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Summary Review of Health Effects Associated with Naphthalene

Health Issue Assessment

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Preface

The Office of Health and Environmental Assessment has prepared this summary health assessment to serve as a source document for EPA use. The summary health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of naphthalene as a hazardous air pollutant.

In the development of the summary health assessment document, the scientific literature has been inventoried through October, 1987, key studies have been evaluated, and summary/conclusions have been prepared so that the chemicals' toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, a considerable effort will be undertaken to obtain appropriate information regarding sources, emissions, and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

Abstract

Naphthalene, a white crystalline solid that is nearly insoluble in water, is released into ambient air via industrial gaseous and particulate emissions, tobacco use, and through consumer use. Naphthalene is the principal ingredient of mothballs.

The data base concerning exposure of humans via inhalation and associated health effects is virtually nonexistent. Human data consist principally of accidental overexposure and occupational case reports. Overexposure often results in acute hemolytic anemia and has been associated with cataract formation. There are no available dose-response data.

In laboratory animals, two principal target tissues have been identified: nonciliated bronchiolar epithelial (Clara) cells and eye tissue. Effects on Clara cells appear to correlate with the degree of covalent binding of reactive metabolites. The absence of such effects in some studies suggest that strain and/or exposure variables may play a role. The metabolite(s) that is responsible for Clara cell damage is unknown. There are no published studies involving inhalation exposure.

Administration of naphthalene by routes other than inhalation has been shown to produce cataracts in rats, rabbits, and one mouse strain. Animal strains with pigmented eyes develop cataracts faster and more severely than albino strains. The likely causative agent is polyphenol oxidase, found only in pigmented eyes, that catalyzes the formation of 1,2-naphthoquinone which binds to lens tissue.

Only a limited number of mutagenicity studies have been conducted. Negative results have been reported for gene mutations (*Salmonella*), unscheduled DNA synthesis in rat hepatocytes and micronuclei in mouse bone marrow. Limited teratology studies in rats and rabbits reported no gross abnormalities. In a single dose (300 mg/kg) study in mice, both maternal and fetal toxicity were reported.

The effects of chronic inhalation exposure of mice to 10 and 30 ppm have been examined in a lifetime study by the National Toxicology Program. Results are not expected to be published until the latter part of 1988. This study should provide for a more definitive judgment of the toxicologic and carcinogenic potential of naphthalene..

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1. Summary

Naphthalene is a white, aromatic crystalline solid that is nearly insoluble in water. It can be released to ambient air via industrial gaseous and particulate emissions, aqueous wastestreams, tobacco use, and through consumer use into indoor environments.

Measurements of its concentration in ambient air are limited. One U.S. EPA report indicated levels are in the range of 0.03 to 0.10 ng/m^3. Levels are known to be considerably higher (in the low ppb range) in the vicinity of industrial sources of naphthalene. In air, naphthalene is subjected to photochemical degradation. During sunlight hours, naphthalene reacts with hydroxyl radicals and has a half-life of 8 hours. During darkness, naphthalene has an estimated half-life of 15 hours as a result of reaction with nitrate radicals. Thus, naphthalene is not expected to be persistent in the atmosphere. In water, naphthalene levels are generally no higher than 2 µg/L. It is subject to degradation by microorganisms and is known to sorb to particulates in aqueous environments.

The data base concerning naphthalene exposure of humans via ambient air and associated health effects is virtually nonexistent. Human data consist principally of accidental overexposure and occupational case reports. In these instances of human overexposure, acute hemolytic anemia has been a frequent finding and there is suggestive evidence that overexposure is associated with cataract formation. One factor identified as increasing risk for hemolytic anemia is glucose-6-phosphate dehydrogenase deficiency. Exfoliative dermatitis also can result upon direct contact with naphthalene. There are no available dose-response data.

Dose-response information relating naphthalene to adverse health effects has been derived principally from limited laboratory animal experimentation. Data available from inhalation exposures are minimal.

Two principal target tissues have been identified: nonciliated bronchiolar epithelial cells (Clara cells) and eye tissue. In mice, single intraperitoneal injections result in a dose-dependent necrosis of Clara cells. The extent and severity of this lesion appears to correlate with the degree of covalent binding of reactive metabolites of naphthalene in the lung. The nature of the reactive metabolite(s) and its source (whether the Clara cell or liver) have not been identified. While naphthols have been identified as being partially responsible for covalent binding observed in Clara cells, they have not been demonstrated to be a causal factor in producing pulmonary necrosis. The absence of such lesions in other mouse studies, including subchronic studies, suggests strain or exposure variables may play a role. The data base for other species (e.g., rat, rabbit, and hamster) is limited but there are indications that the mouse is the most sensitive species tested. Hepatic and renal necrosis has not been observed in the mouse.

There are an extensive number of metabolites (>30) that have been identified in the rat and mouse. The metabolic profile differs between these species. In limited studies with humans, only 1- and 2-naphthol have been conclusively identified. Most metabolites excreted in the urine are conjugates

of glucuronides or mercapturic acids. The metabolic profile between rodents and primates suggests interspecies differences. In rodents, conjugation of naphthalene with glutathione (GSH) appears to be the principal mechanism of excretion. In primates, conjugation with GSH may not represent a major metabolic pathway. It is not known whether this metabolic difference is significant in eliciting differences in adverse responses between the species. The metabolism of naphthalene in primates has been studied only with acute oral exposure. Information from oral studies suggests that reactive metabolites are produced in a stereoselective manner in the liver and have a sufficiently long half-life that enables them to reach the lung and eye, resulting in damage.

The acute oral LD_{50} values for mice and rats indicate that naphthalene is not particularly toxic. For mice, LD_{50} values are in the range of 500 to 700 mg/kg while for rats, the range is 2,009 to 3,310 mg/kg. It is not known what the comparable inhalation LC_{50} values are.

Administration of naphthalene by routes other than inhalation has been shown to produce cataracts in rats, rabbits, and one mouse strain. In rats, eye pigmentation is an important factor in cataract formation. Pigmented strains develop cataracts faster and more severely than albino strains. A likely causative factor is the occurrence of polyphenol oxidase, found only in pigmented tissue, that catalyzes formation of 1,2-naphthoquinone from 1,2-dihydroxynaphthalene. 1,2-naphthoquinone is known to bind to lens tissue. In rabbits, depletion of antioxidants is believed to be the critical step because the reserve of antioxidants is considerably less than in rats. Cataract formation and other damage to the eye have been reported in C57BL/6J mice in feeding experiments.

In inhalation exposures, some naphthalene is likely to enter the systemic circulation. In this event, metabolism by the liver may result in the formation of reactive metabolites similar to those identified in non-inhalation studies and associated with pulmonary cell damage and cataract formation. However, there are insufficient dose-response and pharmacokinetic data to estimate likely effect levels via the inhalation route.

Naphthalene was found to cause a statistically significant increase ($p < 0.05$) in the number of adenomas per tumor-bearing mouse lung but not in the number of adenomas per mouse in female A/J strain mice after 6 months of inhalation exposure. These results are inconclusive with regard to the carcinogenic potential of naphthalene. Effects of chronic exposure of mice (to 10 and 30 ppm naphthalene) have been examined in a 2-year inhalation study by the National Toxicology Program. Results have not yet been published. This study should provide information with which one can evaluate the carcinogenic potential of naphthalene. According to U.S. Environmental Protection Agency Guidelines for Carcinogen Risk Assessment, naphthalene is classified as a Group D carcinogen. The evidence is inadequate to evaluate the carcinogenic potential of naphthalene for man.

Only a limited number of mutagenicity studies have been conducted with naphthalene. Negative results have been reported for gene mutations in *Salmonella*, unscheduled DNA synthesis in rat hepatocytes, and micronuclei in mouse bone marrow.

In a single dose (300 mg/kg) teratology study in mice, both maternal and fetal toxicity were reported. Limited teratology studies in rats and rabbits reported no gross abnormalities from naphthalene exposure.

A more definitive judgment of the impact of naphthalene exposure via ambient air on human health can only be made after completion of the National Toxicology Program (NTP) chronic bioassay and additional studies

on selected biological endpoints. A reassessment of naphthalene effects associated with inhalation exposure should be carried out once the NTP results become available.

2. Background Information

2.1 Chemical Characterization

Naphthalene (CAS No. 91-20-3) has the empirical formula $C_{10}H_8$. It is a white, crystalline solid with a molecular weight of 128.16. Naphthalene is practically insoluble in water (30 mg/L) and has a low vapor pressure (1 mm Hg at 52.6°C) (Toxicology Data Bank). At 25°C, 1 part per million = 5.2 mg/m^3.

Domestic production capacity of naphthalene was estimated to be 660 million pounds annually as of January 1, 1984. Six manufacturers produce the compound at nine plant sites as shown in Table 2-1 (SRI International, 1984). Naphthalene is recovered from coal-tar feedstocks (coal-tar naphthalene), accounting for about 60 percent of production, and from aromatic petroleum refinery streams (petronaphthalene), accounting for the remaining 40 percent (Chemical Economics Handbook, 1981).

Total domestic consumption of naphthalene for 1985 has been estimated to be 540 million pounds; this amount includes imports of 8 million pounds. Exportation volumes are believed to be in the range of 5 million pounds annually. Major captive and merchant applications of naphthalene include use as an intermediate in the production of phthalic anhydride (55 percent of consumption), the insecticide carbaryl (20 percent), beta-naphthol (8 percent), synthetic tanning agents (6 percent), surfactants (5 percent), miscellaneous organic intermediates (2 percent), and use as a moth repellant (2 percent) (Chemical Economics Handbook, 1981).

2.2 Environmental Release and Exposure

Naphthalene is released into the environment via industrial gaseous and particulate emissions, aqueous waste streams, and through consumer uses. The compound has been detected in aerosols from a coal gasification plant (Williams et al., 1982), gaseous emissions from aluminum manufacturing (Hung and Bernier, 1983), rendering plant emissions (Van Langenhove et al., 1982), spent pulp bleaching liquor (Kringstad et al., 1984), and wastewater from oil and gas fields (Middleditch, 1982). Oil spills are another important source of naphthalene release into the aquatic environment (U.S. EPA, 1980). The compound is also released into the atmosphere via the combustion gases of coal-fired boilers (Warman, 1983), residential wood stoves (Jaasma and Pierce, 1983), chain-saw engines (Levin et al., 1984), automobile exhaust (Hampton et al, 1983), cigarettes U.S. EPA, 1980; Schmeltz et al., 1976; Brinkman et al., 1984), landfill gas (Zimmerman et al., 1983) and mothballs (Brinkman et al., 1984).

Naphthalene has been detected in industrial effluents at concentrations up to 32 mg/L, municipal wastewater treatment plant effluents at 22 µg/L, ambient river water at 2.0 µg/L, seawater, drinking water at 1.4 µg/L, well water, and ground water (U.S. EPA, 1980; Shackelford and Keith, 1976; Eganhouse and Kaplan, 1982; Desideri et al., 1984). Stuermer et al. (1982) detected naphthalene in groundwater samples collected near underground

Table 2-1. Current Domestic Manufacturers of Naphthalene and Their Production Capacities (million pounds)

Manufacturer	Annual Capacity
Allied Corporation, Allied Chemical, Ironton, OH	75[d]
Ashland Oil, Inc., Ashland Chemical Company Division, Petrochemicals Division, Catlettsburg, KY	90[a]
E.I. du Pont de Nemours & Company, Inc., Conoco Inc., subsidiary, Conoco Chemicals Company Division, Chocolate Bayou, TX	90[b]
Getty Oil Company, Getty Refining and Marketing Company, subsidiary, Delaware City, DE	60[a]
Koppers Company, Inc., Organic Materials Group, Cicero, IL Follansbee, WV Fontana, CA	190[c]
United States Steel Corporation, USS Chemicals Division, Clairton, PA Gary, IN	155[d]
Total	660

[a]From petroleum; naphthalene is sold on the merchant market.
[b]From petroleum (ethylene coproduct); naphthalene is used used captively.
[c]From coal tar; naphthalene is used captively and sold on the merchant market.
[d]From coal tar; naphthalene is used captively.
Source: SRI International (1984)

coal gasification sites at concentrations of 380 to 1,800 ppb 15 months after gasification activity had ended. Pankow et al. (1984) reported mean dissolved naphthalene concentrations of 11 and 72 ng/L in rainwater samples collected in semirural and residential locations, respectively, in Oregon.

Naphthalene was detected in ambient air samples collected in Denver, CO (Hutte et al., 1984), and near abandoned chemical waste dumps (Durchin and Pendleton, 1983). In 1977, ambient air concentrations were reported to range from 0.03 to 0.10 ng/m^3 (for vapor) and 0.003 to 0.25 ng/m^3 (for particulates) (U.S. EPA, 1980). In a field study of mobile homes, Connor et al. (1985) reported naphthalene levels have been 0.3 and 11.8 ppb. Naphthalene has also been detected in fly-ash samples from municipal waste incinerators in Canada and Norway at concentrations of 130 to 760 ng/g (Viau et al., 1984). The compound has been found to be adsorbed to the particulate matter emitted in diesel engine exhaust; Yergey et al. (1982) determined an average emission rate of 329 µg/g of particle.

