boyland & Sims, 1958
2- Sims, 1959
3- Booth, et al. 1960
4- Young, 1947
5- Booth & Boyland, 1949
6- Corner, et al. 1954
7- Corner & Young, 1954
8- Bourne & Young, 1934
9- Mackell, et al. 1951

cytochrome c (Van Heyningen and Pirie, 1967). 1,2-naphthaquinone also binds irreversibly to lens protein and amino acids (Van Heyningen and Pirie, 1966).

Aryl hydrocarbon hydroxylase, a mixed-function microsomal oxidase, is induced by many carcinogenic polycyclic aromatic hydrocarbons. Alexandrov and Frayssinet (1973) found that the intraperitoneal injection of 40 mg/kg of naphthalene in corn oil into male Wistar rats daily for a period of three days resulted in a 40 percent inhibition of this enzyme's ability to hydroxylate benzo(a)pyrene. Naphthalene also inhibited the inducability of this enzyme by 3-methylcholanthrene. A number of other napthtalene derivatives, including 1-naphthol and 2-naphthol, were tested and were not found to depress the activity of this enzyme.

EFFECTS

Lezenius (1902) described the case of a 36-year-old pharmacist who, after taking 5 g of naphthalene in oil, developed near blindness eight or nine hours later. An examination a year later disclosed constricted visual fields associated with optic atrophy and bilateral cataracts made up of numerous whitish opacities. In 1906 Van der Hoeve further described a case of a 44-year-man who worked with powdered naphthalene and was found to have cataracts and a retinal hemorrhage. A coworker was noted to have chorioretinitis in one eye. Ghetti and Mariani (1956) examined 21 workers in a plant producing a dye intermediate from naphthalene and found cataracts in 8 of them with the following age distribution:

Age	#	# with cataracts
20-30	4	2
30-40	5	3
40-50	8	2
50-60	4	1

A model for the eye toxicity of naphthalene has been developed in rabbits (Van Heyningen and Pirie, 1976) to further investigate the disappearance of reduced glutathione from the lens, first noted by Bourne (1937), and its relationship to the cataractogenicity of naphthalene. The authors found that the metabolites of naphthalene released in the eye were general metabolic and coenzyme inhibitors (Rees and Pirie, 1967); that 1,2-dihydroxynaphthalene or 1,2-naphtha-

quinone combined with amino acids or irreversibly with the thiol groups of lens protein to form a brown precipitate; that the hydroperoxide formed in the oxidation of 1,2-dihydroxynaphthalene and ascorbic acid can act with the high levels of glutathione peroxidase in the eye to oxidize glutathione; that oxidized ascorbic acid easily enters the lens where it readily oxidizes reduced glutathione nonenzymatically (Van Heyningen, 1970); that the oxidized ascorbic acid also oxidizes protein thiols, a mechanism that is normally prevented by reduced glutathione; that the oxidation of NADPH prevents the reduction of oxidized glutathione by glutathione reductase; that 1,2-naphtoquinone quickly combines irreversibly with lens and eye proteins thereby losing its ability to oxidize ascorbic acid (Van Heyningen and Pirie, 1967); that oxidized ascorbic acid breaks down to oxalate which in turn precipitates as calcium oxalate crystals in the vitreous humor and on the retina of the eye; and that lens changes are preceded by evidence of injury to the epithelium of the lens as well as retina (Pirie, 1968).

