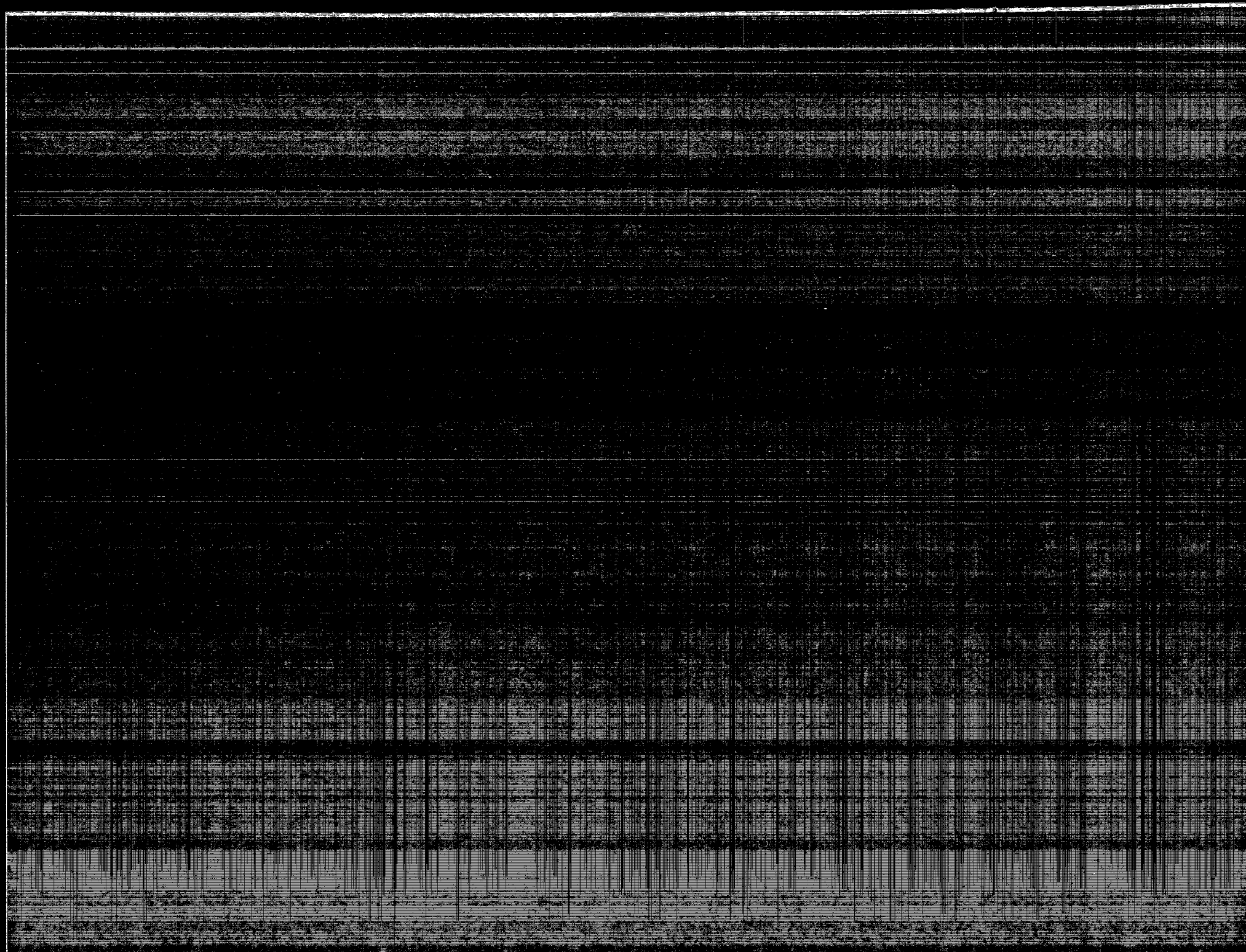
United States
Environmental Protection
Agency

Health Effects Support Document for Naphthalene

External Review Draft



Health Effects Support Document for Naphthalene

EXTERNAL REVIEW DRAFT

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FOREWORD

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Administrator of the Environmental Protection Agency (EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. In addition, the SDWA requires EPA to make regulatory determinations for no fewer than five contaminants by August 2001. The criteria used to determine whether or not to regulate a chemical on the Contaminant Candidate List (CCL) are the following:

> The contaminant may have an adverse effect on the health of persons.
>
> The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
>
> In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The Agency's findings for all three criteria are used in making a determination to regulate a contaminant. The Agency may determine that there is no need for regulation when a contaminant fails to meet one of the criteria. The decision not to regulate is considered a final Agency action and is subject to judicial review.

This document provides the health effects basis for the regulatory determination for naphthalene. In arriving at the regulatory determination, data on toxicokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. In order to avoid wasteful duplication of effort, information from the following risk assessments by the EPA and other government agencies were used in development of this document.

> U.S. EPA 1987. U.S. Environmental Protection Agency. Summary Review of Health Effects Associated with Naphthalene. Washington, D.C.: Office of Health and Environmental Assessment, EPA/600/8-87/005F
>
> U.S. EPA. 1990. U.S. Environmental Protection Agency. Naphthalene Drinking Water Health Advisory. Office of Water. March.
>
> ATSDR. 1995. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Naphthalene (update). Department of Health and Human Services. CRC Press, Boca Raton, FL 1997.
>
> U.S. EPA 1998a. U.S. Environmental Protection Agency. Toxicological Review of Naphthalene (CAS 91-20-3) in support of summary information on the Integrated Risk Information System (IRIS). August 1998.

U.S. EPA 1998b. U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS): Naphthalene. Cincinnati, OH. September 17, 1998.

Information from the published risk assessments was supplemented with information from recent studies of naphthalene identified by literature searches conducted in 1999 and 2000 and the primary references for key studies.

Generally a Reference Dose (RfD) is provided as the assessment of long-term toxic effects other than carcinogenicity. RfD determination assumes that thresholds exist for certain toxic effects, such as cellular necrosis. It is expressed in terms of milligrams per kilogram per day (mg/kg-day). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The carcinogenicity assessment for naphthalene includes a formal hazard identification. Hazard identification is a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen via the oral route and of the conditions under which the carcinogenic effects may be expressed.

Guidelines that were used in the development of this assessment may include the following: the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA,1986a), *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a), *Proposed Guidelines for Carcinogen Risk Assessment* (1996a), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996b), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998c); *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988); *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995); and Memorandum from EPA Administrator, Carol Browner, dated March 21, 1995.

The chapter on occurrence and exposure to naphthalene through potable water was developed by the Office of Ground Water and Drinking Water. It is based primarily on unregulated contaminant monitoring (UCM) data collected under SDWA. The UCM data are supplemented with ambient water data, as well as information on production, use, and discharge.

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1.0 EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) has prepared this Drinking Water Support Document to assist in determining whether to establish a National Primary Drinking Water Regulation (NPDWR) for naphthalene. Case study reports from humans and laboratory studies with animals demonstrate that naphthalene can have adverse effects on the oxidation state of hemoglobin (methemoglobinemia), the structural integrity of the red blood cell membrane (hemolysis), the activity of selected hepatic enzymes, and body weight gain following oral exposure. It also contributes to the formation of cataracts in certain species and strains of laboratory animals. These effects tend to occur at moderate-to-high doses that are unlikely to be found in public water systems. Accordingly, regulation of naphthalene in public water does not present a meaningful basis for health risk reduction. Prolonged inhalation exposure to naphthalene, such as can occur in the workplace, may present risks to humans, but risk from other exposure routes is minimal.

Naphthalene (Chemical Abstracts Services Registry Number 91-20-3) is a bicyclic aromatic hydrocarbon with the chemical formula $C_{10}H_8$. In purified form, naphthalene is a white crystalline solid that is sparingly soluble in water (0.031 g/L). Naphthalene is a natural constituent of coal tar and crude oil. It is obtained in purified form from these raw materials by fractional distillation. The available historical data suggest that both production and consumption of naphthalene are declining in the United States. Crystalline naphthalene is used by consumers as a moth repellant and as a deodorizer in toilets and diaper pails. Approximately 60% of the naphthalene consumed in the United States is used commercially in the manufacture of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellants, and other products.

Direct releases to air account for more than 90% of the naphthalene entering environmental media. In comparison, about 5% of the naphthalene entering the environment is released to water and about 2.7% is discharged to land. Releases to water occur primarily from coal tar production and distillation processes. Other contributing sources include effluents from wood preserving facilities and oil spills. Over half of the releases to water occur to surface water.

Naphthalene is lost from surface water primarily by volatilization. Estimates for half-life range from 4.2 to 7.3 hours. A small fraction (less than 10%) is associated with organic material and settles into sediments. Naphthalene remaining in the water column is degraded by photolysis (half-life = 71 hours) and/or biodegradation processes (highly variable half-life depending on naphthalene concentration, nutrient supply, and water temperature).

Naphthalene has been detected in untreated ambient ground water samples reviewed and/or analyzed by the U.S. Geological Survey National Ambient Water Quality Assessment (NAWQA) program. Detection frequencies and concentrations for all wells are relatively low; however, occurrence is considerably higher for urban wells when compared to rural wells. Naphthalene has been detected at slightly higher frequencies in urban and highway runoff. Concentrations in runoff are low. Naphthalene has also been found at Agency for Toxic Substances and Disease Registry (ATSDR) HazDat and Comprehensive Environmental

Response, Compensation and Liability Act (CERCLA) National Priority List (NPL) sites across the country, and releases have been reported through the Toxic Release Inventory.

Naphthalene has been detected in public water system (PWS) samples collected under the provisions of the Safe Drinking Water Act (SDWA), although only 0.43% and 0.24% of total samples from two rounds of sampling showed detections. Significantly, the values for the 99th percentile and median concentrations of all samples are less than the Minimum Reporting Level (MRL). For Round 1 samples with detections, the median concentration is 1.0 µg/L and the 99th percentile concentration is 900 µg/L. Median and 99th percentile concentrations for Round 2 detections are 0.74 µg/L and 73 µg/L, respectively. Public water systems with detections constitute only 1.2% of Round 1 systems and 0.8% of Round 2 systems, representing an estimated 769 systems (Round 1) and 491 systems (Round 2) when extrapolated to the national level. National estimates for the population served by PWSs with detections are also low, especially for detections greater than the Health Reference Level (HRL).

Nationally aggregated data for naphthalene in media other than water are generally not available. The available data from localized studies suggest that naphthalene levels in fish and non-fish food items are generally low unless they have been smoked or grilled. Estimates for daily intake of naphthalene via the diet ranged from 40.7 to 237 ng/kg-day for a 70 kg adult and 204 to 940 ng/kg-day for a 10 kg child. Comparison of the available data indicates that, based on rough estimates of average intakes for naphthalene, most exposure occurs through inhalation. Estimated intakes from air are approximately 5 to 45-fold greater than those from food and water.

Naphthalene is absorbed when administered orally, although no studies were identified that quantified the rate or extent of uptake. Dermal absorption of naphthalene has been inferred from toxicity observed in human neonates who were reportedly exposed by dermal contact with clothing that had been stored with naphthalene mothballs or naphthalene flakes. No empirical data that describe the rate or extent of naphthalene absorption following inhalation exposure were identified in the materials reviewed for this report. Physiologically-based pharmacokinetic modeling results suggest that inhaled naphthalene is absorbed rapidly into the blood.

After distribution, naphthalene is extensively metabolized. As many as 21 metabolites (including oxidized derivatives and conjugates) have been identified in the urine of humans and animals exposed to naphthalene. The factors that influence the relative proportions of individual metabolites include species, tissue type, and tissue concentration of naphthalene. The available evidence suggests that the naphthalene metabolites 1,2-naphthoquinone and 1,4-naphthoquinone are the primary toxic species.

Information on the human health effects of naphthalene have been obtained from medical case reports of accidental or intentional ingestion. These reports identify hemolytic anemia as the significant outcome of oral exposure to large doses of naphthalene in humans. There is one report of cataracts in humans, but it was published in the early twentieth century and, thus, has limited applicability because of uncertainties regarding compound purity and exposure conditions. There are no reliable human toxicity data for subchronic or chronic exposure to naphthalene.

Studies of occupational exposure to naphthalene are limited to a single report of possible naphthalene-related cataracts in chemical workers and two limited epidemiological studies that provide ambiguous evidence of associations between occupational naphthalene exposure and cancer. Owing to their numerous limitations, none of these studies is useful in characterizing the potential risks associated with human exposures to naphthalene.

Individuals deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) have been identified as a potentially sensitive population for naphthalene exposure. Individuals with this deficiency have lower erythrocyte levels of reduced glutathione, a compound that normally protects red blood cells against oxidative damage. G6PD-deficient neonates, infants, and the fetus are particularly sensitive to naphthalene toxicity because the metabolic pathways responsible for conjugation of toxic metabolites (a prerequisite for excretion) are not yet well developed. In addition, they have low levels of methemoglobin reductase. This enzyme catalyzes the reduction of methemoglobin, an oxidized form of hemoglobin that occurs in association with hemolytic anemia.

Short-term administration of an average daily dose of 262 mg/kg-day to a single dog resulted in signs of hemolytic anemia, including decreased hemoglobin concentration, decreased hematocrit, presence of Heinz bodies, extreme leukocytosis, and reticulocytosis. Other signs noted included pronounced lethargy and ataxia. In mice, short-term oral exposure to naphthalene at doses up to 53 mg/kg-day had no apparent adverse effects. Adverse effects observed in mice exposed to 267 mg/kg-day included increased mortality and decreased terminal body weights (4–10%) in males and females, decreased absolute thymus weights (30%) in males, increased bilirubin in females, and increased spleen and lung weights (relative and absolute) in females. Neither red cell hemolysis nor cataract formation was observed in the naphthalene-exposed mice. Liver changes (increased liver weight, increased lipid peroxidation, moderate increases in serum enzyme activity) have been reported in rats exposed to relatively high doses of naphthalene (approximately 1,000 mg/kg-day or more) when administered for durations of 10 days to 9 weeks. However, no effects on liver weight were noted in a 14-day gavage study at doses up to 267 mg/kg-day. Naphthalene-related cataract formation has been reported in rabbits, mice and rats following acute and short-term oral exposures.

The subchronic oral toxicity of naphthalene has been investigated in rats and mice. Male and female rats administered 400 mg/kg-day by corn oil gavage for 13 weeks exhibited diarrhea, lethargy, hunched posture, and rough coats during the study, and one high-dose male rat died during the last week of exposure. Body weights were significantly decreased in males at 200 mg/kg-day and in males and females at 400 mg/kg-day. In a similar study conducted in mice, transient signs of toxicity (lethargy, rough coats, decreased food consumption) were observed at 200 mg/kg-day and above. Female mice exposed to naphthalene exhibited dose-related decreases in body weight reaching a maximum of 24.5% in females receiving 200-mg/kg-day. A second oral exposure study in mice observed changes in organ weight and enzyme alterations indicative of impacts on liver function at 133 mg/kg-day.

Relatively little information is available regarding the neurological effects of naphthalene exposure in experimental animals. Two studies (one each in rabbits and pregnant rats) have noted

treatment-related signs of neurotoxicity (lethargy, slow respiration including periods of apnea, body drop and labored breathing, and/or inability to move after dosing) at doses of 50 to 450 mg/kg-day. These effects were transient in pregnant rats at doses of 50 to 150 mg/kg-day. However, the subchronic studies discussed above found no clinical signs of neurotoxicity at similar doses.

The reproductive and developmental toxicity of naphthalene has been evaluated in rats, mice and rabbits. The results of these studies suggest that naphthalene is a very weak reproductive and developmental toxicant, with detectable effects occurring only at doses associated with substantial maternal toxicity.

The 2-year inhalation National Toxicology Program (NTP) bioassays of naphthalene reported increased incidences of non-neoplastic nasal lesions in male rats exposed for 6 hours/day to 10 ppm. In mice, there was chronic inflammation of the lungs and nasal epithelium accompanied by hyperplasia

There are no oral exposure studies that are considered adequate to fully assess the carcinogenic potential of naphthalene. No tumors were identified in a study of rats orally administered 42 mg/kg-day for over 2 years. However, the published report contains limited experimental detail. NTP concluded that there was some evidence of carcinogenic potential in female mice exposed by inhalation to 30 ppm naphthalene for 2 years. Clear evidence for carcinogenic potential was observed in male and female rats exposed to 60 ppm naphthalene (approximately 20 mg/kg-day) by inhalation for 2 years. However, statistical significance was achieved only for tumors of the respiratory track (lungs in mice; nasal cavity in rats). Several studies have been conducted in which naphthalene was administered by routes of exposure other than inhalation or diet. No carcinogenic responses were observed in these studies and each has at least one limitation that makes it inadequate for assessing the potential for lifetime risk.

The mutagenic and genotoxic potential of naphthalene has been evaluated in numerous *in vitro* and *in vivo* assays. The results of most studies were negative, suggesting that the mutagenic and genotoxic potential of naphthalene and its metabolites are weak.

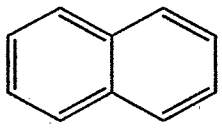
When naphthalene was evaluated for EPA's Integrated Risk Information System (IRIS), prior to completion of the NTP bioassay in rats, it was classified in Group C: possible human carcinogen. This classification was based on inadequate human data for exposure to naphthalene via the oral and inhalation routes and on limited evidence of carcinogenicity in animals exposed via the inhalation route. Using the 1996 Proposed Guidelines for Carcinogen Risk Assessment, the human carcinogenic potential of naphthalene via oral or inhalation routes "cannot be determined." Following completion of the IRIS review, the NTP bioassay in rats showed clear evidence for carcinogenic activity within the nasal cavity, but not in other tissues. The new data strengthen the association of carcinogenicicty with the inhalation route of exposure and weaken the tenuous association with the oral route. For this reason, the carcinogenic potential of naphthalene via the inhalation route may need to be re-evaluated.

A quantitative cancer dose-response assessment for naphthalene was not conducted for IRIS. This decision was made because adequate chronic oral animal data are lacking and because the available human data are inadequate to evaluate a plausible association with cancer. Although statistically significant increases in the incidence of respiratory system tumors were reported in female mice (lung) and rats (nasal cavity) exposed to naphthalene via inhalation for 2 years, this evidence is considered insufficient to assess the carcinogenic potential of naphthalene in humans exposed via the oral route. The existing data on the tumorigenic effects of naphthalene by the oral route of exposure are inadequate to support a judgment and, therefore, would be categorized as Group D, "not classifiable".

2.0 IDENTITY: CHEMICAL AND PHYSICAL PROPERTIES

Naphthalene is a bicyclic aromatic hydrocarbon with the chemical formula $C_{10}H_8$ (Figure 2-1). Pure naphthalene is a white, water-insoluble solid in crystalline or marble-like form and has a distinct mothball odor. The chemical and physical properties of naphthalene are summarized in Table 2-1.

Figure 2-1. Chemical Structure of Naphthalene



Naphthalene

Table 2-1. Chemical and Physical Properties of Naphthalene

Property	Information
Chemical Abstracts Registry (CAS) No.	91-20-3
Registry of Toxic Effects of Chemical Substances No.	QJ0525000
RCRA Waste No.	U165
EPA Pesticide Chemical Code	055801
Synonyms	Tar Camphor; Albocarbon; Naphthene; Naphthalin; Naphthaline; Mothballs; Mothflakes; White Tar; Dezodorator; Mighty 150; Mighty RD1
Registered Trade Name	Caswell No. 587 ®
Chemical Formula	$C_{10}H_8$
Molecular Weight	128.19
Boiling Point	218°C
Melting Point	80.5°C
Vapor Pressure	0.087 mm Hg
Partition Coefficients	Log K_{ow} 3.29 Log K_{oc} 2.97
Solubility in Water	0.0031 g/100 mL
Organic Solvents	Benzene, Alcohol, Ether, Acetone

Source: ATSDR (1995); ChemIDplus (2000)

3.0 USES AND ENVIRONMENTAL FATE

3.1 Production and Use

Naphthalene is naturally present in fossil fuels such as petroleum and coal, and is generated when wood or tobacco are burned. Naphthalene is produced in commercial quantities from either coal tar or petroleum. Most of the naphthalene produced in the United States comes from petroleum by the dealkylation of methylnaphthalenes in the presence of hydrogen at high temperature and pressure. Another common production method is the distillation and fractionation of coal tar.

Naphthalene is a natural constituent of coal tar and crude oil (11% and 1.3%, respectively) (Merck Index, 1996). Purified naphthalene is obtained from coal tar or petroleum products by fractional distillation. Fractional distillation is the process of heating a liquid until its more volatile constituents pass into the vapor phase. This vapor is then cooled to recover constituents by condensation (Encarta, 2000). Different constituents will vaporize at different boiling points, thus permitting separation of constituents. Most naphthalene is recovered in the middle fraction (ATSDR, 1995). This fraction is subsequently purified by treatment with sulfuric acid, sodium hydroxide, and water, followed by sublimation or a second fractional distillation. U.S. manufacturers produced 1.09×10^5 metric tons of naphthalene in 1996 (CEH, 2000).

Naphthalene production in the United States dropped from 900 million pounds per year (lbs/yr) in 1968 to 354 million lbs/yr in 1982. Approximately 7 million lbs of naphthalene were imported and 9 million lbs were exported in 1978. By 1989, imports had dropped to 4 million lbs, and exports increased dramatically to 21 million lbs (ATSDR, 1995).

U.S. consumption of naphthalene was 1.08×10^5 metric tons in 1996 (CEH, 2000). Naphthalene is used in the production of phthalic anhydride, which is an intermediate in the manufacture of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellants, and other products (U.S. EPA, 1998a). These uses account for approximately 60% of naphthalene consumption in the United States (CEH, 1997). Crystalline naphthalene is used as a moth repellant and as a deodorizer for diaper pails and in toilets (U.S. EPA, 1998a). In the past, naphthalene was used medicinally as an antiseptic, expectorant, and anthelminthic, and for treatment of gastrointestinal and skin disorders (ATSDR, 1995). Most naphthalene consumption (60%) is through use as an intermediary in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, and insect repellents. Crystalline naphthalene is used as a moth repellent and a solid block deodorizer for diaper pails and toilets. Naphthalene is also used to make the insecticide carbaryl, synthetic leather tanning agents, and surface active agents (ATSDR, 1995).

3.2 Environmental Release

Naphthalene is listed as a toxic release inventory (TRI) chemical. In 1986, the Emergency Planning and Community Right-to-Know Act (EPCRA) established the Toxic Release Inventory (TRI) of hazardous chemicals. Created under the Superfund Amendments and Reauthorization

Act (SARA) of 1986, EPCRA is also sometimes known as SARA Title III. The EPCRA mandates that larger facilities publicly report when TRI chemicals are released into the environment. This public reporting is required for facilities with more than 10 full-time employees that annually manufacture or produce more than 25,000 pounds, or use more than 10,000 pounds, of TRI chemical (U.S. EPA, 1996d, 2000a).

Under these conditions, facilities are required to report the pounds per year of naphthalene released into the environment both on- and off-site. The on-site quantity is subdivided into air emissions, surface water discharges, underground injections, and releases to land (see Table 3-1). For naphthalene, air emissions constitute most of the on-site releases. Also, surface water discharges exhibit no obvious trend over the period for which data is available (1988–1998), but discharges hit a low in 1996 and 1997, and increased again in 1998. These TRI data for naphthalene were reported from 47 States (excluding ID, NH, and VT), indicating the widespread production or use of this chemical (U.S. EPA, 2000b).

Table 3-1. Environmental Releases (in pounds) for Naphthalene in the United States (1988–1998).

Year	On-Site Releases				Off-Site Releases	Total On- & Off-site Releases
	Air Emissions	Surface Water Discharges	Underground Injection	Releases to Land		
1998	3,374,439	34,148	191,677	1,251,040	827,708	5,679,012
1997	2,449,488	13,333	187,927	82,204	491,124	3,224,076
1996	2,863,431	11,836	296,776	301,513	582,717	4,056,273
1995	2,690,669	43,311	44,318	32,085	474,106	3,284,489
1994	2,889,514	28,557	97,186	47,017	496,501	3,558,775
1993	2,744,887	31,179	79,814	49,886	334,985	3,240,751
1992	2,626,986	28,925	78,227	1,667,150	667,556	5,068,844
1991	2,927,511	31,508	39,112	55,278	983,371	4,036,780
1990	3,912,253	36,821	28,130	143,196	919,225	5,039,625
1989	3,523,562	146,983	39,552	118,409	1,054,602	4,883,108
1988	5,165,426	22,518	50,946	123,697	1,359,184	6,721,771

source: U.S. EPA (2000b)

Although the TRI information can be useful in giving a general idea of release trends, it is far from exhaustive and has significant limitations. For example, only industries that meet TRI criteria (at least 10 full-time employees and manufacture and processing of quantities exceeding 25,000 lbs/yr, or use of more than 10,000 lbs/yr) are required to report releases. These reporting criteria do not account for releases from smaller industries. Threshold manufacture and processing quantities also changed from 1988–1990 (dropping from 75,000 lbs/yr in 1988 to 50,000 lbs/yr in 1989 to 25,000 lbs/yr in 1990), creating possibly misleading data trends. Finally, the TRI data are meant to reflect releases and should not be used to estimate general exposure to a chemical (U.S. EPA, 2000c, d).

Naphthalene is also included in the Agency for Toxic Substances and Disease Registry's (ATSDR) Hazardous Substance Release and Health Effects Database (HazDat). This database records detections of listed chemicals in site samples. Naphthalene was detected in 44 States;

States without detections are AK, AZ, HI, NV, ND, and UT (ATSDR, 2000). The National Priorities List (NPL) of hazardous waste sites, created in 1980 by the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), is a listing of some of the most health-threatening waste sites in the United States. Naphthalene was again detected at sites in all but six States (HI, NE, NV, NM, ND, and WV) (U.S. EPA, 1999a).

3.3 Environmental Fate

Direct releases to the air account for more than 90% of the naphthalene entering environmental media (ATSDR, 1995). The primary discharge source is residential combustion of wood and fossil fuels. Other residential sources of naphthalene include tobacco smoke and the vaporization of moth repellants. Naphthalene may also be released to air during coal tar production and distillation, aeration processes in water treatment plants, and from use of naphthalene during chemical manufacturing (ATSDR, 1995).

About 5% of environmental naphthalene is released into water, primarily from coal tar production and distillation processes (ATSDR, 1995). Other contributors to water releases include effluents from wood preserving facilities and oil spills. More than half of these releases are to surface water (ATSDR, 1995). According to ATSDR (1995), only about 2.7% of naphthalene releases are discharged to land, but that number increased to 37% in the most recent year for which data are available (Table 3-1). Sources for release to land include coal tar production, naphthalene production, publicly operated treatment works (POTWs) sludge disposal, and the use of naphthalene-containing organic chemicals.