Estimates of occupational exposures to naphthalene have been reported in industrial hygiene surveys performed by the National Institute for Occupational Safety and Health (NIOSH). According to the National

Occupational Hazard Survey (NOHS), 121,977 workers were potentially exposed to naphthalene in domestic workplace environments in 1970. Preliminary data for 1980 in the National Occupational Exposure Survey (NOES) indicate that 10,047 workers, including 1,535 women, were exposed to the compound.

The Occupational Safety and Health Administration (OSHA, 1983) established an 8-hour time-weighted average (TWA) permissible exposure limit of 10 ppm (50 mg/m3) for naphthalene; the American Conference of Governmental Industrial Hygienists (ACGIH, 1984) recommended an 8-hour TWA threshold limit value (TLV) of 10 ppm and a 15-minute short-term exposure limit-TLV of 15 ppm (75 mg/m^3).

Van Langenhove et al. (1982) detected naphthalene in the workplace atmosphere of a rendering plant. Bjorseth et al. (1978a) reported naphthalene vapor concentrations of 0.7 to 60 ppb (4 to 311 µg/m^3) in atmospheric samples and 0.01 to 0.7 ppb (0.09 to 4 µg/m^3) (as particulates) in personal samples taken at an aluminum reduction plant. Atmospheric samples at a coke plant showed mean naphthalene concentrations of 0.2 ppb (1.2 µg/m^3) (particulates) and 125 ppb (646 to 653 µg/m^3) (gaseous) (Bjorseth et al., 1978b). In a 1951 study, naphthalene vapor concentrations up to 230 ppm (1.2 µg/m^3) were reported in workplace atmospheres where molten naphthalene was used (U.S. EPA, 1980).

A 1977 report (U.S. EPA, 1980) listed groups of workers that were among those having potential exposure to naphthalene. These workers were involved in the use or manufacture of beta naphthol, celluloid, coal tar, dye chemicals, fungicides, hydronaphthalene, lampblack, moth repellants, phthalic anhydride, smokeless powder, tannery products, textile chemicals, and aluminum reduction.

Gas chromatography (GC) coupled with mass spectrometry (MS) is the method most commonly used to characterize naphthalene in environmental media and workplace atmospheres; flame ionization detection has been used in conjunction with GC/MS to obtain quantitative concentration data (Pankow et al., 1984; Tong et al., 1984; Viau et al., 1984; Stuermer et al., 1982; Yergey et al., 1982; Bjorseth et al., 1978a).

2.3 Environmental Fate and Effects

Naphthalene is expected to be released into the atmosphere from sources that include petroleum fuel combustion (Biermann et al., 1985) and mothball sublimation. In the atmosphere, the compound exists predominantly in the vapor phase, as compared to being bound to particulates (Biermann et al., 1985). It is subject to various photo-oxidative or oxidative reactions.

Several recent articles suggest that naphthalene may be subject to hydroxyl (OH) radical attack during the daytime and to nitrate (NO_3) radical attack at night (Biermann et al., 1985; Atkinson et al., 1984). Biermann et al. found that naphthalene reacts rapidly with OH radicals at room temperature; they determined a rate constant of 2.35×10^{-11} cm^3/mol-sec, which gives a daytime half-life of approximately 8 hours (lifetime of 12 hours), assuming an atmospheric OH radical concentration of 1×10^6 mol/cm^3. Atkinson et al. presumably provided the first direct evidence for the gas phase reaction of NO_3 radicals with naphthalene and determined a rate constant of 6.4×10^{-15} cm^3/mol-sec. Recent evidence suggests that NO_3 radicals may be a common constituent of nighttime air over many U.S. continental areas, with maximum concentrations in excess of 10 ppt and probably close to 100 ppt in populated areas (Platt et al., 1984). Assuming an atmospheric NO_3 radical

concentration of 80 ppt, the nighttime half-life for naphthalene is approximately 15 hours.

Atkinson et al. (1987) observed that gas-phase reactions of naphthalene with OH radicals in the presence of nitrogen oxides resulted in the production of 1- and 2-nitronaphthalenes and 1- and 2-naphthols. Nitronaphthalenes have been detected in ambient air (Arey et al., 1987).

The mechanisms and products of these reactions have not been fully elucidated. These reactions are likely to proceed via initial radical addition to the aromatic ring, but subsequent reaction mechanisms and products under atmospheric conditions are not known (Biermann et al., 1985; Atkinson et al., 1984). For the OH radical, analogies can be made with monocyclic hydrocarbons. Initially, the aromatic ring would stay intact, with products such as hydroxynaphthalene and nitronaphthalene expected to form. However, it is possible that the aromatic ring could cleave, leading to products such as dibenzaldehyde (Biermann et al., 1985).

Naphthalene is expected to enter the aqueous environment from both natural and anthropogenic sources (U.S. EPA, 1979). The initial fate of the compound is determined by three competing physical processes: sorption to particulates, evaporation, and water solubility. Sorption to organic matter is linearly related to the log octanol/water partition coefficient for naphthalene concentrations up to 60 to 70 percent of its water solubility (30 mg/L), whereas increased sorption occurs at higher concentrations (Karickhoff et al., 1979). Given naphthalene's log octanol/water partition coefficient of 3.37, adsorption to particulates would seem to be moderately strong; however, at low naphthalene concentrations, this may not be true. At a concentration of 25 µg/L, Lee et al. (1978) found that only 2 percent of naphthalene bound to suspended particulates in seawater following a 3-hour incubation period. No data on the organic content or the concentrations of the particulates in the seawater were reported.

Southworth (1979) calculated volatilization rates of naphthalene from a model stream with a depth of 1.0 m. The half-life for volatilization varied from about 80 hours for a stream with a velocity of 0.1 m/sec and a wind velocity of 0.25 m/sec, to about 3 hours for a stream with a velocity of 1.0 m/sec and a wind velocity of 4 m/sec. He concluded that the rate of volatilization would be low in relatively deep, slow-moving rivers but that it may be competitive with other removal processes such as adsorption in clear, rapidly flowing shallow streams.

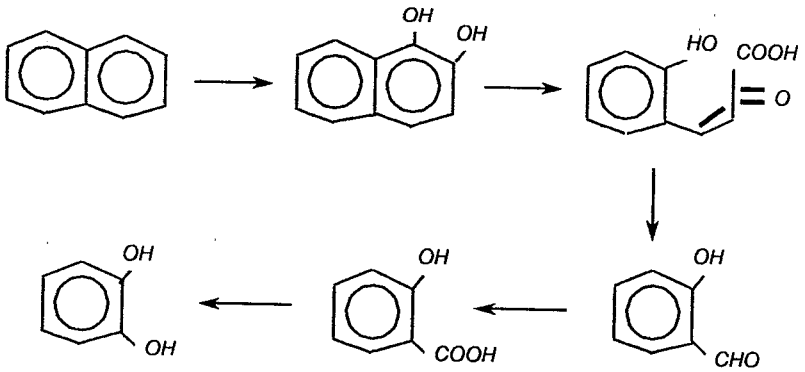
Lee and Anderson (1977) studied the fate of naphthalene in a model ecosystem. When 2 g of naphthalene were added to the ecosystem to make a concentration of 34 µg/L, 220 mg were detected in the sediment after 4 days. Thus, about 11 percent of the naphthalene settled to the sediment, approximately 44 percent remained in the water column, and the remaining 45 percent was unaccounted for. The naphthalene may have evaporated, photo-oxidized, or adsorbed to the sides of the container, but the authors suggested that biodegradation played the major role.

A laboratory method for measuring the volatilization rate of naphthalene and other low volatility chemicals from water has been described by Smith et al. (1981). The use of XAD-2 resin as an adsorbent for trace quantities of naphthalene in water was described by Wigilius et al. (1987).

Many microorganisms found in the environment are capable of degrading naphthalene. These include algae (Cerniglia et al., 1979), fungi (Cerniglia et al., 1978), and bacteria (Gibson, 1972; Davies and Evans, 1964). In addition, treatment of wastewater effluents has been shown to effectively degrade naphthalene (Tabak et al., 1981; Malaney et al., 1967). At concentrations of 5

and 10 mg/L, complete primary degradation of naphthalene was observed in a 7-day static culture test with domestic wastewater used as an inoculum (Tabak et al., 1981). Biodegradation of naphthalene to CO_2 has been demonstrated with bacteria in an activated sludge system where 2,500 mg/L of naphthalene had a 6-day biochemical oxygen demand ranging from 32.8 to 64.2 percent of the theoretical oxygen demand (Malaney et al., 1967). Lee and Anderson (1977) determined the biodegradation rates of naphthalene by microorganisms present in marine water at depths of 5 to 10 m. These samples were fortified with ^{14}C-naphthalene at a concentration of 50 µg/L and incubated for 3 days. Rapid adaptation to naphthalene as a carbon source was observed; the degradation rates changed from 0.1 µg/L/day on day 1 to 3.3 µg/L/day on day 3. Under anaerobic conditions, however, biodegradation of naphthalene is not likely. Delaune et al. (1980) found that naphthalene does not biodegrade under anaerobic conditions that are prevalent at depths below 2 cm in sediments.

Some of the microbial biodegradative pathways of naphthalene have been elucidated. For pseudomonads and most other bacteria, naphthalene is broken down to catechol as shown below.



Catechol is further degraded by these microorganisms to CO_2 and H_2O, although the metabolic pathways vary among differing species (Barnsley, 1976). For these bacteria, the initial metabolite of naphthalene is *cis*-1,2-dihydro-1,2-dihydroxynaphthalene, in contrast to naphthalene-1,2-oxide, which is thought to be the initial metabolite for fungi, eukaryotes, and other bacteria (Cerniglia et al., 1984). This arene oxide is very unstable and can undergo other reactions, predominantly to 1-naphthol. It rearranges, probably nonenzymatically, to 1-naphthol; some 2-naphthol is also formed. The oxide also will react nonenzymatically or enzymatically with water to form

1,2-dihydroxy-1,2-dihydronaphthalene with glutathione to form the glutathione analog of the dihydrodiol.

3. Metabolism

3.1 Pharmacokinetics and Metabolism

With the exception of one study (Mackell et al., 1951), there is no information concerning the metabolism of naphthalene in man. There are, however, a number of studies that have investigated the *in vitro* and *in vivo* metabolism of naphthalene pertinent to laboratory animals, particularly the rabbit and rat. These data, coupled with limited information from subhuman primates, appear sufficient to enable one to draw relevant conclusions for man.

3.1.1 Absorption

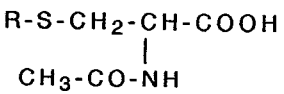
The few case reports available in the literature suggest that ingestion of naphthalene results in absorption and subsequent acute toxicity (Gidron and Leurer, 1956; Chusid and Fried, 1955; Mackell et al., 1951; Zuelzer and Apt, 1949). A recent case report identified naphthalene ingestion as the cause of death (Ijiri et al., 1987). Dermal absorption also is likely based on the reports by Dawson et al. (1958), Cock (1957), and Schafer (1951). Only one inhalation case report associated with toxicity has been identified (Valaes et al., 1963).

Bock et al. (1979) studied the absorption and metabolism of naphthalene in the rat jejunum *in situ*. ^{14}C-naphthalene was injected into the isolated intestinal loop, and the concentrations of naphthalene and its metabolites in the lumen and portal blood were determined after a 30-minute incubation. Naphthalene was rapidly absorbed and found mostly unchanged (about 84 percent of the dose) in portal blood. The major ether-soluble metabolites were identified as naphthalene-1,2-dihydrodiol and 1-naphthol. Conjugates comprised about 40 percent of the metabolites and were mostly glucuronides of the dihydrodiol and 1-naphthol. This study indicates that metabolism can occur prior to first-pass through the liver.

3.1.2 In Vivo Metabolism

3.1.2.1 Oral Administration

Recently, Bakke et al. (1985) studied the metabolism of ^{14}C-naphthalene in male Sprague-Dawley rats in an effort to determine the catabolism of premercapturic acid pathway metabolites of naphthalene to naphthols and methylthio-containing metabolites. Mercapturic acids are n-acetyl cysteinyl thioethers of the form:



R represents an aryl radical.

^{14}C-naphthalene (2 mg/0.5 µCi in 0.5 ml ethanol) was administered orally to two groups of control rats, 4 groups of bile duct-cannulated rats and

to 4 germ-free rats (2 mg/1.0 μCi). Bile, urine, and feces from control and cannulated rats were collected for 72 hr (urine and bile samples from each group were separately pooled for metabolite identification). In control rats, the recovered dose in urine was 77 to 93 percent and 6 to 7 percent in feces; in cannulated rats, urine represented 25 to 43 percent while bile represented 49 to 76 percent (feces contained < 1 percent).

