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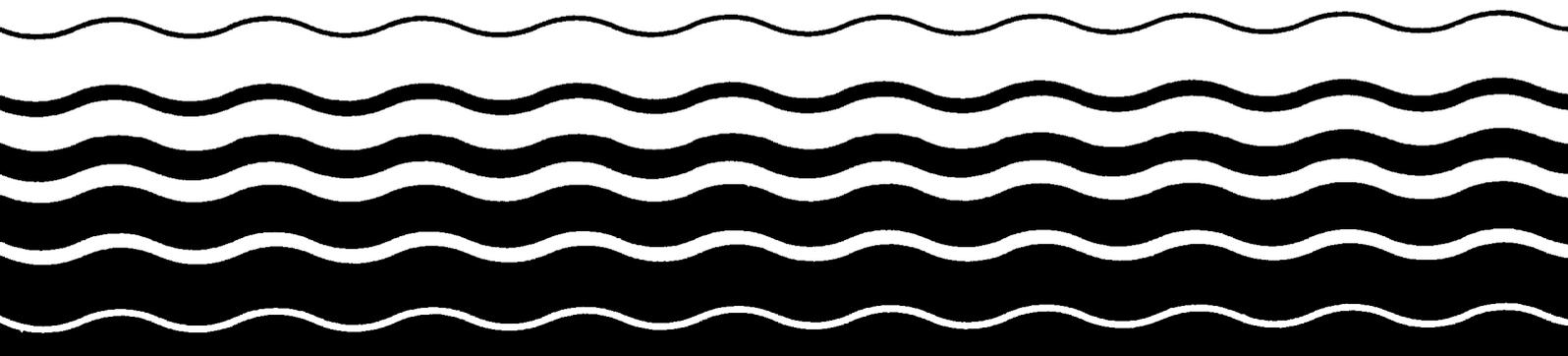
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Office of Water
Regulations and Standards
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Ambient Water Quality Criteria for Naphthalene



AMBIENT WATER QUALITY CRITERIA FOR
NAPHTHALENE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisfaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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CRITERIA DOCUMENT

NAPHTHALENE

CRITERIA

Aquatic Life

The available data for naphthalene indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 2,300 and 620 $\mu\text{g/l}$, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for naphthalene indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 2,350 $\mu\text{g/l}$ and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of naphthalene to sensitive saltwater aquatic life.

Human Health

Using the present guidelines, a satisfactory criterion cannot be derived at this time because of the insufficiency in the available data for 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 repellent and insecticide as well as an antihelminthic, vermicide, and an intestinal antiseptic.

Naphthalene 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°C 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 $\mu\text{g/l}$ (Mitchell, 1926) and 40,000 $\mu\text{g/l}$ (Josephy and Radt, 1948) at 25°C . The solubility of naphthalene in seawater will vary according to the degree of salinity; in seawater of average composition the solubility of

naphthalene is approximately 33,000 $\mu\text{g/l}$ (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 naphthoquinone 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 alkoxyhydroperoxides are formed. In an acidic medium, these peroxides will be converted to methyl phthalaldehyde; in a basic medium, they are converted to phthalaldehydic acid (Bailey, et al. 1964). When combined with nitrate salts with metals 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 degradation rate under laboratory conditions of up to 3.3 $\mu\text{g/l}$ (Lee and Anderson, 1977).

Naphthalene has a varied environmental distribution and has been detected in ambient water (up to 2.0 $\mu\text{g/l}$), sewage plant effluents (up to 22 $\mu\text{g/l}$), and drinking water supplies (up to 1.4 $\mu\text{g/l}$) (U.S. EPA, 1971-1977).

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INTRODUCTION

A variety of aquatic species has been exposed to naphthalene and most acute tests were under static procedures with unmeasured test concentrations. All but two fifty percent effect levels for fish and invertebrate species are in the range of 2,300 to 8,900 $\mu\text{g/l}$. One embryo-larval test with the fathead minnow demonstrated adverse effects at a test concentration of 850 $\mu\text{g/l}$.