A hemolytic anemia with associated jaundice and occasionally renal disease from precipitated hemoglobin has been described both in children and adults (Haggerty, 1956; Chusid and Fried, 1955; Abelson and Henderson, 1951; Zuelzer and Apt, 1949; Gidron and Leurer, 1956; Nash, 1903; Mackell, et al. 1951) as well as in newborn infants (Cock, 1957; Schafer, 1951) after exposure to naphthalene by ingestion, inhalation or, possibly, by skin contact. Dawson, et al. (1958) identified two newborn children who had both a naphthalene hemolytic anemia as well as a combined glucose-6-phosphate

dehydrogenase deficiency and glutathione reductase deficiency. The former defect was more prominent. Glucose-6-phosphate dehydrogenase (G6PD) in the presence of glucose-6-phosphate reduces NAPD to NADPH which in turn is required by glutathione reductase to maintain glutathione in the reduced state. In the absence of reduced glutathione there can be oxidative denaturation of hemoglobin with precipitation of globin as Heinz bodies and the associated stiffening of red blood cell membranes. These abnormal red cells are then removed from the circulation by the spleen and liver. NADPH is also a cofactor for the reduction of methemoglobin (Kellermeyer, et al. 1962). This can lead to the buildup of methemoglobin or methemalbumin in the serum with excretion of these compounds in the urine (Schafer, 1951). Both Valaes, et al. (1963) and Naiman and Kosoy (1964) have noted that although most infants with naphthalene-associated acute hemolytic anemia have G6PD deficiency, there was a group of neonates that had a milder form of hemolysis and did not have the enzyme deficiency. Both groups noted high levels of bilirubin in the serum of their cases with associated brain damage (kernicterus) and even death in several infants. Gross, et al.(1958) noted that red blood cells lose G6PD activity with aging in G6PD deficient individuals such that older populations of red blood cells are more susceptible to hemolysis than young ones. In some forms of G6PD deficiency, this can result in a self-limited form of hemolysis (Wintrobe, et al. 1974).

Hemolytic anemia has also been noted in individuals exposed to a metabolite of naphthalene, 2-naphthol. Smillie (1920) treated 79 Brazilians with 2-naphthol for hookworm disease. Adults received a 6 g a day orally for three days while children received a smaller dose. Four of those treated were found to develop a hemolytic anemia, two associated with splenomegaly. He identified three of those affected as being black.

Acute, Sub-acute, and Chronic Toxicity

The acute lethality of naphthalene has been assessed by several routes in several species as shown in Table 5. The greater toxicity by an oral versus subcutaneous route might be due to species variation in susceptibility but might also indicate that naphthalene first has to be metabolized by the liver to produce maximum toxicity.

Several other studies have been performed to assess sublethal effects of naphthalene or its metabolites. Zuelzer and Apt (1949) administered naphthalene in a solid form to dogs by the oral route. One dog received 1800 mg/kg in divided doses over a period of five days with resultant lethargy, ataxia, a drop in hemoglobin by 83 percent and a leukamoid reaction (white blood cell count of 119,000). Two other dogs received 1530 mg/kg and 420 mg/kg in single doses with a resultant drop in hemoglobin by 33 percent and 29 percent respectively.

TABLE 5

Tests of the Acute Toxicity of Naphthalene

Test Animal	#	Route	LD50 (mg/kg)	Reference
Mice	---	Subcut.	5100	Irie, et al. 1973
Sherman rats				
male	40	Oral[a]	2200	Gaines, 1969
female	40	Oral[a]	2400	Gaines, 1969
male	10	Skin[b]	>2500	Gaines, 1969
female	10	Skin[b]	>2500	Gaines, 1969
Rat	---	Oral	1780	NIOSH, 1977
Rat	---	Oral	9430	Union Carbide Corp., 1968
Rat	---	Inhalation	>100 ppm x 8 hr.	Union Carbide Corp., 1968

[a] Dissolved in peanut oil

[b] Dissolved in xylene

Mahvi, et al.(1977) administered naphthalene in corn oil intraperitoneally to C57 Bl/6J mice. Two groups of 63 mice received corn oil alone or remained untreated. Groups of 21 mice each were given 67.4, 128, or 256 mg/kg. Three animals from each dosage group were sacrificed at ten minutes, 1 hour, 6 hours, 12 hours, 24 hours, 48 hours, and 7 days following treatment. Lung tissue was rapidly fixed and examined by light, scanning electron microscopy, and transmission electron microscopy. No changes were noted in either control group. Minor bronchiolar epithelial changes were noted in the group receiving 6.4 mg/kg. Mice in the higher dosage groups developed necrosis of secretory nonciliated bronchiolar cells. Epithelial structure returned to normal within seven days in all cases.