Urinary naphthols and naphthol glucuronides represented 4.6 percent of the dose administered (methylthioglucuronide also represented 4.6 percent) in control rats. In contrast, bile and urine from cannulated rats and urine from germ-free rats contained no labeled methylthio derivative and only trace amounts of labeled naphthols or conjugates. The principal metabolites in control urine were identified as 1,2-dihydro-1-hydroxy-2-S-(N-acetyl) cysteinyl naphthalene (38 percent) and 1,2-dihydro-1,2-dihydroxynaphthalene glucuronide (24 percent). In germ-free rats, the major urinary metabolite was 1,2-dihydro-1-hydroxyl-2-S(N-acetyl)-cysteinyl ^{14}C-naphthalene (89 percent). Identified metabolites are shown in Table 3-1.

Figure 3-1 highlights the proposed *in vitro* and *in vivo* pathways, with a focus on the pre-mercapturic acid pathway. As shown in Figure 3-1, it is likely that naphthol formation in rats is derived from pre-mercapturic acid metabolites, possibly from the action of intestinal microflora. Oral administrations of compounds I or II to control rats resulted in the formation of both naphthols and the methylthio derivatives; elimination of acid hydrolysis in the stomach as a mechanism was confirmed when compounds I and II were injected intracecally. Both naphthol and methylthio derivative increased significantly above oral values.

Rozman et al. (1982) determined the urinary, fecal, and biliary excretion of thioethers and hepatic GSH content (by liver biopsy) in rhesus monkeys following administration of a single oral dose of naphthalene (in sesame oil) at 0, 30, 75, or 200 mg/kg. Naphthalene had no significant effect on the urinary and fecal excretion of thioethers or the hepatic GSH content. Bile excretion of thioethers increased from 6.4 to 14.6 μmol/kg/24 hours, but the amount corresponded to only 0.5 percent of the administered dose. Bakke et al. (1985) found that methylthio derivatives were about 5 percent of administered dose to rats. The data of Rozman et al. (1982) suggest that naphthalene conjugation with GSH is apparently not a major metabolic pathway in rhesus monkeys. Similarly, a single dose of naphthalene in sesame or corn oil at 200 mg/kg did not increase the urinary excretion of mercapturic acids in four chimpanzees (Summer et al., 1979). However when SPF Wister rats were administered naphthalene (0, 30, 75 or 200 mg/kg), up to 39 percent of the dose (30 mg/kg) was excreted in the urine as mercapturic acids (Summer et al., 1979).

There were no GSH conjugates of naphthalene in the bile and only trace amounts were found in the urine of humans receiving a single oral dose of 0.5 g naphthalene (Boyland and Sims, 1958). These data are consistent with the hypothesis that primates do not conjugate naphthalene with GSH to the extent that rodents do (Rozman et al., 1982; Summer et al., 1979), possibly because of a slow rate of naphthalene-epoxide formation or a higher epoxide hydrolase activity in primates (Rozman et al., 1982). Increased epoxide hydrolase activity would result in increased formation of naphthols at the expense of mercapturic acids. Lower activities of GSH transferases in primates, as suggested by the studies of Chasseaud (1973), also may be an additional factor. It also is known that a variety of isozymes of GSH transferases exist and which may differ among species (Ketterer, 1986).

Table 3-1. Metabolism of [^{14}C]Naphthalene in Control and Bile-Duct-Cannulated Rates

Metabolite(s)	% of ^{14}C dose		
	Control	Bile duct cannulated	
	Urine	Urine	Bile
1,2-Dihydro-1-hydroxy-2-S-cysteinyl-naphthalene (I)*	---	---	16.9
1,2-Dihydro-1-hydroxy-2-S-(N-acetyl) cysteinylnaphthalene (II)*	38.1	14.1	0.7
1,2-Dihydro-1-hydroxy-2-S-cysteinylglycine-naphthalene*	---	---	9.6
Dihydroxynaphthalene	4.9	1.5	---
Dihydrodihydroxylnaphthalene	---	---	6.4
1,2-Dihydro-1,2-dihydroxynaphthalene glucuronide(III)	23.9	14.5	26.8
1,2-Dihydro-1-hydroxy-2-methylthionaphthalene glucuronide*	4.6	---	---
Naphthols	1.6	---	---
Naphthol glucuronides	3.0	---	---
Uncharacterized**	2.4	3.0(4)	6.0(5)

Urine from control rats and urine and bile from bile-duct-cannulated rats were collected for 24 hr after dosing; these contained 75.6, 29.9, and 66.8% of the ^{14}C dose, respectively. ---not detected (limit of detection was <0.5% of the ^{14}C dose).

**Assumed to have the 1,2-dihydro-1-hydroxy structure as deducted by Jeffery and Jerina (1975).*

***Numbers in parentheses indicate the number of chromatographic fractions.*

Source: Bakke (1985).

In a study by Corner and Young (1954) the comparative metabolism of naphthalene in male rabbits, male guinea pigs, hooded male rats, and male white mice was assessed by paper chromatographic identification of urinary metabolites. All animals were given a single dose of naphthalene in arachis oil at 500 mg/kg. Rabbits were dosed by stomach tube; guinea pigs and mice were dosed by intraperitoneal injection; and rats were dosed by both intraperitoneal injection and stomach tube. The same metabolites were found in the urine of rats dosed with naphthalene intraperitoneally or orally. All four species converted naphthalene to 1- and 2-naphthol, 1,2-dihydronaphthalene-1,2-diol, 1-naphthyl-sulfuric acid, and 1-naphthylmercapturic acid. In addition, rabbits and rats excreted 1-naphthylglucuronic acid and 1,2-dihydronapthalene-1,2-diol glucuronic acid; mice excreted 1-naphthylglucuronic acid; and guinea pigs excreted 1,2-dihydroxynaphthalene. Chromatographic analyses suggested

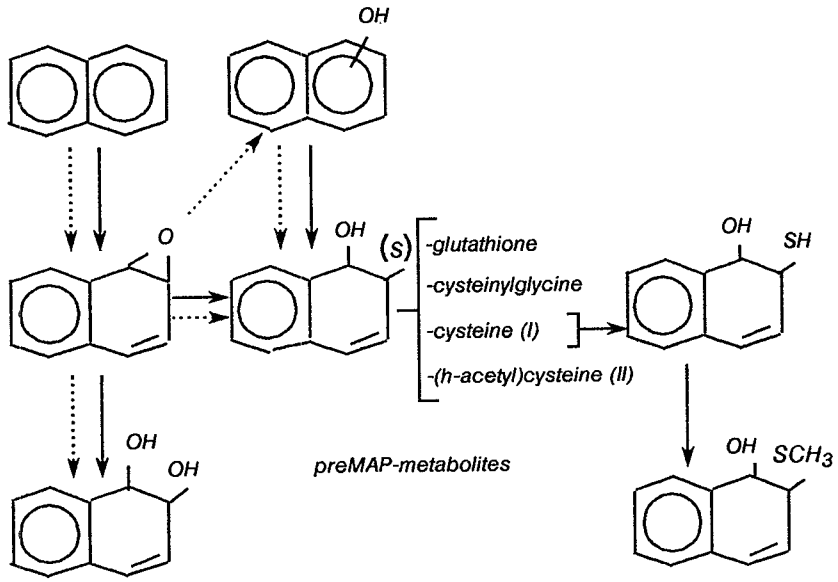


Figure 3-1 *Proposed* in vitro (·····➤) *and* in vivo (——➤) *pathways for the metabolism of naphthalene by rats.*
Source: Bakke et al. (1985).

interspecies difference in the amounts of 1- and 2-naphthol produced. Hooded rats were found to secrete glucuronic acid conjugates of both levo- and dextro-rotary forms of 1,2-dihydronaphthalene-1,2-diol. In rabbits, the glucuronic acid conjugate (Corner et al., 1954) was found. No evidence was found for the occurrence of the glucuronic acid conjugates in either guinea pigs or mice (Corner and Young, 1954).

Boyland and Sims (1958) detected 1-naphthyl-mercapturic acid in the acidified urine of rabbits dosed with naphthalene in arachis oil (5 ml of 20%, w/v). Acidification of urine also resulted in the concomitant production of naphthols and indications that N-acetylcysteine may have been formed. The precursor of 1-naphthylmercapturic acid was suggested to be N-acetyl-S-(1,2-dihydro-2-hydroxynaphthyl)-L-cysteine. Other species shown to form this precursor included both male and female rats, mouse, hamster, guinea pig, and man. Bourne and Young (1934) detected α-naphthylmercapturic acid in urine of rabbits administered naphthalene in warm paraffin.

In a study designed to elucidate the impaired metabolic step in an inherited disorder, Kodama et al. (1974) found high concentrations of cystine, N-monoacetylcystine, and S-(2-hydroxy-2-carboxyethylthio)cysteine in the urine of rabbits dosed orally with 3 g of naphthalene (approximately 1.2 g/kg) daily for 3 weeks.

3.1.2.2 Intraperitoneal Administration

In a study with female Sprague-Dawley rats, 24 and 60 percent of the 1-^{14}C-naphthalene dose (100 mg/kg) administered intraperitoneally was found in the urine 24 and 72 hours after dosing, respectively (Chen and Dorough, 1979). In addition, about 14 percent of the dose was found in the feces 72 hours after dosing. 1,2-Dihydro-1,2-dihydroxynaphthalene (naphthalene-1,2-dihydrodiol) and 1-naphthol were the major ether-extractable metabolites in the urine, accounting for about 6 percent of the administered dose. This is similar to the amount formed by control rats in the oral dosing study by Bakke et al. (1985). Four water-soluble radiolabeled metabolites were found in the urine of rats after 72 hours. These metabolites were tentatively identified as 1-naphthol, 1,2-dihydro-1,2-dihydroxy-1-naphthyl sulfate (most probably the 1,2-dihydro-2-hydroxy-1-naphthyl sulfate), N-acetyl-S-(1,2-dihydro-2-hydroxy-1-naphthyl)cysteine, (most probably N-acetyl-S-(1,2-dihydro-1-hydroxyl-2-naphthyl)cysteine or possibly N-acetyl-S-(2-naphthyl)cysteine), and 1,2-dihydro-2-hydroxy-1-naphthyl glucuronide, and accounted for 5.0, 8.0, 65.0, and 16.8 percent, respectively, of the total radiolabel found in the water-soluble fraction. It was concluded that in rats, glutathione (GSH) and mercapturic acid derivatives were the major conjugates in the metabolism of naphthalene.

Several studies were conducted on the metabolism of 1-^{14}C-naphthalene in male Sprague-Dawley rats following intraperitoneal injection at a dosage of 100 mg/kg in 0.5 ml corn oil (Horning et al., 1980a; Horning et al., 1980b; Stillwell et al., 1978). Of the administered radiolabeled dose, 20 to 30 and 3 to 11 percent was excreted in the urine in 0 to 24 and 24 to 48 hours, respectively. Unconjugated (neutral) and conjugated (acidic) metabolites accounted for 5 to 20 and 80 to 95 percent, respectively, of the total metabolites excreted in urine. Of the radioactivity excreted as conjugates, 20 to 40 percent was liberated after glucuronide and sulfate hydrolysis; the remainder was accounted for as mercapturic and premercapturic acids (Horning et al., 1980b). Twenty-one suggested metabolites were isolated and characterized by GC and GC/MS. The major metabolites were 1-naphthol, 2-naphthol, *trans*-1,2-dihydrodiol (1β,2α-dihydroxy-1,2-dihydronaphthalene), *trans*-1,4-dihydrodiol (*rac-trans*-1,4-dihydroxy-1,4-dihydronaphthalene), and 1,2-, 1,7-, and 2,6-dihydroxynaphthalene. Other metabolites included O-methylcatechol, trihydroxynaphthalenes, trihydroxydihydronaphthalenes, tetrahydroxynaphthalenes, and tetrahydroxy-tetrahydronaphthalenes. The authors also suggested that in addition to naphthalene-1,2-oxide, several other epoxides, including two naphthalene dihydrodiol epoxides, one diepoxide, and a cyclic peroxide, were intermediates in the *in vivo* metabolism of naphthalene. These epoxides and the cyclic peroxide, in turn, lead to the formation of the di, tri-, and tetrahydroxynaphthalenes, dihydronaphthalenes, and tetrahydronaphthalenes as urinary excretion products (Horning et al., 1980a; Horning et al., 1980b). In addition, 10 methylthio metabolites were isolated (Horning et al., 1980a; Stillwell et al., 1978). These metabolites were identified as 1-methyl-thionaphthalene, methylthiohydroxynaphthalene, and methylthio derivatives with a dihydronaphthalene or a tetrahydronaphthalene structure. The methylthio derivatives accounted for only a minor part of the metabolites excreted. The two major methylthio metabolites (methylthiodihydrodiol and dimethylthiotetrahydrodiol) accounted for 0.2 to

1.0 percent of the administered dose (Stillwell et al., 1978). This finding is in contrast to that of Summer et al. (1979) in which Wistar rats converted about 39 percent of the dose to thioethers.