Histopathological changes in the saltwater mummichog were observed at naphthalene concentrations as low as 2 $\mu\text{g/l}$.

EFFECTS

Acute Toxicity

Daphnia magna is the only tested freshwater invertebrate species (U.S. EPA, 1978) and the 48-hour EC_{50} is 8,570 $\mu\text{g/l}$ (Table 1).

DeGraeve et al. (1980) conducted flow-through tests with measured concentrations for the rainbow trout and the fathead minnow. The trout appeared to be a little more sensitive with a 96-hour LC_{50} of 2,300 $\mu\text{g/l}$ (Table 1). The 96-hour LC_{50} for the fathead minnow tested at 14°C was 4,900 $\mu\text{g/l}$ and at 24°C the LC_{50} was 8,900 $\mu\text{g/l}$. The LC_{50} of 150,000 $\mu\text{g/l}$ for the mosquitofish appears to be atypical but the result cannot be discounted.

Ninety-six-hour LC_{50} values for the polychaete, Neanthes arenaceo-
dentata, Pacific oyster, and the grass shrimp are 3,800, 199,000, and 2,350 $\mu\text{g/l}$, respectively (Table 1). The 24-hour LC_{50} values for one fish and two saltwater shrimp species range from 2,400 to 2,600 $\mu\text{g/l}$ (Table 6).

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses 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 calculations for deriving various measures of toxicity as described in the Guidelines.

With the exception of the mosquitofish and the Pacific oyster, all LC₅₀ and EC₅₀ values, regardless of test method, fall within the narrow range of 2,300 to 8,900 µg/l for 9 freshwater and saltwater species.

Chronic Toxicity

An embryo-larval test has been conducted with the fathead minnow and the resultant chronic value is 620 µg/l (Table 2). When this concentration is divided by the geometric mean LC₅₀ value of 6,600 µg/l for this species (Table 1) an acute-chronic ratio of 11 is obtained. No other species have been tested under chronic conditions.

A summary of species mean acute and chronic values is presented in Table 3.

Plant Effects

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

Residues

There is only one reported test (Harris, et al. 1977b) that determined an apparent equilibrium bioconcentration factor for naphthalene. After nine days, the bioconcentration factor for a copepod was 5,000 (Table 5). Bioconcentration data for other species for exposures of one hour to one day are listed in Table 6. These factors range from 32 to 77 and indicate that equilibrium does not occur rapidly when those results are compared to the nine-day value of 5,000 (Table 5).

Miscellaneous

Soto, et al. (1975a) observed the death in 24 hours of 61 percent of the cells of the alga, Chlamydomonas angulosa, at a concentration of 34,400 µg/l (Table 6). There was 50 percent mortality of coho salmon after an exposure of less than six hours to 5,600 µg/l (Holland, et al. 1960).

Saltwater species have been more extensively tested, probably the result of more interest in oil pollution. Berdugo et al. (1977) exposed the copepod, Eurytemora affinis, to a concentration of 1,000 $\mu\text{g/l}$ and observed effects on egg production and ingestion rate. The most significant data were produced by DiMichele and Taylor (1978). Gill hyperplasia in the mummichog was observed in 80 percent of the fish after a 15-day exposure to 2 $\mu\text{g/l}$; there was a 30 percent occurrence in the controls. All of the fish exposed to 20 $\mu\text{g/l}$ demonstrated necrosis of the tastebuds, a change not observed in any of the controls.

Summary

The LC_{50} and EC_{50} values for one freshwater invertebrate and two fish species are within the range of 2,300 to 8,900 $\mu\text{g/l}$. The LC_{50} for the mosquitofish is 150,000 $\mu\text{g/l}$, which result appears to be atypical but cannot be rejected at this time. The results of an embryo-larval test with the fathead minnow demonstrated adverse effects at a naphthalene concentration of 850 $\mu\text{g/l}$. The resultant chronic value, 620 $\mu\text{g/l}$, provides an acute-chronic ratio of 11. Freshwater algae appear to be less sensitive with effect concentrations of about 33,000 to 34,000 $\mu\text{g/l}$. The bioconcentration factor for naphthalene and a copepod is 5,000 and this high result suggests a need for additional testing.