The primary removal process for naphthalene in air is through reactions with hydroxyl radicals. Naphthalene will also react with atmospheric N_2O_5, nitrate radicals, and ozone. The major products of these reactions are 1- and 2-naphthol and 1- and 2-nitronaphthalene. The half-life of atmospheric naphthalene is less than 1 day (ATSDR, 1995).

Naphthalene is lost from surface water via several mechanisms. Volatilization into the air is the most important route of loss from surface water (ATSDR, 1995). Mackay and Leinonen (1975) estimated a half-life of 7.2 hours for the volatilization of naphthalene (quantity not stated) from an aqueous solution 1 meter deep. Southworth (1979) estimated that a 10-fold increase in current velocity would accelerate volatilization 2 to 3 times. Rodgers et al. (1983) estimated a volatilization rate constant of 0.16 $hour^{-1}$, which resulted in a half-life of 4.3 hours (U.S. EPA, 1986d).

A small fraction (less than 10%) of naphthalene in water will be associated with particulate matter and will settle into sediments (ATSDR, 1995). Naphthalene that remains in surface water will be degraded through photolysis and biodegradation processes. Naphthalene undergoing photolysis has a half-life of about 71 hours (ATSDR, 1995). Biodegradation of this chemical also occurs quite rapidly, although degradation time will vary with naphthalene concentration, water temperature, and the availability of nutrients (U.S. EPA, 1986d). In general, the rate of biodegradation increases as the concentration of naphthalene increases. The half-life of

naphthalene in oil-polluted water versus unpolluted water is approximately 7 and 1,700 days, respectively (ATSDR, 1995).

Volatilization from soil surfaces and biodegradation are important processes for the removal of naphthalene from soil (U.S. EPA, 1986d). The estimated volatilization half-lives for naphthalene from soil containing 1.25% were 1.1 day from soil 1 cm deep and 14 days from soil 10 cm deep. Maximum biodegradation is reported to occur at a pH of 8 and in the presence of a positive redox potential (U.S. EPA, 1986d). Naphthalene is degraded to carbon dioxide and salicylate by aerobic microorganisms (ATSDR, 1995). Therefore, soil aerobic conditions strongly influence the half-life of the chemical. In addition, soil organic matter is an important factor in degradation time because the adsorption of naphthalene to organic matter significantly decreases its bioavailability to microorganisms.

3.4 Summary

In summary, most of naphthalene's consumption is through its use as an intermediary in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, and insect repellents. Its production in the United States declined from 1968 to 1982; however its import decreased and export increased from 1978 to 1989. The widespread use and production of naphthalene in the United States is evidenced by its presence in hazardous waste sites in at least 44 States (at NPL sites), its presence in site samples in at least 44 States (listed in ATSDR's HazDat), and its direct release into the environment in at least 47 States (based on TRI data).

4.0 EXPOSURE FROM DRINKING WATER

4.1 Introduction

This section of the report examines the occurrence of naphthalene in drinking water. While no complete national database exists of unregulated or regulated contaminants in drinking water from public water systems (PWSs) collected under the Safe Drinking Water Act (SDWA), this report aggregates and analyzes existing state data that have been screened for quality, completeness, and representativeness. Populations served by PWSs exposed to naphthalene are estimated, and the occurrence data are examined for regional or other special trends. To augment the incomplete national drinking water data and to aid in the evaluation of occurrence, information on the ambient occurrence of naphthalene is also reviewed.

4.2 Ambient Occurrence

To understand the presence of a chemical in the environment, an examination of ambient occurrence is useful. In a drinking water context, ambient water is source water existing in surface waters and aquifers before treatment. The most comprehensive and nationally representative data describing ambient water quality in the United States are being produced through the United States Geological Survey's (USGS) National Ambient Water Quality Assessment (NAWQA) program. However, as NAWQA is a relatively young program, complete national data are not yet available from their entire array of sites across the nation.

4.2.1 Data Sources and Methods

The USGS instituted the NAWQA program in 1991 for the purpose of examining water quality status and trends in the United States. NAWQA is designed and implemented in such a manner to allow consistency and comparison between representative study basins located around the country, facilitating interpretation of natural and anthropogenic factors affecting water quality (Leahy and Thompson, 1994).

The NAWQA program consists of 59 significant watersheds and aquifers referred to as "study units." The study units represent approximately two-thirds of the overall water usage in the United States and a similar proportion of the population served by public water systems. Approximately one-half of the nation's land area is represented (Leahy and Thompson, 1994).

To facilitate management and make the program cost-effective, approximately one-third of the study units at a time engage in intensive assessment for a period of 3 to 5 years. This is followed by a period of less intensive research and monitoring that lasts between 5 and 7 years. This way all 59 study units rotate through intensive assessment over a ten-year period (Leahy and Thompson, 1994). The first round of intensive monitoring (1991–1996) targeted 20 watersheds. This first group was more heavily slanted toward agricultural basins. A national synthesis of results from these study units and other research initiatives focusing on pesticides and nutrients is being compiled and analyzed (Kolpin et al., 1998; Larson et al., 1999).

For volatile organic chemicals (VOCs), the national synthesis will compile data from the first and second rounds of intensive assessments. Study units assessed in the second round represent conditions in more urbanized basins, but initial results are not yet available. However, VOCs were analyzed in the first round of intensive monitoring and data are available for these study units (Squillace et al., 1999). The minimum reporting level (MRL) for most VOCs, including naphthalene, was 0.2 µg/L (Squillace et al., 1999). Additional information on analytical methods used in the NAWQA study units, including method detection limits, are described by Gilliom and others (in press).

Furthermore, the NAWQA program has compiled, by study unit, data collected from local, State, and other Federal agencies to augment its own data. The data set provides an assessment of VOCs in untreated ambient groundwater of the coterminous United States for the period 1985–1995 (Squillace et al., 1999). Data were included in the compilation if they met certain criteria for collection, analysis, well network design, and well construction (Lapham et al., 1997). They represent both rural and urban areas, but should be viewed as a progress report as NAWQA data continue to be collected that may influence conclusions regarding occurrence and distribution of VOCs (Squillace et al., 1999).

The National Highway Runoff Data and Methodology Synthesis has reviewed 44 highway and urban runoff studies implemented since 1970 (Lopes and Dionne, 1998). Two national studies were included in this review: the National Urban Runoff Program (NURP) and studies associated with the U.S. EPA National Pollution Discharge Elimination System (NPDES) municipal stormwater permits. NURP, conducted in the 1970s and early 1980s, had the most extensive geographic distribution. The NPDES studies took place in the early to mid-1990s (Lopes and Dionne, 1998). Naphthalene was an analyte in both studies.

4.2.2 Results

Naphthalene was detected in both rural and urban wells of the local, State, and Federal data set compiled by NAWQA (Table 4-1). The data represent untreated ambient ground water of the coterminous United States for the years 1985–1995 (Squillace et al., 1999). Detection frequencies and median concentrations are low, especially for rural areas. Occurrence of naphthalene in rural areas is an order of magnitude lower than in urban areas, a trend generally observed for VOCs throughout the United States (Miller, 2000). The exception to this trend for naphthalene is the maximum concentration, a parameter more likely to be influenced by extreme values (outliers) that do not well represent the overall data.

The NURP and NPDES studies analyzing urban and highway runoff also found naphthalene (Lopes and Dionne, 1998). Naphthalene was detected in 11% of NURP samples, making it among the 3 most detected VOCs in the study. Its detection frequency was 7% in the NPDES studies. The maximum concentration was 2.3 µg/L in NURP samples and 5.1 µg/L in NPDES samples.

Table 4-1. Naphthalene Detections and Concentrations in Ground Water.

Location	Detection frequency (% of sampled wells > MRL*)	Concentration percentiles (of detections; µg/L)		Percent exceeding HAL** (20 µg/L)	
		median	maximum	all wells	drinking water wells
Urban	3.0 %	3.9	43	0.4	0
Rural	0.2 %	0.4	70	0.1	0

after Squillace et al.(1999).
** MRL for naphthalene in water: 0.001 µg/L*
*** U.S. EPA (1996e); ATSDR (1996)*

The maximum values for urban and highway runoff are well below the Health Advisory Level (HAL) of 20 µg/L cited by Lopes and Dionne (1998), the HAL in effect at the time (U.S. EPA, 1996e). The ground water studies also reported few exceedances of the 20 µg/L HAL (Squillace et al., 1999). The maximum values for runoff and groundwater are considerably less than the current HAL of 100 µg/L (U.S. EPA, 2000e) and even more so for the Health Reference Level (HRL) of 140 µg/L used as a preliminary health effects level for the drinking water data analysis presented below.

4.3 Drinking Water Occurrence

The Safe Drinking Water Act, as amended in 1996, required PWSs to monitor for specified "unregulated" contaminants, on a five-year cycle, and to report the monitoring results to the States. Unregulated contaminants do not have an established or proposed National Primary Drinking Water Regulation (NPDWR), but they are contaminants that were formally listed and required for monitoring under federal regulations. The intent was to gather scientific information on the occurrence of these contaminants to enable a decision as to whether or not regulations were needed. All non-purchased community water systems (CWSs) and non-purchased non-transient non-community water systems (NTNCWSs), with greater than 150 service connections, were required to conduct this unregulated contaminant monitoring. Smaller systems were not required to conduct this monitoring under federal regulations, but were required to be available to monitor if the State decided such monitoring was necessary. Many States collected data from smaller systems. Additional contaminants were added to the Unregulated Contaminant Monitoring (UCM) program in 1991 [56 FR 3526] (U.S: EPA, 1991b) for required monitoring that began in 1993 [57 FR 31776] (U.S. EPA, 1992).

Naphthalene has been monitored under the SDWA UCM program since 1987 (52 FR 25720) (U.S. EPA, 1987a). Monitoring for naphthalene under UCM continued throughout the 1990s, but ceased for small public water systems (PWSs) under a direct final rule published January 8, 1999 (64 FR 1494) (U.S. EPA, 1999b). Monitoring ended for large PWSs with promulgation of the new Unregulated Contaminant Monitoring Regulation (UCMR) issued September 17, 1999 (64 FR 50556) (U.S. EPA, 1999c) and effective January 1, 2001. At the time the UCMR lists were developed, the Agency concluded there were adequate monitoring data

for a regulatory determination. This obviated the need for continued monitoring under the new UCMR list.

4.3.1 Data Sources, Data Quality, and Analytical Methods

Currently, there is no complete national record of unregulated or regulated contaminants in drinking water from public water systems collected under SDWA. Many States have submitted their unregulated contaminant PWS monitoring data to EPA databases, but there are issues of data quality, completeness, and representativeness. Nonetheless, a significant amount of State data are available for UCM contaminants that can provide estimates of national occurrence.

The National Contaminant Occurrence Database (NCOD) is an interface to the actual occurrence data stored in the Safe Drinking Water Information System (Federal version; SDWIS/FED) and can be queried to provide a summary of the data in SDWIS/FED for a particular contaminant. The data used in this report were derived from the data in SDWIS/FED and another database called the Unregulated Contaminant Information System (URCIS).

The data in this report have been reviewed, edited, and filtered to meet various data quality objectives for the purposes of this analysis. Hence, only data meeting the quality objectives described below were used, rather than all available data from a particular source. The sources of these data, their quality and national aggregation, and the analytical methods used to estimate a given contaminant's national occurrence (from these data) are discussed in this section (for further details see Cadmus, 2000a, b):

UCM Rounds 1 and 2

The 1987 UCM contaminants include 34 volatile organic compounds (VOCs), divided into two groups: one with 20 VOCs for mandatory monitoring, and the other with 14 VOCs for discretionary monitoring [52 FR 25720]. Naphthalene was among the 14 VOCs included for discretionary monitoring. The UCM (1987) contaminants were first monitored coincident with the Phase I regulated contaminants, during the 1988–1992 period. This period is often referred to as "Round 1" monitoring. The monitoring data collected by the PWSs were reported to the States (as primacy agents), but there was no protocol in place to report these data to EPA. These data from Round 1 were collected by EPA from many States over time.

The Round 1 data were put into a database called the Unregulated Contaminant Information System, or URCIS. Most of the Phase 1 regulated contaminants were also VOCs. Both the unregulated and regulated VOCs are analyzed using the same sample and the same laboratory methods. Hence, the URCIS database includes data on all of these 62 contaminants: the 34 UCM (1987) VOCs, the 21 regulated Phase 1 VOCs, 2 regulated synthetic organic contaminants (SOCs), and 5 miscellaneous contaminants that were voluntarily reported by some States (e.g., isomers of other organic contaminants).

The 1993 UCM contaminants include 13 SOCs and 1 inorganic compound (IOC) [56 FR 3526]. Monitoring for the UCM (1993) contaminants began coincident with the Phase II/V

regulated contaminants in 1993 through 1998. This is often referred to as "Round 2" monitoring. The UCM (1987) contaminants were also included in the Round 2 monitoring. As with other monitoring data, PWSs reported these results to the States. During the past several years, EPA has requested that the States submit these historic data to EPA.

The details of the actual individual monitoring periods are complex. The timing of required monitoring was staggered relative to different size classes of PWSs, and the program was implemented somewhat differently by different States. While Round 1 includes the period from 1988–1992, it also includes results from samples analyzed prior to 1988 that were "grandfathered" into the database (for further details see Cadmus, 2000a, b).

Developing a Nationally Representative Perspective

The Round 1 and Round 2 databases contain contaminant occurrence data from a total of 40 and 35 primacy entities (largely States), respectively. However, data from some States are incomplete and biased. Furthermore, the national representativeness of the data is problematic because the data were not collected in a systematic or random statistical framework. These State data could be heavily skewed to low-occurrence or high-occurrence settings. Hence, the State data were evaluated based on pollution-potential indicators and the spatial/hydrologic diversity of the nation. This evaluation enabled the construction of a cross-section from the available State data sets that provides a reasonable representation of national occurrence.

A national cross-section from these State Round 2 contaminant databases was established using the approach developed for the EPA report *A Review of Contaminant Occurrence in Public Water Systems* (U.S. EPA, 1999d). This approach was developed to support occurrence analyses for EPA's Chemical Monitoring Reform (CMR) evaluation. It was supported by peer reviewers and stakeholders. The approach cannot provide a "statistically representative" sample because the original monitoring data were not collected or reported in an appropriate fashion. However, the resultant "national cross-section" of States should provide a clear indication of the central tendency of the national data. The remainder of this section provides a summary description of how the national cross-sections for the URCIS (Round 1) and SDWIS/FED (Round 2) databases were developed. The details of the approach are presented in other documents (Cadmus, 2000a, b), to which readers are referred for more specific information.

Cross-Section Development

As a first step in developing the cross-section, the State data contained in the URCIS database (that contains the Round 1 monitoring results) and SDWIS/FED database (that contains the Round 2 monitoring results) were evaluated for completeness and quality. For both the URCIS (Round 1) and SDWIS/FED (Round 2) databases, some State data were unusable for a variety of reasons. Some States reported only detections, or their data had incorrect units. Datasets only including detections are obviously biased. Other problems included substantially incomplete data sets without all PWSs reporting. Also, data from Washington, D.C. and the Virgin Islands were excluded from this analysis because it was difficult to evaluate them for the current purposes in relation to complete State data (Cadmus, 2000b, Sections II and III).

The balance of the States remaining after the data quality screening were then examined to establish a national cross-section. This step was based on evaluating the States' pollution potential and geographic coverage in relation to all States. Pollution potential is considered to ensure a selection of States that represent the range of likely contaminant occurrence and a balance with regard to likely high and low occurrence. Geographic consideration is included so that the wide range of climatic and hydrogeologic conditions across the United States are represented, again balancing the varied conditions that affect transport and fate of contaminants, as well as conditions that affect naturally occurring contaminants (Cadmus, 2000a, Sections III.A. and III.B.).

The cross-section States were selected to represent a variety of pollution potential conditions. Two primary pollution potential indicators were used. The first factor selected indicates pollution potential from manufacturing/population density and serves as an indicator of the potential for VOC contamination within a State. Agriculture was selected as the second pollution potential indicator because the majority of SOCs of concern are pesticides (Cadmus, 2000a, Section III.A.). The 50 individual States were ranked from highest to lowest based on the pollution potential indicator data. For example, the State with the highest ranking for pollution potential from manufacturing received a ranking of 1 for this factor and the State with the lowest value was ranked as number 50. States were ranked for their agricultural chemical use status in a similar fashion.

The States' pollution potential rankings for each factor were subdivided into four quartiles (from highest to lowest pollution potential). The cross-section States were chosen from all quartiles for both pollution potential factors to ensure representation, for example, from: States with high agrochemical pollution potential rankings and high manufacturing pollution potential rankings; States with high agrochemical pollution potential rankings and low manufacturing pollution potential rankings; States with low agrochemical pollution potential rankings and high manufacturing pollution potential rankings; and States with low agrochemical pollution potential rankings and low manufacturing pollution potential rankings (Cadmus, 2000a, Section III.B.). In addition, some secondary pollution potential indicators were considered to further ensure that the cross-section States included the spectrum of pollution potential conditions (high to low). The cross-sections were then reviewed for geographic coverage throughout all sectors of the United States.

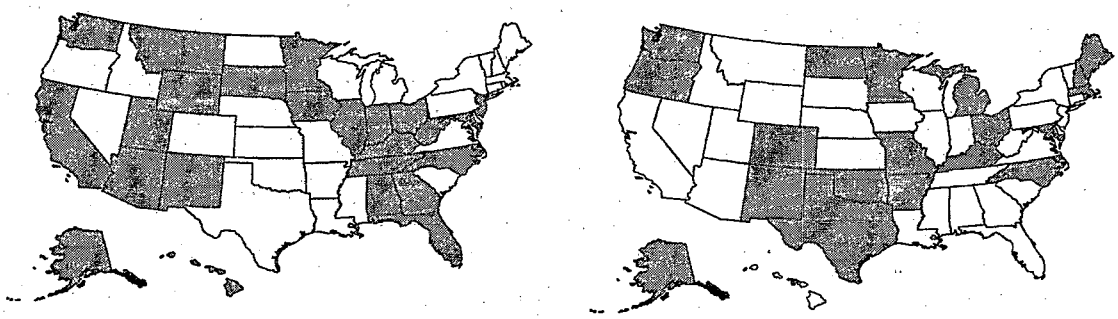
The data quality screening, pollution potential rankings, and geographic coverage analysis established national cross-sections of 24 Round 1 (URCIS) States and 20 Round 2 (SDWIS/FED) States. In each cross-section, the States provide good representation of the nation's varied climatic and hydrogeologic regimes and the breadth of pollution potential for the contaminant groups (Table 4-2 and Figure 4-1).

Table 4-2. Cross-section States for Round 1 (24 States) and Round 2 (20 States).

Round 1 (URCIS)		Round 2 (SDWIS/FED)	
Alabama	Minnesota*	Alaska*	New Hampshire
Alaska*	Montana	Arkansas	New Mexico*
Arizona	New Jersey	Colorado	North Carolina*
California	New Mexico*	Kentucky*	North Dakota
Florida	North Carolina*	Maine	Ohio*
Georgia	Ohio*	Maryland*	Oklahoma
Hawaii	South Dakota	Massachusetts	Oregon
Illinois	Tennessee	Michigan	Rhode Island
Indiana	Utah	Minnesota*	Texas
Iowa	Washington*	Missouri	Washington*
Kentucky*	West Virginia		
Maryland*	Wyoming		

** cross-section State in both Round 1 and Round 2*

Figure 4-1. Geographic Distribution of Cross-section States. Round 1 (left) and Round 2 (right).



Cross-Section Evaluation

To evaluate and validate the method for creating the national cross-sections, the method was used to create smaller State subsets from the 24-State, Round 1 cross-section and aggregations. Again, States were chosen to achieve a balance from the quartiles describing pollution potential, as well as a balanced geographic distribution, to incrementally build subset cross-sections of various sizes. For example, the Round 1 cross-section was tested with subsets of 4, 8 (the first 4 State subset plus 4 more States), and 13 (8 State subset plus 5) States. Two additional cross-sections were included in the analysis for comparison: a cross-section composed of 16 biased States eliminated from the 24-State cross-section for data quality reasons and a cross-section composed of all 40 Round 1 States (Cadmus, 2000a, Section III.B.1).

These Round 1 incremental cross-sections were then used to evaluate occurrence for an array of both high- and low-occurrence contaminants. The comparative results illustrate several points. The results are quite stable and consistent for the 8-, 13- and 24-State cross-sections. They are much less so for the 4-State, 16-State (biased), and 40-State (all Round 1 States) cross-sections. The 4-State cross-section is apparently too small to provide balance both geographically and with pollution potential, a finding that concurs with past work (U.S. EPA, 1999d). The CMR analysis suggested that a minimum of 6–7 States was needed to provide balance both geographically and with pollution potential, and the CMR report used 8 States out of the available data for its nationally representative cross-section. The 16-State and 40-State cross-sections, both including biased States, provided occurrence results that were unstable and inconsistent for a variety of reasons associated with their data quality problems (Cadmus, 2000a, Section III.B.1).

The 8-, 13-, and 24-State cross-sections provide very comparable results, are consistent, and are usable as national cross-sections to provide estimates of contaminant occurrence. Including data from more States improves the national representation and the confidence in the results, as long as the States are balanced relative to pollution potential and spatial coverage. The 24- and 20-State cross-sections provide the best nationally representative cross-sections for the Round 1 and Round 2 data.

Data Management and Analysis

The cross-section analyses focused on occurrence at the water system level; i.e., the summary data presented discuss the percentage of public water *systems* with detections, not the percentage of *samples* with detections. By normalizing the analytical data to the system level, skewness inherent in the sample data, particularly over the multi-year period covered in the URCIS data, is avoided. System level analysis was used since a PWS with a known contaminant problem usually has to sample more frequently than a PWS that has never detected the contaminant. Obviously, the results of a simple computation of the percentage of samples with detections (or other statistics) can be skewed by the more frequent sampling results reported by the contaminated site. This level of analysis is conservative. For example, a system need only have a single sample with an analytical result greater than the MRL, i.e., a detection, to be counted as a system with a result "greater than the MRL."

Also, the data used in the analyses were limited to only those data with confirmed water source and sampling type information. Only standard SDWA compliance samples were used; "special" samples, or "investigation" samples (investigating a contaminant problem that would bias results), or samples of unknown type were not used in the analyses. Various quality control and review checks were made of the results, including follow-up questions to the States providing the data. Many of the most intractable data quality problems encountered occurred with older data. These problematic data were, in some cases, simply eliminated from the analysis. For example, when the number of data with problems was insignificant relative to the total number of observations, they were dropped from the analysis (for further details see Cadmus, 2000c).

As indicated above, New Hampshire generally is included in the 20-State, Round 2 national cross-section. Naphthalene occurrence data from the State of New Hampshire, however, are biased. New Hampshire reported only 5 samples from 3 systems for naphthalene with each system showing a detection. Though these results are simple detections not violating a health effect standard, and inclusion of the data does not significantly affect overall summary statistics, to maintain a consistent method for managing biased data, New Hampshire's naphthalene data were omitted from Round 2 cross-section occurrence analyses and summaries presented in this report.

Occurrence Analysis

To evaluate national contaminant occurrence, a two-stage analytical approach has been developed. The first stage of analysis provides a straight-forward, conservative, broad evaluation of occurrence of the CCL regulatory determination priority contaminants as described above. These descriptive statistics are summarized here. Based on the findings of the Stage 1 analysis, EPA will determine whether more intensive statistical evaluations, the Stage 2 analysis, may be warranted to generate national probability estimates of contaminant occurrence and exposure for priority contaminants (for details on this two-stage analytical approach, see Cadmus, 2000c).

The summary descriptive statistics presented in Table 4-3 for naphthalene are a result of the Stage 1 analysis and include data from both Round 1 (URCIS, 1987–1992) and Round 2 (SDWIS/FED, 1993–1997) cross-section States (minus New Hampshire). Included are the total number of samples, the percent samples with detections, the 99th percentile concentration of all samples, the 99th percentile concentration of samples with detections, and the median concentration of samples with detections. The percentages of PWSs and population served indicate the proportion of PWSs whose analytical results showed a detection(s) of the contaminant (simple detection, > MRL) at any time during the monitoring period; or a detection(s) greater than half the Health Reference Level (HRL); or a detection(s) greater than the Health Reference Level. The Health Reference Level, 140 µg/L, is a preliminary estimated health effect level used for this analysis.

The HRL was derived as a preliminary estimated health effect level using the Reference Dose (RfD) for naphthalene of 2×10^{-2} mg/kg-day. The RfD is an estimate (within an order of magnitude) of the daily oral dose to the human population that is likely to be without appreciable

Table 4-3. Summary Occurrence Statistics for Naphthalene.