Stillwell et al. (1982) conducted a similar study with male Swiss mice dosed intraperitoneally with naphthalene dissolved in corn oil at 100 or 150 mg/kg. Approximately 65 percent of the administered dose was excreted in the urine after 24 hours and 3 percent between 24 and 48 hours. Neutral metabolites accounted for only 4 percent of the metabolites excreted in the urine, whereas 96 percent were excreted as conjugates with approximately 20 percent of these as glucuronides or sulfates. Three major neutral metabolites were identified in the urine after enzyme hydrolysis; these were 1-naphthol (I), *trans*-1-hydroxy-2-methylthio-1,2-dihydronaphthalene (II), and 1β,2α-dihydroxy-1,2-dihydro-naphthalene (III). In addition, eight minor sulfur-containing metabolites were isolated.

Most of the neutral metabolites isolated from mouse urine also were present in rat urine, but the profiles of the urinary metabolites were quite different for the two species. 1-Naphthol was the major neutral metabolite in hydrolyzed urine from mice (8 to 10 percent of the dose), whereas the *trans*-1,2-dihydrodiol was the major metabolite in hydrolyzed urine from rats (18 to 24 percent of the dose). In mice, the order of excretion of the five major metabolites was I > II > III > 1-methylthionaphthalene > 2-naphthol. In rats, the order of excretion of the four major metabolites was II > I > 2-naphthol > 1,7-dihydroxynaphthalene (III is a minor metabolite). It was suggested that these differences between mice and rats were associated with differences in mono-oxygenase and epoxide hydrolase activities for each species.

Seven acidic sulfur-containing metabolites were also identified. A product identified as N-acetyl-S-(1-hydroxy-1,2-dihydro-2-naphthalenyl)-cysteine was the major metabolite and accounted for 38 percent of the administered dose of naphthalene. A number of other sulfur-containing metabolites, accounting for approximately 1 percent of the dose, were isolated.

A variety of naphthalene metabolites also has been identified in the bile of cannulated rats dosed i.p. (until rats became ill) with solutions of naphthalene (75 mg), 1,2-dihydro-naphthalene (50 mg), or 1,2-epoxy-1:2:3:4 tetrahydronaphthalene (25 mg) in 0.5 ml arachis oil (Boyland et al., 1961). The bile of rats treated with naphthalene contained 1- and 2-naphthol, 1-naphthylglucuronic acid, 1,2-dihydroxynaphthalene and 1- and 2-glucuronic acid conjugates of *trans* naphthalene. Sulfuric esters 1,2-dihydrodiol were not detected. In rats treated with 1,2-dihydronapthalene, bile contained all metabolites seen upon naphthalene administration as well as S-(1:2:3:4-tetrahydro-2-hydroxy-1-naphthyl) glutathione. Large amounts of 2-naphthol were produced. Detection was made by paper chromatography.

The metabolites identified in the *in vivo* studies are presented in Table 3-2.

3.1.3 In Vitro Metabolism

The *in vitro* metabolism of naphthalene has been studied by several investigators (Booth et al., 1960; Jerina et al., 1968, 1970; Chen and Dorough, 1979; Holtzman et al., 1967a,b; Oesch and Daly, 1972; Bock et al., 1976; van Bladeren et al., 1984, 1985; Hesse and Mezger, 1979; Hesse et al., 1982). Jerina et al. (1970, 1968) demonstrated, in radioisotope trapping experiments

Table 3-2. Naphthalene Metabolites in Urine

Metabolite	Found in:					
	Rabbit	Guinea Pig	Mouse	Rat	Hamster	Man
1-naphthol	1,7	7	5,7	2,3,7		8
2-naphthol	1,7	7	7	2,7		8
1-naphthyl sulfate	1,7	7	7	7		
1-naphthyl glucuronic acid	1,7		7	7		
S-(1-naphthyl)-L-cysteine						
1-naphthyl mercapturic acid	1,7	1,7	1,7	1.7	1	
1,2-dihydro-1,2-dihydroxy naphthalene	1,7	7	5,7	3,4,7		
1,2-dihydro-2-hydroxy-1-naphthyl-glucuronic acid	1,7			2,3,7		
1,2-dihydro-1-hydroxy-2-naphthyl-glucuronic acid				2		
N-acetyl-S-(1,2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine	1	1	1,5	1,2,3		
2-hydroxy-1-naphthyl sulfate	1					
1-hydroxy-2-naphthyl sulfate	2					
1,2-dihydroxynaphthalene		7		2		
1,2-dihydro-1-hydroxy-2-methylthiono-naphthalene glucuronide				2		
1,2-dihydro-2-hydroxy-1-naphthyl sulfate				3		
1,4-dihydrodiol, naphthalene				4		
1,7-dihydrodiol, naphthalene				4		
2,6-dihydrodiol, naphthalene				4		
0-methy catechol				4		
trihydroxynaphthalene				4		
trihydroxydihydro-naphthalene				4		
tetrahydroxynaphthalene				4		
tetrahydroxytetrahydro-naphthalene				4		
1,2-dihydro-1-hydroxy-2-methylthio-naphthalene			5			
1-methylthiononaphthalene			5			
S-(2-hydroxy-2-carboxyethylthio)cysteine	6					

References: 1. Boyland and Sims (1958); 2. Bakke et al. (1985); 3. Chen and Dorough (1979); 4. Horning et al. (1980a,b); Stillwell et al.(1978); 5. Stillwell et al. (1982); 6. Kodama et al. (1974); 7. Corner and Young (1954); and 8. Mackell et al. (1951).

and by direct isolation, the formation of 1,2-naphthalene oxide from naphthalene following incubation with rat liver microsomes. Incubations of rabbit liver microsomes with the oxide resulted in the formation of the trans-dihydrodiol with a 35 to 40 percent yield (see Figure 3-2). The formation of

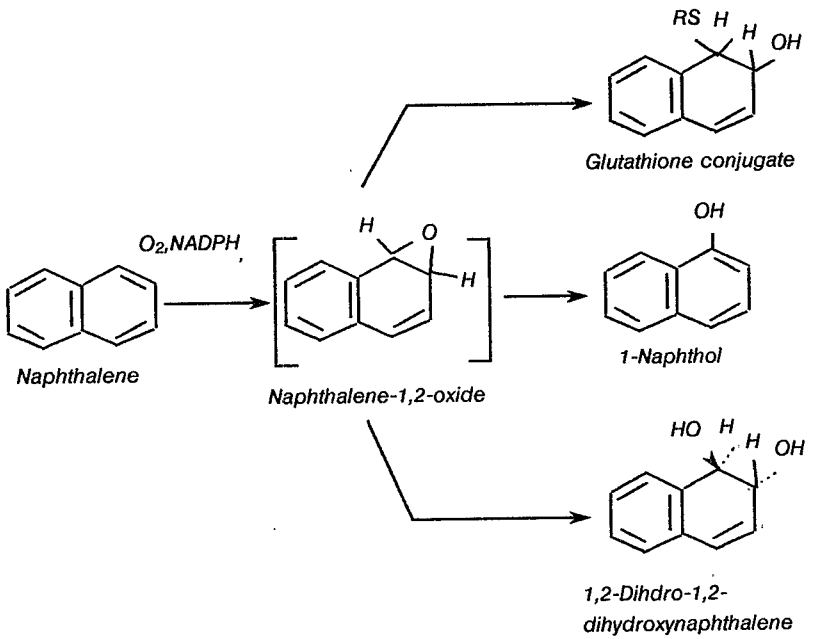


Figure 3-2 In vitro *metabolism of naphthalene. Source: Jerina et al. (1968).*

small amounts of naphthol is apparently a result of a nonenzymatic isomerization of the oxide during incubation. When the GSH-conjugating system and GSH were added to the microsomal preparations, the GSH conjugate increased at the expense of the other two metabolites. Thus, 1,2-naphthalene oxide appears to be obligatory in the formation of all three metabolites. When racemic 1,2-naphthalene oxide was incubated with microsomes, an optically active diol identical with the diol from naphthalene with respect to stereochemistry and source of the oxygen atom in the 2 position, was produced (Jerina et al., 1970). Inhibition of epoxide hydrase increased the yield of naphthol at the expense of the diol. Small amounts of 2-naphthol were shown to be formed during non-enzymatic isomerization of 1,2-naphthalene oxide.

Similar results were reported by Chen and Dorough (1979). Formation of water-soluble products from the metabolism of 1-^{14}C-naphthalene *in vitro* was increased from 34 to 61 and 74 percent upon addition of 300 and 600 µg of GSH, respectively. Buckpitt (1985) has suggested that 2-glutathione

conjugates formed *in vitro* upon incubation of naphthalene with lung and liver microsomes from mice were stereoisomers of 1-hydroxy-1,2-dihydro-2-s-glutathionyl-naphthalene.

Holtzman et al. (1967a; 1967b) utilized ^{18}O-enriched air and demonstrated that the enzymatic conversion of naphthalene to naphthalene dihydrodiol proceeds with the incorporation of one oxygen atom from molecular oxygen; the second oxygen atom is derived from water. The initial attack on naphthalene occurs at the 1-position, and the product formed is the *trans*-diequatorial diol as shown by nuclear magnetic resonance (NMR) spectroscopy.

Oesch and Daly (1972) studied the *in vitro* metabolism of naphthalene with liver preparations from male guinea pigs, utilizing naphthalene and 1,2-naphthalene oxide as substrates and a variety of biochemical (metabolic inhibitors and inducers) and radiolabel tracing techniques. They reported the presence of a coupled monooxygenase-hydrase system in liver microsomal preparations that catalyzes the overall conversions of naphthalene to the dihydrodiol. Bock et al. (1976) studied the glucuronidation of naphthalene 1,2-dihydrodiol in isolated hepatocytes and liver microsomal fraction from male Sprague-Dawley rats. Naphthalene 1,2-dihydrodiol glucuronide was a major metabolite in hepatocytes incubated with naphthalene, NADPH regenerating system, and UDP-glucuronic acid. In microsomes, the glucuronide conjugate was formed only when UDP-N-acetylglucosamine, the positive allosteric effector of UDP-glucuronyltransferase was added. The authors suggested that the activation of UDP-glucuronyltransferase by UDP-N-acetylglucosamine may be an important factor in the coupling of glucuronidation to functionally linked microsomal enzyme reaction.

Strong evidence against such a coupled mechanism has recently been presented by Jerina and colleagues (van Bladeren et al., 1984, 1985), who showed that a more likely alternative is an enantioselectivity by epoxide hydrolase toward the enantiomers of naphthalene-1,2-oxide formed in different ratios by specific isozymes of cytochrome P-450. Through the application of trapping techniques for establishing the enantiomer ratios of metabolically formed arene oxides, it was found that cytochrome P-450b (the major isozyme induced in rats by phenobarbital) metabolized naphthalene predominantly to the (-)-(1S,2R) epoxide isomer (74 percent of total), while cytochrome P-450c (the isozyme induced in rats treated with 3-methylcholanthrene) metabolized naphthalene primarily to the (+)-(1R,2S) epoxide isomer (73->95 percent). Epoxide hydrolase preferentially metabolized the (+)-naphthalene oxide to the (-)-1R,2R-dihydrodiol. In comparison, the (-)-(1S,2R)-naphthalene oxide was metabolized by epoxide hydrolase to both the (-)-(1R,2R) and the (+)-(1S,2S)-dihydrodiols. The apparent K_m for the epoxide hydrolase-mediated hydration of (+)-(1R,2S)-naphthalene oxide was 1 μM, while for (-)-(1S,2R)-naphthalene oxide the apparent K_m was 12 μM.

The identification of 1-napthol as an intermediate in the metabolism has led several groups of investigations to explore further the conversion of 1-naphthol to additional metabolites.

Hesse and Mezger (1979), using [1-^{14}C]-1-naphthol in a rat liver microsomal preparation, identified covalently bound products which they suggested might be naphthoquinones and/or naphthosemiquinones. Because binding was not decreased by SKF-525A or 7,8-benzoflavone, they concluded 1-naphthol metabolism was not mediated by cytochrome P450. The studies of Doherty and Cohen (1984), using a similar protocol, found that [1-^{14}C]-1-naphthol was metabolized to methanol-soluble products

including 1,4-naphthoquinone and covalently bound species. It was suggested that 1,4-naphthoquinone most probably was formed via autooxidation of 1,4-dihydroxy naphthalene. Hesse et al. (1982) reported that inhibition of glucuronidation and sulfation in isolated rat hepatocytes led to several fold increase in covalent binding of ^{14}C-naphthalene-derived metabolites. Results suggested saturation of detoxification pathways may play an important role at high levels of naphthalene.

To more fully evaluate the role of cytochrome P450, Doherty et al. (1985) conducted additional experiments with purified P450 from hepatic microsomes of male Wistar albino rats, that had been pretreated with sodium phenobarbitone in drinking water for 6 days.