Reid, et al. (1973) gave naphthalene dissolved in sesame oil to C57 Bl/6J mice by the intraperitoneal route and found coagulative necrosis of the bronchiolar and bronchial epithelium at a dose of 600 mg/kg. Controls received sesame oil alone and no adverse effects were reported for this group. The size of the treatment groups was not stated.

Pilotti, et al. (1975) treated ascites sarcoma BP8 cells <u>in vitro</u> by incubating with naphthalene solutions for 48 hours. The authors noted 100 percent growth inhibition at a concentration of 128 mg/l and 10 percent growth inhibition at a concentration of 12.8 mg/l.

Several studies have also been done on the metabolites of naphthalene. Van Heyningen and Pirie (1967) dosed one rabbit with 300 mg of the dihydrodiol intravenously in divided doses over three days and noted retinal lesions. They also noted lens changes in four rabbits dosed externally with one percent eye drops of the same compound (dissolved in water) over a period of two to five days for a total dose of 40-70 mg per rabbit.

Mackell, et al. (1951) incubated blood from normal human donors with naphthalene or its metabolites in various concentrations. Hemolysis was noted as shown in Table 6. These agents were also injected intravenously into white male rabbits in concentrations of 0.25, 0.5, 1.0 and 1.25 mg/kg. Naphthalene, 2-naphthol,1,2-naphthaquinone and 1,4-napthaquinone produced no hemolysis at 15 minutes after the injection; 1-naphthol, however, produced six percent and 9 percent hemolysis at the two higher dosages. Zinkham and Childs (1958) performed similar in vitro experiments with the same metabolites but measured drop in reduced glutathione as an end point. They also investigated the effect of these metabolites on blood from a patient who had hemolysis after contact with naphthalene and who had red blood cells sensitive to an oxidant (presumed G6PD) deficiency. All four metabolites resulted in depression of reduced glutathione levels. Naphthalene resulted in minor depression of reduced glutathione levels at concentrations of 5000 mg/l or greater.

TABLE 6

In vitro Hemolysis of Red Blood Cells Exposed to Naphthalene and its Metabolites (Mackell, et al. 1951)

Compound	Percent Hemolysis						
	Concentration (mg/l blood)						
	10	13.3	20	40	100	200	1000
1-naphthol	< 2	6	14	46	53	65	74
2-naphthol	0	0	3	11	32	48	60
1,4-naphtha-quinone	0	0	0	0	0	4	18
1,2-naphtha-quinone	0	0	0	0	0	< 1	12
Naphthalene	0	0	0	0	0	0	0

Several studies have been done on the subacute and chronic toxicity of naphthalene, all involving a single dose/day regime. Fitzhugh and Buschke (1949) fed five weanling rats two percent of naphthalene or 2-naphthol in their diets for a period of at least 60 days and noted early cataracts in both groups.

Van Heyningen and Pirie (1976) dosed rabbits daily by gavage with 1000 mg/kg of naphthalene for various periods of time for a maximum of 28 days. They noted lens changes developing after the first dose and retinal changes developing after the second dose.

Ghetti and Mariani (1956) fed five rabbits 1000 mg/kg/day of naphthalene and noted the development of cataracts between days 3 and 46. Topical application of a ten percent solution in oil to the eyes of two rabbits did not produce cataracts after a period of 50 days. Intraperitoneal injection of 500 mg/day of naphthalene in an oily solution to one rabbit over a period of 50 days produced weight loss but no cataracts.