The saltwater fish and invertebrate species tested are of about similar sensitivity to the freshwater species, with LC_{50} values of 3,800 $\mu\text{g/l}$ for a polychaete and 2,350 $\mu\text{g/l}$ for the grass shrimp. There was an apparently atypical 48-hour value for the Pacific oyster of 199,000 $\mu\text{g/l}$. The most critical data are those on histopathological effects on a high percentage of mummichog exposed to concentrations of naphthalene between 2 and 20 $\mu\text{g/l}$.

CRITERIA

The available data for naphthalene indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 2,300 and 620 $\mu\text{g}/\text{l}$, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for naphthalene indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 2,350 $\mu\text{g}/\text{l}$ and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of naphthalene to sensitive saltwater aquatic life.

Table 1. Acute values for naphthalene

<u>Species</u>	<u>Method*</u>	<u>LC50/EC50 (µg/l)</u>	<u>Species Acute Value (µg/l)</u>	<u>Reference</u>
<u>FRESHWATER SPECIES</u>				
<u>Cladoceran, Daphnia magna</u>	S, U	8,570	8,570	U.S. EPA, 1978
<u>Rainbow trout, Salmo gairdneri</u>	FT, M	2,300	2,300	DeGraeve, et al. 1980
<u>Fathead minnow, Pimephales promelas</u>	FT, M	4,900	-	DeGraeve, et al. 1980
<u>Fathead minnow, Pimephales promelas</u>	FT, M	8,900	6,600	DeGraeve, et al. 1980
<u>Mosquitofish, Gambusia affinis</u>	FT, M	150,000	150,000	Wallen, et al. 1957
<u>SALTWATER SPECIES</u>				
<u>Polychaete, Neanthes arenaceodentata</u>	S, U	3,800	3,800	Rossi & Neff, 1978
<u>Pacific oyster, Crassostrea gigas</u>	S, U	199,000	199,000	LeGore, 1974
<u>Grass shrimp, Palaemonetes pugio</u>	S, M	2,350	2,350	Tatem, 1976

* S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for naphthalene (DeGraeve, et al. 1980)

<u>Species</u>	<u>Method*</u>	<u>Limits (µg/l)</u>	<u>Chronic Value (µg/l)</u>
<u>FRESHWATER SPECIES</u>			
Fathead minnow, <u>Pimephales promelas</u>	E-L	450- 850	620

* E-L = embryo-larval

<u>Acute-Chronic Ratio</u>			
<u>Species</u>	<u>Chronic Value (µg/l)</u>	<u>Acute Value (µg/l)</u>	<u>Ratio</u>
Fathead minnow, <u>Pimephales promelas</u>	620	6,600	11

Geometric mean acute-chronic ratio = 11

Table 3. Species mean acute and chronic values for naphthalene

<u>Number</u>	<u>Species</u>	<u>Species Mean Acute Value* (µg/l)</u>	<u>Species Mean Chronic Value (µg/l)</u>	<u>Acute-Chronic Ratio**</u>
<u>FRESHWATER SPECIES</u>				
4	<u>Mosquitofish, Gambusia affinis</u>	150,000	-	-
3	<u>Cladoceran, Daphnia magna</u>	8,570	-	-
2	<u>Fathead minnow, Pimephales promelas</u>	6,600	620	11
1	<u>Rainbow trout, Salmo gairdneri</u>	2,300	-	-
<u>SALTWATER SPECIES</u>				
3	<u>Pacific oyster, Crassostrea gigas</u>	199,000	-	-
2	<u>Polychaete, Neanthes arenaceodentata</u>	3,800	-	-
1	<u>Grass shrimp, Palaemonetes pugio</u>	2,350	-	-

* Rank from high concentration to low concentration by species mean acute value.