Frequency Factors	24-State Cross-Section[1] (Round 1)	20-State Cross-Section[2] (Round 2)	National System & Population Numbers[3]	
Total Number of Samples	45,567	94,915	--	
Percent of Samples with Detections	0.43%	0.24%	--	
99th Percentile Concentration (all samples)	< (Non-detect)	< (Non-detect)	--	
Health Reference Level	140 µg/L	140 µg/L	--	
Minimum Reporting Level (MRL)	Variable[4]	Variable[4]	--	
99th Percentile Concentration of Detections	900µg/L	73 µg/L	--	
Median Concentration of Detections	1.0 µg/L	0.74 µg/L	--	
Total Number of PWSs	13,452	22,926	65,030	
Number of GW PWSs	12,034	20,525	59,440	
Number of SW PWSs	1,502	2,401	5,590	
Total Population	77,209,916	67,498,059	213,008,182	
Population of GW PWSs	42,218,746	25,185,032	85,681,696	
Population of SW PWSs	41,987,010	42,313,027	127,326,486	
			National Extrapolation[5]	
Occurrence by System			**Round 1**	**Round 2**
% PWSs with detections (> MRL)	1.18%	0.75%	769	491
Range of Cross-Section States	0–28.24%	0–4.48%	N/A	N/A
GW PWSs with detections	1.08%	0.62%	642	368
SW PWSs with detections	1.93%	1.92%	108	107
% PWSs > 1/2 Health Reference Level (HRL)	0.01%	0.01%	10	6
Range of Cross-Section States	0–1.53%	0–0.06%	N/A	N/A
GW PWSs > 1/2 Health Reference Level	0.02%	0.01%	10	6
SW PWSs > 1/2 Health Reference Level	0.00%	0.00%	0	0
% PWSs > Health Reference Level	0.01%	0.00%	10	0
Range of Cross-Section States	0–1.53%	0.00%	N/A	N/A
GW PWSs > Health Reference Level	0.02%	0.00%	10	0
SW PWSs > Health Reference Level	0.00%	0.00%	0	0

Table 4-3 (continued)

Frequency Factors	24-State Cross-Section[1] (Round 1)	20-State Cross-Section[2] (Round 2)	National System & Population Numbers[3]	
			National Extrapolation[5]	
Occurrence by Population Served			Round 1	Round 2
% PWS Population Served with detections	2.910%	4.790%	6,198,000	10,204,000
Range of Cross-Section States	0– 37.22%	0– 31.41%	N/A	N/A
GW PWS Population with detections	4.005%	1.162%	3,431,000	995,000
SW PWS Population with detections	1.323%	6.950%	1,685,000	8,849,000
% PWS Population Served > 1/2 Health Ref Level	0.007%	0.002%	16,000	5,000
Range of Cross-Section States	0– 0.23%	0– 0.01%	N/A	N/A
GW PWS Population > 1/2 Health Ref Level	0.013%	0.007%	11,000	6,000
SW PWS Population > 1/2 Health Ref Level	0.000%	0.000%	0	0
% PWS Population Served > Health Ref Level	0.007%	0.000%	16,000	0
Range of Cross-Section States	0– 0.23%	0.000%	N/A	N/A
GW PWS Population > Health Ref Level	0.013%	0.000%	11,000	0
SW PWS Population > Health Ref Level	0.000%	0.000%	0	0

1. Summary Results based on data from 24-State Cross-Section, from URCIS, UCM (1987) Round 1.
2. Summary Results based on data from 20-State Cross-Section (minus New Hampshire), from SDWIS/FED, UCM (1993) Round 2.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook.
4. See text for discussion
5. National extrapolations are from the 24-State data and 20-State data using the Baseline Handbook system and population numbers.

- PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; MRL = Minimum Reporting Level (for laboratory analyses);
- Health Reference Level = Health Reference Level, an estimated health effect level used for preliminary assessment for this review; N/A = Not Applicable
- The Health Reference Level used for naphthalene is 140 µg/L. This is a draft value for working review only.
- Total Number of Samples = the total number of analytical records for naphthalene.
- 99th Percentile Concentration = the concentration value of the 99th percentile of either all analytical results or just the samples with detections (in µg/L).
- Median Concentration of Detections = the median analytical value of all the detections (analytical results greater than the MRL) (in µg/L).
- Total Number of PWSs = the total number of public water systems with records for naphthalene.
- Total Population Served = the total population served by public water systems with records for naphthalene.
- % PWS with detections, % PWS > ½ Health Reference Level, % PWS > Health Reference Level = percent of the total number of public water systems with at least one analytical result that exceeded the MRL, ½ Health Reference Level, Health Reference Level, respectively.
- % PWS Population Served with detections, % PWS Population Served >½ Health Reference Level, % PWS Population Served > Health Reference Level = percent of the total population served by PWSs with at least one analytical result exceeding the MRL, ½ Health Reference Level, or the Health Reference Level, respectively.

risk of adverse effects over a lifetime of exposure. This dose was converted to a drinking water equivalent concentration of 700 μg/L by multiplying the RfD by the default body weight for an adult (70 kg) and dividing the result by the default daily intake of drinking water for an adult (2 L). For derivation of the HRL, it was assumed that about 20% of an individual's total exposure to naphthalene was attributable to drinking water. Multiplication of the drinking water equivalent concentration by 0.2 yields the HRL of 140 μg/L. The HRL was derived as follows:

$$HRL = \frac{RfD \times BW \times RSC}{DI}$$

Where:

RfD	=	Reference dose for HCBD in drinking water, 2×10^{-4} mg/kg-day
BW	=	Body weight of an adult, 70 kg
DI	=	Daily intake of water for an adult, 2 L
RSC	=	Relative Source Contribution, default value of 20%

Therefore:

$$HRL = \frac{(2 \times 10^{-2}\ mg/kg\text{-}day) \times (70\ kg) \times 0.20}{2\ L}$$

$$= 140\ \mu g/L \text{ (rounded to 1 significant number).}$$

The 99th percentile concentration is used here as a summary statistic to indicate the upper bound of occurrence values because maximum values can be extreme values (outliers) that sometimes result from sampling or reporting error. The 99th percentile concentration is presented for both the samples with detections and for all of the samples, because the value for the 99th percentile concentration of all samples is below the MRL (denoted by "<" in Table 4-3). The 95th percentile concentration of all samples and the median (or mean) concentration of all samples are omitted because these also are below the MRL. Only 0.43% and 0.24% of all samples recorded detections of naphthalene in Round 1 and Round 2, respectively.

As a simplifying assumption, a value of half the MRL is often used as an estimate of the concentration of a contaminant in samples/systems whose results are less than the MRL. With a contaminant with relatively low occurrence, such as naphthalene in drinking water occurrence databases, the median or mean value of occurrence using this assumption would be half the MRL (0.5 × MRL). However, for these occurrence data, this is not straightforward. For Round 1 and Round 2, States have reported a wide range of values for the MRLs. This is in part related to State data management differences as well as real differences in analytical methods, laboratories, and other factors.

The situation can cause confusion when examining descriptive statistics for occurrence. For example, for Round 2, most States reported non-detections as zeros, resulting in a modal

MRL value of zero. By definition the MRL cannot be zero. This is an artifact of State data management systems. Because a simple meaningful summary statistic is not available to describe the various reported MRLs, and to avoid confusion, MRLs are not reported in the summary table (Table 4-3).

In Table 4-3, national occurrence is estimated by extrapolating the summary statistics for the 24 and 20 State cross-sections (minus New Hampshire) to national numbers for systems and population served by systems, using the *Water Industry Baseline Handbook, Second Edition* (U.S. EPA, 2000f). From the handbook, the total number of CWSs plus NTNCWSs is 65,030, and the total population served by CWSs plus NTNCWSs is 213,008,182 persons (see Table 4-3). To arrive at the national occurrence estimate for a particular cross-section, the national estimate for PWSs (or population served by PWSs) is simply multiplied by the percentage for the given summary statistic [i.e., for Round 1, the national estimate for the total number of PWSs with detections (769) is the product of the percentage of Round 1 PWSs with detections (1.18%) and the national estimate for the total number of PWSs (65,030)].

Round 1 (1987–1992) and Round 2 (1993–1997) data were not merged because they represent different time periods and different States (only eight States are represented in both rounds). Also, each round has different data management and data quality problems. The two rounds are only merged for the simple spatial analysis overview presented in Section 4.3.2 and Figures 4-2 and 4-4.

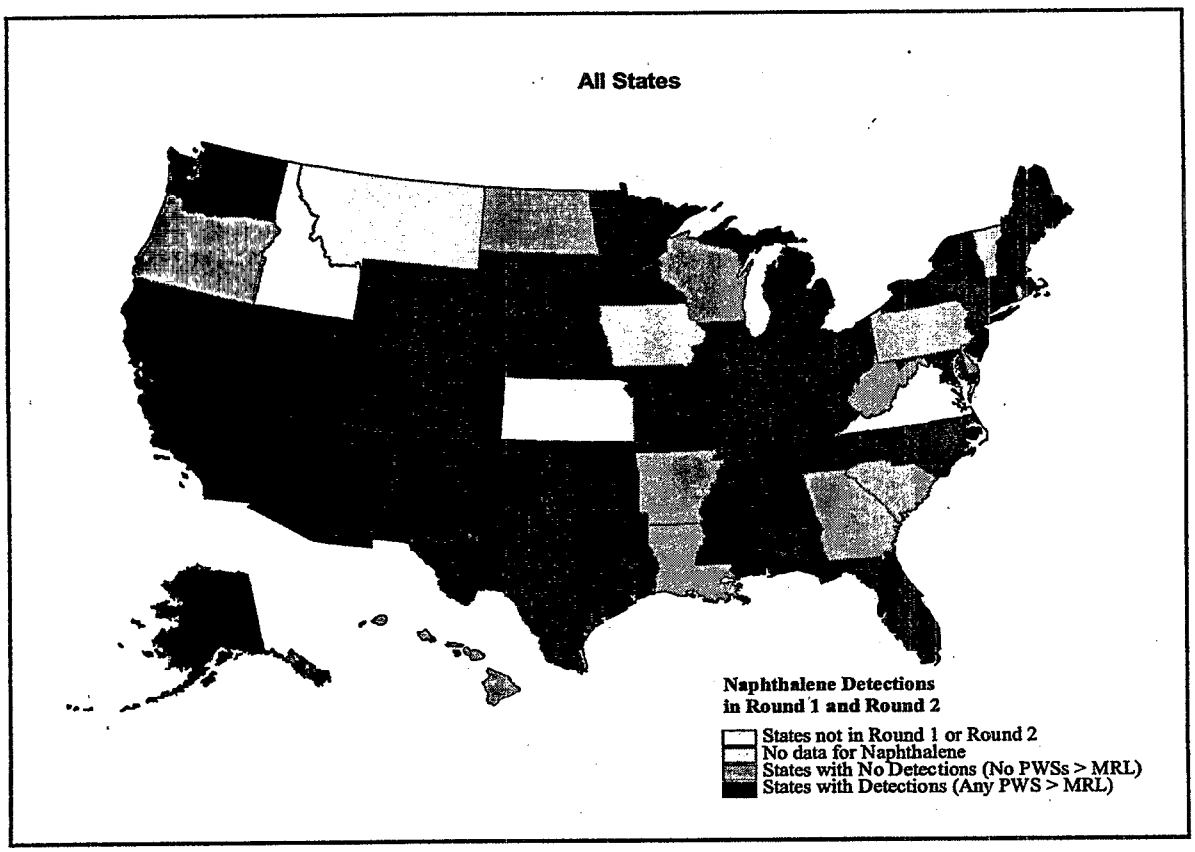
4.3.2 Results

Occurrence Estimates

While States with detections of naphthalene are widespread (Figure 4-2), the percentages of PWSs by State with detections are modest (Table 4-3). In aggregate, the cross-sections show that approximately 0.8–1.2 % of PWSs in both rounds experienced detections (> MRL), affecting 3.0–4.8 % of the population served (approximately 6–10 million people). Percentages of PWSs with detections greater than half the Health Reference Level (> ½ HRL) are much lower for both rounds: 0.01%. The percentage of PWSs exceeding the Health Reference Level (> HRL) is also very small (Table 4-3). Detections > HRL were only reported in Round 1: 0.01% percent of PWSs, affecting a population of approximately 16,000. There were no samples in Round 2 with concentrations above the HRL.

Note that for the Round 1 cross-section, the total number of PWSs (and the total population served by the PWSs) is not the sum of the number of ground water and surface water systems (or the populations served by those systems). Because some public water systems are seasonally classified as either surface or ground water, some systems may be counted in both categories. The population numbers for the Round 1 cross-section are also incomplete. Not all of the PWSs for which occurrence data were submitted reported the populations they served. (However, the population numbers presented in Table 4-3 for the Round 1 cross-section are reported from approximately 95% of the systems.)

Figure 4-2. States with PWSs with Detections of Naphthalene for all States with Data in URCIS (Round 1) and SDWIS/FED (Round 2).



The national estimates extrapolated from Round 1 and Round 2 PWS numbers and populations are not additive either. In addition to the Round 1 classification and reporting issues outlined above, the proportions of surface water and ground water PWSs, and populations served by them, are different between the Round 1 and 2 cross-sections and the national estimates. For example, approximately 63% of the population served by PWSs in the Round 2 cross-section States are served by surface water PWSs (Table 4-3). Nationally, however, that proportion changes to 60%.

Both Round 1 and Round 2 national cross-sections show a proportionate balance in PWS source waters compared to the national inventory. Nationally, 91% of PWSs use ground water (and 9% surface waters): Round 1 shows 89% and Round 2 shows 90% of systems using ground water. The relative populations served are not as closely comparable. Nationally, about 40% of the population is served by PWSs using groundwater (and 60% by surface water). Round 2 data is most representative with 37% of the cross-section population served by ground water; Round 1 shows about 55%.

There are differences in the occurrence results between Round 1 and Round 2, as should be expected. The differences are not great, however, particularly when comparing the proportions of systems affected. The results range from 0.8 to 1.2% of PWSs with detections of naphthalene and range from 0.00 to 0.01% of PWSs with detections greater than the HRL of 140 µg/L. These are not substantively different, given the data sources. The differences in the population extrapolations appear greater, but still constitute relatively small proportions of the population. Less than 5.0% of the population served by PWSs in either round were served by systems with detections and only 0.01% of the population served by Round 1 PWSs were served by systems with detections greater than the HRL.

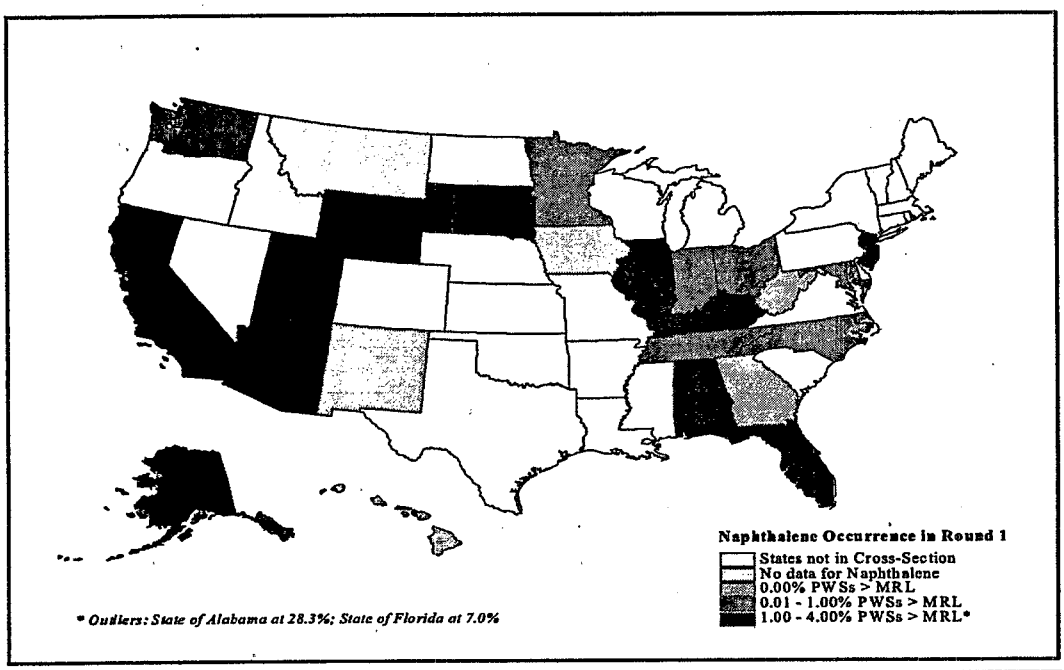
The Round 2 cross-section provides a better proportional balance relative to the national population of PWSs and may have fewer reporting problems than Round 1. The non-zero estimate of the national population served by PWSs with detections greater than the HRL using Round 1 data can also provide an upper-bound estimate in considering the data.

Regional Patterns

Occurrence results are displayed graphically by State in Figures 4-2, 4-3, and 4-4 to assess whether any distinct regional patterns of occurrence are present. Combining Round 1 and Round 2 data (Figure 4-2), there are 47 States reporting. Four of those States have no data for naphthalene, while another 11 have no detections of the chemical. The remaining 32 States have detected naphthalene in drinking water and are well distributed throughout the United States. In contrast to the summary statistical data presented in the previous section, this simple spatial analysis includes the biased New Hampshire data.

The simple spatial analysis presented in Figures 4-2, 4-3, and 4-4 suggests that special regional analyses are not warranted because naphthalene occurrence at concentrations below the HRL is widespread. While no clear geographical patterns of occurrence are apparent, comparisons with environmental use and release information are useful (see also Chapter 3).

Figure 4-3. States with PWSs with Detections of Naphthalene (any PWSs with Results Greater than the Minimum Reporting Level [MRL]) for Round 1(above) and Round 2 (below) Cross-section States.



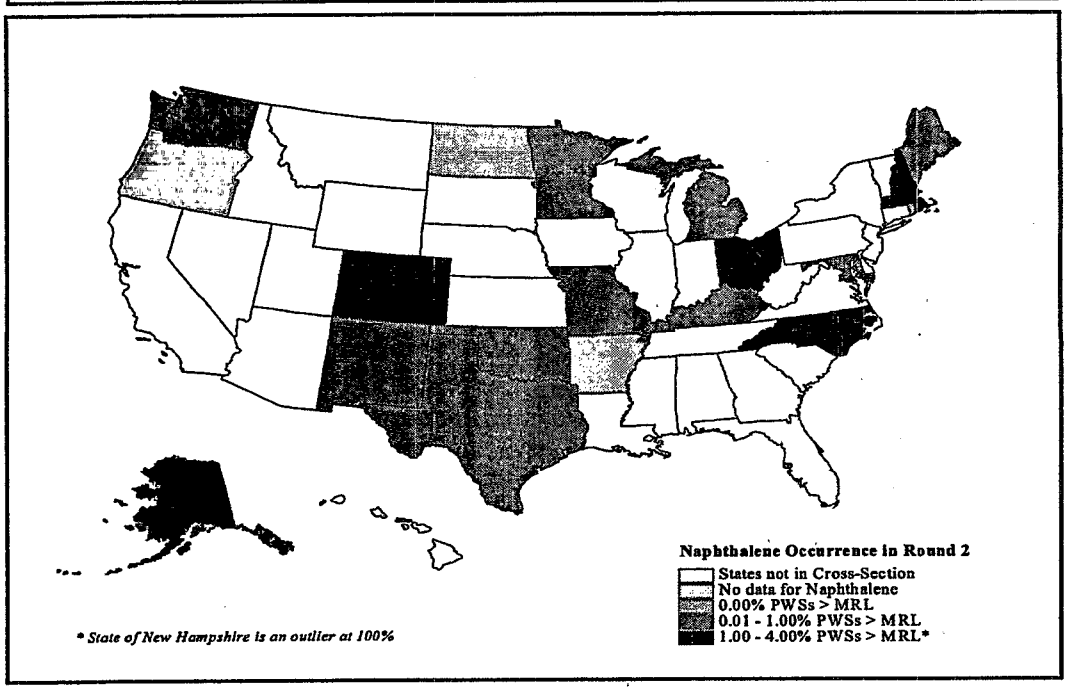
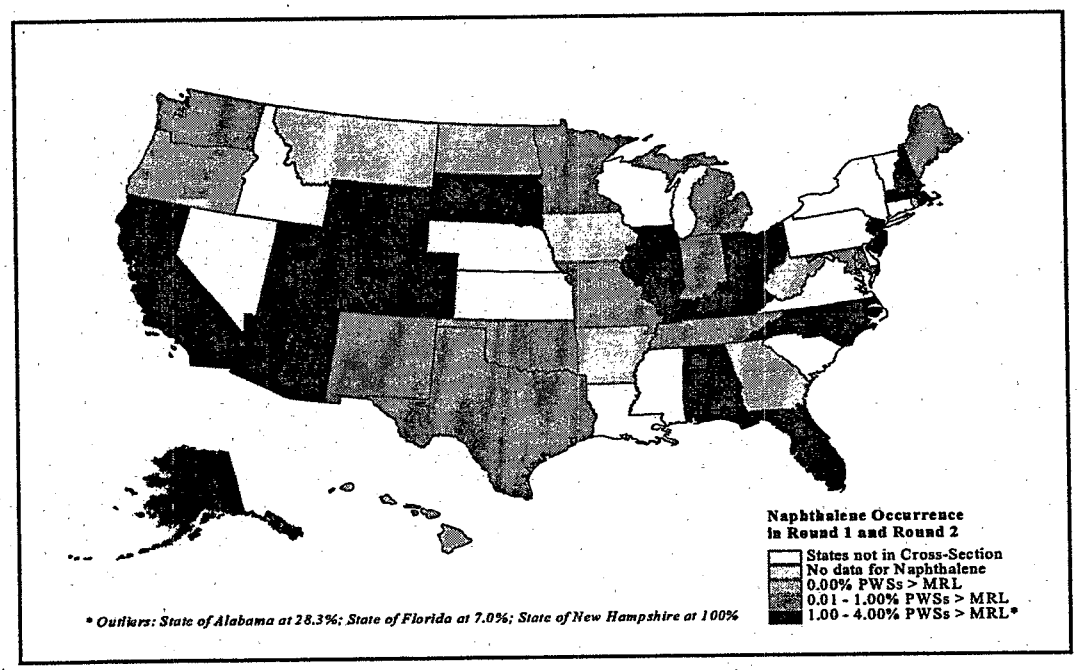
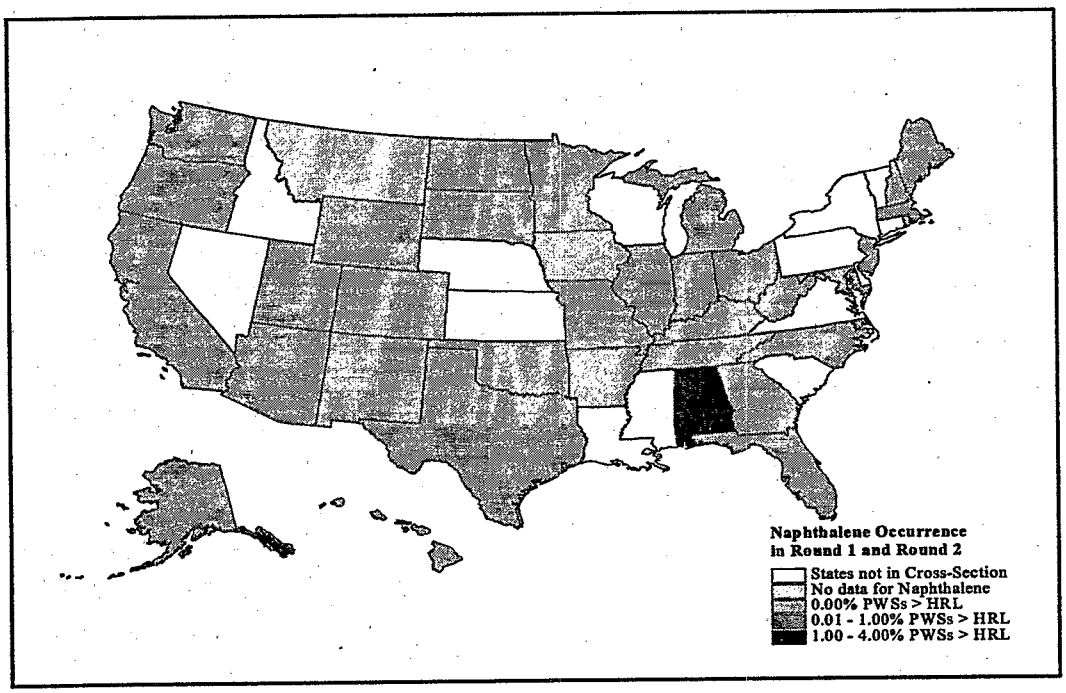


Figure 4-4. Cross-section States (Round 1 and Round 2 Combined) with PWSs with Detections of Naphthalene (above) and Concentrations Greater than the Health Reference Level (HRL; below).





The 47 TRI States reporting releases of naphthalene to the environment include all of the States that detected it in drinking water except New Hampshire. Also, four of the six States that have not detected naphthalene in site samples reported to ATSDR's HazDat database, and three of the six States where it was not detected at CERCLA NPL sites, have detected it in drinking water.

4.4 Conclusion

Naphthalene is naturally present in fossil fuels, such as petroleum and coal, and is generated when wood or tobacco are burned. Naphthalene is produced in commercial quantities from either coal tar or petroleum. Most naphthalene consumption (60%) is through use as an intermediary in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, and insect repellents. Crystalline naphthalene is used as a moth repellent and a solid block deodorizer for diaper pails and toilets. Naphthalene is also used to make the insecticide carbaryl, synthetic leather tanning agents, and surface active agents.

Naphthalene has been detected in untreated ambient ground water samples reviewed and/or analyzed by the USGS NAWQA program. Detection frequencies and concentrations for all wells are relatively low; however, occurrence is considerably higher for urban wells when compared to rural wells. Naphthalene has been detected at slightly higher frequencies in urban and highway runoff. Concentrations in runoff are low, with maximum concentrations well below the current HAL of 20 µg/L. Naphthalene has also been found at ATSDR HazDat and CERCLA NPL sites across the country and releases have been reported through the Toxic Release Inventory.

Naphthalene has also been detected in PWS samples collected under SDWA. Occurrence estimates are low for Round 1 and Round 2 monitoring with only 0.43% and 0.24% of all samples showing detections, respectively. Significantly, the values for the 99th percentile and median concentrations of all samples are less than the MRL. For Round 1 samples with detections, the median concentration is 1.0 µg/L and the 99th percentile concentration is 900 µg/L. Median and 99th percentile concentrations for Round 2 detections are 0.74 µg/L and 73 µg/L, respectively. Systems with detections constitute only 1.2% of Round 1 systems and 0.8% of Round 2 systems (an estimate of 769 (Round 1) and 491 (Round 2) systems nationally). National estimates for the population served by PWSs with detections are also low, especially for detections greater than the HRL. It is estimated that less than 0.01% of the national PWS population is served by systems with detections greater than the HRL (approximately 16,000 people).

5.0 EXPOSURE FROM MEDIA OTHER THAN WATER

5.1 Exposure from Food

5.1.1 Concentration in Non-Fish Food Items

Naphthalene contamination levels in non-fish food items are generally low, unless they have been exposed to smoke. Naphthalene was detected in two of 13,980 samples of foods analyzed in six U.S. states (Minyard and Roberts, 1991). Naphthalene and methylnaphthalene levels in meat samples that were not exposed to fire or smoke are listed in Table 5-1 below. Naphthalene and methylnaphthalene levels were observed to be higher in foods contaminated by smoke during fire exposure (Johnston et al., 1994; Snyder et al., 1996). Naphthalene levels in homogenized milk samples stored in low-density polyethylene (LDPE) bottles were low (0.02 μg/mL) at the time of purchase, increased to 0.1 μg/mL 30 days later, and averaged 0.25 μg/mL at the expiration date (Lau et al., 1994). Lau et al. (1994) hypothesized that residual naphthalene present in the LDPE packaging (1.5 to 2.0 μg/g) was the source of the naphthalene contamination in the milk samples. A later study by the same authors (Lau et al., 1995) observed that the level of naphthalene in LDPE milk bottle material had been reduced to 0.1 to 0.4 μg/g due to a new packaging method.