Synergism and Antagonism

There is little information on the synergistic or antagonistic effects of naphthalene. In a single case report Harden and Baetjer (1978) described finding aplastic anemia in a 68-year-old black female exposed to mothproofing compounds. Yearly for a period of 39 years she had intermittently worked in storing garments with mothproofing compounds. One month prior to becoming ill she worked for a period of three weeks in a hot, unventilated room mothproofing garments. She handled a total of 7 kg of naphthalene and 5.5 kg of para-

dichlorobenzene. It was estimated that she was exposed to at or near 1400 ppm of paradichlorobenzene and 184 ppm of napthalene. The time of her exposure was consistent with the onset of her bone marrow depression, estimated from her hematologic findings on admission two months after first becoming ill. No other cases of aplastic anemia have been described with either a naphthalene or paradichlorobenzene exposure either alone or in combination with another chemical.

Teratogenicity

Naphthalene or its metabolites can cross the placenta in sufficient amounts to cause fetal toxicity. Both Zinkham and Childs (1958) and Anziulewicz, et al. (1959) noted toxic effects in infants where the only exposure was to the mother during pregnancy. When a metabolite of naphthalene, 2-naphthol, was administered to pregnant rabbits, their offspring were born with cataracts and evidence of retinal damage (Van der Hoeve, 1913).

Mutagenicity

Naphthalene has been found to be nonmutagenic in several microsomal/bacterial assay systems as outlined in Table 7. Metabolites of naphthalene have not been tested.

Carcinogenicity

Wolf (1976) reported six cases of malignant tumors among 15 workers exposed to vapors of naphthalene and coal tar for a period of up to 32 years at a coal tar naphthalene production facility. Four workers contracted laryngeal carcinoma and were all smokers. The other 2 workers developed neoplasms of the pylorus and cecum. There was no con-

TABLE 7

Mutagenicity of Naphthalene in Various In Vitro Microsomal Assay Systems

System	Strain	Result	Reference
Rat microsomes/ Salmonella typhimurium	TA100	Negative[a]	McCann, et al. 1975
	TA1535	Negative[a]	McCann, et al. 1975
	TA1537	Negative[a]	McCann, et al. 1975
	TA98	Negative[a]	McCann, et al. 1975
Mouse microsome/ Salmonella typhimurium[b]	G46	Neative	Kraemer, et al. 1974
Mouse microsome/ E. coli	K12	Negative	Kraemer, et al. 1974

[a]Less than 0.09 revertants/nmol. Tested at 10, 100, 500 and 1000 ug/plate

[b]Naphthalene-1,2-oxide used in the test system

trol group.

Knake (1956) treated 40 white rats with 500 mg/kg of coal tar naphthalene in sesame oil subcutaneously every two weeks for a total of seven treatments; 34 rats survived the treatment and five developed invasive or metastatic lymphosarcoma prior to death. There was a two percent incidence of malignancies in an untreated control group with a similar incidence in a group treated with sesame oil alone. His data are detailed in Table 8. The sites of the injections of the naphthalene/sesame oil and sesame oil treated groups were painted with carbolfuchsin (a known experimental carcinogen) prior to each injection. The naphthalene contained 0.07 gram molecular weight impurities per 100 g (equivalent to 10 percent methyl naphthalene).

In a second study, Knake (1956) painted a group of mice with either benzene or a solution of coal tar naphthalene in benzene and noted an excess of lymphatic leukemia in the naphthalene/benzene group compared to the benzene treated group or a group of untreated controls. His results are detailed in Table 9.