**See the Guidelines for derivation of this ratio.

Table 4. Plant values for naphthalene (Kauss & Hutchinson, 1975)

<u>Species</u>	<u>Effect</u>	<u>Result</u> <u>(µg/l)</u>
<u>FRESHWATER SPECIES</u>		
Alga, <u>Chlorella vulgaris</u>	Extrapolated cell numbers 48-hr EC50	33,000

Table 5. Residues for naphthalene (Harris, et al. 1977b)

<u>Species</u>	<u>Tissue</u>	<u>Bioconcentration Factor*</u>	<u>Duration (days)</u>
<u>SALTWATER SPECIES</u>			
Copepod, <u>Eurytemora affinis</u>	whole body	5,000	9

* Dry weight to wet weight conversions.

Table 6. Other data for naphthalene

<u>Species</u>	<u>Duration</u>	<u>Effect</u>	<u>Result (µg/l)</u>	<u>Reference</u>
<u>FRESHWATER SPECIES</u>				
Alga, <u>Chlamydomonas angulosa</u>	24 hrs	Death of 61% of cells	34,400	Soto, et al. 1975a
Alga, <u>Chlamydomonas angulosa</u>	24 hrs	Loss of photo- synthetic capacity	10% saturation	Soto, et al. 1975b
Coho salmon, <u>Oncorhynchus kisutch</u>	<6 hrs	50% mortality	5,600	Holland, et al. 1960
<u>SALTWATER SPECIES</u>				
Copepod, <u>Eurytemora affinis</u>	0.16 days	Reduction in ingestion rate of 10% (P = 0.05)	1,000	Berdugo, et al. 1977
Copepod, <u>Eurytemora affinis</u>	1 day	Reduction in egg production by 83% (P = 0.05)	1,000	Berdugo, et al. 1977
Copepod, <u>Calanus helgolandicus</u>	1 day	Bioconcentration factor = 50	-	Harris, et al. 1977b
Copepod, <u>Calanus helgolandicus</u>	1 day	Bioconcentration factor = 60	-	Harris, et al. 1977a
Blue mussel, <u>Mytilus edulis</u>	4 hrs	Bioconcentration factor = 44	-	Lee, et al. 1972b
Grass shrimp, <u>Palaemonetes pugio</u>	24 hrs	LC50	2,600	Anderson, et al. 1974
Brown shrimp, <u>Penaeus aztecus</u>	24 hrs	LC50	2,500	Anderson, et al. 1974
Sheepshead minnow, <u>Cyprinodon variegatus</u>	24 hrs	LC50	2,400	Anderson, et al. 1974

Table 6. (Continued)

<u>Species</u>	<u>Duration</u>	<u>Effect</u>	<u>Result ($\mu\text{g/l}$)</u>	<u>Reference</u>
<u>Mummichog, Fundulus heteroclitus</u>	15 days	Gill hyperplasia	2	DIMichele & Taylor, 1978
<u>Mummichog, Fundulus heteroclitus</u>	15 days	Tastebud necrosis	20	DIMichele & Taylor, 1978
<u>Sand goby, Giliichthys mirabilis</u>	1 hr	Bioconcentration factor = 63	-	Lee, et al. 1972a
<u>Sculpin, Oligocottus maculosus</u>	3 hrs	Bioconcentration factor = 32	-	Lee, et al. 1972a
<u>Sand dab, Citharichthys stigmæus</u>	1 hr	Bioconcentration factor = 77	-	Lee, et al. 1972a

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

Naphthalene, $C_{10}H_8$, is an aromatic hydrocarbon with two ortho-condensed benzene rings. In 1965, 74.4 percent of the naphthalene produced in this country was used for the manufacture of phthalic anhydride. Phthalic anhydride was used in the manufacture of alkyd and polyester resins, dyes, pigments, pharmaceuticals, and insecticides. In the manufacture of insecticides, 12.2 percent was used to make insecticides such as 1-naphthyl-N-methylcarbamate (carbaryl). Eleven percent was used for the production of mothballs and 2-naphthol which is used as an intermediate in the manufacturing of dyestuffs, pigments, and pharmaceuticals. 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 decahydronaphthalenes (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 distillates 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).