Incubation of [1-^{14}C]-1-napthol in the fully reconstituted P450 system and NADPH led to the formation of methanol-soluble products. The predominant metabolite, identified by HPLC, was 1,4-naphthoquinone. 1,2-naphthoquinone was not found in any significant amount. Production of 1,4-naphthoquinone was rapid and dependent on the P450 concentration. The apparent K_m for 1-naphthol was 17 μm and in agreement with the value previously obtained (Doherty and Cohen, 1984; Hesse and Mezger, 1979). The metabolism was inhibited by classic P450 inhibitors: metyrapone, SKF-525A and $CO:O_2$ (9:1). The apparent discrepancy with the results of Hesse and Mezger (1979) may have been due to the higher concentration of 1-naphthol used in the Hesse and Mezger study. When GSH, which reacts with both 1,2- and 1,4-naphthoquinone was added, the radioactivity associated with the HPLC peak for 1,4-naphthoquinone disappeared and new metabolites formed. When ethylenediamine, which reacts specifically with 1,2-naphthoquinone was added, the metabolite profile was not altered.

Addition of ethylenediamine to the reaction mixture was found to significantly inhibit covalent binding indicating that 1,2-naphthoquinone may have been involved. Inhibition of binding was greater when GSH was used. The authors suggested that 1,2-naphthoquinone *per se* may not be involved but rather another metabolic product possessing quinone groups. Such a product could arise from further metabolism of 1,4-naphthoquinone or 1,4-dihydroxynaphthalene.

The *in vitro* metabolism of naphthalene by human lung microsomes was investigated by Buckpitt and Bahnson (1986). Fresh lung tissue was obtained from two elderly individuals, one of which was identified as a smoker. The preparation from patient 1 catalyzed the metabolism of naphthalene to the dihydrodiol and three GSH conjugates. The rate of dihydrodiol formation nearly equalled the total rate of formation of the GSH conjugates. This observation is consistent with that of Oesch et al. (1980) who demonstrated high activities of epoxide hydrolase in lung microsomes. Cyclohexene oxide, an inhibitor of dihydrodiol formation, was added to the preparation from patient 2 and was found to shunt metabolism, as expected, to formation of the three GSH conjugates. Addition of lung microsomes (patient 1) to a mouse liver microsomal preparation resulted in a marked inhibition of naphthalene metabolism. This was not seen when microsomes from patient 2 were substituted. The existence of an inhibitor, possibly released during tissue homogenization was hypothesized as an explanation for the inhibition observed.

Because studies (Cohen et al., 1983; Wilson et al., 1985) had shown that 1-naphthol has potential selective toxicity to human colonic tumor tissue, Doherty et al. (1986) examined the peroxidase activation of 1-naphthol. Horseradish peroxidase was incubated with [1-^{14}C]-1-naphthol and H_2O_2 in the presence and absence of bovine serum albumin (BSA). The amount of

radiolabelled material covalently bound to BSA also was assessed. The mechanism of action was evaluated by spectrophotometry and electron spin resonance (ESR). Results indicated that 62 percent of the radiolabel was covalently bound to protein following a 60 min incubation. GSH inhibited binding in a dose-dependent manner. Evidence indicated that GSH acts as a radical scavenger (napthoxy or naphthoxy-derived). In the absence of GSH, ESR studies showed that napthoxy radicals decayed extremely readily and resulted in polymeric products and covalently bound species. At high GSH levels, naphthoxy radicals are repaired with concomitant formation of GS radicals. GS radicals react to form GSSG, resulting in depletion of GSH with very little loss of 1-naphthol.

In an *in-vitro* system with a human colonic adenocarcinoma cell line, the toxic action of 1-naphthol was potentiated by dicoumarol, an inhibitor of NADPH quinone reductase (Cohen et al., 1983). Wilson et al. (1985) found that normal colon, *in vitro* formed significantly more 1-naphthyl sulfate than 1-naphthyl-B-D-glucuronide.

3.2 Mechanisms of Metabolite-Induced Toxicities

3.2.1 Ocular Toxicity

Ocular toxicity, particularly cataract formation, has long been associated with naphthalene administration in rodents and other laboratory animals (Adams, 1930; van Heyningen and Pirie, 1966; Lindberg, 1922; Koch et al., 1976).

Oral administration of naphthalene is believed to result in its metabolism in the liver and metabolites then travel through the bloodstream to the eye where further metabolism takes place (van Heyningen, 1979). Evidence in rats and rabbits suggest that 1,2-dihydroxy naphthalene is enzymatically converted to 1,2-napthoquinone which then reacts with eye proteins, resulting in damage (Pirie and van Heyningen, 1966; Rees and Pirie, 1967; Pirie, 1968).

Van Heyningen (1979), in her review of the literature, hypothesized that susceptibility to naphthalene-induced cataracts is more pronounced in rat and rabbit strains with lightly pigmented or dark eyes, due to the presence of polyphenol oxidase. This nonspecific enzyme, found only in pigmented tissues, catalyzes the formation of melanin from tyrosine. Nagata (1984) detected o-diphenol oxidase activity in strain ACI rats, which have pigmented eyes but not in albino Wistar rats.

A significant increase in o-diphenol oxidase activity in the lens tissue of naphthalene-fed rabbits also was reported by Srivastava and Nath (1969).

Van Heyningen and Pirie (1967) suggested that the toxic metabolite is 1,2-dihydroxy naphthalene. In gavage studies in which naphthalene was administered daily to 39 rabbits at 1 gm/kg, they detected 1,2-dihydroxy naphthalene and 1,2-naphthoquinone in the eyes and three metabolites in blood: (1) naphthalene 1,2-dihydrodiol, (2) 1,2-dihydro-1,2-dihydroxy-1-naphthyl glucuronic acid and (3) 2-hydroxy-1-naphthyl sulfate. It was shown that each blood-borne metabolite could be converted by a different enzyme in the eye to 1,2-dihydroxynaphthalene. In more than half the rabbits, lens opacities and degeneration of the retina were observed. Occasional hemorrhages of the ear and intestine were also observed. In addition, 1,2-naphthoquinone can oxidize ascorbic acid present in the aqueous and vitreous humors, resulting in oxalic acid formation as the ascorbic acid concentration decreases (van Heyningen, 1970a,b). Although ascorbic acid decreases in aqueous and vitreous humors, the level is

maintained or increases in the eye lens itself (van Heynigen, 1970b). Presumably dehydroascorbic acid, formed by oxidation by naphthoquinones, penetrates the lens and is reduced to ascorbic acid. Ascorbic acid diffuses only slowly from the lens (Wachtl and Kinsey, 1958). Excessive depletion of ascorbic acid may account for the appearance of calcium oxalate crystals (Pirie and van Heyningen, 1966). GSH appears to be maintained at high levels in the eye lens in spite of extensive oxidative reactions (van Heyningen, 1970b).

Although ocular toxicity of naphthalene is similar in both rat and rabbit, the severity of effect may differ to some extent because of interspecies differences.

van Heyningen (1970a) found that the albino Wistar rat has only about 3 percent of the concentration of catechol reductase (an enzyme which catalyzes the interconversion of quinones and diols) found in the rabbit lens. The rat also has less ascorbic acid in aqueous humor than the rabbit (van Heyningen, 1979). This would result in a higher level of 1,2-naphthoquinone. Thus, polyphenol oxidase may be the most important factor in the rat eye while catechol reductase may play a crucial role in ocular toxicity in the rabbit.

Rao and Pandya (1981) reported increased lipid peroxidation in the eyes of male albino rats administered 1 gm naphthalene daily for 10 days. Alkaline phosphatase showed a slight increase and aniline hydroxylase activity was not detected. Liver peroxide levels were elevated but serum lipid peroxides were not measured.

Lipid peroxides have been suggested as a causal factor in cataract formation. Yamauchi et al. (1986) investigated this aspect in relation to naphthalene. Naphthalene (1 gm/kg) in acacia oil was administered to male Wistar rats daily for up to 18 days. GSH content in lens and serum and liver lipid peroxide levels were measured during interim sacrifice. Serum peroxide levels increased significantly on the 4th day and reached a maximum on the 7th day. Liver peroxide levels had a similar pattern. GSH content in lenses decreased to about 64 percent on the fourth day and remained depressed. The authors suggested that lipid peroxides are stable enough to reach the lens and cause ocular damage. Microscopic observation indicated slight cataractous changes in some rats on the 14th day when serum lipid peroxide levels were elevated (Yamauchi et al., 1986). It was suggested that peroxides may play a role in cataract formation, in addition to role played by 1,2-naphthaquinone. A decrease in nonprotein sulfhydryl content in lens has previously been associated with naphthalene-induced cataracts in rabbits (Ikemoto and Iwata, 1978).

3.2.2 Pulmonary Toxicity

Various investigators have observed that i.p. administration of naphthalene to rodents results in selective pulmonary bronchiolar epithelial cell (Clara) necrosis, but not hepatic or renal necrosis (Tong et al., 1982; Warren et al., 1982; Tong et al., 1981; Mahvi et al., 1977; Reid et al., 1973). Rats and hamsters were reported to be much less sensitive than mice (Buckpitt et al., 1984).

In an effort to determine the mechanism of action, numerous studies have focused on the biochemistry of naphthalene and the covalent binding characteristics of its metabolites.

Shank et al. (1980) found that mice pretreated with diethyl maleate prior to i.p. injection of naphthalene had three times the level of covalently-bound

naphthalene metabolites in lung, liver, kidney, and spleen. Studies with ^{14}C-naphthalene injected into mice revealed a similar binding pattern: binding was highest in the lung but low in spleen. Increased binding corresponded to rapid and significant depletion of GSH in lung and liver, and to a lesser extent in kidney. Covalent binding was dose-dependent and exhibited a threshold at dosages between 200 and 400 mg/kg. Warren et al. (1982) suggested that lung damage may be mediated by P450 dependent metabolism and GSH depletion.

Buckpitt and Warren (1983) extended these studies, utilizing a variety of metabolic inhibitors. The results suggested that some of the metabolites involved in GSH depletion and covalent binding in extrahepatic tissues originated in the liver. *In vitro* studies (Buckpitt et al., 1984) with mouse liver and lung microsomes indicated the formation of three GSH conjugates. Evidence indicated that two conjugates are stereoisomers of 1-hydroxy-1,2-dihydro-2-S-glutathionyl naphthalene (Buckpitt, 1985). The rates of formation differed; conjugate 2 was predominant in lung but not liver preparations and was considered due to P450 selectivity or epoxide hydrolases. Buckpitt (1985) suggested that the differences in the rates of formation between target and nontarget tissues may reflect the stereochemistry of epoxidation by the tissue-specific P450 isozymes. This may, in turn, relate to the selective pulmonary necrosis observed in mice.

Van Bladeren et al. (1984) found that P450 catalyses the formation of naphthalene 1,2-oxide in a stereoselective manner (see Section 3.1.1) and that epoxide hydrolase determines the enantiomeric composition of the 1,2-dihydrodiols formed.

Confirmation that P450 was involved in pulmonary necrosis was obtained in the studies of Buckpitt et al. (1986). Liver microsomes from phenobarbitol-induced mice administered 300 mg naphthalene/kg i.p. exhibited 73 percent less covalent binding in the presence of piperonyl butoxide, a P450 inhibitor, than controls. A similar degree of inhibition also was observed with SKF 525A. It was reported that piperonyl butoxide also blocked the pulmonary injury exhibited by naphthalene in controls. Covalent binding was higher in nontarget tissues. Differences in covalent binding between tissues were attributed to the possibility that only some metabolites are toxicologically active and that reactive metabolites are stable enough to circulate in the blood (Buckpitt and Warren, 1983; Richieri and Buckpitt, 1985).

Buckpitt et al. (1985) provided evidence that 1-naphthol is not an obligate intermediate in the covalent binding or pulmonary necrosis caused by naphthalene. While 1-naphthol is formed at a higher rate by mouse lung rather than liver microsomes, the rate of covalent binding after ^{14}C-1-naphthol administration was not higher than that after ^{14}C-naphthalene administration. In addition, pulmonary necrosis was not observed after either intraperitoneal or intravenous administration of 1-naphthol.

Naphthalene (i.p., 225/kg) was shown to reduce the activity of a number of rat lung, but not liver, microsomal enzymes (Tong et al., 1981, 1982). Enzymes studied included benzphetamine N-demethylase, arylhydrocarbon hydrolyase, NADPH cytochrome c reductase, 17-ethoxyresorufin o-deethylase, and styrene epoxide hydrolase. Inhibition ranged from 30 to 70 percent and lasted from 8 to 15 days. Changes in enzyme activity were reported to correlate with morphologic changes in the bronchiolar epithelium. There were no morphologic changes noted in liver tissue.