Druckey and Schmahl (1955) used naphthalene as a vehicle for testing the carcinogenic effects of anthracene. In a preliminary study they looked at the potential carcinogenic effects of naphthalene alone. BD I and BD III strain rats were used. One group of 28 rats was given 10 gm of naphthalene orally per rat over a period of time and followed for an excess of 1000 days. A second group of ten rats was given a total dose of 0.82 gm of naphthalene per rat subcutaneously and followed for a similar period of time. No

TABLE 8

Incidence of Tumors in White Rats Treated with 0.5 gm/kg Naphthalene Subcutaneously (15% in sesame oil) Every Two Weeks for 14 Weeks and then Followed for 18 months[a] (Knake, 1956)

	Number of Animals				
Treatment	Total	Survivors	Lymphosarcoma	Fibroadenoma	Other Malignant Tumor
Naphthalene in sesame oil	40	0	5	1	0
Sesame oil[b]	40	4	1	1	0
No treatment	101	0 (lifetime)	1	0	1

[a] 34 naphthalene/sesame oil treated rats survived the initial treatment. 32 rats treated with sesame oil alone survived the initial 14 weeks of treatment

[b] 3.3 ml/kg/treatment

TABLE 9

Incidence of Tumors in Inbred Black Mice Painted with 0.5% Naphthalene in Benzene or Benzene Alone 5 days/week for Life (Knake, 1956)

Treatment	Number	Leukemia	Lymphosarcoma	Sarcoma (other)	Other Malignancy	Lung Adenoma
Naphthalene in Benzene	25	4[a]	1	0	1	3
Benzene	21	0	1	1	0	1
No Treatment	1227	5	3	1	44	0

[a] All lymphocytic leukemia

tumors were noted in either group.

Boyland, et al. (1964) found a four percent incidence of bladder carcinoma in mice with naphthalene implaced in their bladders. As seen in Table 10, there was a similar or higher incidence of bladder carcinoma in mice treated with various inert control substances including glass.

Kennaway (1930) and Kennaway and Hieger (1930) tested the carcinogenicity of naphthalene in mice by a skin painting experiment. They found that naphthalene was noncarcinogenic, but did not give the details of their protocols.

Bogdat'eva and Bid (1955) painted naphthalene onto the skin of rabbits at a dose sufficient to cause systemic toxicity. No carcinomatous changes were noted after this chronic study. Details of the protocol were not given.

Takizawa (1940) painted the skin of mice with a metabolite of naphthalene, 1,4-naphthaquinone. They noted an incidence of 15 to 20 percent skin papillomas with some degenerating into malignant epithelomas in mice surviving 200 days. Further details of the protocol were not given.

Pirie (1968) treated Dutch and albino rabbits with 1g/kg/day of naphthalene by gavage. After three doses they noted mitotic arrest of the epithelial cells of the lens. The arrest persisted for 15 days when replication of the epithelial cells was first noted. At 16 days numerous abnormal mitotic figures in metaphase were noted in the epithelial layer in association with cell overgrowth. This work is significant in that one of the effects of 2 metabolites of naphthalene, 1-naphthol and 2-naphthol, is to interfere with the mitotic spindle function, as seen in root tips

TABLE 10

Bladder Tumors in Mice with Naphthalene Bladder Implants
(Boyland, et al. 1964)

Substance	# Mice Surviving to 30 weeks	Carcinoma	Adenoma/Papilloma
Naphthalene	23	1	0
Inert Controls			
Magnesium stearate	41	1	1
n-Hexadecanol	69	6	2
n-Octadecanol	50	6	7
Smooth glass	67	3	---
Roughened glass	63	18	---

of Vicia faba (Dean, 1978). Both metabolites cause a chromosomal lagging in anaphase and 1-naphthol results in a colchicine-like accumulation of chromosomes in metaphase.

Naphthalene has also been tested for carcinogenic activity in in vitro test systems using rodent embryo cells pretreated with Rauscher leukemia virus. No effects were seen at doses up to 100,000 µg/l (Table 11).