EXPOSURE

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 ug/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 ug/l naphthalene (U.S. EPA, Region IV, unpublished data).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of

the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 350 was obtained for naphthalene using Eurytemora affinis (Harris, et al., 1977). Another species of copepod produced a lower BCF but may not have reached steady-state. This BCF was calculated on a lipid basis, and so corresponds to 100 percent lipids. An adjustment factor of $3.0/100 = 0.030$ can be used to adjust the measured BCF from the 100 percent lipid basis of the BCF to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for naphthalene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be $350 \times 0.030 = 10.5$.

Inhalation

Unusual exposure to naphthalene can occur to cigarette smokers, naphthalene being identified as one of the polynuclear aromatic hydrocarbons found in cigarette smoke condensate (Akin, et al. 1976). Under industrial conditions individuals can be exposed to levels of naphthalene up to 1.1 g/m^3 (220 ppm) as vapor and up to $4.4 \text{ } \mu\text{g/m}^3$ as particulates (Table 1). Potential exposure categories in this group are outlined in Table 2.

Dermal

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

TABLE 1
Air Levels of Naphthalene

Area Investigated	Vapor	Air Level ($\mu\text{g}/\text{m}^3$) Particulate	Reference
<u>Industrial:</u>			
Naphthalene melt present	1,600 - 1.1×10^6	---	Robbins, 1951
Coke Oven	11.35 - 1,120	0-4.40	Bjørseth, et al. 1978a
Aluminum Reduction Plant	.72 - 311.3	.090-4.00	Bjørseth, et al. 1978b
Providence, R.I.	0.0001	0.00025	Krstulovic, et al. 1977
Kingston, R.I.	0.00003	0.00003	Krstulovic, et al. 1977
Narragansett Bay, R.I.	0.00005	0.000003	Krstulovic, et al. 1977

TABLE 2

Workers with Potential Naphthalene Exposure*

Beta naphthol makers
Celluloid makers
Coal tar workers
Dye chemical makers
Fungicide makers
Hydronaphthalene makers
Lampblack makers
Moth repellent workers
Phthalic anhydride makers
Smokeless powder makers
Tannery workers
Textile chemical workers
Aluminum reduction plant workers

*Source: Tabershaw, et al., 1977

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-naphthoquinone, is increased at least 5-fold when dissolved in oil and administered to rabbits, as compared to an aqueous solution (Talakin, 1966). Sanborn and Malins (1977) found a marked decrease in absorption of protein bound naphthalene in shrimp. The authors give this as evidence that naphthalene would be less likely 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 in mammals has been extensively studied. 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 with sulfate or glucuronic acid or spontaneously oxidized to form another highly reactive compound, 1,2-naphthoquinone.