Buckpitt et al., (1986) also investigated the role of prostaglandin synthetases in mediating the pulmonary toxicity of naphthalene. Prostaglandin synthetases have been shown to catalyze the metabolism of aromatic

hydrocarbons and dihydrodiols and detectable activities have been measured in Clara cells, a site of naphthalene-induced toxicity. Naphthalene was administered to phenobarbitol-induced mice at a dose of 300 mg/kg. Indomethacin, an inhibitor of prostaglandin synthetases but not P450, was administered both 1 hr before and 6 hr after naphthalene. In an *in vitro* microsomal system containing either an NADPH-generating system or arachidonic acid (the precursor to prostaglandin production), it was observed that arachidonic acid failed to catalyze the formation of covalently bound metabolites in any of the tissues studied. Indomethacin treatment of the mice failed to protect against bronchiolar necrosis.

4. Health Effects

4.1. Acute Toxicity

The acute effects of naphthalene have been studied in rats, mice, rabbits, cats, and dogs following administration of the compound by various routes. The acute toxicity values of naphthalene for these laboratory animals are summarized in Table 4-1. Additional information is presented in Section 3.2.

Table 4-1. Acute Toxicity Values of Naphthalene in Laboratory Animals

Route of Administration	Species/Sex	Lethal Concentration mg/kg[a] LD_{50}	Lethal Concentration mg/kg[a] LC_{50}	Reference
Oral	Rat/M	2,009	--	Mallory et al. (1985a)
	Rat/F	3,310	--	Mallory et al. (1985a)
	Rat/M	2,200	--	Gaines (1969)
	Rat/F	2,400	--	Gaines (1969)
	Rat/--b	1,780	--	TDB
	Rat/--	9,430	--	U.S. EPA (1980)
	Mouse/M	533	--	Shopp et al. (1984)
	Mouse/F	710	--	Shopp et al. (1984)
	Mouse/F	353	--	Plasterer et al. (1985)
	Cat/--	1,000	--	TDB
	Dog/--	400	--	TDB
	Rabbit/--	3	--	TDB
Dermal	Rat/M	>2,500	--	Gaines (1969)
	Rat/F	>2,500	--	Gaines (1969)
	Rabbit/M	>2,000	--	Mallory et al. (1985b)
	Rabbit/F	>2,000	--	Mallory et al. (1985b)
Inhalation	--	--	--	
Intraperitoneal	Mouse/M	380	--	Warren et al. (1982)
Subcutaneous	Mouse/--	969	--	Irie et al. (1973)

[a]Unless otherwise noted.
[b]Data not available.

4.1.1. Oral

The acute LD_{50} values of naphthalene dissolved in peanut oil for male and female Sherman rats were 2,200 and 2,400 mg/kg, respectively (Gaines, 1969). In two other studies, the LD_{50} values for rats were 1,780 (Toxicology

Data Bank) and 9,430 mg/kg (U.S. EPA, 1980), but the strain and sex of the animals were not specified. For male and female CD-1 mice, the acute oral LD_{50} values of naphthalene in corn oil were 533 and 710 mg/kg, respectively (Shopp et al., 1984). In a recent study (unpublished) conducted by Mallory et al. (1985a), the acute LD_{50} values of naphthalene in corn oil for male and female Sprague-Dawley rats were reported to be 2,009 and 3,310 mg/kg, respectively. In a sub-acute study, at doses ranging from 125 to 2,000 mg/kg given daily for 8 days, an LD_{50} of 353 mg/kg was determined for CD-1 mice (Plasterer et al., 1985).

Although cataract formation following oral administration of naphthalene has been known for many years (Fitzhugh and Buschke, 1949), recent studies have shown that ocular changes can result from a single dose of naphthalene. Van Heyningen and Pirie (1967) found that lens changes developed in the eyes of rabbits after a single dose of naphthalene (1,000 mg/kg) was administered by gavage. In CD-1 mice, oral doses of $\geq$400 mg/kg for males and $\geq$600 mg/kg for females resulted in ptosis with clear, red secretions around the eyes within 1 hr of dosing (Shopp et al., 1984).

Ikemoto and Iwata (1978) reported that oral administration of naphthalene (1 gm/kg) to male and female albino rabbits for 2 consecutive days resulted in cataract formation. Occurrence of cataracts was accompanied by a decrease in sulfhydryl content in both soluble and insoluble lens protein.

4.1.2. Dermal

No deaths occurred when 2,500 mg/kg of naphthalene was applied to the skin of male and female Sherman rats (Gaines, 1969). The application of 2,000 mg naphthalene/kg (dissolved in acetone to the skin of New Zealand white rabbits) did not cause mortality; the LD_{50} was >2,000 mg/kg (Mallory et al., 1985b). This study suggests that naphthalene may not be as readily absorbed through the skin as it is through the intestinal mucosa.

4.1.3. Inhalation

It previously had been reported that the 8-hour LC_{50} value for naphthalene was 100 ppm (Union Carbide, 1968). However, Buckpitt (1985) suggested that this value may be too low. He estimated that in 8 hours the body burden would be less than 30 mg/rat, or about 150 to 200 mg/kg. This concentration is far less than the oral or intraperitoneal LD_{50} values for rats. Fait and Nachreiner (1985) reported that exposure of male and female Wistar rats to 78 ppm for 4 hr resulted in no mortalities, nor any lung, liver, kidney, or nasal passage abnormalities. In an unpublished inhalation study with male Swiss-Webster mice, no deaths were noted following nose-only exposures to 90 ppm for 4 hours. However, lung lesions were reported to be prominent (Buckpitt, 1985).

4.1.4. Intraperitoneal

The 24-hour LD_{50} value of naphthalene in Swiss-Webster mice was 380 (350 to 413) mg/kg following intraperitoneal injection (Warren et al., 1982; Shank et al., 1980). All deaths occurred within 24 hours, with survivors being observed for an additional 6 days. The target organ was identified as the lungs (see Section 4.1.6 below).

Tong et al. (1982) found remarkable histological changes in the lungs of C57BL/6J mice dosed intraperitoneally with naphthalene at 225 mg/kg. One day after dosing, the Clara cells in the terminal bronchioles were pyknotic,

and hypereosinophilic nuclei were apparently detaching from the bronchiolar wall. Three days after dosing, some surfaces appeared to be completely denuded of Clara cells, whereas other surfaces appeared to have immature Clara cells scattered circumferentially. Five days after treatment, there was still evidence of incomplete recovery; by 8 days, most of the terminal bronchioles were reepithelialized; and by 15 days, mature Clara cells were common, but recovery was evidently not complete. Similar findings had previously been reported by Reid et al. (1973) in C57BL/6J mice dosed i.p. with approximately 350 mg naphthalene/kg.

Shank et al. (1980) found that GSH plays an important role in naphthalene toxicity. When male Swiss-Webster mice were pretreated with diethyl maleate prior to i.p. injection of naphthalene doses ranging from 0 to 500 mg/kg, severely damaged lungs were seen in mice given 40 mg/kg. None of the animals given 300 mg/kg survived 24 hr. In contrast, piperonyl butoxide decreased toxicity.

See Section 3.2.2 for additional information related to pulmonary toxicity and metabolite formation.

4.1.5. Subcutaneous

Irie et al. (1973) studied the effects of naphthalene in mice (strain not specified) following single subcutaneous injections at doses of 650 to 1,348 mg/kg. Vigorous tremors were noted in the mice for 3 to 4 days following dosing. The LD_{50} value was calculated to be 969 (891 to 1053) mg/kg.

4.1.6. Eye Irritation

Acute ocular irritation was noted in two of six New Zealand white rabbits receiving no postdose rinse after 24 and 48 hours of exposure to 0.1 mg naphthalene (Mallory et al., 1985c). This response included slight iritis, moderate redness and slight swelling and discharge. All animals were normal by 72 hours postdosing. No positive response was noted in rabbits (three) receiving a postdose rinse.

4.1.7. Dermal Irritation and Sensitization

Naphthalene (moistened with 2 mL of acetone) was found to be slightly to moderately irritating to the skin of male and female New Zealand white rabbits 30 to 60 minutes postdosing (Mallory et al., 1985d). Dermal irritation was still evident up to 5 days after test material application. Fissuring of the skin was also noted.

Naphthalene (100 percent) did not cause delayed hypersensitivity in Hartley guinea pigs (Mallory et al., 1985e).

4.2. Subchronic Toxicity

Naphthalene toxicity has been investigated in repeated dose studies following oral administration. Additional studies have been conducted to determine the ocular effects of naphthalene following administration by various routes.

4.2.1. Oral

Shopp et al. (1984) conducted a 14-day and a 90-day study on groups of male and female CD-1 mice administered naphthalene in corn oil by oral

gavage. In the 14-day study, six groups of male and female mice (40 to 112/group) were given doses of 0 (naive), 0 (vehicle), 27, 53, or 267 mg/kg/day; the highest dose was one-half the LD_{50} for male mice. Male mice demonstrated lower survival rates than females, apparently due to the aggressive behavior of group-housed male mice; however, the mortality in the high-dose groups of male and female mice was 5 to 10 percent higher than the control groups. There was a significant decrease (7 to 13 percent) in body weight in male and female mice receiving the high dose. The high-dose males exhibited a 30 percent decrease in thymus weight, while females exhibited a decrease in spleen weight and an increase in lung weight. Gross pathology but not histopathology was performed. No biologically relevant changes were noted in treated animals for hematology, clinical chemistry, hexabarbital sleeping time, or immunotoxicity (humoral immune response, lymphocyte responsiveness, popliteal lymph node response, and bone marrow function).

For the 90-day study, five groups of 112 male and 112 female mice were given doses of 0 (naive), 0 (vehicle), 5.3, 53, or 133 mg/kg/day. A positive control for immunotoxicity received 50 mg/kg cyclophosphamide intraperitoneally on days 87, 88, 89, and 90. The mortality seen among all groups of male mice appeared to be due to the aggressive behavior of group-housed male mice.

No significant effects on body weight were noted for males or females. A significant decrease in the absolute weight of the brain, spleen, and liver was noted for females receiving 133 mg/kg; however, organ-to-body weight ratios were significantly different only for the spleen. Of the changes noted in the clinical chemistry data, the increase in blood protein content in males and females receiving 53 or 133 mg/kg, the decrease in blood urea nitrogen in all treated female groups, and the decrease in calcium ion concentrations in males receiving 53 or 133 mg/kg were considered to be treatment related. No significant changes were noted in hematology, the mixed-function oxidase activity, or immunotoxicity assays for either sex. Histopathology data were not presented and it is not known if naphthalene caused bronchiolar lesions.

No evidence of cataract formation or hemolytic anemia was observed in CD-1 mice. Since the CD mouse is an albino strain, cataract formation was not expected.

In a subchronic oral toxicity study performed for the NTP (1980a), naphthalene in corn oil was administered by gavage to male and female F344 rats (10/sex/dose) at dose levels of 0, 25, 50, 100, 200 or 400 mg/kg/day, 5 day/week for 13 weeks. At 400 mg/kg, two males died during the first week and the treatment caused diarrhea, lethargy, hunched posture and roughened haircoats in rats of both sexes. A significant (i.e., >10%) decrease in body weight gain was observed among males and females at 200 and 400 mg/kg and in females at 100 mg/kg. Food consumption was not affected.

All the rats in the study were necropsied and comprehensive histopathological examinations were performed on rats from the 0 and 400 mg/kg groups. Histopathological examinations of the kidneys and thymus were performed on rats from the 200 mg/kg group (according to the histopathology tables; the 100 mg/kg group according to the text). The authors stated that lesions of the kidney in males and thymus in females of the 400 mg/kg group may have been compound-induced, and that no eye lesions were found. The incidences of lesions of kidney and thymus were, however, very low. The renal lesions, which did not occur in females, were observed at incidences of 0/10 in controls, 2/10 in the 200 mg/kg group and 1/10 in the 400 mg/kg group. These renal lesions consisted of focal cortical

lymphocytic infiltration or focal tubular regeneration in the two 200 mg/kg males and diffuse tubular degeneration in the one 400 mg/kg male. Lymphoid depletion of the thymus occurred in 2/10 females of the 400 mg/kg group and in none of the control or 200 mg/kg females and in none of the males of these groups. Hematological analyses revealed marginal decreases in hemoglobin and hematocrit in males and females of the 400 mg/kg group, and a moderate increase in the number of mature neutrophils and a decrease in the number of lymphocytes in males of the 400 mg/kg group, relative to controls. No hematological changes were observed at the lower dosages.

In a similar study, naphthalene was administered in corn oil by gavage at 0, 12.5, 25, 50, 100 or 200 mg/kg/day, 5 day/week, to B6C3F1 mice (10/sex/dose) for 13 weeks (NTP, 1980b). Seven mice (three males and two females of the 200 mg/kg group, one female of the 25 mg/kg group and one control male) died during the 2nd, 3rd and 4th weeks of the study from gavage trauma or accident. Transient signs of toxicity (lethargy, rough haircoats and decreased food consumption) occurred at weeks 3 to 5 in the 200 mg/kg groups. All treated groups of male mice gained somewhat more weight than did control males. Dose-related decreases in body weight gain were seen in females, but were not significant. All the mice were necropsied and comprehensive histopathological examinations were performed on the mice from the 0 and 200 mg/kg groups. No compound-related lesions were observed in any organs, including kidneys, thymus, eyes and lungs. Hematological analyses, performed on all groups, revealed no significant, compound-related changes.