Dietary naphthalene concentrations were evaluated using duplicate diet food samples from adults and children residing in low-income housing in North Carolina (Chuang et al., 1999). In the adult diets, naphthalene concentrations were found to average 3.75 ± 5.35 μg/kg (range = 0.01 to 18.7), whereas in the child diets, naphthalene concentrations were 4.08 ± 10.9 (range = 0.01 to 54.9).

Naphthalene concentrations from vegetables grown in an industrial area of Thessaloniki, Greece are summarized in Table 5-2 (Kipopoulou et al., 1999). As shown in the tabulated data, naphthalene was detected in all tissue samples and ranged from 0.37 to 63 μg/kg dry weight depending on the vegetable type.

Naphthalene and methylnaphthalene (isomer not specified) were detected in five male and five female harp seals (*Phoca groenlandica*) caught in southern Labrador on the eastern coast of Canada in 1994 (Zitko et al., 1998). Reported median concentrations of naphthalene and methylnaphthalene in harp seal tissues are presented in Table 5-3.

5.1.2 Concentrations in Fish and Shellfish

In the United States, naphthalene was not detected in 83 biota samples (median detection limit 2.5 mg/kg) reported from 1980 to 1982 in the STORET database (Staples et al., 1985). Reported naphthalene concentrations ranged from 5 to 176 nanograms per gram (ng/g) in oysters, from 4 to 10 ng/g in mussels, and from less than 1 to 10 ng/g in clams obtained from United States waters (Bender and Huggett, 1989). In shore crabs collected from the San Francisco Bay area, average naphthalene concentrations were 7.4 ng/g (Miles and Roster, 1999). Naphthalene was detected in all samples of seven fish and two shellfish species taken from Kuwaiti waters

Table 5-1. Naphthalene And Methylnaphthalene Concentrations in Meat Samples.

SAMPLE	NAPHTHALENE CONCENTRATION (ng/g)	METHYLNAPHTHALENE[a] CONCENTRATION (ng/g)	REFERENCE
Fried chicken	26	27	Johnston et al., 1994
Beef	26	26	Johnston et al., 1994
Hot dog	25	5	Johnston et al., 1994
Young turkey breast	17	6	Johnston et al., 1994
Smoked chicken	11.7	Not evaluated	Snyder et al., 1996
Smoked chicken	5	13	Johnston et al., 1994
Boneless beef	5	2	Johnston et al., 1994
Boneless turkey breast	4	0	Johnston et al., 1994
Cooked beef	3	2	Johnston et al., 1994
Corned beef	3	2	Johnston et al., 1994
Ham	2.5	Not evaluated	Snyder et al., 1996
Corned beef	1.7	Not evaluated	Snyder et al., 1996
Boneless beef	LOQ[b]	Not evaluated	Snyder et al., 1996
Turkey breast	LOQ[b]	Not evaluated	Snyder et al., 1996
Beef roast	0	Not evaluated	Snyder et al., 1996
Boneless turkey	0	Not evaluated	Snyder et al., 1996

[a] The isomer of methylnaphthalene was not specified.
[b] LOQ = limit of quantitation (1 ng/g (1 part per billion)) for the method used, which involved supercritical fluid extraction followed by gas chromatograph-mass spectrometer analysis; the concentration was determined using naphthalene-d8 as an internal standard.

that were polluted with crude oils; reported concentrations of naphthalene ranged from 2.06 to 156.09 ng/g dry weight (Saeed et al., 1995).

2-Methylnaphthalene was reported at concentrations ranging from 0.4 to 320 µg/g in fish from Ohio waters, but neither isomer of methylnaphthalene was detected in muscle tissue of fish from polluted areas of Puget Sound (GDCH, 1992). Methylnaphthalenes were detected in oysters collected in Australia at less than 0.3 to 2 µg/g.

5.1.3 Intake of Naphthalene from Food

Factors that may contribute to high dietary naphthalene intake include consumption of grilled foods. Assuming food ingestion of 0.76 to 4.43 kg per day for adults, (Chuang et al., 1999) a daily average intake of 2.85 to 16.6 µg of naphthalene can be calculated from the dietary concentration data of Chuang et al. (1999). Assuming food ingestion of approximately 0.5 to 2.3 kg per day for children (Chuang et al., 1999), an average daily intake of 2.04 to 9.4 µg of naphthalene can be calculated from the dietary concentration data of Chuang et al. (1999).

Table 5-2. Concentrations of Naphthalene in Vegetables

VEGETABLE TYPE	CONCENTRATION (µg/kg dry weight)	
	Range	Median
Cabbage (n=8)	0.37–15	5.0
Carrot (n=6)	8.9–30	21
Leek (n=5)	6.3–35	18
Lettuce (n=8)	4.9–53	42
Endive (n=3)	27–63	29

Source: Kipopoulou et al. (1999)

Table 5-3. Median Concentrations of Naphthalene and Methylnaphthalene in Harp Seals

Compound	Tissue Concentration (ng/g wet weight)							
	Muscle		Kidney		Liver		Blubber	
	Female	Male	Female	Male	Female	Male	Female	Male
Naphthalene	3.10	2.90	4.30	4.15	4.70	4.15	21.00	23.50
Methylnaphthalene	1.50	1.55	1.70	1.40	1.70	1.40	8.30	8.85

Source: Zitko et al. (1998)

Using the average ranges of naphthalene intake determined above, an estimated daily intake of 40.7 to 237 ng/kg-day can be calculated for a 70-kg adult, and an average daily intake of 204 to 940 ng/kg-day can be calculated for a 10-kg child. Values for individuals will vary depending upon dietary composition.

5.2 Exposure from Air

5.2.1 Concentration of Naphthalene in Air

The average reported concentration for 67 ambient air samples in the United States was 0.991 parts per billion (ppb) (5.19 $\mu g/m^3$), and the majority (60) of these samples and the highest concentrations were collected at source-dominated locations (Shah and Heyerdahl, 1988). Howard (1989) reported a median naphthalene level in urban air in 11 U.S. cities of 0.18 ppb (0.94 $\mu g/m^3$). Chuang et al. (1991) reported an average naphthalene concentration of 170 $\mu g/m^3$ in outdoor air in a residential area of Columbus, Ohio. Naphthalene was detected in ambient air in Torrance, California, at a concentration of 3.3 $\mu g/m^3$ (Propper, 1988). Patton et al. (1997) reported a naphthalene concentration of 1.50×10^{-4} $\mu g/m^3$ in an air sample collected from the Department of Energy's Hanford site in Washington State. Average naphthalene concentrations detected in ambient air at five hazardous waste sites and one landfill in New Jersey ranged from 0.08 to 0.88 ppb (0.42 to 4.6 $\mu g/m^3$) (La Regina et al., 1986). Atmospheric concentrations of naphthalene in total suspended particles were reported to range from 0.003 to 0.095 $\mu g/m^3$ (median = 0.017) in the city of Ionia, Greece and from 0.002 to 0.179 $\mu g/m^3$ (median = 0.030) in the city of Sindos, Greece (Kipopoulou et al., 1999).

1-Methylnaphthalene and 2-methylnaphthalene have also been detected in ambient air. Shah and Heyerdahl (1988) reported average concentrations of 0.086 and 0.011 ppb (0.51 and 0.065 $\mu g/m^3$) for 1-methylnaphthalene and 2-methylnaphthalene, respectively. ATSDR (1995) indicated that these data were obtained from source-dominated areas where the highest concentrations were detected. Methylnaphthalene (isomer not specified) was detected in ambient air at a hazardous waste site in New Jersey; however the concentration was not reported (La Regina et al., 1986). A mean concentration of 0.252 ppb (1.5 $\mu g/m^3$) 2-methylnaphthalene was reported for indoor air (Shah and Heyerdahl, 1988).

Naphthalene has been detected in indoor air samples, and residential indoor concentrations are sometimes higher than outdoor air levels. Published average indoor concentrations of naphthalene in various locations within homes range from 0.860 to 1,600 $\mu g/m^3$ (Chuang et al., 1991; Hung et al., 1992; Wilson et al., 1989; Lau et al., 1995). However, ATSDR (1995) suggested that the upper range value reported in Chuang et al. (1991) might be erroneous and indicated that a more representative upper limit concentration for indoor air might be 32 $\mu g/m^3$, recorded in buildings in heavily trafficked urban areas of Taiwan (Hung et al., 1992). Lau et al. (1995) reported mean naphthalene vapor concentrations of 5 to 41 $\mu g/m^3$ and less than 3 to 100 $\mu g/m^3$ in office and laboratory air, respectively. Concentrations of naphthalene vapor were also found to be high (350 $\mu g/m^3$) in a flat that had been freshly painted with lacquer paint (Lau et al., 1995). Measurements of naphthalene concentrations in both indoor and outdoor air were obtained from 24 low-income homes in North Carolina in 1995 (Chuang et al., 1999). Indoor air

concentrations ranged from 0.33 to 9.7 μg/m^3 (mean ± Std Dev = 2.2 ± 1.9), whereas outdoor air concentrations were lower and ranged from 0.057 to 1.82 μg/m^3 (mean ± Std Dev = 0. 43 ± 0.51).

In homes with residents who smoke, indoor and outdoor air concentrations of naphthalene were reported to be 2.2 μg/m^3 and 0.3 μg/m^3, respectively (Gold et al., 1991; IARC, 1993). A similar analysis of air in homes without smokers detected indoor and outdoor air concentrations of 1.0 μg/m^3 and 0.1 μg/m^3, respectively. Lofgren et al. (1991) reported an average concentration of naphthalene inside automobiles in commuter traffic of about 4.5 μg /m^3.

5.2.2 Intake of Naphthalene from Air

Assuming an average ambient concentration level of 5.19 μg naphthalene/m^3 and an average inhalation rate of 15.2 m^3/day (U.S. EPA, 1996c), an average daily dose of 1,127 ng/kg-day can be calculated for a 70-kg adult. An estimated average daily dose of 4,515 ng/kg-day can be calculated for a 10-kg child assuming an inhalation rate of 8.7 m^3/day (U.S. EPA, 1996c). Individual intake will vary depending on factors including activity, geographic location, and inhalation rate.

5.3 Exposure from Soil

5.3.1 Concentration of Naphthalene in Soil

Chuang et al. (1995) analyzed house dust samples obtained from carpet in homes in Columbus, Ohio. They reported mean naphthalene levels of 530 μg/kg (measured following Soxhlet extraction) and 350 μg/kg (measured using sonication extraction). Measurements of naphthalene concentrations in household dust were obtained from 24 low-income homes in North Carolina in 1995 (Chuang et al., 1999). Concentrations ranged from < 10 to 4,300 μg/kg, depending on the location of sampling (Table 5-4).

Table 5-4. Concentrations of Naphthalene in Residential Dust (mg/g)

LOCATION	CONCENTRATION (μg/kg)	
	Range	Mean ± Std Dev
House Dust	20 - 4,300	330 ± 850
Entryway Dust	10 - 1,310	110 ± 260
Pathway Soil	<10 - 40	10 ± 10

Source: Chuang et al. (1999)

Low levels of naphthalene and methylnaphthalenes have been found in uncontaminated soils and sediments, while higher levels have been reported for samples taken near sources of contamination. Wild et al. (1990) reported that naphthalene levels in untreated agricultural soils ranged from 0 to 3 μg/kg. Published naphthalene concentrations in contaminated soils included up to 66 μg/kg in sludge-treated soils (Wild et al., 1990), 6,100 μg/kg in coal tar-contaminated soil (Yu et al., 1990) and 16,700 μg/kg in soil from a former tar-oil refinery (Weissenfels et al., 1992). Kipopoulou et al. (1999) reported naphthalene concentrations in agricultural soil from Thessaloniki, Greece ranging from 3.1 to 78 μg/kg dry weight (median = 17). For methylnaphthalene (isomer not specified), Yu et al. (1990) reported a concentration of 2,900 μg/kg in coal tar-contaminated soil.

For sediments, naphthalene was detected in 7 percent of 267 sediment samples entered into the STORET database (1980 to 1982); the median concentration for all samples was reported to be less than 500 μg/kg (Staples et al., 1985). Coons et al. (1982) performed a separate analysis of the STORET data and reported that concentrations in positive sediment samples ranged from 0.02 to 496 μg/kg.

Naphthalene and methylnaphthalene have been detected in marine and estuarine sediments near petroleum production and transport facilities. Brooks et al. (1990) reported average concentrations of 54.7 and 61.9 μg/kg naphthalene and 50.4 and 55.3 μg/kg methylnaphthalenes at 10 and 25 miles, respectively, from an offshore multi-well drilling platform. The study also reported that naphthalene and methylnaphthalene concentrations in nearby noncontaminated estuarine sediments were 2.1 and 1.9 μg/kg, respectively. Sharma et al. (1997) analyzed sediments from 52 sites in the upper part of the Laguna Madre system, a large coastal basin located south of Corpus Christi, Texas, that supports the Gulf Coast Intracoastal Waterway and petroleum production wells and pipelines. They detected methylnaphthalene at four sites, and the mean concentrations identified at these four sites ranged from 9,400 to 81,000 μg/kg dry weight. The Laguna Madre site with the highest concentration of methylnaphthalene receives dredged material from the waterway and other canals.

5.3.2 Intake of Naphthalene from Soil

Humans may be exposed to soil naphthalene by inhalation of airborne soil particles, by ingestion of food-borne soil residues, by ingestion of household dust, or by direct ingestion of soil. Exposure by inhalation of airborne soil particles is accounted for in Section 5.4. Infants and toddlers ingest soil and household dust by hand-to-mouth transfer during everyday activities, and may therefore be exposed to higher levels of soil naphthalene than the general population.

Assuming average ingestion of 50 milligram (mg) of soil per day by adults (U.S. EPA, 1996c), and house dust concentrations from 0.02 to 4.3 milligram per kilogram (mg/kg) (average = 0.33), the estimated average daily intake for a 70-kg adult is calculated to be 0.00001 to 0.003 mg/kg-day (average = 0.00002). An estimated intake range of 0.0002 to 0.043 mg/kg-day (average = 0.0033) was calculated for a 10-kg child, assuming ingestion of 100 mg of soil per day (U.S. EPA, 1996c). For comparison with intake from other media, these ranges have been

converted to units of 10 to 3,000 ng/kg-day (average = 20) for adults, and 200 to 43,000 ng/kg-day (average = 3,300) for a 10-kg child (Table 5-5).

5.4 Other Residential Exposures

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have been identified in cigarette smoke (HSDB, 1999). Schmeltz et al. (1978) reported levels of 3 μg napthalene, 1 μg 1-methylnaphthalene, and 1 μg 2-methylnaphthalene in the smoke from one commercial U.S. unfiltered cigarette. Sidestream smoke levels of 46 μg, 30 μg, and 32 μg per cigarette were reported for these three compounds, respectively (Schmeltz et al., 1976).

Use of naphthalene-containing moth repellents also contributes to naphthalene in indoor air. Lau et al. (1995) measured 350 $\mu g/m^3$ naphthalene in the air inside a cupboard containing approximately 36 grams of mothballs. Unvented kerosene space heaters, gas cooking and heating appliances, as well as wood-burning fireplaces, might also contribute to indoor air concentrations of naphthalene (HSDB, 1999; Chuang et al., 1995).

In Taiwan, mosquito coils are frequently burned despite being categorized as a source of indoor air pollution. Lin and Lee (1997) identified naphthalene in smoke resulting from the burning of two prevalent brands of mosquito coils. Burning one gram of the mosquito coils yielded 20.98 or 30.45 μg of naphthalene vapor and 7.35 or 9.23 μg of particulate-bound naphthalene, depending on the brand. The study authors estimated that the concentration of naphthalene in the air would be up to 3.35 $\mu g/m^3$ after burning a mosquito coil for 6 hours in a 40 cubic meter (m^3) room.

5.5 Summary

Estimated concentration and intake values for naphthalene in media other than water are summarized in Table 5-5. Inspection of the data reveals that, based on average intakes, most exposure occurs through inhalation, with average intakes being approximately 5- to 27-fold greater than those from food and up to about 5-fold greater than those from soil. However, soil may be a significant route of exposure for children living in areas with soils containing high levels of naphthalene.

Table 5-5. Exposure to Naphthalene in Media Other than Water

PARAMETER	MEDIUM					
	Food		Air		Soil*	
	Adult	Child	Adult	Child	Adult	Child
Concentration in medium [average]	[3.75] µg/kg	[4.08] µg/kg	[5.19] µg/m^3		0.02–4.3 [0.33] mg/kg	
Estimated daily intake (ng/kg-day) [average]	[40.7–237] **	[204–940] **	[1,127]	[4,515]	10–3,000 [235]	200–43,000 [3,300]

*based on household dust concentrations

** range based on different total food intakes (0.076 to 4.43 kg/day adults; 0.5 to 2.3 kg/day child) (Chuang et al., 1999)

6.0 TOXICOKINETICS

6.1 Absorption

Oral Exposure

Naphthalene is readily absorbed when administered orally as inferred from the occurrence of adverse effects after exposure. Toxic effects have been reported in dogs, mice, rats, and rabbits following oral exposures to naphthalene, although the extent of absorption was not quantified (ATSDR, 1995).

Bock et al. (1979) instilled ^{14}C-naphthalene into isolated rat intestinal loops. When assayed 30 minutes after instillation, 84% of the administered dose was recovered unmetabolized in the portal blood, while only 1% remained in the luminal contents. Absorption is believed to occur by passive diffusion across the intestinal membranes, with the rate of absorption determined by the partition coefficient between the contents of the intestinal lumen and the lipids of the intestinal membranes (ATSDR, 1995).

No studies were identified that quantified the rate and extent of naphthalene absorption in humans following ingestion. However, the results of case reports confirm that significant amounts of naphthalene ingested by humans may be absorbed and that adverse effects may result (Zuelzer and Apt, 1949; Mackell et al., 1951; Bregman, 1954; MacGregor, 1954; Chusid and Fried, 1955; Gidron and Leurer, 1956; Haggerty, 1956; Santhanakrishnan et al., 1973; Gupta et al., 1979; Shannon and Buchanan, 1982; Ojwang et al., 1985; Kurz, 1987).

Dermal Exposure

Evidence of naphthalene toxicity has been described in human neonates who reportedly were exposed by dermal contact with diapers that had been stored with naphthalene mothballs or naphthalene flakes (Schafer, 1951; Dawson et al., 1958). However, inhalation of naphthalene vapors could not be excluded as a contributing route of exposure (ATSDR, 1995; U.S. EPA, 1998a).

Turkall et al. (1994) applied 3.3 $\mu g/cm^2$ of naphthalene to the shaved skin of male rats and sealed the area of application under a glass cap for 48 hours. Dermal absorption occurred rapidly, with approximately 50% of the dose being absorbed in 2.1 hours.

Inhalation Exposure

No empirical data that describe the rate or extent of naphthalene absorption following inhalation exposure were identified in the materials reviewed for this report. NTP (2000) developed a physiologically-based pharmacokinetic model to describe the uptake of naphthalene in rats and mice following inhalation exposure. The model was calibrated using blood time course data for naphthalene (parent compound). Results from this model suggest that inhaled naphthalene is absorbed rapidly into the blood (Blood:air partition coefficient of 571). On the

basis of estimates of naphthalene metabolism generated by the model, approximately 22% to 31% of inhaled naphthalene is absorbed by rats and 65% to 73% of inhaled naphthalene is absorbed by mice.

6.2 Distribution

Oral Exposure

Absorbed naphthalene is expected to be distributed throughout the body (U.S. EPA, 1998a). Eisele (1985) evaluated the distribution of naphthalene following oral administration to pigs, to chickens, or to a single cow. A single 0.123 mg dose of radiolabeled naphthalene/kg (4.8 Ci/kg) was administered to young pigs, and distribution was monitored at 24 and 72 hours. Adipose tissue had the highest percentage of the label (3.48 ± 2.16% dose/mg tissue) at 24 hours post-administration. Lower percentages were reported in the kidney (0.96% dose/mg tissue), liver (0.26 ± 0.06% dose/mg tissue), lungs (0.16% dose/mg tissue), heart (0.09 ± 0.04% dose/mg tissue) and spleen (0.07 ± 0.01% dose/mg tissue). At 72 hours, the percentage of the label in adipose tissue had decreased to 2.18 ± 1.16% dose/mg tissue, while the activity in the liver was 0.34 ± 0.24% dose/mg tissue. Activities of 0.96% dose/mg tissue were determined in the kidneys and lung.

Eisele (1985) also administered oral doses of 0.006 mg radiolabeled naphthalene/kg-day (0.22 Ci/kg-day) to pigs daily for 31 days. Repeated administration resulted in a pattern of distribution that differed from the pattern observed following a single oral dose. Following repeated doses, the highest tissue concentration of naphthalene occurred in the lung (0.15% dose/mg tissue). The heart and liver each contained 0.11% dose/mg tissue, and 0.03% dose/mg tissue was reported in adipose tissue. The spleen and the kidney had 0.09 ± 0.05% and 0.09% dose/mg tissue, respectively.

Following single or repeated administration to one dairy cow, naphthalene was reported to distribute to milk, with the highest concentration in the lipid fraction (Eisele, 1985). After 31 days, the highest tissue concentration was reported in the liver, and the lowest concentration was reported in adipose tissue.

Data for distribution of naphthalene or its metabolites in humans are unavailable. However, there is evidence that naphthalene can cross the placenta in humans. Erythrocyte hemolysis of sufficient magnitude to cause anemia was reported in infants born to mothers that had consumed naphthalene while pregnant (Zinkham and Childs, 1957, 1958; Anziulewicz et al., 1959). The glucose-6-phosphate dehydrogenase status (see Section 7.4.5) of the infants was not indicated in the materials reviewed for this document.

Dermal Exposure

No data describing the distribution of naphthalene following dermal exposures in humans were identified in the materials reviewed for this document.

Turkall et al. (1994) applied ^{14}C-radiolabeled naphthalene (3.3 $\mu g/cm^2$) to the skin of rats. At 48 hours post-application, the highest concentration (0.56% of the initial dose) was observed at the application site. Approximately 0.01%-0.02% of the initial dose was recovered in the ileum, duodenum, and kidney. Presence of the radiolabel in the ileum and duodenum was considered by the authors as evidence for biliary excretion of naphthalene metabolites.

Inhalation Exposure

A recent case report of hemolytic anemia in a neonate whose mother inhaled naphthalene during the 28th week of gestation suggests that inhaled naphthalene can cross the placenta (Athanasiou et al., 1997). No other data describing the distribution of naphthalene in humans or animals following inhalation exposure were identified in the materials reviewed for this document.

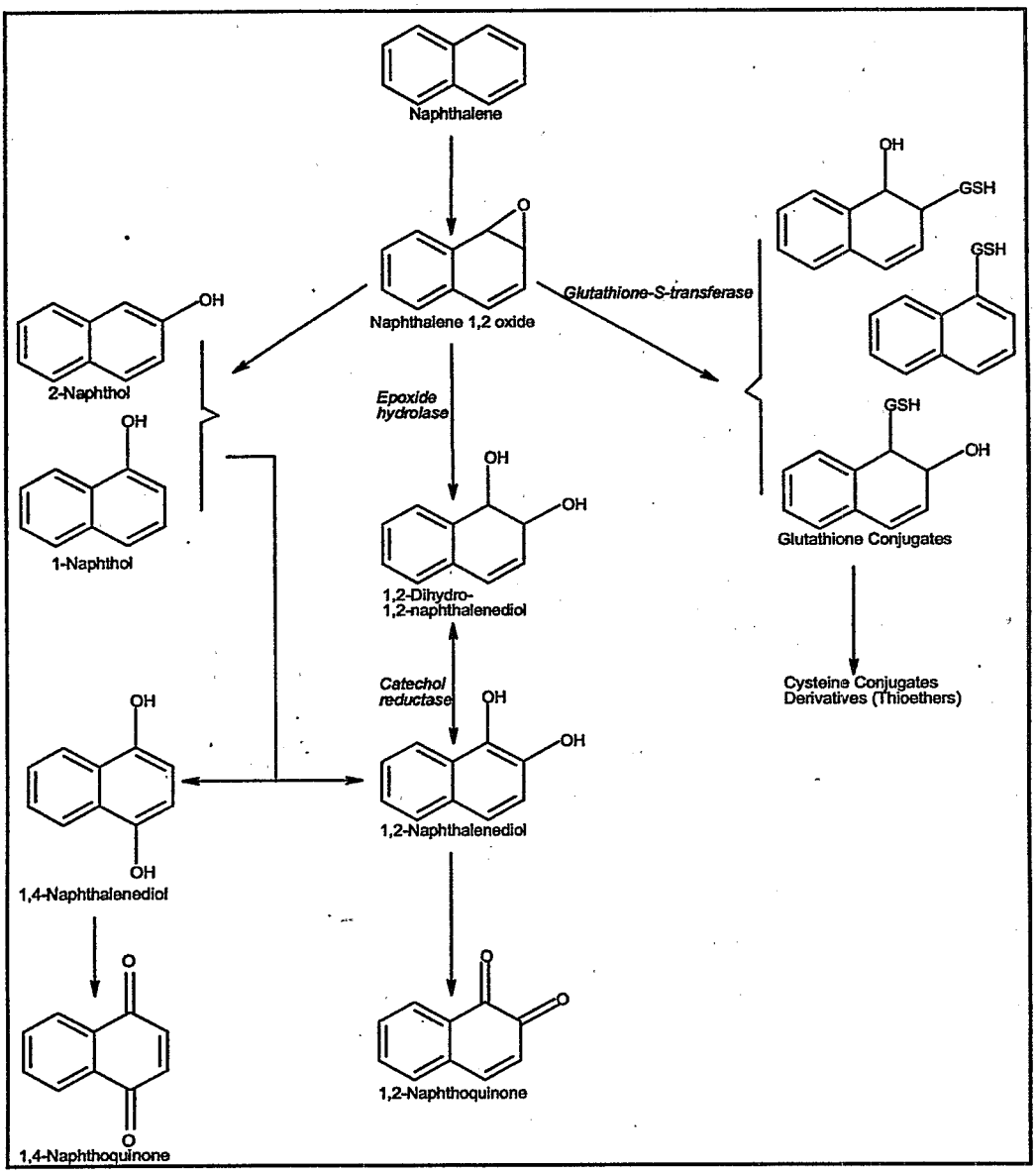
6.3 Metabolism

Overview of Metabolic Pathways

The *in vivo* and *in vitro* metabolism of naphthalene in mammalian systems has been extensively studied (U.S. EPA 1998a). As many as 21 metabolites, including oxidized derivatives and conjugates, have been identified in the urine of animals exposed to naphthalene (Horning et al., 1980; Wells et al., 1989; Kanekal et al., 1990). Factors that potentially influence the relative proportions of individual metabolites include species, tissue type, and tissue concentration of naphthalene (U.S. EPA, 1998a). The initial step in naphthalene metabolism is catalyzed by cytochrome P-450 monooxygenases, and results in the formation of the arene epoxide intermediate 1,2-naphthalene oxide (Figure 6-1). 1,2-Naphthalene oxide can undergo spontaneous rearrangement to form naphthols (predominately 1-naphthol). The resulting intermediates may be further metabolized by oxidation reactions, resulting in the formation of di-, tri-, and tetrahydroxylated intermediates (Horning et al., 1980). Some metabolites may undergo conjugation with glutathione, glucuronic acid, or sulfate (ATSDR, 1995; U.S. EPA, 1998a). Glutathione conjugates undergo additional reactions to form cysteine derivatives (thioethers). These cysteine derivatives may be further metabolized to mercapturic acids and may be excreted in the bile (U.S. EPA, 1998a).