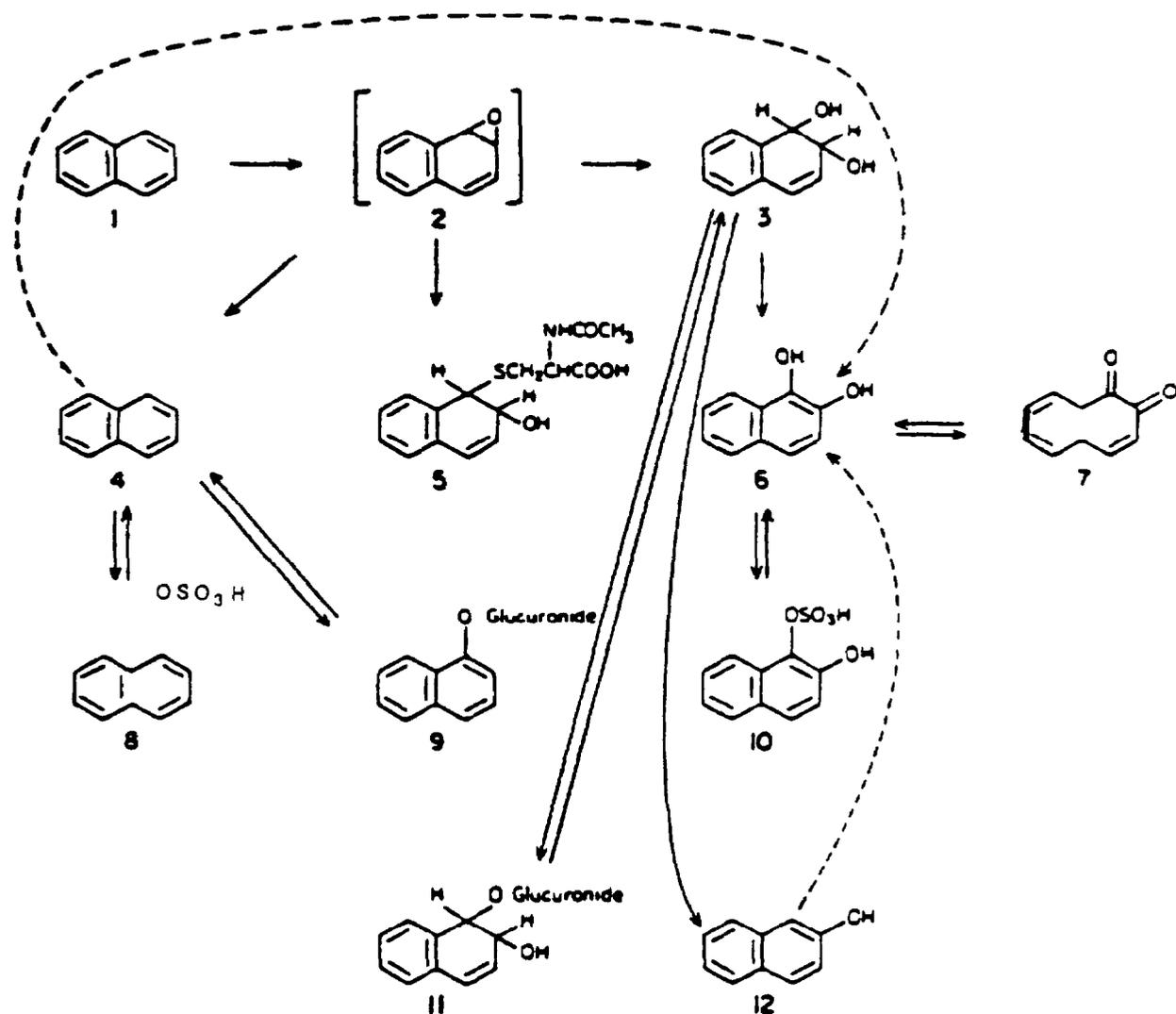


FIGURE 1

Metabolism of Naphthalene. (1) Naphthalene; (2) naphthalene epoxide; (3) 1,2-dihydro-1,2-dihydroxynaphthalene (naphthalene diol); (4) 1-naphthol; (5) N-acetyl-S-(1,2-dihydro-2-hydroxynaphthyl) cysteine; (6) 1,2-dihydroxynaphthalene; (7) 1,2-naphthoquinone (*β*-naphthoquinone); (8) 1-naphthyl sulphate; (9) 1-naphthyl glucuronide; (10) 2-hydroxy-1-naphthyl sulphate; (11) 1-glucosiduronide of (3); (12) 2-naphthol.

Source: Van Heyningen, 1979

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).