Fitzhugh and Buschke (1949) noted the formation of cataracts, within 3 weeks of treatment, in rats fed diets containing 2 percent naphthalene or one of several naphthalene derivatives. The effects of pigmentation on cataract formation in rats and rabbits have been summarized by van Heyningen (1979): Albino rats do not readily convert naphthalene to 1,2-dihydroxynaphthalene, which auto-oxidizes to form 1,2-naphthoquinone (the naphthalene metabolite known to bind to the lens of the eye), possibly because polyphenol oxidase is found only in pigmented tissues. Secondary effects occur in the retinas of both albino and pigmented rats. For rabbits, pigmentation is not as important, since the reserve of ascorbic acid and other antioxidants is considerably less than in the rat. Thus, the depletion of antioxidants is a critical step in rabbits.

When rabbits were given oral doses of 1,000 mg/kg for various periods up to 28 days, lens changes were noted after the first dose and retinal changes were noted after the second dose (van Heyningen and Pirie, 1967). The progression of retinal changes include the finding of abnormal amounts of protein in the aqueous humor and crystalline deposits in the vitreous body, followed by complete degeneration of the retina. Considerable variation exists among rabbits in their response to naphthalene. Cataract formation was not noted following topical application of a 10 percent solution of naphthalene in oil or intraperitoneal injection of 500 mg/day for 60 days (Ghetti and Mariani, 1956). A detailed elucidation of these effects is presented in Section 3.2, Biochemical Effects.

Cataract formation in C57BL/6J and DBA/2N mice was evaluated by Shichi et al. (1980) and Shichi and Nebert (1982). Groups of 15 mice were fed *ad libitum* laboratory chow which had been soaked for at least 24 hr in corn oil containing 5 or 10 mg/ml naphthalene. Feeding regimen was continued for 60 days. Daily ingestion was not calculated by the authors. Concomitant doses of 3-methylcholanthrene or β-naphthoflavone were given twice weekly. A 6.7% incidence in cataract formation was observed in C57BL/6J

mice at each dose. No cataracts were observed in DBA/2N mice. All mice treated with 3-methylcholanthrene died within 6 weeks. In addition to cataract formation, tissue degeneration in the choroid, ciliary body, and iris occurred.

4.3. Chronic Toxicity

A chronic inhalation study of naphthalene in mice has recently been conducted by the National Toxicology Program (NTP, 1985). The exposure phase of the 2-year inhalation study has been completed, but the histopathology data and the final report are not yet available. No other chronic toxicity data were found.

4.4. Carcinogenicity

There is only limited information available on the carcinogenic potential of naphthalene following oral, dermal or subcutaneous administration to laboratory animals. The results of an inhalation study in mice conducted by the National Toxicology Program (NTP) have not yet been published. Histopathology is currently being evaluated. Exposure levels in this study were 10 and 30 ppm (NTP, 1985).

Recently, Adkins et al. (1986) exposed groups of 30 female A/J strain mice via inhalation to naphthalene at concentrations of 0, 10, or 30 ppm, 6 hours a day, 5 days a week for 6 months. At the beginning of the study, the mice were 6 to 8 weeks of age and weighed 15 to 25 g each. After the 6-month exposure period, a pulmonary tumor bioassay was performed on excised lungs. Naphthalene did not result in changes in tumors per mouse but did cause a statistically significant increase ($p < 0.05$) in the number of adenomas per tumor-bearing mouse lung (Table 4-2). The tumors were described as alveolar adenomas consisting of large cuboidal or columnar epithelial cells supported by a sparse fibroblastic stroma and arranged in poorly defined acinar structures with papillary formations. No apparent dose-response was observed. Alveolar epithelial hyperplasia was present in lungs of most treated mice with adenomas. This lesion was considered as a possible precursor to adenomas. Bronchiolar epithelial hyperplasia was not observed.

Schmahl (1955) reported that naphthalene, administered in food or by i.p. injection was not carcinogenic in rats (in-house strains BDI and BDIII). Naphthalene was dissolved in oil and given six times weekly in food. The daily dose was between 10 and 20 mg. After reaching a total dose of 10 gm/rat (food intake was not reported), treatment was stopped and animals observed until spontaneous death, between 700 and 800 days of age. In the i.p. experiments, 10 control rats were used and 10 were injected i.p. The daily dose was 20 mg/rat. Injections were given weekly for 40 weeks. Animals were observed until spontaneous death. Tissues were examined histologically in each experiment. It was reported that naphthalene caused no carcinogenic effects.

Boyland et al. (1964) implanted naphthalene into the bladder of stock Chester Beatty mice (23) and followed the mice for 30 weeks. Tumor incidence was as low as when paraffin wax was used and lower than with cholesterol. Naphthalene was judged to be inert and to have no advantage over cholesterol as a base for implantation pellets.

A study was conducted on carcinogenicity testing of coal tar derived naphthalene that contained about 10 percent unidentified impurities (Knake, 1956). White rats (40, sex unspecified) were given 7 subcutaneous injections

Table 4-2. Tumor Incidence in Female A/J Strain Mice Exposed to Naphthalene via Inhalation for 6 Months [a,b]

Exposure Level (ppm)	Survivors[c]	Surviving Animals: Total No. of Tumors	Surviving Animals: Animals with Tumors (%)	Surviving Animals: Tumors/ Mouse[d]	Surviving Animals: Tumor/ Tumor-Bearing Mouse Lung [d]
0	29/30	6	21	0.21 ± 0.39	1.00 ± 0.00
10	27/30	10	29	0.35 ± 0.55	1.25 ± 0.07*
30	29/30	11	30	0.37 ± 0.55	1.25 ± 0.07*

[a]Taken from Adkins et al. (1986).
[b]Based on animals that survived to study termination.
[c]Number of survivors at end of study/number of animals at start of study.
[d]Mean ± SD.
*Significantly different from control ($p < 0.05$).

of 500 mg/kg naphthalene in sesame oil at 2-week intervals. Lymphosarcomas were found in 5 of 34 surviving rats at 18 months (14.7 percent), whereas vehicle controls had a 2 percent incidence of these tumors. Mice (25, inbred black mice) were painted with 0.5 percent naphthalene in benzene 5 days a week for life. Four treated mice developed leukemias in contrast to 0 of 21 vehicle controls; the negative control incidence was 0.4 percent. The value of these studies for assessing carcinogenicity is very limited because the impurities may very well be carcinogenic. The vehicle in the mouse study has been shown to cause leukemias and the site of injection in the rat study was painted, prior to injection, with carbofuchsin, a known carcinogen.

Kennaway (1930) reported that naphthalene was not carcinogenic in skin painting studies in mice. The concentration, purity, dosing regimen, and other details were not provided. The reaction product of naphthalene and aluminum trichloride was carcinogenic but the product was not identified.

Schmeltz et al. (1978) tested the carcinogenic activity of benzo(a)pyrene (BaP) and naphthalene in female ICR/HA (Sprague-Dawley) mice. A 100-µl test solution containing 0.25 percent naphthalene and 0.003 percent BaP was painted on the shaved backs of 30 mice 3 times a week for 78 weeks. Naphthalene inhibited BaP-induced tumors; approximately 42 percent of the mice had skin tumors with BaP alone, and about 20 percent had skin tumors when naphthalene and BaP were administered together.

Naphthalene was not active in causing cellular transformation in a Fischer rat embryo cell line at a level of 100 µg/mL (Freeman et al., 1973) or in an AKR leukemia, virus-infected Swiss mouse embryo cell line at 5 µg/mL (Rhim et al., 1974).

Tsuda et al. (1980) administered a single gavage dose of 100 mg/kg naphthalene in corn oil to a group of 10 young adult F344 rats (sex not specified) at 12 hours after partial hepatectomy. A vehicle control group of 10 rats was included. At 2 weeks after surgery, 2-acetylaminofluorene was added to the diet at 200 ppm to inhibit proliferation of "nonresistant" hepatocytes. After 1 week of dietary 2-acetylaminofluorene, a single 2.0 ml/kg dose of carbon tetrachloride was given to necrotize "nonresistant"

hepatocytes and permit proliferation of "resistant" hepatocytes. Feeding of 2-acetylaminofluorene continued for 1 week, followed by a basal diet for 1 week. The rats were then sacrificed and livers were sectioned and histochemically examined for the number and size of gamma-glutamyl transpeptidase (GGT) positive foci. These foci contain cells that are "resistant" to the necrotizing effects of carbon tetrachloride and to the proliferation-inhibiting effects of 2-acetylaminofluorene and are considered to represent preneoplastic transformations. Neither the number nor the size of GGT foci appeared to be increased in naphthalene-treated rats compared with vehicle controls. The role of GGT as a biochemical marker of preneoplastic foci has recently been assessed by Hendrich and Pitot (1987).

4.5. Mutagenicity

Naphthalene was reported to be nonmutagenic in *Salmonella* strains TA98, A100, TA1535, and TA1537 when tested with or without S9 activation at levels of up to 1,000 µg/plate (McCann et al., 1975). Similarly, Godek et al. (1985) reported that naphthalene at concentrations up to 300 µg/plate was negative in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 with or without metabolic activation. Connor et al. (1985) reported naphthalene was not mutagenic in two DNA-repair deficient strains of *S. typhimurium*, TA100 and TA98 and two other strains UTH8414 and UTH8413 which have full DNA repair capacity, both with and without S9 activation.

Naphthalene at 250 mg/kg in corn oil did not induce micronuclei in bone marrow of CD-1 mice (Sorg et al., 1985). This dose level was determined to be the maximum tolerated dose in a range-finding study and is approximately 50 percent of the oral LD_{50} for CD-1 mice (Shopp et al., 1984). Barfknecht et al. (1985) reported that naphthalene at concentrations up to 16 µg/mL (0.32 µg) did not induce unscheduled DNA synthesis in rat hepatocytes. Concentrations greater than 16 µg/mL were found to be extremely cytotoxic.

4.6. Teratogenicity and Reproductive Effects

In what appears to be the results of the same study (Plasterer et al., 1985; Booth et al., 1983), single oral doses (300 mg/kg) of naphthalene were administered daily for 8 consecutive days to 50 pregnant mice beginning on day 7 of gestation. This dose was estimated to be at or just below the maximum tolerated dose for acute lethality. A significant increase in maternal lethality ($p < 0.05$) and a decrease in mean maternal body weights as well as the number of live pups per litter ($p < 0.05$) on postpartum day 1 were noted when compared to the controls. There was not a concomitant increase in dead pups. There were no effects on pup survival and mean body weights. No gross congenital abnormalities were detected in the pups, although the method used to examine the pups was not reported.

Hardin et al. (1981) administered naphthalene i.p. (395 mg/kg) in corn oil to pregnant Sprague-Dawley rats on day 1 of gestation. Daily injections continued through day 15. Treatment-related effects were reported to be limited to evidence of maternal or fetal toxicity.

In a pilot range-finding study, 20 artificially inseminated New Zealand white rabbits (at least 24 weeks of age and weighing 4 to 5 kg) were orally dosed with naphthalene (in 1% methylcellulose vehicle) at 50 to 1,000 mg/kg from gestational days (GD) 6 to 18. Maternal lethality and/or abortion were increased at doses of 630 mg/kg or greater, but no data were collected. No

differences in reproductive parameters were noted, and no malformations or fetal death occurred at the lower dose levels (Naismith and Matthews, 1985).

In the main study by Naismith and Matthews (1986), 18 artificially inseminated New Zealand white rabbits per group were orally dosed with naphthalene (1% methylcellulose vehicle) at 0, 40, 200, or 400 mg/kg from GD 6 to 18 (age was not specified; body weights were reported but data were incomplete). Maternal body weights and body weight gains were comparable among all test groups and controls. Food consumption of high-dose (400 mg/kg) animals was significantly greater ($p \leq 0.05$) than controls during GD 7 to 15 and significantly greater ($p \leq 0.05$) than controls during GD 23 to 25 and 27 to 29. Pharmacotoxic signs observed during the study included decreased activity, dyspnea, weight loss, cyanosis, salivation, and loose stools or diarrhea, and occurred in an apparent dose-related manner. Gross examination of dams and controls indicated no differences in reproductive parameters: number of corpora lutea, total number of implantations, viable or nonviable fetuses, pre- or postimplantation loss, fetal body weights, and fetal sex distribution. Several malformations and variations were observed. However, they were equally distributed among groups; no dose-related trends were apparent. The study authors concluded that oral administration of naphthalene to pregnant rabbits did not evoke a teratogenic effect. However, the teratogenic potential could not be adequately assessed because of lack of information on the methods of fetal sacrifice and of visceral and skeletal examinations.

Matarova (1982) reported that naphthalene administered by oral gavage (0.015, 0.15, and 1.5 mg/kg) on a chronic basis to pregnant female albino rats was associated with adverse effects on reproductive function and development of progeny (English translation of complete study). The reported threshold for effects was 0.075 mg/kg. Because of a lack of information on protocol design, tests for significance, experimental data, these reported results should be viewed with caution until substantiated.