TABLE 11

Carcinogenic Activity of Naphthalene with *In Vitro* Test Systems

Test System	Dose (ug/l)[b]	Result	Reference
Rat embryo cells/ Rauscher leukemia virus[a]	50	Negative	Freeman, et al. 1973
	1,000	Negative	Freeman, et al. 1973
	5,000	Negative	Freeman, et al. 1973
	10,000	Negative	Freeman, et al. 1973
	50,000	Negative	Freeman, et al. 1973
	100,000	Negative	Freeman, et al. 1973
Mouse embryo cells/ AKR leukemia virus[a]	100	Negative	Rhim, et al. 1974
	500	Negative	Rhim, et al. 1974
	1,000	Negative	Rhim, et al. 1974
	5,000	Negative	Rhim, et al. 1974

[a] In addition to transforming ability, treated cells injected into newborn rats or mice, respectively, without any evidence of tumorigenicity

[b] Dissolved in acetone

CRITERIA FORMULATION

Existing Guidelines and Standards

The only existing U.S. standard for naphthalene is the Occupational Safety and Health Administration standard of 10 ppm (50 mg/m^3) of vapor exposure for a time-weighted industrial exposure (39FR23540). This standard was adopted from the American Conference of Governmental Industrial Hygienists' Threshold Limit Value which in turn was based on an irritant threshold for naphthalene of 15 ppm (ACGIH, 1971). At present the ACGIH also suggests a maximum 15 minute exposure value of 15 ppm (75 mg/m^3) (ACGIH, 1978).

The maximum permissible concentration of naphthalene in fishery water bodies of the USSR is 4 µg/l (Mosevich, et al. 1976).

Current Levels of Exposure

Natural waters have been found to contain up to 2 µg/l of naphthalene while drinking water supplies have been found to contain up to 1.4 µg/l of naphthalene (U.S.EPA, Region IV, unpublished data). Ambient air levels have been measured at .00035 $\mu g/m^3$ in an urban area and .00006 $\mu g/m^3$ in a small town (Krstulovic, et al. 1977). Industrial exposures can range as high as 1.1×10^6 $\mu g/m^3$ for naphthalene-using industries (Robbins, 1951) with exposures up to 1120 $\mu g/m^3$ for coke oven workers (Bjorseth, et al. 1978a) and 310 $\mu g/m^3$ for aluminum reduction plant workers (Bjørseth, et al. 1978b). No measurements of naphthalene have been reported for market basket foods.

Special Groups at Risk

Approximately 100 million people worldwide have G6PD deficiency which would make them more susceptible to hemolytic anemia on exposure to naphthalene. At present more than 80 variants of this enzyme deficiency have been identified (Wintrobe, et al. 1974). The incidence of this deficiency is 0.1 percent in American and European Caucasians but can range as high as 20 percent in American blacks and greater than 50 percent in certain Jewish groups (Table 12).

Newborn infants have a similar sensitivity to the hemolytic effects of naphthalene, even without G6PD deficiency. Zinkham and Childs (1957) surveyed 26 normal white and black newborn infants and found that their blood reduced glutathione levels dropped moderately to severely in all of the samples tested when incubated with acetylphenylhydrazine, suggestive of a glutathione reductase deficiency. Brown and Burnett (1957) also noted that newborn infants have a decreased capacity to conjugate chemical metabolites with glucuronide secondary to an absolute decrease in the activity of UDP-glucuronyl dehydrogenase and transferase. Such a lack in glucuronidation can allow the build-up of toxic amounts of 1,2-dihydroxynaphthalene and 1,2-naphthaquinone.

A small percentage of the population might have an allergic hypersensitivity to naphthalene. Fanburg (1940) described a 43-year-old physician with a generalized exfoliative dermatitis who was found to be allergic to naphthalene. Both the clinical and histologic picture resembled a malignancy, mycosis fungoides. A patch test with naphthalene

TABLE 12

Frequency of G6PD Deficiency in Populations
(Wintrobe, et al. 1974)

Population	G6PD Deficiency (%)
Northern European	0.1
American black male	13
American black female	20
Brazilian black male	8.2
Bantu male	37
Sardinian	14.35
Maltese	2.7
Italian	0.4
Greek	9.5
Sephardic, Oriental or Kurdish Jews	$\geq$50

was positive, resulting in urticaria. When all exposure to naphthalene was discontinued, the skin condition cleared rapidly and did not recur over a three year period of followup.