An alternative pathway of naphthol metabolism involves enzymatic hydration by epoxide hydrolase. This reaction results in the formation of trans-1,2-dihydro-dihydroxynaphthalene, also referred to as naphthalene-1,2-dihydrodiol (U.S. EPA, 1998a). Trans-1,2-dihydro-dihydroxynaphthalene can be converted to 1,2-naphthalenediol by catechol reductase, and with subsequent oxidation to 1,2-naphthoquinone and hydrogen peroxide. In addition, 1,2-naphthoquinone may rearrange to form 1,4-naphthoquinone and vice versa (U.S. EPA, 1998a). The 1,2-naphthoquinone and 1,4-naphthoquinone metabolites may be the primary toxic metabolites, rather than the 1,2-naphthalene-epoxide intermediate. This conclusion is based on observations that 1,2-naphthoquinone and 1,4-naphthoquinone were cytotoxic and genotoxic to human lymphocytes, and that they depleted glutathione. In contrast, the epoxide was not cytotoxic or genotoxic, and did not deplete glutathione (Wilson et al., 1996).

Figure 6-1. Proposed Pathways For Naphthalene Metabolism



Source: U.S. EPA (1998a)

Studies of Naphthalene Metabolism in Humans

Data describing the metabolism of naphthalene in humans are limited. Human lung microsome preparations from three individuals aged 60 to 77 years metabolized naphthalene to dihydro-1,2-naphthalenediol and three glutathione adducts (Buckpitt and Richieri, 1984; Buckpitt and Bahnson, 1986). There was considerable variation in the amount of each metabolite formed by each of the three individuals. Buonarati et al. (1990) subsequently identified these adducts as trans-1-(S)-hydroxy-2-(S)-glutathionyl-1,2-dihydronaphthalene; trans-1-(R)-glutathionyl-2-(R)-hydroxy-1,2-dihydronaphthalene; and trans-1-(S)-hydroxy-2-S-glutathionyl-1,2-dihydronaphthalene.

Tingle et al. (1993) investigated naphthalene metabolism using microsomes prepared from six histologically normal human livers. The primary stable metabolite was 1,2-dihydro-1,2-naphthalenediol, generated by the action of epoxide hydrolase on 1,2-naphthalene oxide, whereas, 1-naphthol was a minor metabolite. Inhibition of epoxide hydrolase increased the amount of 1-naphthol formed.

Analysis of urine indicates that naphthols (specifically 1- and 2-naphthol), 1,2-naphthoquinone, and 1,4-naphthoquinone are formed in humans exposed to naphthalene (Zuelzer and Apt, 1949; Mackell et al., 1951).

Animal Studies of Naphthalene Metabolism

There is some evidence that metabolism of naphthalene may vary among species. Urinary mercapturic acid excretion increased in a dose-dependent manner following the administration of naphthalene to rats via gavage (Summer et al., 1979). In comparison, glucuronic acid and sulfate conjugates were the primary conjugates excreted in the urine of chimpanzees, based on limited data collected from two animals (Summer et al., 1979).

Urinary metabolites identified in rats and rabbits following the oral administration of naphthalene included 1- and 2-naphthol, 1,2-dihydro-1,2-naphthalenediol, 1-naphthyl sulfate, and 1-naphthylglucuronic acid (Corner and Young, 1954). With the exception of 1-naphthylglucuronic acid in the urine of guinea pigs, the same metabolites were also identified in the urine of mice, rats and guinea pigs following intraperitoneal injection. A glucuronic acid conjugate of 1,2-naphthalenediol was also likely present in all species; however, the presence of this metabolite was not confirmed. In addition, the urine of rats and rabbits contained 1,2-dihydro-2-hydroxy-1-naphthyl glucuronic acid, while in guinea pigs, unconjugated 1,2-naphthalenediol was excreted.

Horning et al. (1980) administered a 100 mg/kg intraperitoneal dose of naphthalene to male Sprague-Dawley rats. The majority of the administered dose (80-95%) was excreted in the urine as conjugated glucuronide, sulfate, and thioether metabolites; the major metabolites identified were: 1-naphthol, 2-naphthol, 1,2-naphthalenediol, cis- and trans-1,2-dihydro-1,2-naphthalenediol, cis- and trans-1,4-dihydro-1,4-naphthalenediol, and 1,1-, 2,7- and 2,6-naphthalenediol.

Stillwell et al. (1982) identified 1-naphthol, trans-1-hydroxy-2-methylthio-1,2-dihydroxynaphthalene, trans-1,2-dihydro-1,2-naphthalenediol, methylthionaphthalene, and 2-naphthol as the major metabolites in the urine of male mice that received naphthalene by intraperitoneal injection. Seven sulfur-containing metabolites were identified, with the N-acetyl-S-(1-hydroxy-1,2-dihydro-2-naphthenyl) cysteine being the primary sulfur metabolite identified.

Bakke et al. (1990) identified the glucuronic acid conjugate and the dihydro-1-hydroxy-2-cysteine derivative of dihydronaphthalenediol in the urine of calves. The cysteine derivative was excreted in slightly larger amounts. The two metabolites accounted for approximately 81% of the administered dose.

6.4 Excretion

Oral Exposure

Limited information exists on the excretion of orally ingested naphthalene by humans. The results of a case-study indicated that naphthol was present in human urine four days post-ingestion (Zuelzer and Apt, 1949). Smaller amounts were found at five days post-ingestion. Naphthol was not present in subsequent specimens. Mackell et al. (1951) reported that 1- and 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone were present in the urine of an 18-month-old infant 9 days after ingestion. At 13 days post-ingestion, all metabolites except 1,4-naphthoquinone were still detectable. These results suggest that urinary excretion may be extended following the ingestion of naphthalene. In some exposure scenarios, delayed dissolution and absorption from the gastrointestinal tract may also contribute to an extended pattern of excretion. Zuelzer and Apt (1949) noted that naphthalene was visible in fecal matter after the ingestion of naphthalene flakes or mothballs in several individuals.

Boyland and Sims (1958) reported that only trace amounts of mercapturic acids were detected in the urine of a man who ingested a 500 mg dose of naphthalene, an observation that is consistent with the findings in non-human primates described above.

Animal studies indicate that the majority of ingested naphthalene is eliminated as metabolites in the urine, with a small fraction eliminated in the feces (U.S. EPA, 1998a). Bakke et al. (1985) administered oral doses of radiolabeled naphthalene to rats. At 24 hours post-administration, the majority of the label (77-93%) was recovered in the urine, while 6-7% was recovered in the feces.

Urinary excretion of premercapturic acids and mercapturic acids represents a major excretory pathway (accounting for approximately 80% of urinary metabolites) in rodents (Stillwell et al., 1978; Chen and Dorough, 1979). However, thioethers were not detected in the urine of chimpanzees (Summer et al., 1979) or rhesus monkeys (Rozman et al., 1982) administered oral doses of up to 200 mg naphthalene/kg. This result suggests that minimal glutathione conjugation occurs in these species (ATSDR, 1995). Urinary metabolite data collected from two chimpanzees suggests that naphthalene is excreted primarily as glucuronide and sulfate conjugates in this species (Summer et al., 1979).

Animal evidence exists for enterohepatic recirculation of naphthalene metabolites. Experiments with normal bile-duct-cannulated and germ-free rats (Bakke et al., 1985) suggest that premercapturic acid metabolites of naphthalene are excreted in the bile and subsequently converted by the intestinal microflora to 1-naphthol. The newly formed 1-naphthol is then subject to absorption and re-circulation.

Dose-dependent increases in urinary thioether levels were reported in rats that received gavage doses of 30, 75, or 200 mg naphthalene/kg (Summer et al., 1979). The levels of thioethers excreted accounted for approximately 39%, 32%, and 26%, respectively, of the dose levels tested.

Dermal Exposure

No studies were located that documented the excretion of naphthalene in humans following dermal exposures.

Turkall et al. (1994) evaluated the excretion of dermally applied ^{14}C-labeled naphthalene by rats over a 48-hour period. A dose of 3.3 $\mu g/cm^2$ of neat naphthalene or naphthalene adsorbed to clay or sandy soils was applied to the shaved skin of rats under a sealed plastic cap. In all cases, excretion was primarily through the urine (70-87%). Exhaled air accounted for 6-14% of the administered dose, and 2-4% was recovered in feces. Less than 0.02% of the label was exhaled as carbon dioxide.

Inhalation Exposure

Bieniek (1994) analyzed the excretion patterns of 1-naphthol in three groups of workers occupationally exposed to naphthalene. The mean excretion rate for these workers was 0.57 mg/hour, with a calculated excretion half-life of approximately 4 hours. The highest urinary levels of 1-naphthol were reported for workers in a naphthalene oil distribution plant. Peak 1-naphthol levels were detected in urine collected one hour after finishing the shift.

7.0 HAZARD IDENTIFICATION

7.1 Human Effects

7.1.1 Short-Term Studies and Case Reports

General Population

Intentional and Accidental Acute Ingestion

The earliest account of acute oral exposure to naphthalene (Lezenius, 1902) describes the ingestion of impure naphthalene by a man over the course of 13 hours in an attempt to cure an abdominal ailment (ATSDR, 1995). The dose of naphthalene was not known precisely, but was estimated to be approximately 5 grams. Assuming a body weight of 70 kg for an adult, this amount corresponds to a dose of approximately 71 mg/kg. Within 8 to 9 hours, vision became severely impaired. No evidence of hematological impacts was reported, but painful urination and urethral swelling were noted. Upon examination 1 month later, bilateral zonular cataracts were seen, visual fields were constricted, and the subject could count fingers up to a distance of only 1.5 meters. The contribution of impurities in the naphthalene to the observed toxic effects is unknown.

Several reports describe cases in which accidental or intentional ingestion of naphthalene resulted in death. Gupta (1979) reported a case of a 17-year-old male who had ingested an unknown quantity of mothballs. He died after exhibiting symptoms that included vomiting, gastrointestinal bleeding, blood-tinged urine, jaundice, and coma. Additional observations included liver enlargement, elevated creatine and blood urea nitrogen, and reduction in urine output. Death occurred 5 days after ingestion. Proximal tubular damage and general tubular necrosis were recorded at autopsy.

Kurz (1987) reported the death of a 30-year-old woman after she ingested a large number of moth balls. The patient reported consuming at least 40 mothballs, 25 of which were recovered at autopsy. The patient exhibited abdominal pain, blood in the urine, and vomiting of blood. Neurological signs included malaise, loss of response to painful stimuli, and muscular twitching or convulsions. Hemolytic anemia was diagnosed prior to death, and the increased plasma level of liver enzymes indicated potential hepatic injury. Death occurred 5 days after ingestion. Limited areas of mucosal hemorrhage in the small bowel and colon were seen at autopsy.

Two cases describe the death of a child following the ingestion of naphthalene. In the first case, a Japanese child died after ingesting approximately 5 grams of mothballs (Ijiri et al., 1987). Assuming a body weight of 10 kg (the age of the child is unknown), this amount corresponds to a dose of approximately 500 mg/kg. The blood level of naphthalene was reported to be 0.55 mg/L. Pulmonary edema, congestion, and hemorrhage of the lungs were found to be present at autopsy. Liver pathology included fatty changes, and leucocyte and lymphocyte infiltration. In the second case, a 6-year-old child died after ingesting an estimated 2 grams of naphthalene over

approximately 2 days (Gerarde, 1960). Assuming a body weight of 21 kg (U.S. EPA, 1996c), this amount corresponds to an estimated dose of 95 mg/kg.

Gidron and Leurer (1956) reported sublethal acute effects in the case of a 16-year-old girl who consumed 6 g of naphthalene in a suicide attempt. Assuming a body weight of 55 kg, this dose corresponds to 109 mg/kg. Symptoms and treatment were recorded during 18 days of hospitalization. Indications of hemolytic anemia (low hemoglobin concentration, low erythrocyte count, discolored urine), fever, and pain in the kidney region were observed.

Dreisbach and Robertson (1987) reported a fatal dose from oral exposure to be approximately 2 grams, although this information was not well documented. This dose is equivalent to about 28 mg/kg for a 70-kg reference human.

Additional reports of sublethal acute naphthalene poisoning have been summarized in ATSDR (1995) and U.S. EPA (1998a). Most of these cases involved naphthalene ingestion by children. Case reports document hemolytic anemia characterized by methemoglobinemia, the occurrence of Heinz bodies, reduced hemoglobin levels, reduced hematocrit, increased reticulocyte counts, and increased serum bilirubin levels. None of these cases provides estimates of the dose levels associated with the development of hemolytic anemia.

Acute and Short-Term Inhalation Exposure

Household inhalation exposures to naphthalene have also been associated with adverse effects. Eight adults and one child reported gastrointestinal (nausea, vomiting, abdominal pain) and neurological (headache, malaise, confusion) symptoms after exposure to large numbers of mothballs in their homes (Linick, 1983). The duration of exposure was not specified, and a single measurement of the level of naphthalene in indoor air (20 ppb) was taken at a time when exposures were thought to be lower because the mothballs were not "fresh." Symptoms were relieved when the mothballs were removed (U.S. EPA, 1998a).

Short-Term Exposure by Other Pathways

Dermal exposure to naphthalene has occasionally been associated with adverse effects in humans. Valaes et al. (1963) reported adverse health effects in an infant exposed to naphthalene by wearing diapers that had been stored with mothballs. The infant developed severe hemolytic anemia accompanied by jaundice, enlarged liver, methemoglobinemia, and cyanosis. A similar case was reported by Schafer (1951). In the latter case, symptoms persisted after cessation of exposure, and death resulted. Levels of exposure were not estimated in either case.

Three reports (Zinkham and Childs, 1958; Anziulewicz et al., 1959; Athanasiou et al., 1997) describe apparent transplacental exposure of a fetus during pregnancy, which resulted in neonatal hemolysis. In the two older cases, unspecified amounts of naphthalene had been ingested by the mother during pregnancy. The more recent report by Athanasiou et al. (1997) documented the occurrence of hemolytic anemia in a neonate whose mother had inhaled naphthalene during the 28th week of pregnancy.

Sensitive Populations

Short-term inhalation exposures to naphthalene have been associated with hemolytic anemia, and occasionally, death. Valaes et al. (1963) reported adverse effects in 21 Greek infants exposed to naphthalene from clothing, diapers, blankets, and other items that had been stored in contact with mothballs. Durations of exposure ranged from 1 to 7 days. Inhalation was identified as the primary route of exposure because 19 of the 21 infants did not have dermal contact with the naphthalene-contaminated materials. A total of 21 infants developed hemolytic anemia and two infants died from kernicterus, a severe neurological condition that was thought to be a consequence of massive hemolysis. Ten of the 21 anemic children and 1 of the 2 infants that died from naphthalene exposure had a genetic polymorphism that resulted in a deficiency in glucose-6-phosphate dehydrogenase (G6PD). This enzyme helps to protect red blood cells from oxidative damage, and G6PD deficiency makes the cells more sensitive to a wide variety of toxicants, including naphthalene.

7.1.2 Long-Term and Epidemiological Studies

General Populations

Ghetti and Mariani (1956) reported the development of pin-point lens opacities in 8 of 21 individuals employed for five years at a dye manufacturing plant. The individuals were involved in the heating of large amounts of naphthalene in open vats. Exposure of these workers likely occurred primarily via inhalation and dermal contact, but exposure levels were not estimated. Although cataracts may develop spontaneously with age, seven of the affected individuals were younger than 50 years old. The probability of spontaneous cataract development in these individuals was therefore considered to be low. The lesions, which did not affect visual acuity, were attributed to naphthalene exposure because no correlation existed between incidence and age, and because they occurred in the crystalline lens (ATSDR, 1995).

Two epidemiological studies addressed a potential relationship between occupational exposure to naphthalene and cancer in German workers. An abstract of a case-control study by Kup (1978) described 12 cases of laryngeal carcinomas, 2 cases of epipharyngeal cancer, and one case of nasal carcinoma. All but three workers were smokers. Four of the patients with laryngeal cancer also had a history of occupational exposure to naphthalene. Limitations to this study include the small number of patients studied, uncertainty about how naphthalene exposures were identified, and known exposures to other potential carcinogens. Consequently, this study does not provide strong evidence for an association between naphthalene exposure and pharyngeal cancer. The author suggested that most of the observed cancers were probably due to nonoccupational causes (U.S. EPA, 1998a).

The second epidemiological study reported the finding of 6 cases of cancer among 15 workers exposed to naphthalene vapors at a coal tar and naphthalene production facility (Wolf, 1976). The duration of exposure ranged from 7 to 32 years. Four workers developed carcinomas of the larynx. Two workers developed cancer of the stomach and cecum. All of the subjects were smokers. Limitations to this study include lack of a control population, the small numbers of

workers involved, lack of quantitative exposure data, and the presence of both occupational and nonoccupational exposures to other potential carcinogens. Therefore, this study does not provide strong evidence for a relationship between naphthalene exposure and cancer incidence (U.S. EPA, 1998a).

Sensitive Populations

No long-term studies conducted in sensitive populations were identified in the materials reviewed for this document.

7.2 Animal Studies

This section presents the results of toxicity studies of naphthalene in animals. The first four subsections provide study results by duration of exposure. Acute studies are those which address exposure durations of 24 hours or less. Short-term studies are those in which the exposure duration is greater than 24 hours but less than approximately 90 days. The exposure duration of subchronic studies is typically 90 days, and chronic studies are those in which exposure lasts one year or more. Some studies fall into more than one category because they measure impacts over several exposure periods. The discussion of acute, short-term, subchronic, and chronic studies summarizes observed toxicological effects on all body systems.

The last four subsections of Section 7.2 provide toxicological data related to specific organ systems and types of endpoints: ocular toxicity, neurotoxicity, developmental/reproductive toxicity, and carcinogenicity.

7.2.1 Acute Toxicity

Oral Exposure

Acute lethality data have been reported for rats and mice. LD_{50} values in various strains of rats typically range between 1,780 mg/kg and 2,800 mg/kg (Gaines, 1969; NIOSH, 1977; Papciak and Mallory, 1990), although LD_{50} values as high as 9,430 mg/kg have been reported in one study (Union Carbide Corp., 1968). Shopp et al. (1984) reported LD_{50} values of 533 mg/kg for male mice and 710 mg/kg for female mice.

Zuelzer and Apt (1949) administered single dietary doses of 410 mg/kg or 1,530 mg/kg naphthalene to two dogs. Both dogs developed signs of hemolytic anemia including a 29–33% reduction in hemoglobin concentrations, decreased hematocrit, presence of Heinz bodies, and reticulocytosis.

Shopp et al. (1984) administered 0, 200, 400, 600, 800, or 1,000 mg/kg naphthalene via oral gavage (in a corn oil vehicle) to CD-1 mice (8 animals/sex/dose). Mice displayed ptosis (drooping of eyelids) and red discharge soon after receiving doses of 400 mg/kg or higher (males) or 600 mg/kg or higher (females). These findings suggest NOAEL and LOAEL values for this

study of 200 and 400 mg/kg, respectively, based on the occurrence of ptosis (drooping of the eyelids) in male mice.

Naphthalene-related cataract formation has been reported in animals following acute oral exposure. Van Heyningen and Pirie (1976) administered naphthalene by gavage at 1,000 mg/kg-day to rabbits and observed cataract formation in some animals after a single dose. Ikemoto and Iwata (1978) observed that oral administration of 1,000 mg/kg to albino rabbits of both sexes for two consecutive days resulted in cataract formation. The ocular toxicity of naphthalene is further discussed in Section 7.3.2.

Dermal Exposure

Acute toxicity testing in rabbits revealed that 2,000 mg/kg of naphthalene causes moderate dermal irritation (erythema, edema, and/or fissuring that resolved within 7 days) when applied directly to intact or abraded skin (Papciak and Mallory, 1990). Application of 500 mg/kg to intact or abraded skin resulted in slight irritation (some reversible erythema at 24 and 72 hours after application) (Papciak and Mallory, 1990). In a separate study, application of 500 mg to intact shaved skin (area not specified) resulted in mild to well-defined erythema and some fissuring (PRI, 1985). Mild ocular irritation occurred following the instillation of 100 mg of naphthalene into the eye (PRI, 1985; Papciak and Mallory, 1990). These effects were reversed within 7 days, and they occurred only when naphthalene was left on the eye surface rather than rinsed off after application (ATSDR, 1995).

Inhalation Exposure

U.S. EPA (1987b) has previously summarized acute inhalation data for naphthalene. Union Carbide (1968) reported that the 8-hour LC_{50} value for naphthalene was 100 ppm. Buckpitt (1985) suggested that this value may be too low, on the basis of calculated body burdens. Buckpitt (1985) calculated that following 8 hours of inhalation exposure at 100 ppm, the body burden would be less than 30 mg/rat, or approximately 150 to 200 mg/kg. This value is considerably 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 naphthalene for 4 hours did not result in mortalities or any abnormalities in the lung, liver, kidney, or nasal passages. Buckpitt (1985) conducted an inhalation study with male Swiss-Webster mice. No deaths were observed after exposure to 90 ppm naphthalene for 4 hours, but lung lesions were reported to be prominent.

No new data for acute inhalation toxicity were identified in the materials reviewed for this document.

7.2.2 Short-Term Studies

Oral Exposure

Zuelzer and Apt (1949) administered seven consecutive daily doses of naphthalene in the diet to a single dog. The daily doses ranged from 74 to 441 mg/kg, with an average daily dose of 262 mg/kg-day. The dog developed signs of hemolytic anemia, including decreased hemoglobin concentration, decreased hematocrit, presence of Heinz bodies, extreme leukocytosis, and reticulocytosis. Other signs noted included pronounced lethargy and ataxia.

Shopp et al. (1984) administered 0, 27, 53, or 267 mg/kg-day naphthalene in corn oil via oral gavage to CD-1 mice (76–112 males/dose, 40–76 females/dose) for 14 days. Gross pathology was performed, but a histopathological examination was not conducted. No adverse effects were noted at doses of 53 mg/kg-day or less. Adverse effects observed in animals exposed to 267 mg/kg-day included increased mortality and decreased terminal body weights (4–10%) in males and females, decreased absolute thymus weights (30%) in males, increased bilirubin in females, and increased spleen and lung weights (relative and absolute) in females. Serum enzyme activities (lactic dehydrogenase and serum glutamic-oxaloacetic transamidase) and electrolyte levels were not altered in a dose-dependent pattern. There were no effects on hexobarbital sleeping time or on various immunological screening parameters (with the exception of decreased lymphocyte response to concanavalin A in high-dose females). Values for hematological and coagulation parameters were similar to controls, with the exception of decreased prothrombin time in high-dose females, and a small but significant increase in eosinophils in high-dose males. Neither red cell hemolysis nor cataract formation was observed in the naphthalene-exposed mice, and the authors suggested that this mouse strain appears to be resistant to these toxic effects. This study identified a NOAEL of 53 mg/kg-day and a LOAEL of 267 mg/kg-day.

Plasterer et al. (1985) administered doses of 0, 125, 250, 500, 1,200, and 2,000 mg/kg-day to non-pregnant female CD-1 mice (10 per dose group) by gavage in corn oil. A steep dose-response relationship was observed for lethality in naphthalene-exposed mice. After 8 daily gavage doses, an LD_{50} value of 354 mg/kg was determined for male and female mice. This value is based on 100% mortality at 500 mg/kg-day and no deaths at 250 mg/kg-day. In pregnant mice, 15% mortality was observed in the 300-mg/kg-day group. In contrast, no mortality was reported in 2 strains of rabbits that received 1,000 mg/kg naphthalene via gavage, twice a week for 12 weeks (Rossa and Pau, 1988), suggesting that there are species differences in response to naphthalene exposure.

Liver changes have been reported in rats exposed to relatively high doses of naphthalene (approximately 1,000 mg/kg-day or more) when administered for durations of 10 days to 9 weeks (ATSDR, 1995). Rao and Pandya (1981) reported hepatic toxicity in rats administered 1,000 mg/kg-day naphthalene (LOAEL) for 10 days. Observed effects included a 39% increase in liver weight, increased lipid peroxidation, and a modest increase in aniline hydroxylase activity (ATSDR, 1995). Increased lipid peroxidation was also reported in rats that received 1,000 mg/kg-day naphthalene for 18 days (Yamauchi et al., 1986), and in rats that received escalating doses of naphthalene up to 750 mg/kg-day over a 9-week period (Germansky and Jamall, 1988).

No effects on liver weight were noted in the 14-day gavage study reported by Shopp et al. (1984) at tested doses as high as 267 mg/kg-day.

Dermal Exposure

No short-term animal studies evaluating the dermal route of exposure were identified in the materials reviewed for this document.

Inhalation Exposure

No short-term inhalation studies of naphthalene exposure were identified in the materials reviewed for this document.

7.2.3 Subchronic Studies

Oral Exposure

Naphthalene (>99% in corn oil) was administered to Fischer 344 rats (10/sex/dose), 5 days per week for 13 weeks (BCL, 1980a). Unadjusted daily dose levels were 0, 25, 50, 100, 200, and 400 mg/kg-day. Weekly food consumption and body weights were measured, and rats were examined twice daily for clinical signs of adverse effects. Hematological parameters (hemoglobin, hematocrit, total and differential white cell count, red blood cell count, mean cell volume and mean cell hemoglobin) were measured in all animals at the end of the study. All rats were necropsied, and detailed histopathological examinations on 27 tissues were performed on all rats in the control and 400 mg/kg-day groups. The tissues examined included eyes, stomach, liver, reproductive organs, thymus, and kidneys. In the 100-mg/kg-day group, male kidneys and female thymus tissues were subject to detailed histopathological examinations.