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 acidic 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

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 naphthalene	2	3,4	5
1,2-dihydro-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-L-naphthyl)-L-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-naphthyl)-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
2-Jerina, et al. 1970 5-Roubal, et al. 1978
3-Boylard, et al. 1961

TABLE 4

Naphthalene Metabolites: Kidney/Urine

Metabolite	Found in:				
	Rabbit	Guinea Pig	Mice	Rat	Man
1-naphthol	1,2	7	7	7	8
2-naphthol	1	7	7	7	8
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-naphthyl)-L-cysteine	1	1	1	1,3	
2-hydroxy-1-naphthyl sulfate	1				
1-hydroxy-2-naphthyl sulfate	2				
1,2-dihydroxynaphthalene		7			
1,2-naphthoquinone					8
1,4-naphthoquinone					8
References:	1- Boyland & Sims, 1958	4- Young, 1947	7- Corner & Young, 1954		
	2- Sims, 1959	5- Booth & Boyland, 1949	8- Mackell, et al. 1951		
	3- Booth, et al. 1960	6- Corner, et al. 1954			

1,2-naphthoquinone with the concomitant release of hydrogen peroxide. 1,2-Naphthoquinone 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-naphthoquinone is reduced by the reaction with ascorbic acid to 1,2-dihydroxynaphthalene, it oxidizes NADPH. The dihydroxide will rapidly reduce cytochrome c (Van Heyningen and Pirie, 1967). 1,2-Naphthoquinone 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 induction of this enzyme by 3-methylcholanthrene. A number of other naphthalene 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:

<u>Age (years)</u>	<u>Number of workers</u>	<u>Number with cataracts</u>
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 and its relationship to the cataractogenicity of naphthalene. Bourne (1937) was the first to note the disappearance of reduced glutathione from the lens. Rees and Pirie (1967) reported that the metabolites of naphthalene released in the eye were general metabolic and coenzyme inhibitors. Van Heyningen (1970) found that 1,2-dihydroxynaphthalene or 1,2-naphthoquinone 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; and that oxidized ascorbic acid easily enters the lens where it readily oxidizes reduced glutathione nonenzymatically. Van Heyningen and Pirie (1967) reported 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; and that 1,2-naphthoquinone quickly combines irreversibly with lens and eye proteins thereby losing its ability to oxidize ascorbic acid. Pirie (1968) observed 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.

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 NADP 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 6 g of 2-naphthol per 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, Subacute, 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 1,530 mg/kg and 420 mg/kg in single doses with a resultant drop in hemoglobin by 33 percent and 29 percent, respectively.

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 67.4 mg/kg. Mice in the higher dosage groups developed necrosis of secretory nonciliated bronchiolar

TABLE 5
Tests of the Acute Toxicity of Naphthalene

Test Animal	Number	Route	LD ₅₀ (mg/kg)	Reference
Mice	--	Subcut.	5,100	Irie, et al. 1973
Sherman rats				
male	40	Oral ^a	2,200	Gaines, 1969
female	40	Oral ^a	2,400	Gaines, 1969
male	10	Skin ^b	2,500	Gaines, 1969
female	10	Skin ^b	2,500	Gaines, 1969
Rat	--	Oral	1,780	NIOSH, 1977
Rat	--	Oral	9,430	Union Carbide Corp., 1968
Rat	--	Inhalation	100 ppm x 8 hr.	Union Carbide Corp., 1968

^a Dissolved in peanut oil
^b Dissolved in xylene

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 tumor BP8 cells in vitro 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-naphthoquinone, and 1,4-naphthoquinone produced no hemolysis at 15 minutes after the injection; 1-naphthol, however, produced 6 percent

TABLE 6

In vitro Hemolysis of Red Blood Cells Exposed to Naphthalene and its Metabolites*

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

*Source: Mackell, et al., 1951

and 9 percent hemolysis at the two higher dosages. Zinkham and Childs (1958) performed similar in vitro experiments with the same metabolites but measured a 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.

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 2 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 10 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/or 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 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 paradichlorobenzene. It was estimated that she was exposed to near 1,400 ppm of paradichlorobenzene and 184 ppm of naphthalene. 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 control 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 5 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.