Basis and Derivation of Criterion

All chronic toxicity studies using naphthalene have failed to demonstrate any carcinogenic activity except for those performed by Knake (1956). This author found an excess occurrence of lymphosarcoma when naphthalene was given by the subcutaneous route to rats, and of lymphocytic leukemia when naphthalene was chronically painted on the skin of mice using benzene as a solvent. However, the naphthalene used in this study was derived from coal tar and contained ten percent or more unidentified impurities. Furthermore, a known experimental carcinogen, carbolfuchsin, was applied prior to each injection of naphthalene in the former study. In light of these defects, carcinogenicity data derived from this study cannot be used as a basis for a naphthalene water criterion.

No other chronic toxicity studies are available that can be used as an adequate basis for a naphthalene criterion. Furthermore, there are no adequate epidemiologic studies that can be used as a basis.

The ACGIH (1971) has recommended a time-weighted threshold limit value for an industrially exposed population of 50 mg/m^3 (50 ug/l) of naphthalene vapor in air. This value was set to prevent workers with exposure to naphthalene vapors from getting eye irritation. It is unclear, however, whether exposures to water containing naphthalene in excess of this level (50 ug/l) might also result in mucous membrane

irritation. Until further information is available on the direct irritant properties of naphthalene in water, the ACGIH threshold limit value cannot be used as a basis for a naphthalene water criterion.

Mahvi, et al. (1977) noted a dose related response by C57 Bl/6J mice given intraperitoneal injections of naphthalene in sesame oil. No bronchiolar epithelial changes were noted in two control groups. The authors noted minimal bronchiolar epithelial changes in the treated group receiving 6.4 mg/kg of naphthalene. Severe, reversible damage to bronchiolar epithelial cells was noted among two higher dosage groups. The results of this study can be used as the basis for the criterion. The minimal effect level of 6.4 mg/kg is equivalent to a 448 mg dose for a 70 kg man and can reasonably be used as a basis for calculating an acceptable daily dosage if it is reduced by a factor of 1000, which equals 448 ug, to protect sensitive individuals (Natl. Acad. Sci., 1977).

No pharmacokinetic data are available on the absorption of naphthalene by the oral route. Because of its high octanol: water partition coefficient (Krishnamurthy and Wasik, 1978), it is reasonable to expect that naphthalene in water should be nearly completely absorbed and an absorption efficiency of 100 percent can be assumed.

For the purposes of establishing a water quality criterion, human exposure to napthalene is considered to be based on ingestion of 2 liters of water and 18.7 g of fish. Fish bioaccumulate naphthalene from water by a factor of 60.

With these considerations in mind, the following equation can be used to calculate a criterion value:

$$2\ L \cdot X + (0.0187 \times 60) \cdot X = 448\ ug$$

Where:

448 ug = limit on daily exposure for a 70 kg person (ADI)

2 L = amount of drinking water consumed

0.0187 kg = amount of fish consumed

60 = bioaccumulation factor

Solving for X:

$$X = 143\ ug/l$$

Thus, the recommended ambient water quality criterion is 143 ug/l.

This calculation assumes that 100 percent of man's exposure is assigned to the ambient water pathway. Although it is desirable to arrive at a criterion level for water based on contribution to total exposure, data on other routes of exposure is not sufficient to support a factoring of the criterion level.

In summary, based on the use of toxicologic data for mice, the criterion level corresponding to an acceptable daily intake of 448 ug/day, is 143 mg/l. Drinking water contributes 64 percent of the assumed exposure while eating contaminated fish products accounts for 36 percent. The criterion can alternatively be expressed as 400 ug/l if exposure is assumed to be from the consumption of fish and shellfish alone.

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