Male and female rats in the 400 mg/kg-day dose group exhibited diarrhea, lethargy, hunched posture, and rough coats during the study, and one high-dose male rat died during the last week of exposure. Food consumption was not affected in any dose group, but body weights were significantly decreased in several of the groups (Table 7-1). Males in the high-dose group experienced a 94% increase in the number of mature neutrophils and a 25.1% decrease in circulating lymphocytes, as compared to control group rats. No other differences were observed in hematological parameters. Histopathological examination of kidney and thymus tissues revealed the following changes: focal cortical lymphocyte infiltration was observed in 1 of 10 males in the 200-mg/kg-day group; focal tubular degeneration was observed in 1 of 10 males in the 200-mg/kg-day group; diffuse renal tubular degeneration was observed in 1 male in the 400-mg/kg-day group; and lymphoid depletion of the thymus was seen in 2 of 10 females in the high-dose group. No other tissue abnormalities were seen in any group. The NOAEL and LOAEL values derived from this study were 100 and 200 mg/kg-day, respectively, on the basis of reduced body weight (>10%) in males (U.S. EPA, 1998a). These NOAEL and LOAEL values correspond to duration-adjusted doses of 71 and 143 mg/kg-day, respectively.

Table 7-1. Terminal Body Weights in Controls and in Fischer 344 Rats Exposed to Naphthalene by Gavage for 13 Weeks

Dose (mg/kg-day)		Average Terminal Body Weight Males (g)	Average Terminal Body Weight Females (g)
Unadjusted	Duration-adjusted		
0	0	348.9	203.4
25	17.9	353.4	197.8
50	35.7	351.2	203.5
100	71.4	333.4	197.2
200	142.9	306.7*	190.5
400	285.7	250.6*	156.7*

*Decrease > 10% relative to controls
Source: U.S. EPA (1998a)

In a second study (BCL, 1980b), the same investigators exposed $B6C3F_1$ mice to naphthalene in corn oil by gavage. The administered doses were 0, 12.5, 25, 50, 100, and 200 mg/kg-day, 5 days per week for 13 weeks. Seven mice died during the exposure period, all from gavage trauma unrelated to naphthalene dose. In weeks 3 and 5 of the exposure period, transient signs of toxicity (lethargy, rough coats, decreased food consumption) occurred in the highest-dose groups. The average weight gain during the study was higher for all of the exposed male groups than for the control group. Female mice exposed to naphthalene, in contrast, gained less weight than the control group. The reduction in weight gain was dose-related, ranging from 2.5% in the 12.5-mg/kg-day females to 24.5% in the 200-mg/kg-day females. The authors of the study indicated that the weight gain reduction "was not large enough to conclusively indicate a toxic effect". Complete histological evaluations were performed on all control and high-dose animals at the end of the study. No exposure-related lesions were observed in any organ system. Mild focal or multifocal subacute pneumonia was observed in similar proportions for both control and high-dose animals. Hematological evaluation indicated an increase in circulating lymphocytes of 18% in the high-dose males relative to these in control groups. A decrease of 38.8% in segmented neutrophils was also noted in high-dose males. No significant differences were observed in hematological parameters.

The authors of the study indicated that given the "marked indication" of sex differences in body weight responses, the observed weight gain differences did not constitute an adverse effect. If this interpretation is accepted, a LOAEL of 200 mg/kg-day (adjusted dose: 143 mg/kg-day) can be identified from this study based on the occurrence of transient clinical signs of toxicity

discussed above (U.S. EPA, 1998a). The corresponding NOAEL would be 100 mg/kg-day (adjusted dose 71 mg/kg-day).

Shopp et al. (1984) employed larger numbers of mice to evaluate the subchronic toxicity of naphthalene. Groups of 76 male and 40 female CD-1 mice were exposed by gavage to daily doses of 5.3 or 53 mg/kg-day naphthalene in corn oil for 90 consecutive days. In addition, a high-dose group of 96 male and 60 female mice received a daily dose of 133 mg/kg-day. Toxicological responses were measured against naive control groups of 76 male and 40 female mice, and against vehicle control groups of 112 male and 76 female animals. No differences in survival or terminal body weights were seen between the control and exposed groups. In the high-dose females, significant decreases were seen in absolute weights of the brain, liver, and spleen, and in the relative spleen weight. No differences in organ weights were seen in males in any exposure group. Histopathological examinations were not performed, but the authors noted an absence of cataracts in all dose groups. In general, serum chemistry parameters for naphthalene treatment groups did not differ significantly from control groups. However, hematological evaluation showed slight but significant increases in hemoglobin levels in high-dose females. All of the exposed female groups had significantly decreased blood urea nitrogen (BUN) levels. Significant changes in serum globulin levels were observed in females, but a consistent dose-response relationship was not evident. Hematological parameters for males were normal. No exposure-related impacts on immunological function were observed. Assays for enzyme activity indicated that hepatic benzo(a)pyrene hydroxylase activity was decreased significantly in males and females treated with the 53 and 133 mg/kg-day doses, and in males treated with the 5.3 mg/kg-day dose. Aniline hydroxylase activity was significantly increased in females receiving the 133 mg/kg-day dose. The authors of this study did not report a NOAEL. Because the effects on serum chemistry parameters and hepatic enzymes are not clearly adverse, U.S. EPA (1998a) identified a NOAEL of 53 mg/kg-day. The LOAEL of 133 mg/kg-day reflects the observed effects on organ weight and suggestive evidence for impacts on hepatic enzyme function.

Dermal Exposure

Frantz et al. (1986) applied doses of 0, 100, 300, or 1,000 mg naphthalene/kg-day to the skin of albino rats for 6 hours/day, 5 days/week, for 13 weeks. Following exposure, clinical signs, food consumption, body weight, clinical chemistry, hematology, and urinalysis were evaluated. A significantly increased incidence of excoriated skin lesions and papules was reported in the high-dose group relative to those in the controls. Similar lesions were observed in the control group and low-dose groups. The severity of the lesions appeared to increase with dose.

Inhalation Exposure

No studies that addressed subchronic exposures by inhalation were identified in the materials reviewed for this document.

7.2.4 Neurotoxicity

Relatively little information is available regarding the neurological effects of naphthalene exposure in experimental animals. PRI (1986) observed treatment-related signs of labored breathing, body drop, and decreased activity (incidence data not provided) in New Zealand White rabbits exposed to 200 or 400 mg/kg-day. In a study of developmental toxicity (NTP, 1991), pregnant Sprague-Dawley rats received daily gavage doses of 0, 50, 150, or 450 mg/kg-day naphthalene for 10 days during organogenesis (gestation days 6 to 15). Animals in all dose groups showed signs of neurotoxicity, including lethargy, slow respiration (including periods of apnea), and apparent inability to move after dosing. Incidence of symptoms in the low-dose group was 73%, while incidence in the highest-dose group was over 90%. These effects were transient, however, and diminished as the animals apparently acclimatized to the treatment. Animals in the low-dose group appeared to acclimatize to naphthalene exposures after a few days. Incidence in the higher-dose groups declined with continued exposure, but never dropped below 15% (ATSDR, 1995).

Male mice exposed to 10 or 30 ppm naphthalene in a two-year inhalation study exhibited increased huddling behavior during exposure and a reduced inclination to fight (NTP,1992a). Although the observed activities may indicate neurological effects, the authors of this study did not speculate on the underlying basis for the behavioral changes, and no additional signs of neurotoxicity were reported.

Other large studies found no evidence of neurotoxicity at naphthalene doses similar to those producing symptoms mentioned in the studies above. No neurological effects were found in Fischer 344 rats (BCL, 1980a) or B6C3F$_1$ mice (BCL, 1980b), at gavage doses up to 400 mg/kg-day and 200 mg/kg-day, respectively.

7.2.5 Developmental/Reproductive Toxicity

Studies of the reproductive and developmental toxicity of naphthalene are summarized in Table 7-2.

PRI (1985) conducted a range-finding developmental study in New Zealand White rabbits. Gavage doses of 0, 50, 250, 630, or 1,000 mg/kg-day were administered to pregnant rabbits (4/dose) by gavage in 1% methylcellulose on gestation days (GD) 6 to 18. All does in the high-dose group died. At 630 mg/kg-day, 2 of 4 animals died. The surviving animals experienced decreased weight gain and aborted their pregnancies. No exposure-related changes were observed in the incidence of early resorption, postimplantation loss, number of corpora lutea, fetal survival, or gross fetal structural development.

In a subsequent study of developmental toxicity, PRI (1986) administered doses of 0, 40, 200, or 400 mg/kg-day by gavage in 1% methyl cellulose to pregnant New Zealand White rabbits (18/dose). Dosing occurred on GD 6–18. Caesarean sections were performed on GD 29.

Table 7-2. Summary of Developmental and Reproductive Data on Naphthalene

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL mg/kg-day	LOAEL mg/kg-day	Effect
PRI (1985)	Rabbit (New Zealand White)	Female 4	0 50 250 630 1,000	Gavage Methyl-cellulose	GD 6–18	Maternal 250 Fetal 250	Maternal 630 (FEL) Fetal 630 (abortion)	Maternal: Mortality and decreased wt. gain at 630 mg/kg-day Fetal: Aborted at 630 mg/kg-day
PRI (1986)	Rabbit (New Zealand White)	Female 18	0 40 200 400	Gavage Methyl-cellulose	GD 6-18	Maternal 400 Fetal 400	Maternal - Fetal -	Maternal: survival, body wt. and body wt. gain unaffected Fetal: No effect on reproduction or development of fetus
Plasterer et al. (1985)	Mouse (CD-1)	Female 33–40	0 300	Gavage oil	GD 7–14	-	300 (FEL)	Maternal: Reduced wt. gain; reduced survival Fetal: Reduced no. of pups/litter; no abnormalities in surviving pups

Table 7-2 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
NTP (1991)	Rat (Sprague-Dawley CD)	Female 25–26	0 50 150 450	Gavage	GD 6–15	Maternal – Fetal 450	Maternal 50 (central nervous system depression) Fetal --	Maternal: Two deaths; central nervous system depression manifested as lethargy, slow breathing, prone body posture, and increased rooting Fetal: no finding of fetoxicity or embryotoxicty
NTP (1992b)	Rabbit (New Zealand White)	Female 25–27	0 20 80 120	Gavage oil	GD 6–19	Maternal 120 Fetal 120	Maternal - Fetal -	Maternal: No consistently observed toxicity Fetal: No effect on reproduction or development of fetus
Shopp et al. (1984)	Mouse (CD-1)	Male 76–112	0 27 53 267	Gavage oil	14	267	-	No effect on testicular weight
		Male 76–96	53 133	Gavage oil	90	133	-	No effect on testicular weight

Table 7-2 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
BCL (1980a)	Rat (F344)	Male 10/dose	0 25 50 100 200 400	Gavage oil	13 weeks 5 days/week	400	-	Absence of gross testicular lesions
BCL (1980b)	Mouse ($B6C3F_1$)	Male 10/dose	0 12.5 25 50 100 200	Gavage oil	90 days	200	-	Absence of gross testicular lesions

GD = gestation day
FEL = fetal effect level

Maternal survival, body weight, and body weight gain were unaffected by naphthalene treatment. Treatment-related signs of labored breathing, cyanosis, body drop, decreased activity and salivation were reportedly noted in animals receiving the 200 and 400 mg/kg-day doses, but incidence data were not provided. No effect of treatment was noted on number of corpora lutea, total implantations, fetal viability, pre- or postimplantation loss, fetal body weight, fetal sex distribution, or fetal skeletal or visceral abnormalities.

Plasterer et al. (1985) examined the developmental toxicity of naphthalene in CD-1 mice. Doses of 0 or 300 mg/kg-day (40 and 33 animals/group, respectively) were administered by gavage in corn oil on GD 7 to 14. Mortality occurred in 5/33 exposed dams, while all control dams survived the treatment. Average weight gain was significantly reduced in exposed dams when compared with controls. The average number of live pups per litter was significantly reduced by naphthalene treatment, but the average body weight of the living pups was not affected by exposure. No treatment-related gross structural abnormalities were seen in the surviving pups. The 300 mg/kg-day dose is considered a frank effect level (FEL) based on maternal (death and reduced body weight) and fetal (decreased live pups per litter) effects.

NTP (1991) conducted a developmental study of naphthalene toxicity in pregnant Sprague-Dawley CD rats (25–26/dose). Doses of 0, 50, 150,or 450 mg/kg naphthalene were administered by gavage in corn oil on gestational days 6 to 15. The dams were examined daily for clinical signs until sacrifice on GD 20. Fetuses were examined on GD 20 for gross, visceral, and skeletal malformations. Maternal mortality was limited to two deaths in the low-dose group. Treatment with naphthalene produced clinical signs of toxicity, including lethargy, slow breathing, prone body posture, and increased rooting behavior. The effects subsided in the 50 and 150 mg/kg-day groups before the end of the treatment period, but persisted throughout the treatment period in the 450 mg/kg-day treatment group. Dams exposed to the 150 and 450 mg/kg doses showed significant decreases in weight gain. The average reductions in weight gain were 31% and 53% respectively. No unequivocal treatment-related effects on fetal development were noted. The study authors identified the highest dose of 450 mg/kg-day as a NOAEL for fetal effects. U.S. EPA (1998a) identified 50 mg/kg-day as the LOAEL for maternal toxicity in this study.

Mild developmental abnormalities were noted in some offspring of New Zealand rabbits that were administered 0, 20, 80, or 120 mg/kg-day naphthalene on gestation days 6–19 (NTP, 1992b). Slight increases in the incidence of fused sternebrae were seen in the female pups in 2 of 20 litters of animals given 80 mg/kg-day, and in 3 of 20 litters of animals given 120 mg/kg-day. However, these increases were not statistically significant. No significant differences were observed for average litter size, average fetal body weight, or incidence of other malformations on a per fetus or per litter basis. The highest dose in this study was the NOAEL for maternal and developmental toxicity.

Naphthalene does not cause testicular lesions in rats or mice. Testicular weight was unaffected in B6C3F_1 mice given 267 mg/kg naphthalene for 14 days or 133 mg/kg for 90 days (Shopp et al., 1984). Two other subchronic studies also found no gross histopathological

testicular lesions in Fischer 344 rats receiving up to 400 mg/kg-day naphthalene (BCL, 1980a) or in B6C3F$_1$ mice receiving up to 200 mg/kg-day (BCL, 1980b) for 13 weeks.

7.2.6 Chronic Toxicity

The few chronic animal studies that are available for naphthalene were conducted primarily to characterize its carcinogenic potential effects. Noncancer endpoints reported in these studies are summarized below.

Oral Exposure

Schmähl (1955) examined the long-term (300–700 day) exposure of rats (in-house strain BDI or BDII) to naphthalene in food. High-purity naphthalene (as judged by absorption spectra) was dissolved in oil, mixed in the diet, and administered to 28 rats, 6 times a week. Estimated daily doses were between 10 and 20 mg/rat. Assuming that the body weight of the test strain was similar to the reference weight of 0.36 kg for a male Fischer 344 rat (U.S. EPA, 1988), the average daily dose was approximately 42 mg/kg-day. Dosing was stopped at 700 days when the total dose for each animal reached 10 grams. Animals were then observed until spontaneous death, usually between the 700th and 800th experimental day. Survival of the exposed animals was similar to that of the control group. Autopsy and histological results did not identify signs of adverse noncancer effects in any organ system, including the eye. This study is not considered adequate to support the development of a NOAEL or LOAEL value (U.S. EPA, 1998a), on the basis of the administration of a single dose level, inadequate reporting of results, incomplete histopathological examinations, lack of hematological examinations, and examination of some animals at time points up to 300 days following termination of exposure.

Dermal Exposure

No studies evaluating chronic naphthalene exposure by the dermal route were identified.

Inhalation Exposure

Adkins et al. (1986) investigated the impacts of less-than-lifetime inhalation exposures to naphthalene on rats. Groups of 30 female A/J strain rats were exposed to 0, 10, or 30 ppm naphthalene vapors for 6 hours per day, 5 days per week, for 6 months. All animals were sacrificed at the end of the exposure period and their lungs excised and examined for tumors. No adverse noncancer effects on the lung were reported (U.S. EPA, 1998a). Other organs were not examined in study.

A chronic inhalation study of naphthalene toxicity was conducted in B6C3F$_1$ mice by NTP (1992a). Naphthalene exposure concentrations in air were 0, 10 ppm, or 30 ppm. The concentration of 10 ppm was chosen because it was equal to the ACGIH TLV® for naphthalene, while the 30 ppm concentration was chosen because it was one-half the air saturation concentration. The control and low-exposure groups consisted of 75 mice of each sex, while the

high-exposure group consisted of 150 mice of each sex. Exposure was for 6 hours per day, 5 days per week, for 2 years. Comprehensive histopathological evaluations were performed on all control and high-exposure mice, and on all low-exposure mice that died or were sacrificed during the first 21 months of exposure. The original study plan called for 50 animals per sex to be exposed for 2 years, and 5 animals per sex to be sacrificed for hematological evaluations at 14 days, 3, 6, 12, and 18 months. However, as a result of excessive mortality in the control males, only the 14-day hematological evaluation was conducted. All of the remaining animals were incorporated into the two-year study.

A statistically significant decrease in survival was noted in the male control group (Table 7-3). This phenomenon was attributed to the frequent fighting that occurred among the control group mice. In contrast, the exposed groups tended to huddle together during exposure periods, and fought less. Statistically significant increases were seen in several types of noncancer respiratory tract lesions in both exposed groups (Table 7-3). The observed responses included chronic lung inflammation, chronic nasal irritation with hyperplasia of the nasal epithelium, and metaplasia of the olfactory epithelium. The authors of the study described the lung lesions as a chronic inflammatory response with granuloma. These lesions consisted of "focal intra-alveolar mixed inflammatory cell exudates and interstitial fibrosis." The more advanced lesions consisted primarily of "large foamy macrophages sometimes accompanied by giant cells."

No changes in hematological parameters were seen among the exposed animals at 14 days. No cataract formation was observed after 2 years of exposure. Histopathological examination did not reveal treatment-related effects on the liver, gastrointestinal system, reproductive system, brain, or any other organs. The results of this study have been interpreted by U.S. EPA (1998a) to support a chronic LOAEL for nasal and respiratory irritation of 10 ppm.

Table 7-3. Survival and Incidence of Non-neoplastic Lesions in B6C3F$_1$ Mice Exposed to Naphthalene by Inhalation for Their Lifetime

Dose (ppm)	Survival		Chronic Lung Inflammation		Chronic Nasal Inflammation, Hyperplasia of Nasal Epithelium		Metaplasia of Olfactory Epithelium	
	Male	Female	Male	Female	Male	Female	Male	Female
0	26/70	59/69	0/70	3/69	0/70	0/69	0/70	1/69
10	52/69*	57/65	21/69*	13/65*	66/69*	65/65*	67/69*	65/65*
30	118/133*	102/135	56/135*	52/135*	134/135*	135/135*	133/135*	135/135*

Source: NTP (1992a)
*Significantly different from control by logistic regression ($p \leq 0.001$).

NTP (2000) conducted a chronic inhalation study in F344/N rats. Male and female rats (49/sex/dose) were exposed to naphthalene vapor concentrations of 0, 10, 30, and 60 ppm for 6 hours per day plus T_{90} (the theoretical time to achieve 90% of the target concentration in the vapor chamber: 12 minutes), 5 days per week for 105 weeks. Additional groups of rats were similarly exposed for up to 18 months for evaluation of toxicokinetic parameters. Dose calculations were based upon model estimates of the amount of naphthalene inhaled by rats at the exposure concentrations used in the two-year study, the total amount of naphthalene metabolized following a six-hour exposure period (21% to 31% of inhaled naphthalene), and average weights of 125 grams (male rats) and 100 grams (female rats). Because essentially all of the naphthalene that is absorbed into the bloodstream is metabolized, the total amount of naphthalene metabolized was assumed to represent the internalized dose to rats from the exposure concentrations used in this two-year study. The estimated daily doses determined by this method were 0, 3.6, 10.7, 20.1 mg/kg-day for males, and 0, 3.9, 11.4, and 20.6 mg/kg-day for females.

Rats were clinically examined twice daily and findings were recorded every four weeks beginning at week 4 and every two weeks beginning at week 92. Body weights were recorded at study initiation, every four weeks beginning at week 4, and every two weeks beginning at week 92. Full necropsies and complete histopathologies were performed on all core study animals.

There were no clinical findings related to naphthalene exposure from the two-year inhalation study. The mean body weights all exposed groups of male and female rats were similar to those observed in the appropriate control chamber group. No significant difference in survival rate was observed for any exposed group when compared to the chamber control. The mean body weights of female rats were generally similar to the body weights of the control group, while the mean body weights of naphthalene-exposed male rats were generally less than the chamber control for all exposed groups.

Although naphthalene is a known cataractogen and ocular irritant (see Section 7.3.2), no naphthalene-related cataractogenic effects or ocular abnormalities were observed in rats during this study. Treatment-related non-neoplastic lesions were observed in the nose and lungs of male and female rats. The incidence and average severity of nasal lesions (glands, goblet cells, respiratory epithelium and olfactory epithelium) are summarized in Table 7-4. The incidences of these lesions were significantly greater than those in the chamber controls for all male and female exposed groups, with the exception of squamous metaplasia of glands in male and female rats in the 10 ppm exposure groups (NTP, 2000). In general, the severities of olfactory epithelial and glandular lesions increased with increasing exposure concentrations.

Two noteworthy type of lesions occurred in the lungs of exposed rats: alveolar epithelial hyperplasia and minimal chronic inflammation. Female rats in all exposure groups had increased incidences of alveolar epithelial hyperplasia when compared to the chamber control (chamber control: 4/49, 10ppm: 11/49, 30 ppm: 11/49, 60 ppm: 9/49). This effect reached statistical significance in the 10 and 30 ppm exposure groups. The incidences of alveolar epithelial hyperplasia in male rats (chamber control: 23/49, 10 ppm: 12/49, 30 ppm: 9/48, 60

Table 7-4. Incidence and Severity of Nonneoplastic Lesions in the Noses of Rats in a Two-year Naphthalene Inhalation Study

Lesion Type	Incidence and Severity (average) of Lesions			
	Chamber Control	10 ppm	30 ppm	60 ppm
MALE				
Atypical Hyperplasia of the Olfactory Epithelium	0/49	48/49* (2.1)	45/48* (2.5)	46/48* (3.0)
Atropy of the Olfactory Epithelium	3/49 (1.3)	49/49* (2.1)	48/48* (2.8)	47/48* (3.5)
Chronic Inflammation of the Olfactory Epithelium	0/49	49/49* (2.0)	48/48* (2.2)	48/48* (3.0)
Hyaline Degeneration of the Olfactory Epithelium	3/49 (1.3)	45/49* (1.7)	40/48* (1.7)	38/48* (1.5)
Hyperplasia of the Respiratory Epithelium	3/49 (1.0)	21/49* (2.2)	29/48* (2.0)	29/48* (2.2)
Squamous Metaplasia of the Respiratory Epithelium	0/49	15/49* (2.1)	23/48* (2.0)	18/48* (1.8)
Hyaline Degeneration of the Respiratory Epithelium	0/49	20/49* (1.2)	19/48* (1.4)	19/48* (1.2)
Hyperplasia of the Respiratory Epithelium Goblet Cells	0/49	25/49* (1.3)	29/48* (1.2)	26/48* (1.2)
Hyperplasia of Glands	1/49 (1.0)	49/49* (2.2)	48/48* (2.9)	48/48* (3.5)
Squamous Metaplasia of Glands	0/49	3/49 (3.0)	14/48* (2.1)	26/48* (2.5)
FEMALE				
Atypical Hyperplasia of the Olfactory Epithelium	0/49	48/49* (2.0)	48/49* (2.4)	43/49* (2.9)
Atropy of the Olfactory Epithelium	0/49	49/49* (1.9)	49/49* (2.7)	47/49* (3.2)
Chronic Inflammation of the Olfactory Epithelium	0/49	47/49* (1.9)	47/49* (2.6)	45/49* (3.4)
Hyaline Degeneration of the Olfactory Epithelium	13/49 (1.1)	46/49* (1.8)	49/49* (2.1)	45/49* (2.1)
Hyperplasia of the Respiratory Epithelium	0/49	18/49* (1.6)	22/49* (1.9)	23/49* (1.7)
Squamous Metaplasia of the Respiratory Epithelium	0/49	21/49* (1.6)	17/49* (1.5)	15/49* (1.8)
Hyaline Degeneration of the Respiratory Epithelium	8/49 (1.0)	33/49* (1.2)	34/49* (1.4)	28/49* (1.2)
Hyperplasia of the Respiratory Epithelium Goblet Cells	0/49	16/49* (1.0)	29/49* (1.2)	20/49* (1.0)
Hyperplasia of Glands	0/49	48/49* (1.9)	48/49* (3.1)	42/49* (3.3)
Squamous Metaplasia of Glands	0/49	2/49 (2.0)	20/49* (2.5)	20/49* (2.8)

Source: Adapted from *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene in Rats (Inhalation Studies)*, Table 6 (NTP, 2000).

*Significantly different ($P < 0.01$) from chamber control using the Poly-3 test

ppm: 16/49) were significantly decreased in the 10 and 30 ppm exposure groups. The incidences of minimal chronic inflammation of the lung were increased in males and females exposed to naphthalene. This lesion is characterized by small focal interstitial and intra-alveolar collections of macrophages, neutrophils, and lymphocytes and minimal interstitial fibrosis. As noted by the NTP study authors, foci of minimal inflammation are common in chamber control rats (as evident in this study). Therefore, this change could not be confidently related to naphthalene exposure.

The study conducted by NTP (2000) identified an estimated inhalation LOAEL of 3.6 mg/kg-day based on the occurrence of nasal lesions in male rats in the 10 ppm exposure group. A NOAEL was not identified in this study. The 10 ppm concentration associated with the LOAEL corresponds to the threshold limit value for naphthalene (ACGIH, 2000).