4.7. Neurotoxicity

No reports were found in the available literature that described any neurotoxic effects due to naphthalene exposure except for retinal effects in rats and rabbits, which are discussed in Section 4.4.2.

4.8. Effects on Humans

4.8.1 Hemotoxicity

Acute hemolytic anemia is the most frequent manifestation of naphthalene poisoning in humans. Case reports have described the appearance of acute hemolytic anemia after: 1) naphthalene ingestion by children (Jacobziner and Raybin, 1964; Athreya et al., 1961; Gross et al., 1958; Zinkham and Childs, 1958; Zinkham and Childs, 1957; Haggerty, 1956; Chusid and Fried, 1955; Bregman, 1954; MacGregor, 1954; Abelson and Henderson, 1951; Mackell et al., 1951; Zuelzer and Apt, 1949;) and adults (Anziulewicz et al., 1959, Zinkham and Childs, 1958; Zinkham and Childs, 1957; Gidron and Leurer, 1956); 2) combined dermal absorption and inhalation of naphthalene vapor by neonates (Grigor et al., 1966; Naiman and Kosoy, 1964; Valaes et al., 1963; Dawson et al., 1958; Cock, 1957; Schafer, 1951) and adults (Younis et al., 1957); 3) inhalation of naphthalene vapor by neonates (Hanssler, 1964; Irle, 1964); 4) inhalation of naphthalene vapor by a child and adults (Linick, 1983); and 5) transplacental exposure of the fetus to

naphthalene that had been ingested by the mother (Anziulewicz et al., 1959; Zinkham and Childs, 1958; Zinkham and Childs, 1957).

The reported mechanisms and range of exposure to naphthalene in these case studies were: 1) chewing, sucking, or swallowing of mothballs (one to numerous) as a single incident or for periods up to 3 months; 2) ingestion of toilet bowl deodorant cakes (pure naphthalene) by a child over a period of a year; 3) ingestion of naphthalene-containing deodorant in a diaper pail for an unspecified period; 4) combined dermal absorption and inhalation for a few days of naphthalene vapor from apparel and bed clothing that had been stored in mothballs; 5) inhalation of vapor from a naphthalene-containing medication; 6) inhalation of naphthalene vapor for several years from excessive numbers of mothballs kept throughout the home; and 7) transplacental exposure, for about 3 months, of fetuses to naphthalene ingested by the mother.

Doses of naphthalene were not generally reported in these case studies because of the poorly defined nature of the exposure. Tests to detect naphthalene derivatives in the urine of the anemic individuals were negative in some cases (Zinkham and Childs, 1958; Cock, 1957) and positive in others (Athreya et al., 1961; Mackell et al., 1951; Zuelzer and Apt, 1949). Some reports noted the odor of naphthalene in the urine at the time of hospitalization (Cock, 1957; Mackell et al., 1951).

Symptoms of naphthalene toxicity that frequently precede the diagnosis of acute hemolytic anemia in persons of all ages include mild to severe jaundice, dark urine (red, orange, or port wine colored), pallor, and lethargy (Linick, 1983; Grigor et al., 1966; Irle, 1964; Jacobziner and Raybin, 1964; Naiman and Kosoy, 1964; Anziulewicz et al., 1959; Dawson et al., 1958; Zinkham and Childs, 1958; Cock, 1957; Younis et al., 1957; Zinkham and Childs, 1957; Gidron and Leurer, 1956; Haggerty, 1956; Chusid and Fried, 1955; Bregman, 1954; MacGregor, 1954; Abelson and Henderson, 1951; Mackell et al., 1951; Schafer, 1951; Zuelzer and Apt, 1949; Nash, 1903). Severe jaundice is often the reason for hospitalization, since the jaundice often develops before severe anemia becomes manifest (Valaes et al., 1963). However, it is clear that anemia and jaundice can develop in parallel as shown by a time-course study of hematologic changes in a 16-year-old girl who had ingested about 6 g of naphthalene in a suicide attempt (Gidron and Leurer, 1956). Vomiting and tachycardia are occasionally observed as preclinical signs of naphthalene poisoning in persons of all ages (Linick, 1983; Grigor et al., 1966; Athreya, 1961; Zinkham and Childs, 1958; Dawson et al., 1958; Younis et al., 1957; Zinkham and Childs, 1957; Haggerty, 1956; Bregman, 1954; MacGregor, 1954; Abelson and Henderson, 1951; Zuelzer and Apt, 1949). Preclinical signs of naphthalene toxicity observed primarily in neonates or children include anorexia, cyanosis, shallow respiration or apnea, convulsions, and diarrhea (Grigor et al., 1966; Hanssler, 1964; Jacobziner and Raybin, 1964; Naiman and Kosoy, 1964; Athreya et al., 1961; Anziulewicz et al., 1959; Zinkham and Childs, 1958; Cock, 1957; Zinkham and Childs, 1957; Haggerty, 1956; Chusid and Fried, 1955; Abelson and Henderson, 1951; Mackell et al., 1951; Schafer, 1951; Zuelzer and Apt, 1949). Preclinical symptoms of naphthalene poisoning reported by children or adults include fever, confusion, pain in abdominal or kidney region, pain at urination, nausea, headache, fainting, and vertigo (Linick, 1983; Athreya et al., 1961; Zinkham and Childs, 1958; Zinkham and Childs, 1957; Younis et al., 1957; Haggerty, 1956; Gidron and Leurer, 1956; Chusid and Fried, 1955; MacGregor, 1954; Bregman, 1954; Mackell et al., 1951; Abelson and Henderson, 1951; Zuelzer and Apt, 1949; Nash, 1903).

Frequent laboratory findings indicative of severe hemolytic anemia after naphthalene poisoning in persons of all ages include depressed hemoglobin, hematocrit, and erythrocyte count; elevated leukocyte and reticulocyte counts; erythrocyte anisocytosis, polychromatophilia, fragmentation, spherocytosis, and microspherocytosis; and occasional hemoglobinuria (Grigor et al., 1966; Hanssler, 1964; Irle, 1964; Naiman and Kosoy, 1964; Valaes et al., 1963; Athreya et al., 1961; Anziulewicz et al., 1959; Zinkham and Childs, 1958; Dawson et al., 1958; Younis et al., 1957; Cock, 1957; Haggerty, 1956; Chusid and Fried, 1955; MacGregor, 1954; Bregman, 1954; Mackell et al., 1951; Zuelzer and Apt, 1949).

Additional laboratory findings indicative of severe hemolytic anemia after exposure of primarily neonates or children to naphthalene include erythrocyte poikilocytosis and microcytosis; elevated serum bilirubin; occasional observation of Heinz bodies, nucleated erythrocytes, and Howell-Jolly bodies; and occasional observation of methemoglobinuria (Grigor et al., 1966; Hanssler, 1964; Irle, 1964; Naiman and Kosoy, 1964; Valaes et al., 1963; Athreya et al., 1961; Anziulewicz et al., 1959; Zinkham and Childs, 1958; Dawson et al., 1958; Cock, 1957; Haggerty, 1956; Chusid and Fried, 1955; MacGregor, 1954; Bregman, 1954; Mackell et al., 1951; Zuelzer and Apt, 1949).

Many of the studies of naphthalene toxicity in neonates included tests to determine whether Rh sensitization was a complicating factor; these tests gave no evidence of blood group incompatibility (Hanssler, 1964; Naiman and Kosoy, 1964; Valaes et al., 1963; Athreya et al., 1961; Anziulewicz et al., 1959; Dawson et al., 1958; Zinkham and Childs, 1958; Cock, 1957; Haggerty, 1956; Bregman, 1954; Schafer, 1951). When investigated in some of these studies, sickle cell anemia also was not a complicating factor except in one of the four subjects studied by Zuelzer and Apt (1949).

In most studies of persons who have developed severe hemolytic anemia after exposure to naphthalene, treatment with blood transfusions, treatment with blood transfusions plus alkali therapy, or observation without either of these treatments has led to complete patient recovery with no observed complications (Grigor et al., 1966; Hanssler, 1964; Irle, 1964; Jacobinzer and Raybin, 1964; Valaes et al., 1963; Athreya et al., 1961; Anziulewicz et al., 1959; Dawson et al., 1958; Zinkham and Childs, 1958; Cock, 1957; Younis et al., 1957; Gidron and Leurer, 1956; Haggerty, 1956; Chusid and Fried, 1955; Bregman, 1954; MacGregor, 1954; Mackell et al., 1951; Abelson and Henderson, 1951; Zuelzer and Apt, 1949). However, deaths have been observed after naphthalene-induced hemolytic anemia (Schafer, 1951; Younis et al., 1957; Valaes et al., 1963; Naiman and Kosoy, 1964).

Two groups of individuals have been shown to be especially susceptible to naphthalene-induced hemolytic anemia:

1. Persons whose erythrocytes are deficient in glucose 6-phosphate dehydrogenase (G6PDH) or persons in whom erythrocyte GSH is rapidly depleted by certain oxidant chemicals (Grigor et al., 1966; Naiman and Kosoy, 1964; Valaes et al., 1963; Athreya et al., 1961; Dawson et al., 1958; Gross et al., 1958; Zinkham and Childs, 1958). The precise mechanism by which GSH is depleted or a deficiency of G6PDH leads to naphthalene-induced hemolysis in these cases is not clear. A deficiency of G6PDH will decrease the rate of conversion of nicotinamide adenine dinucleotide phosphate from its oxidized (NADP) to its reduced form (NADPH). One hypothesis for increased naphthalene sensitivity in G6PDH-deficient individuals is that the decreased availability of NADPH

will decrease the conversion of oxidized glutathione to GSH, reduce the rate of conjugation and excretion of naphthalene metabolites and increase the accumulation of naphthalene metabolites in the body. A similar hypothesis may explain increased naphthalene sensitivity in individuals in which erythrocyte GSH can be rapidly depleted by certain oxidant chemicals (Naiman and Kosoy, 1964; Kellermeyer et al., 1962; Dawson et al., 1958; Gross et al., 1958; Zinkham and Childs, 1958). Gross et al. (1958) demonstrated a quantitative correlation between G6PDH deficiency and diminished levels of GSH in infants beyond 55 hours of age; however, diminished levels of erythrocyte GSH were observed in infants of less than 55 hours of age despite high levels of G6PDH activity. A second hypothesis for increased naphthalene sensitivity in G6PDH-deficient individuals is that the decreased availability of NADPH will, in the presence of oxidant metabolites of naphthalene, allow the accumulation of methemoglobin and products of its further irreversible oxidation (Kellermeyer et al., 1962).

2. Neonates (Grigor et al., 1966; Naiman and Kosoy, 1964; Valaes et al., 1963; Dawson et al., 1958; Gross et al., 1958; Zinkham and Childs, 1958). The sensitivity of neonates to naphthalene is explained in part by the same factors that confer sensitivity to children and adults; namely, G6PDH deficiency and/or diminished levels of GSH as described above. Additional naphthalene sensitivity in newborns may be conferred by the immaturity of pathways necessary for the conjugation and excretion of naphthalene metabolites (Valaes et al., 1963). Evidence for the latter hypothesis is suggested by the finding that glucuronide excretion by human newborn infants increased gradually during the first week of life and that the initial levels and the rate of increase were lower in the premature infant than in the full-term infant (Brown and Burnett, 1957).

A single report described a case of aplastic anemia in a 68 year-old woman who had been exposed to naphthalene in the workplace (Harden and Baetjer, 1978). The interpretation of this finding is difficult, since the woman had been simultaneously exposed to p-dichlorobenzene.

4.8.2. Skin Sensitization

Fanburg (1940) described the case of a man who had developed an allergic reaction to naphthalene from clothing that had been stored in mothballs. The reaction was an exfoliative dermatitis resembling mycosis fungoides. The elimination of naphthalene from the patient's environment resulted in prompt recovery, which lasted uninterruptedly for a 7-year period of observation.

4.8.3. Ocular Toxicity

Case studies that describe the presence of cataracts in persons exposed to naphthalene by the oral, dermal, or inhalation routes have been summarized in an ambient water quality criteria document for naphthalene (U.S. EPA, 1980). Ghetti and Mariani (1956) associated the occurrence of cataracts in 8 of 21 workers with naphthalene exposure in a manufacturing plant. Other cases of occupational instances of cataract formation have been described by Hollwich et al. (1975).

4.8.4. Carcinogenicity

Wolf (1976) reported 6 cases of carcinomas among 15 workers exposed to vapors of naphthalene and coal tar for 7-32 years at a coal-tar naphthalene production facility. Four of the workers developed carcinomas of the larynx and all were smokers; the other two developed carcinomas of the pylorus and cecum. There was no control group. Experiments in animals, however, suggest that coal tar fractions with boiling points higher than 270°C contain most of the carcinogenic activity of the coal tar, and fractions with lower boiling points, which include naphthalene, are generally not carcinogenic (Kennaway, 1930).

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