TABLE 7

Mutagenicity of Naphthalene in Various In Vitro Microsomal Assay Systems

System	Strain	Result	Reference
Rat microsomes/ <u>Salmonella typhimurium</u>	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/ <u>Salmonella typhimurium</u> ^b	G46	Negative	Kraemer, et al. 1974
Mouse microsome/ <u>E. coli</u>	K12	Negative	Kraemer, et al. 1974

^aLess than 0.09 revertants/nmol. Tested at 10, 100, 500, and 1000 µg/plate

^bNaphthalene-1,2-oxide used in the test system

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}

Treatment	Number of Animals				Other Malignant Tumor
	Total	Survivors	Lymphosarcoma	Fibroadenoma	
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

*Source: Knake, 1956

^a34 naphthalene/sesame oil treated rats survived the initial treatment. 32 rats treated with sesame oil alone survived the initial 14 weeks of treatment.

^b3.3 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*

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

*Source: Knake, 1956

^a All lymphocytic leukemia

Druckrey 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 1,000 days. A second group of 10 rats was given a total dose of 0.82 gm of naphthalene per rat subcutaneously and followed for a similar period of time. No tumors were noted in either group.

Boyland, et al. (1964) found a 4 percent incidence of bladder carcinoma in mice with naphthalene implanted 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.

The investigations of Schmeltz, et al. (1978) have indicated the di-, tri-, and tetramethyl naphthalenes, common contaminants of coal tar naphthalene, all show cocarcinogenic activity when applied by painting to mouse skin in conjunction with benzo(a)pyrene. Pure naphthalene did not show cocarcinogenic activity when tested in

TABLE 10

Bladder Tumors in Mice with Naphthalene Bladder Implants*

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

*Source: Boyland, et al., 1964

this manner. The alkyl-naphthalenes which had shown positive activity in combination with benzo(a)pyrene for mouse skin tumors were shown to accelerate in vitro metabolism of benzo(a)pyrene by 3-methylcholanthrene induced liver homogenates, while naphthalene produced an inhibition of this in vitro liver metabolizing activity.

Takizawa (1940) painted the skin of mice with a metabolite of naphthalene, 1,4-naphthoquinone. 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 1.0 g/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 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 mg/l (Table 11).

TABLE 11

Carcinogenic Activity of Naphthalene with In Vitro Test Systems

Test System	Dose ($\mu\text{g}/\text{l}$) ^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

Tonelli, et al. (1979) tested naphthalene in a marine mammary gland organ culture system, and were unable to demonstrate cell transformation at compound levels up to 1,000 mg/l of culture medium.

CRITERION FORMULATION

Existing Guidelines and Standards

The only existing U.S. standard for naphthalene is the Occupational Safety and Health Administration (OSHA) standard of 10 ppm (50 mg/m³) as a time-weighted average (39 FR 23540). 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 (1978) also suggests a maximum 15 minute exposure value of 15 ppm (75 mg/m³).

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 0.35 ng/m³ in an urban area and 0.06 ng/m³ in a small town (Krstulovic, et al. 1977). Industrial exposures can be as high as 1,100 mg/m³ for naphthalene-using industries (Robbins, 1951), with exposures up to 1.12 mg/m³ for coke oven workers (Bjørseth, et al. 1978a), and 0.31 mg/m³ 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 glucose-6-phosphate dehydrogenase (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 moderately to severely reduced glutathione levels in blood samples incubated with acetylphenylhydrazine. This effect was 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-naphthoquinone.

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 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.

TABLE 12

Frequency of G6PD Deficiency in Populations*

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	≥ 50

*Source: Wintrobe, et al., 1974

Basis and Derivation of Criteria

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 10 percent or more unidentified impurities. Furthermore, a known experimental carcinogen, carbol-fuchsin, 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 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 equivalent exposures to water containing naphthalene 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.

Because of the above deficiencies as well as deficiencies in the other toxicity studies on naphthalene, a criterion cannot be derived. Because of the potential cocarcinogenicity of this compound, it should be regarded with concern and an effort should be made to generate adequate toxicity data on which a criterion could be based.

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