7.2.7 Carcinogenicity

Oral Exposure

One study was available that evaluated the carcinogenic potential of naphthalene following oral exposure in experimental animals. Schmähl (1955) administered 10 to 20 mg naphthalene/rat (dissolved in oil) in the diet for 6 days/week to a group of 28 rats. Compound administration was continued until a total dose of 10 g/rat was achieved. A concurrent control group was reported, but the number of animals was not specified. Administration of the diet containing naphthalene was terminated on the 700th day of the study, with animals observed until spontaneous death (approximately 700–800 days of age). An average daily dose of 42 mg/kg body weight/day was estimated by U.S. EPA (1998a) for this study, assuming that animals ingested 15 mg naphthalene/day and had an average default body weight of 0.36 kg (U.S. EPA, 1988). Gross necropsies were conducted on all animals, with histopathological examinations conducted only on those organs that appeared unusual. Reported results were limited to a statement that indicated that no toxic effects were observed, including eye damage or tumors. This study has inadequacies in study design, implementation, and reporting that limit the conclusions that can be drawn regarding the carcinogenicity of naphthalene. These limitations include administration of only one dose level, inadequate reporting of results, incomplete histopathological examinations, lack of hematological examinations, and examination of some animals at time points up to 300 days following termination of exposure. Based on the absence of toxicity, the dose tested is not considered an adequately high dose for detection of carcinogenic effects (U.S. EPA, 1998a).

Inhalation Exposure

Three studies were identified which evaluated the carcinogenic potential of inhalation exposure to naphthalene in animals. Adkins et al. (1986) exposed groups of 30 female A/J mice to 0, 10, or 30 ppm naphthalene via inhalation for 6 hours/day, 5 days/week for 6 months. An additional group of 20 mice served as a positive control, and animals in this group were administered a single intraperitoneal injection of 1g urethane/kg. At termination of exposure, animals were sacrificed and lungs excised and examined for tumors, with tumors examined histologically. Lung tumors were observed in all positive control mice, with an average of 28.9

tumors/animal. An increase in the number of mice with alveolar adenomas was observed in the naphthalene-exposed groups (6, 10, and 11 in the 0, 10, and 30 ppm groups, respectively). The increases were not statistically significant when compared with the incidence of alveolar adenomas observed in the concurrent control group. Statistically significant increases in the number of adenomas per tumor-bearing mouse were reported in the exposed mice; however, there was no increase in response with increasing dose. The average number of tumors per tumor-bearing animal (standard deviation in parentheses) was 1.00 (0.00), 1.25 (0.07), and 1.25 (0.07) for the 0, 10, and 30 ppm groups, respectively. This study is limited for use in evaluating the carcinogenic potential in humans following lifetime exposure due to the less-than-lifetime exposure and observation period and due to the limited histopathological examinations (U.S. EPA, 1998a).

NTP (1992a) conducted a two-year inhalation exposure study in $B6C3F_1$ mice. Groups of male and female mice were housed 5 to a cage and were exposed (whole body) to atmospheres containing 0 (75 mice/sex), 10 (75 mice/sex), or 30 ppm (150 mice/sex) naphthalene (99% pure) for 6 hours/day, 5 days/week for 2 years. The high-dose group contained twice as many animals as the low-dose group to ensure that a sufficient number of animals lived until termination of the study, and because of the insufficient information on the long-term toxicity of naphthalene. Comprehensive histopathological examinations were performed on all control and high-dose mice, and on low-dose mice that died or were sacrificed before 21 months of exposure. In the remaining low-dose animals that survived longer than 21 months of exposure, only the nasal cavity and lung were histologically examined. Initially, 50 animals/sex/dose group were designated for the two-year study, with 5 animals/sex/dose group designated for an interim hematology examination at 14 days, and 3, 6, 12, and 18 months of the study. However, because of high mortality in the male control group (discussed below), only the 14-day hematology examination was conducted, with the remaining animals incorporated into the two-year study.

In the male control group, statistically significant decreases in survival were observed due to wound trauma and secondary lesions resulting from increased fighting in this group, compared to the exposed groups. In the exposed groups, male mice tended to huddle in the cage corners during exposure. At study termination, survival was 37% (26/70), 75% (52/69), and 89% (118/133) for the male mice exposed to 0, 10, or 30 ppm, respectively. Survival percentages in exposed female mice were similar to that of the control group. Survival percentages were 86% (59/69), 88% (57/65), and 76% (102/135) for female mice exposed to 0, 10, or 30 ppm, respectively. The occurrence of nonneoplastic lesions observed in this study is summarized in Table 7-3 (Section 7.2.6 above).

Apparent dose-related increases were noted for the incidence of alveolar/bronchiolar adenomas in female and male mice. In females, the incidence of this tumor type was 5/69, 2/65 and 28/135 at the 0, 10 and 30 ppm concentrations, respectively. An additional female mouse in the 30 ppm group displayed an alveolar/bronchiolar carcinoma. The incidence of alveolar/bronchiolar adenomas reached statistical significance at the 30 ppm concentration and the occurrence of this tumor type was considered compound-related. In male mice, the incidence of alveolar/bronchiolar adenomas was 7/70, 15/69, and 27/135 in the control, 10, and 30 ppm groups, respectively. However, when these incidence data were analyzed using a logistics

regression test (a statistical test that adjusts for intercurrent mortality), the incidence of tumors in the 10 and 30 ppm groups did not differ significantly from the control.

Hemangiosarcomas were also reported in 5/135 female mice in the 30 ppm group. This tumor type was not observed in male mice or in control or 10 ppm female mice. However, this occurrence of hemangiosarcomas did not reach statistical significance, and the incidence of this tumor type was within the range of historical incidence (17/467) observed in control animals in multiple NTP inhalation studies (NTP, 1992a).

NTP (2000) exposed F344/N rats (49/sex/dose) to naphthalene vapor concentrations of 0, 10, 30, and 60 ppm for 6 hours plus T_{90} (the theoretical time to achieve 90% of the target concentration in the vapor chamber: 12 minutes) per day, 5 days a week for 105 weeks. The 10 ppm concentration corresponded to the threshold limit value for naphthalene (ACGIH, 2000). Naphthalene concentrations were monitored by an on-line gas chromatograph and average chamber concentrations were maintained within 1% of the target concentrations throughout the study. A physiologically-based toxicokinetic model was used to estimate the daily doses of naphthalene. Data for modeling were obtained from additional groups of male and female rats exposed to 10, 30, or 60 ppm for up to 18 months. Dose calculations were based upon model estimates of the amount of naphthalene inhaled by rats at the exposure concentrations used in the two-year study, the total amount of naphthalene metabolized following a six-hour exposure period (21% to 31% of inhaled naphthalene), and average body weights of 125 grams (male rats) and 100 grams (female rats). Because essentially all of the naphthalene absorbed into the bloodstream is metabolized, the total amount of naphthalene metabolized was assumed to represent the internalized dose to rats from the exposure concentrations used in this study. The estimated daily doses determined by this method were 0, 3.6, 10.7, and 20.1 mg/kg-day for male rats, and 0, 3.9, 11.4, and 20.6 mg/kg-day for female rats.

The study animals were clinically examined twice daily. Body weights were recorded on day 1, every 4 weeks beginning at week 4, and every 2 weeks beginning at week 92. Clinical findings were recorded every 4 weeks beginning at week 4 and every 2 weeks beginning at week 92. Surviving rats were sacrificed at the end of the study and full necropsies and complete histopathological examinations were performed on all core study animals.

There were no treatment-related clinical findings. All exposed groups of male and female rats had survival rates similar to those of the chamber controls. Mean body weights of females were generally similar to the body weights of the control group. The mean body weights of male rats in all exposure groups were generally less than those of the control group for most of the study. The mean body weights for the 10, 30, and 60 ppm exposure groups of male rats at 4 and 104 weeks were 9% and 5%, 9% and 5%, and 11% and 6% lower than those of chamber controls, respectively.

Neoplasms were observed in the nose of male and female rats in all exposure groups (Table 7-5). However, neoplasm incidence in the lungs was not affected by naphthalene exposure of male or female rats in any exposure group (respective tumor incidences for the chamber

control, 10 ppm, 30 ppm and 60 ppm exposure groups were 2/49, 3/49, 1/48, and 0/49 for males, and 1/49, 0/49, 0/49, and 0/49 for females). The observed nasal neoplasms were identified as neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium. Neuroblastomas of the olfactory epithelium occurred with positive trends in both male and female exposure groups. The incidence of neuroblastomas for female rats in the control, low-, mid- and high-exposure groups were 0/49 (0%), 2/49 (4%), 3/49 (6%), 12/49 (24%), respectively. Tumor incidence for female rats in the 60 ppm exposure group was significantly greater ($p<0.001$) than control. Incidences of neuroblastomas in the male rat control, low-, mid- and high-exposure groups were 0/49 (0%), 0/49 (0%), 4/48 (8%), and 3/48 (6%), respectively. Neuroblastomas of the olfactory epithelium have not been historically observed in chamber control rats in other NTP two-year inhalation studies. Positive trends in the incidence of respiratory epithelium adenomas in the nose were also observed for both male and female exposure groups. Tumor incidences were significantly increased ($p\leq0.01$) in all male rat exposure groups relative to the control group. Male rats in the control, low-, mid-, and high-exposure groups had respiratory epithelium adenoma incidences of 0/49 (0%), 6/49 (12%), 8/48 (17%), and 15/48 (31%), respectively. Female rats exposed to the same concentrations had incidences of respiratory epithelium adenomas of 0/49 (0%), 0/49 (0%), 4/49 (8%), and 2/49 (4%), respectively. The increased tumor incidence observed in female rats in the 30 and 60 ppm exposure groups was not statistically significant. No historical incidence (0/299) of respiratory epithelium adenomas has been observed in chamber control rats utilized in previous NTP studies using the same diet as the current study.

Table 7-5. Incidence of Neoplasms in Male and Female F344/N Rats in a Two-year Naphthalene Inhalation Exposure Study

Tumor Type	Incidences of Neoplasms			
	Chamber Control	10ppm	30ppm	60ppm
MALE				
Adenoma of the Respiratory Epithelium	0/49 (0%)	6/49* (12%)	8/48* (17%)	15/48* (31%)
Neuroblastoma of the Olfactory Epithelium	0/49 (0%)	0/49 (0%)	4/48 (8%)	3/48 (6%)
Alveolar/bronchiolar Adenoma or Carcinoma	2/49 (4%)	3/49 (6%)	1/48 (2%)	0/49 (0%)
FEMALE				
Adenoma of the Respiratory Epithelium	0/49 (0%)	0/49 (0%)	4/49 (8%)	2/49 (4%)
Neuroblastoma of the Olfactory Epithelium	0/49 (0%)	2/49 (4%)	3/49 (6%)	12/49* (24%)
Alveolar/bronchiolar Adenoma	1/49 (2%)	0/49 (0%)	0/49 (0%)	0/49 (0%)

*Significantly different from chamber control ($P<0.01$) from chamber control using the Poly-3 test
Source: NTP (2000)

Based upon the absence of neuroblastomas and adenomas in the chamber control rats of this two-year study and historically in NTP two-year inhalation studies, the increased incidences of these neoplasms are considered to be related to naphthalene exposure. The increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose observed in this study are considered by the study authors to be clear evidence of carcinogenic activity of naphthalene in male and female F344/N rats.

Other Routes of Exposure

In a study conducted by Schmähl (1955), groups of 10 rats were given subcutaneous or intraperitoneal injections of naphthalene in oil (20 mg/rat/injection) once a week, starting at 100 days of age and continuing for 40 weeks, for a total dose of 820 mg/rat. Rats were observed following the administration of naphthalene until natural death (700–900 days). Necropsies were performed on animals at death, and organs that appeared unusual were examined histologically. Results were limited to the statements indicating that no toxic effects or tumors were observed in either treatment group (U.S. EPA, 1998a).

Boyland et al. (1964) implanted naphthalene into the bladders of stock Chester Beatty mice to determine the suitability of naphthalene as a potential vehicle of carcinogenicity testing. Thirty animals received the naphthalene implants, with examinations conducted 30 weeks following implantation. Twenty-three of the 30 animals survived the implantation period. One mouse (1/23 or 4%) implanted with naphthalene developed a bladder carcinoma. No adenomas or papillomas were reported in the naphthalene-implanted group. When compared to the paraffin wax or cholesterol-implanted groups, tumor incidence in the naphthalene-implanted group was as low as the incidence in the paraffin-implanted groups (2–4%), and lower than in groups implanted with cholesterol (12%). The limitations of this study that make it inadequate for assessing the carcinogenic potential of naphthalene include the short exposure and observation periods and the lack of untreated controls (U.S. EPA, 1998a).

La Voie et al. (1988) administered naphthalene dissolved in dimethyl sulfoxide by intraperitoneal injection to a group of 49 male and female newborn CD-1 mice on days 1, 8, and 15 of life. The doses at each injection time were 0.25, 0.5, and 1.0 μmol, for a total dose of 1.75 μmol naphthalene. A separate group of 46 pups served as a vehicle control group and received dimethyl sulfoxide alone. Mice were maintained (10 mice/cage) until moribund, or until study termination at 52 weeks. Histopathological examinations were conducted on all gross lesions and on liver sections. Incidences of liver tumors reported in the mice that lived at least 6 months were 0/16 and 2/31 for exposed females and males, and 0/21 and 4/21 for vehicle control females and males. This study is limited for assessing the carcinogenic potential of naphthalene by the short exposure (2 weeks) and observation (52 weeks) periods, and because complete histopathological examinations were not conducted (U.S. EPA, 1998a).

7.3 Other Key Data

7.3.1 Mutagenicity and Genotoxicity

Numerous *in vitro* and *in vivo* assays have been conducted to evaluate the potential genotoxicity of naphthalene and its metabolites. The results of most studies were negative, suggesting that the genotoxic potential of naphthalene and its metabolites is weak (U.S. EPA, 1998a), and is probably not an area of concern for exposure to naphthalene (ATSDR, 1995). The results of naphthalene genotoxicity studies are summarized below.

Negative Results in vitro

Naphthalene was not mutagenic in several bacterial/microsomal assay systems, including *Salmonella* tester strains TA 97, 98, 100, 199, 667, 1535, and 1537, in the presence or absence of Aroclor-1254-induced hamster or rat liver microsomes (McCann et al., 1975; Kaden et al., 1979; Florin et al., 1980; Gatehouse, 1980; Seixas et al., 1982; Connor et al., 1985; Godek et al., 1985; Sakai et al., 1985; Mortelmans et al., 1986; Nakamura et al., 1987; Narbonne et al., 1987; Bos et al., 1988; NTP, 1992a, 2000). There was no evidence of naphthalene-induced DNA damage in *Escherichia coli* WP2/WP100 (Mamber et al., 1983), PQ37 (Mersch-Sundermann et al., 1992), GY5027/GY4015 (Mamber et al., 1984), or *Salmonella typhimurium* TA 1535/p5K 1002 (Nakamura et al., 1987).

The frequency of sister chromatid exchanges (SCE) was not increased upon incubation of human peripheral lymphocytes in a medium containing naphthalene or in a human liver metabolic activation system, when compared with control frequencies (Tingle et al., 1993; Wilson et al., 1995). Naphthalene did not induce unscheduled DNA synthesis in cultured rat hepatocytes (Barfknecht et al., 1985). Naphthalene did not induce transformations of Fischer rat embryo cells (Freeman et al., 1973) or Swiss mouse embryo cells (Rhim et al., 1974) *in vitro*. Sina et al. (1983) reported that naphthalene did not induce single-strand DNA breaks in cultured rat hepatocytes, as detected by alkaline elution (U.S. EPA, 1998a).

Negative Results in vivo

Several experiments have investigated the genotoxicity of naphthalene *in vivo*. Naphthalene did not increase the number of micronuclei in bone marrow cells of mice following intraperitoneal injection of a single dose of 250 mg naphthalene/kg body weight (Sorg et al., 1985). Harper et al. (1984) reported no increase in the frequency of micronucleated erythrocytes in mice exposed to single oral doses of naphthalene as high as 500 mg/kg when compared to frequencies observed in control mice.

Tsuda et al. (1980) reported no evidence of the neoplastic transformation of liver cells in a group of 10 young adult Fischer 344 rats administered single gavage doses of 100 mg naphthalene/kg in corn oil, when compared with the results from a group of 10 vehicle control animals (U.S. EPA, 1998a). Rats were administered the doses of naphthalene or corn oil

following partial hepatectomy, but prior to dietary treatment with 2-acetylaminofluorene and carbon tetrachloride. Gamma-glutamyl transpeptidase foci were used as an indicator of neoplastic transformation. These foci were observed in both exposed and control animals following the dietary treatments. In contrast to the results observed with naphthalene, a single gavage dose of 200 mg/kg benzo[a]pyrene induced significant increases in the number, area, and size of gamma-glutamyl transpeptidase foci (U.S. EPA, 1998a).

Positive results

Four studies were available that reported a positive genotoxic response (ATSDR, 1995; U.S. EPA, 1998a). NTP (1992a, 2000) reported that naphthalene caused sister chromatid exchanges (concentration range of 27–90 μg/mL) in Chinese Hamster ovary cells when assayed in the presence or absence of metabolic activation with rat liver S9 fraction. Chromosomal aberrations were observed (concentration range of 30–67.5 μg/mL) only in the presence of metabolic activation. Naphthalene was mutagenic in the marine bacterium *Vibrio fischeri* (Arfsten et al., 1994) and in the *Drosophila melanogaster* wing somatic mutation and recombination test (Delgado-Rodriguez et al., 1995). Gollahon et al. (1990) observed a 10-fold increase in chromosomal damage in mouse embryos cultured in a medium containing 0.16 mM naphthalene, when compared with untreated culture controls. This response was amplified by the inclusion of a hepatic metabolic activation system in the medium.

Genotoxicity Studies of Naphthalene Metabolites

Studies have been conducted with several known or possible metabolites of naphthalene, including 1-naphthol, 2-naphthol, naphthoquinone, and naphthalene-1,2-dione (U.S. EPA, 1998a). The metabolites 1-naphthol and 2-naphthol were not mutagenic in *Salmonella typhimurium* with or without metabolic activation (McCann et al., 1975; Florin et al., 1980; Narbonne et al., 1987). The metabolite 1-naphthol gave negative results in several other genotoxicity assays, including tests for sex-linked recessive lethal mutations in *Drosophila melanogaster* (Gocke et al., 1981), tests for mutations in mouse L5178Y cells (Amacher and Turner, 1982), tests for unscheduled DNA synthesis in cultured rat hepatocytes (Probst and Hill, 1980), and acute *in vivo* tests for the induction of micronuclei in the bone marrow cells of mice (Gocke et al., 1981) and rats (Hossack and Richardson, 1977). Naphthoquinone was not mutagenic in several strains of *Salmonella typhimurium*, with or without metabolic activation (Sakai et al., 1985). Flowers-Geary et al. (1994) reported that naphthalene-1,2-dione was mutagenic in strains of *Salmonella typhimurium* without metabolic activation (U.S. EPA, 1998a).

7.3.2 Ocular Toxicity

The ocular toxicity of naphthalene has been studied extensively, and the association between naphthalene exposure and the development of cataracts in animals is well-established. Table 7-6 summarizes the results of representative ocular toxicity studies of naphthalene in various animal species.

Table 7-6. Summary of Studies of Naphthalene Ocular Toxicity in Animals

Study	Species (Strain)	Exposure Route	Dose mg/kg-day	Duration	NOAEL	LOAEL	Result
Van Heyningen and Piric (1976)	Rabbits (Dutch, albino)	Gavage	1,000	3–28 consecutive daily doses	--	1,000	Cataracts in 10/16 Dutch and 11/12 albino animals)
Srivastava and Nath (1969)	Rabbits (NS*)	Gavage	2,000	5 days	--	2,000	Cataracts in 8/8 animals
Rossa and Pau (1988)	Rabbits (Chinchilla Bastard)	Oral	1,000	Single dose	--	1,000	Cataracts
	Rabbit (New Zealand)	Oral	1,000	4 biweekly doses	--	1,000	Cataracts
Orzalesi et al. (1994)	Rabbit (pigmented)	Gavage	500	5 weeks	--	500	Cataracts, retinal degeneration, subretinal neovascularization
Fitzhugh and Buschke (1949)	Weanling rats (NS)	Diet	2,000 (estimated)	2 months (approx.)	--	2000	Mild cataracts
Koch et al. (1976)	Rats (Sprague-Dawley, Wistar, and others)	Gavage	1,000	Total duration unknown*; cataracts developed within 16-28 days. Doses administered on alternate days	--	1,000	Cataracts
Rao and Pandya (1981)	Rat (NS)	Gavage	1,000	10 days	1,000	--	No effects observed
Yamauchi et al. (1986)	Rat (Wistar)	Oral	1,000	18 days	--	1,000	Cataracts
Rathbun et al. (1990)	Rat (Black-Hooded)	Gavage	5,000	79 days	--	5,000	Lens opacities
Tao et al. (1991a, b)	Rat (Brown Norway)	Gavage	700	102 days	--	700	Lens opacities
Kojima (1992)	Rat (Brown Norway)	Gavage	500 (1,000 mg/kg-day every second day)	4 weeks	--	500	Lens opacities

Table 7-6 (continued)

Study	Species (Strain)	Exposure Route	Dose mg/kg-day	Duration	NOAEL	LOAEL	Result
Xu et al. (1992a)	Rat (Long-Evans, Brown Norway, Sprague-Dawley, Wistar, Lewis)	Gavage	1,000	28 days	--	1,000	Cataracts
Ikemoto and Iwata (1978)	Rabbits (Albino)	Oral	1,000	2 days	-	1,000	Cataracts
Murano et al. (1993)	Rat (Sprague-Dawley, Brown Norway)	Gavage	1,000	6 weeks (administered every other day)	--	1000	Cataracts
Schmähl (1955)	Rat (in-house strain BDI, BDIII)	Food	41	2 years	Study not adequate to support LOAEL OR NOAEL	--	No cataracts observed
BCL (1980a)	Rat (Fischer)	Gavage	0 25 50 100 200 400	13 weeks 5 days/week	400	--	No cataracts observed
BCL (1980b)	Mouse ($B6C3F_1$)	Gavage	0 12.5 25 50 100 200	90 days 5 days/week	200	--	No cataracts observed
Shopp et al. (1984)	Mouse (CD-1)	Gavage	0 53 133	90 days	133	--	No cataracts observed
Shopp et al. (1984)	Mouse (CD-1)	Gavage corn oil	0 27 53 267	14 days	267	--	No cataracts observed
NTP (1992a)	Mouse B6CF1	Inhalation	0 ppm* 10ppm 30 ppm	2 years (6 hr/day; 5 days/wk)	30ppm*	--	No cataract formation observed
NTP (2000)	Rat (F344/N)	Inhalation	0 3.6–3.9 10.7–11.4 20.1–20.6	2 years	20.1–20.6	--	No cataractogenic effects or ocular abnormalities observed.

Table 7-6 (continued)

Study	Species (Strain)	Exposure Route	Dose mg/kg-day	Duration	NOAEL	LOAEL	Result
Shichi et al. (1980)	Mouse (C57BL/6N, DBA/2N)	Diet	0 60 120 (injected twice weekly with cyto-chrome P-450 inducer)	60 days	C57BL/6N mice: -- DBA/2N mice: 120	C57BL/6N mice: 60 DBA/2N mice: --	Cataracts observed in 1/15 C57BL/6N mice at each dose. No cataracts observed in DBA/2N mice)
Holmen et al. (1999)	Rat (Brown Norway)	Gavage	0 100 500 1,000 1,500	10 weeks 2 doses/week	100 adjusted: 29	500 adjusted: 143	First signs of ocular changes occurred within 2.5 weeks after start of treatment. All treated with doses of 500 mg/kg or more developed cataracts.

* NS = Not specified
[a] Information obtained from secondary source in which the indicated data were not provided

Cataract formation has been documented primarily in rabbits and rats. Almost all studies have evaluated oral exposures. In rabbits, Van Heyningen and Pirie (1976) noted the formation of cataracts as soon as two days after initiation of daily administration of 1,000 mg/kg by oil gavage. The incidence of cataract formation was higher in albino rabbits (11/12) than in the pigmented (Dutch) strain. Srivastava and Nath (1969) reported cataracts in 8/8 rabbits (strain not stated) treated with naphthalene doses of 2,000 mg/kg-day for 5 days via gavage. Rossa and Pau (1988) found that cataracts appeared in two different strains of rabbits after administering between one and four 1,000 mg/kg oral doses of naphthalene (U.S. EPA 1998a). Orzalesi et al. (1994) found that pigmented rabbits developed cataracts after 5 weeks gavage exposure at 500 mg/kg-day and retinal degeneration starting at 3 weeks. Retinal degeneration was extensive by the end of the exposure period, resulting in almost complete obliteration of the pigmented layer and extensive neovascularization.

In rats, Fitzhugh and Buschke (1949) reported the development of mild cataracts in five weanling rats (strain unspecified) consuming two percent naphthalene in their diet for two months. U.S. EPA (1998a) estimated that this amount is equivalent to a total dose of approximately 2,000 mg/kg per animal. Tao et al. (1991a, b) reported lense opacities (unspecified incidence) in a group of female Brown Norway rats exposed by gavage at 700 mg/kg-day for 102 days.

Holmen et al. (1999) administered doses of 0, 100, 500, 1,000, or 1,500 mg/kg twice weekly by gavage to female pigmented Brown Norway rats (3 to 15 animals/dose group). When adjusted for duration, these doses correspond to 0, 29,143,285, or 429 mg/kg-day, respectively.

Ocular changes were monitored by slit illumination and retro-illumination. All rats treated with doses of naphthalene equal to or greater than 500 mg/kg developed cataracts. The first ocular changes were evident after 2.5 weeks of treatment when eyes were examined by retroillumination. In contrast, no evidence of cataractous change was noted in control rats or rats administered the 100 mg/kg dose.

Strain differences have been reported for the incidence and rate of development of cataracts in rats. Koch et al. (1976) administered 1,000 mg/kg naphthalene per day by gavage to rats of several strains (Sprague-Dawley, Wistar, and others) on alternate days. All of the pigmented rats developed cataracts within 16 to 28 days, whereas cataract incidence was lower in the albino strains. Xu et al. (1992a) administered gavage doses of 1,000 mg/kg naphthalene per day in oil to both pigmented (Long-Evans and Brown Norway) and unpigmented (Sprague-Dawley, Wistar, and Lewis) rats for up to 28 days. Eyes were examined (by slit-lamp with focal and retro-illumination techniques) twice a week for the first 2 weeks and weekly thereafter. All rats of both pigmented and unpigmented strains were found to have cataracts at the end of the exposure period. However, the rate of cataract development differed among strains, with the order being Brown Norway > Long-Evans = Lewis = Sprague-Dawley > Wistar. Murano et al. (1993) found that gavage doses of 1,000 mg/kg naphthalene administered every other day for 6 weeks resulted in the development of cataracts in all exposed male Brown Norway and Sprague-Dawley rats. Cataracts developed more rapidly in the Brown Norway than in the Sprague-Dawley rats, an observation that is consistent with the findings of Xu et al. (1992a), above.

Shichi et al. (1980) observed a very low incidence (1/15) of cataracts in C57BL/6N mice following administration of doses of approximately 60 or 120 mg/kg-day in the diet for 60 days. The mice were injected twice-weekly with an inducer of cytochrome P-450. No cataracts were observed in DBA/2N mice treated under the same regimen.

NOAELs for naphthalene-induced cataract formation have been identified in chronic and subchronic exposure studies in rats and mice. Schmähl (1955) found no cataracts in rats treated orally with naphthalene at 41 mg/kg-day for 2 years, although the method of examination was not documented. BCL (1980a) did not observe cataracts in Fischer rats receiving up to 400 mg/kg-day, 5 days per week for 13 weeks. In $B6C3F_1$ mice, (BCL, 1980b) identified a NOAEL of 200 mg/kg-day (administered 5 days per week). Shopp et al. (1984) found no cataracts (method of cataract examination was not indicated) in CD-1 mice treated by gavage at 133 mg/kg-day for 90 days. Cataracts were not observed in $B6C3F_1$ mice exposed to concentrations of naphthalene as high as 30 ppm by inhalation for two years (NTP 1992a). Cataracts or other ocular changes were not observed in F344/N rats exposed to concentrations up to 60 ppm (estimated dose 20.6 mg/kg-day for males) for two years (NTP, 2000).

Based on the above findings, the relationship between oral naphthalene exposure and the development of cataracts has been clearly demonstrated in rodents. LOAELs range from 500 mg/kg-day (Brown Norway rats) to 5,000 mg/kg-day (black rats) across studies of all durations. NOAELs for naphthalene-induced cataractogenesis in subchronic studies ranged from

29 mg/kg-day (duration-adjusted dose administered to Brown Norway rats on a biweekly dosing regimen) and 133 mg/kg (CD-1 mice) to 400 mg/kg (Fischer rats).

7.3.3 Hematological Effects

Hemolytic anemia has been observed in humans exposed to naphthalene via inhalation, combined inhalation and dermal exposure, and combined oral and inhalation exposure (see Section 7.3.3). In animals, naphthalene-induced hemolytic anemia has been observed only in the dog. Zuelzer and Apt (1949) administered naphthalene incorporated into a meat diet to three dogs. One dog (7.3 kg body weight) received a single dose of 3 g (equivalent to a 410 mg/kg dose). A second dog (5.9 kg body weight) received a single 9 g dose (equivalent to a 1,530 mg/kg dose). The third dog (6.8 kg) was administered seven consecutive daily doses ranging from 0.5 to 3.0 g (equivalent to 74 to 144 mg/kg). The total dose in the third dog was 12.5 g, which is equivalent to an average daily dose of 262 mg/kg-day. The blood of the treated animals was characterized by decreased hemoglobin concentration and hematocrit; development of Heinz bodies in erythrocytes, erythrocyte fragmentation, and reticulocytosis. Similar indications of hemolytic anemia were not observed when hematological parameters were examined in F344 rats treated with gavage doses of up to 400 mg/kg-day (BCL, 1980a), 5 days/week for 13 weeks; in $B6C3F_1$ mice treated with gavage doses of up to 200 mg/kg-day, 5 days/week for 13 weeks (BCL, 1980b); or in CD-1 mice given gavage doses of up to 133 mg/kg-day for 90 consecutive days (Shopp et al., 1984).

7.3.4 Immunotoxicity

A limited number of studies document potential immunotoxic effects of naphthalene exposure. Based on the available data, adverse effects on the immune system do not appear to be a prominent feature of naphthalene toxicity.

An enlarged spleen was reported in one human subject that died as a result of ingesting naphthalene (Kurz, 1987). Enlarged spleens were also observed in two human subjects that were dermally exposed to naphthalene (Schafer, 1951; Dawson et al., 1958). However, these effects were believed to be associated with hemolysis, rather than indicative of a direct toxic effect on the spleen.

Shopp et al. (1984) reported no effects on humoral immune responses, delayed hypersensitivity responses, bone marrow DNA synthesis, or bone marrow stem cell number in CD-1 mice that received naphthalene at oral doses as high as 267 mg/kg-day for 14 days. Thymic weight decreased approximately 30% in the high-dose male mice. In the high-dose females, mitogenic responses to concanavalin A were reported. This effect was not observed with lipopolysaccharide or in mice that received naphthalene at 27 or 53 mg/kg-day. In addition, no immune system effects or alterations in thymic weights were observed in male mice that received 133 mg naphthalene/kg/day for 13 weeks. An approximately 20% decrease in spleen weight was reported in female mice that received 267 mg naphthalene/kg/day for 14 days, while a 25%

decrease was observed in female mice that received 133 mg/kg-day for 13 weeks (Shopp et al., 1984).

In other studies, thymic lymphoid depletion was reported in 2 of 10 female rats that received 400 mg naphthalene/kg/day for 13 weeks (BCL, 1980a). Dermal application of pure naphthalene once weekly for 3 weeks to the skin of rabbits did not result in evidence of a delayed hypersensitivity reaction (PRI, 1985; Papciak and Mallory, 1990). The results of an *in vivo* study in C57B1/6 mice indicated that a single oral dose of naphthalene did not suppress antibody responses (Silkworth et al., 1995).

An *in vitro* study conducted by Kawabata and White (1990) indicated that naphthalene did not have an immunosuppressive effect in the antibody response of splenic cell cultures to sheep red blood cells.

7.3.5 Hormonal Disruption

No studies were located that document disruptive effects on the endocrine system associated with naphthalene exposure.

7.3.6 Physiological or Mechanistic Studies

Information on the mode of action of naphthalene is available for three health effects associated with exposure: hemolysis, cataract formation, and pulmonary toxicity (ATSDR, 1995; U.S. EPA, 1998a).

Hemolysis

Humans and dogs are susceptible to naphthalene-induced hemolysis following inhalation, oral, or dermal exposures. Naphthalene metabolites are believed to be involved in naphthalene-induced hemolytic anemia, but the mode of action of naphthalene induced hemolysis is not clearly understood. Individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) are particularly sensitive to naphthalene hemolysis. G6PD-deficient cells have a reduced capacity to generate reduced nicotinamide adenine dinucleotide phosphate (NADPH), which serves as a cofactor in the reduction of oxidized glutathione. G6PD-deficient cells, therefore, cannot quickly replenish reduced glutathione (Dawson et al., 1958; Gosselin et al., 1984), a compound that plays a key role in defense against oxidative damage, and in the conjugation and excretion of some toxicants. Deficits in reduced glutathione levels are thought to decrease the rate of conjugation and the excretion of naphthalene metabolites, thereby leading to elevated levels of toxic naphthalene metabolic intermediates (U.S. EPA, 1987b). In the absence of glutathione, the metabolites promote damage to red blood cell membranes and the oxidization of hemoglobin to methemoglobin. Both of these actions likely contribute to cell lysis (U.S. EPA, 1998a). Other possible causes of hemolysis include inhibition of the enzymes glutathione peroxidase or glutathione reductase by a naphthalene metabolite (Rathbun et al., 1990; Tao et al., 1991a, b).

Cataract Formation

Experimental evidence suggests that naphthalene cataractogenesis requires cytochrome P-450 catalyzed bioactivation to a reactive intermediate. Some evidence suggests that the ocular toxicity of naphthalene is mediated by the production of 1,2-naphthalenediol *in situ* in the lens (ATSDR, 1995). Alternatively, Van Heyningen and Pirie (1967) proposed that naphthalene was metabolized in the liver to epoxide intermediates and subsequently to stable hydroxy compounds. These hydroxy compounds then enter the circulation and are transported to the lens, where 1,2-naphthalenediol is subsequently oxidized to 1,2-naphthoquinone and hydrogen peroxide. The quinone binds to lens constituents, thus altering the integrity and transparency of the lens (Uyama et al., 1955; Rees and Pirie, 1967; Van Heyningen and Pirie, 1967; Van Heyningen and Pirie, 1976; Van Heyningen, 1979; Wells et al., 1989).

Wells et al. (1989) assessed cataract formation after administration of naphthalene or naphthalene metabolites. Dose-related increases in cataract incidence were observed following administration of 125 to 1,000 mg naphthalene/kg, 5 to 250 mg 1,2-naphthoquinone/kg, 56 to 562 mg 1-naphthol/kg, or 5 to 250 mg 1,4-naphthoquinone/kg to C57BL/6 mice by intraperitoneal injection. In contrast, cataract formation was not observed following the intraperitoneal administration of 56 to 456 mg 2-naphthol/kg. The potency of the quinones was reported to be about 10 times that of naphthalene. Pretreatment with inducers of cytochrome P-450 and a glutathione-depleting compound increased the potency of naphthalene in causing cataracts. Pretreatment with a P-450 inhibitor decreased naphthalene toxicity.

Xu et al. (1992a, b) conducted experiments that employed five different strains of albino rats. Naphthalene was administered via gavage at a dose of 500 mg/kg-day for three days, followed by 1,000 mg/kg-day for 25 days. All of the naphthalene-treated rats developed cataracts. The concentration of reduced glutathione was decreased in the lens following three weeks of treatment, while increases in protein-glutathione mixed disulfides and high molecular weight-insoluble proteins were reported. Analyses of the aqueous humor indicated that the only naphthalene metabolite present was 1,2-dihydro-1,2-naphthalenediol. The authors speculated that this compound may have been metabolized to 1,2-naphthoquinone, the metabolite believed to be responsible for the formation of cataracts.

Xu et al. (1992a) determined that the only metabolite that resulted in formation of morphologically identical cataracts *in vitro* and *in vivo* was 1,2-dihydro-1,2-naphthalenediol. Opacities were also formed by 1,2-naphthalenediol and naphthoquinone. However, these cataracts formed on the cortex rather than the inner surface of the lens.

Xu et al. (1992a) investigated the role of the enzyme aldose reductase in cataract formation in naphthalene exposed rats. Aldose reductase is found in the lens, liver, and in peripheral neurons (McGilvery, 1983) and is thought to oxidize 1,2-naphthalenediol to 1,2-naphthoquinone, the metabolite responsible for cataract formation (Xu et al. 1992a). If this hypothesis is correct, inhibition of the reaction catalyzed by aldose reductase should result in decreased synthesis of 1,2-naphthoquinone, and decreased cataract formation. Groups of rats

were dosed with naphthalene alone, naphthalene plus the aldose reductase inhibitor ALO1576, or ALO1576 alone. All naphthalene-treated rats developed cataracts. Consistent with the proposed hypothesis, rats given the aldose inhibitor alone, or naphthalene plus aldose inhibitor, did not develop cataracts. The authors of this study suggested that the mechanism of naphthalene cataract formation may involve the transport of the dihydrodiol metabolite formed in the liver into the lens, where it is converted by aldol reductase into the very reactive 1,2-naphthoquinone. The naphthoquinone then causes oxidative damage to the lens, resulting in opacity.

This mode of action is supported by the results of Xu et al. (1992b), who found that the aldose reductase inhibitor ALO1537 also prevented naphthalene-related cataract formation. In contrast, Tao et al. (1991a, b) found that the aldose reductase inhibitor TK344 failed to prevent cataracts in naphthalene-treated rats. The researchers hypothesized that the cataract-preventive activity of ALO1537 might result from the inhibition of a naphthalene-metabolizing enzyme other than aldose reductase.

Several studies have investigated biochemical processes that potentially contribute to naphthalene-induced cataract formation. Srivastava and Nath (1969) reported markedly decreased lactate dehydrogenase activity and elevated o-diphenol oxidase activity in the lens and capsule of rabbits (strain not stated) treated with naphthalene doses of 2,000 mg/kg-day. Yamauchi et al. (1986) detected decreased levels of reduced glutathione in lenses of male Wistar rats treated with 1,000 mg/kg-day doses of naphthalene for 18 days. Rathbun et al. (1990) observed reduced total glutathione levels and progressive loss of glutathione peroxidase and glutathione reductase activity in Black-Hooded rats administered approximately 5,000 mg/kg-day in the diet for 79 days, suggesting that naphthalene exposure impairs defenses against oxidative damage. However, Rao and Pandya (1981) did not detect any significant increase in ocular lipid peroxidation following administration of 1,000 mg/kg-day to male rats (strain not stated) for 10 days.

Pulmonary Toxicity

Pulmonary toxicity has been identified in experimental animals exposed to naphthalene via inhalation and parenteral pathways. As noted below, the pulmonary response to naphthalene varies significantly among species. At present, there is no strong evidence that exposure to naphthalene results in pulmonary toxicity in humans (ATSDR, 1995).

Increased incidences of alveolar bronchiolar hyperplasia were observed in F344/N female rats exposed to naphthalene via inhalation for two years (NTP, 2000). A predominantly benign neoplastic response in the alveolar/bronchiolar region following chronic inhalation exposure to naphthalene has been observed in male and female mice (NTP, 1992a). Pulmonary bronchiolar epithelial cells, primarily Clara cells, may be damaged following intraperitoneal administration of naphthalene (Mahvi et al., 1977; Tong et al., 1982; Warren et al., 1982; O'Brien et al., 1985, 1989; Honda et al., 1990; Chichester et al., 1994; Van Winkle et al., 1999). This toxicity has been associated with the metabolism of naphthalene by the cytochrome P-450 system in the lung (Warren et al., 1982; O'Brien et al., 1985; Rasmussen et al., 1986; Buckpitt and Franklin, 1989).

The ultrastructural changes induced by naphthalene are consistent with the type of damage produced by other P-450-bioactivated toxicants (Van Winkle et al., 1999).

The identity of the toxic, P-450-activated metabolite is not known with certainty. However, it is believed to be one or more of the enantiomeric epoxides, naphthoquinones, or free radical intermediates (Buckpitt and Franklin, 1989), which likely bind to the Clara cell proteins or nucleic acids (Chichester et al., 1994). Local pulmonary metabolic processes are thought to be responsible for the observed toxicity, although there is some evidence that other tissues, such as the liver, may metabolize naphthalene to reactive metabolites that enter the circulation, are transported to the lung, and result in pulmonary cytotoxicity (Warren et al., 1982; O'Brien et al., 1989; Kanekal et al., 1990).

Epoxide metabolites are considered strong candidates for causing the pulmonary toxicity observed following exposure to naphthalene. This conclusion is based on the observations that some epoxides are cytotoxic, genotoxic and possibly carcinogenic (U.S. EPA, 1998a), and that cytotoxicity in isolated, perfused mouse lungs was produced by 1,2-naphthalene epoxide at concentrations 10-fold less than naphthalene (Kanekal et al., 1991). In addition, the epoxide is capable of covalently binding to cellular macromolecules resulting in cell damage. In contrast, the naphthalene metabolites 1-naphthol, 1,2-, and 1,4-naphthoquinone were not apparently cytotoxic in the lung at concentrations equal to concentrations of naphthalene that produced cytotoxicity (U.S. EPA, 1998a). However, Zheng et al. (1997) treated mouse lung Clara cells with naphthalene *in vitro* and identified 1,2-naphthoquinone as a major adduct covalently bound to cellular protein, suggesting that this metabolite has the potential to contribute to pulmonary toxicity.

Species differences exist in the pulmonary metabolism and toxicity of naphthalene. Mice are more sensitive to the pulmonary effects of naphthalene than hamsters or rats (Buckpitt and Franklin, 1989; Buckpitt et al., 1992; Plopper et al., 1992a, b). Microsomes prepared from mouse lung metabolized naphthalene approximately 92 times faster than microsomes prepared from Rhesus monkeys (Buckpitt et al., 1992). The primary metabolites formed by the 2 species were also different, with mice and monkeys forming 1R,2S-naphthalene oxide and 1S,2R-naphthalene oxide, respectively. The metabolic rates reported for hamsters and rats were intermediate between those reported for mice and monkeys (Buckpitt et al., 1992). The metabolic rates of human lung microsomes have been reported to be similar to those of monkeys (Buckpitt and Bahnson, 1986).

Detailed comparison of naphthalene metabolic potential and naphthalene-induced cytotoxicity throughout dissected airways confirms that there is a significant degree of species-specificity in metabolism and injury. Clara cells appear to be a primary target cell for naphthalene toxicity in the lung of mice, the most sensitive species among those tested. This is consistent with the putative role of Clara cells as one of the primary sites for cytochrome P-450-mediated xenobiotic metabolism in the lung. Studies by Plopper et al. (1992a) and Buckpitt et al. (1995) evaluated the association between Clara cell toxicity and metabolism in different areas of the tracheobronchial trees of mice, rats, and hamsters. The rate of metabolism of naphthalene and the

extent of 1R,2S-naphthalene oxide enantiomer formation by microsomal preparations from specific areas were reported to correlate with differences in pulmonary cytotoxicity observed in the different species. Metabolism of naphthalene in mouse airways was highly stereoselective, producing the 1R, 2S-naphthalene oxide enantiomer; similar stereospecificity was not observed in the airways of rats or hamsters. Non-ciliated cells in all airway regions of the mouse were heavily labeled when treated with an antibody to cytochrome P-450 2F2, whereas little labeling was observed in any airway region of rats or hamsters.

Studies of species-specific responses to naphthalene toxicity in the nose suggest that factors other than metabolic activation may play a role in cell injury. Plopper et al. (1992a) compared the sensitivity of nasal tissues to naphthalene toxicity in rat, mouse, and hamster. The close correlation observed between the metabolism and stereospecificity of the metabolites in the lung was not evident in the nose. Damage in the nasal cavity of the three species was limited to necrosis of the olfactory epithelium. Cells in this portion of the nose contain high concentrations of several cytochrome P-450 isoforms. Although the target site for naphthalene-induced injury was the same for all three species, the dose that produced necrosis differed among them. The level of total naphthalene metabolizing activity in a given species was not predictive of the dose required to elicit necrosis. This result was interpreted by the study authors as evidence for a role of phase II enzymes (e.g., epoxide hydrolase and/or glutathione-*S*-transferases) in modulating the intracellular levels of naphthalene oxides and thus toxicity in target cells.

Kanekal et al. (1990) reported that Clara cell numbers decreased substantially following a 4-hour exposure to 0.13 mg naphthalene when tested using a perfused rat lung system. It was also noted that the Clara cells exfoliated and were found in the airway lumens. As noted above, non-ciliated Clara cells contain higher levels of mixed function oxidases and thus are believed to be more sensitive to damage from naphthalene. Chichester et al. (1994) reported that Clara cell viability decreased by 39 and 88%, when exposed to 64 or 128 mg/L naphthalene, respectively. No effect was seen in cells exposed to 1.3 or 6.4 mg/L naphthalene for 120 or 340 minutes. Exposure to equivalent molar concentrations of naphthalene oxide resulted in effects similar to those produced by naphthalene. The addition of glutathione and glutathione transferase decreased Clara cell damage.

Relatively little is known about repair of naphthalene-induced pulmonary injury. However, the number of pulmonary neuroendocrine cells and the surface area covered per cell increased markedly within five days of a single intraperitoneal injection of naphthalene administered to male FVB/n mice (Peake et al., 2000). These alterations were interpreted as evidence for a key role of this cell type in epithelial cell renewal after airway injury.

Germansky and Jamall (1988) investigated the organ-specific effects of naphthalene (169 mg/kg-day, time-weighted average) on tissue peroxidation, glutathione peroxidases, and superoxide dismutase in lung tissue of male Blue Spruce pigmented rats. In contrast to results obtained in the liver, no effect of naphthalene exposure was evident on levels of peroxidation or activity of the two enzymes.

7.3.7 Structure-Activity Relationship

There are few studies that systematically examine the toxicological structure-activity relationships among naphthalene and its close structural analogues. U.S. EPA (1998a) has summarized information related to the metabolism and pulmonary toxicity of the naphthalene structural analogues 1- and 2-methylnaphthalene.

The methylation of naphthalene to form 1- and 2-methylnaphthalene presents opportunities for metabolism via additional oxidative pathways. Due to the lack of a functional group to serve as a site for conjugation, naphthalene metabolism proceeds via P-450-catalyzed ring oxidation. Presence of the methyl groups in 1- and 2-methylnaphthalene enables the formation of potentially toxic aldehydes via side-chain oxidation. The potential toxicity of the aldehydes raises the possibility that there are distinct differences between the effects of naphthalene and its methylated derivatives that result from differences in metabolism (U.S. EPA, 1998a).

Buckpitt and Franklin (1989) reviewed the comparative pulmonary toxicity of naphthalene and the related compound 2-methylnaphthalene. The researchers noted that, while 2-methylnaphthalene is less acutely toxic than naphthalene, the dose-response characteristics for subchronic pulmonary toxicity (alveolar proteinosis, Clara cell damage, bronchiolar necrosis) of naphthalene and the 2-methyl derivative are quite similar. They suggested that metabolism by cytochrome P-450 was more clearly implicated in the toxicity of 2-methylnaphthalene than in the case of naphthalene.

Chronic dietary exposure (0.075% and 0.15% in feed) of B6C3F$_1$ mice to either 1-methylnaphthalene and 2-methylnaphthalene for 81 weeks results in an increased incidence of pulmonary alveolar proteinosis (Murata et al., 1993; Murata et al., 1997). Exposure to 1-methylnaphthalene also induced a small but statistically significant increase in the incidence of bronchiolar/alveolar adenomas in the lungs of male, but not female mice (Murata et al, 1993). Dietary exposures to 2-methylnaphthalene were not associated with an increased tumor incidence.

Additional research is required to determine if and how the pulmonary effects of naphthalene and 1- and 2-methylnaphthalene are mechanistically related (U.S. EPA, 1998a).

7.4 Hazard Characterization

7.4.1 Synthesis and Evaluation of Major Noncancer Effects

As discussed in Section 7.1, data concerning the adverse effects of naphthalene exposure in humans are limited. A number of case reports describe acute accidental and intentional naphthalene ingestion (Lezenius, 1902; Gerarde, 1960; Gupta et al., 1979; Ijiri, 1987; Kurz, 1987). The utility of these data for the evaluation of health effects associated with occurrence of naphthalene in drinking water is potentially limited by several factors. Quantitative exposure data are not provided in these incident reports. The extent of naphthalene uptake and the toxic

endpoints resulting from a single, large dose may differ from those that would occur from exposure in drinking water. In addition, the low aqueous solubility of naphthalene may prevent the occurrence of concentrations in drinking water that are acutely toxic to the general population. An additional important source of uncertainty in these considerations is the potentially greater sensitivity of certain subpopulations to naphthalene toxicity, including infants and children, neonates, fetuses, and individuals deficient in G6PD. At present, little information is available to define acutely toxic levels of exposure for these groups.

Case reports of individuals (primarily infants) exposed to naphthalene by inhalation or through dermal contact with mothballs or with items stored with mothballs (Schafer, 1951; Valaes, 1963; Owa, 1989) are more informative. While none of these studies provides information on the exposure levels that are associated with adverse effects, they provide information that establishes hemolytic anemia and its sequelae as the most important toxic effect in humans exposed to naphthalene at levels that might be encountered in the environment. Case reports also indicate that humans with G6PD deficiency are especially susceptible to naphthalene toxicity, particularly infants and the fetus (Valaes, 1963; U.S. EPA, 1987b; Owa, 1989).

Studies of occupational exposure to naphthalene are limited to a single report of possible naphthalene-related cataracts in chemical workers (Ghetti and Mariani, 1956) and to two limited epidemiological studies (Wolf, 1976; Kup, 1978) that provide ambiguous evidence of associations between occupational naphthalene exposure and cancer. Owing to their numerous limitations (see Section 4.2), neither of these studies is useful in characterizing the potential risks associated with human exposures to naphthalene (U.S. EPA, 1998a).

Because there are no reliable human studies to establish dose-response relationships for specific health effects, most dose-response information is derived from animal studies. The results of key toxicological studies are categorized by toxic effect in Table 7-7. An important feature of the data in this table is that hemolytic anemia, which appears to be the critical toxic effect in humans, is not seen in the majority of the animal studies. Thus, mice, rats, and rabbits are less sensitive to naphthalene-induced hematotoxicity than humans. This is consistent with the general observation that dogs and humans are generally more sensitive to chemically-induced hemolytic anemia than are other species (ATSDR, 1995). The physiological and biochemical mechanisms responsible for this difference in sensitivity are not known (U.S. EPA, 1998a). Dogs are apparently more sensitive to naphthalene exposure than other experimental animals, but the single available study in dogs (Zuelzer and Apt, 1949) is quite old, and it used only a very small number of animals. Thus, it cannot be used to estimate a dose-response relationship for naphthalene-induced hemolysis.

In contrast to hemolytic anemia, naphthalene-induced cataract formation is well-studied in experimental animals. Acute, short-term, and subchronic studies of cataractogenesis (see Table 7-6) have established the general features of dose-response relationships in different species and dosing regimens. In addition, these studies have helped to elucidate the biochemical basis of naphthalene-induced cataractogenesis. The general mechanism for cataract formation, like that for hemolysis, appears to involve oxidative damage of cell components. However, greater

progress has been made in identifying the specific metabolic pathways, enzymes, and toxic metabolites that are involved in cataract formation.

Quinone derivatives of naphthalene appear to be the proximate toxic metabolites involved in cataract formation (U.S. EPA,1998a). Naphthalene is first oxidized by cytochrome P-450 monooxygenases to the 1,2-epoxide. The epoxide is then converted into naphthalene dihydrodiol by one or more pathways. These metabolic steps probably occur in the liver, but it is known that naphthalene metabolism also occurs in other organs, notably the lung. It is thought that the dihydrodiol diffuses into the crystalline lens where it is converted into 1,2-naphthoquinone. The naphthoquinone then reacts with lens components to cause damage and opacity. The key enzyme in the conversion of the dihydrodiol to the quinone is aldose reductase, as judged by studies that show reduced cataract formation when reductase inhibitors are administered along with naphthalene to experimental animals. Glutathione depletion may also enhance the development of cataracts (ATSDR, 1995) by preventing detoxifying conjugation reactions.

Species differences in sensitivity to naphthalene-induced cataracts have been attributed to differences in enzyme activity levels. These results have not yet been extrapolated to human toxicity, however. The relatively low severity of the cataracts observed in the single epidemiologic study (Ghetti and Mariani, 1956) of highly-exposed subjects suggests that humans are not extremely sensitive to naphthalene-induced cataract formation after combined inhalation and dermal exposures.

The second specific toxic effect that has been linked to naphthalene exposure in experimental animals is the development of non-neoplastic lesions in the nose and lung (potential carcinogenic responses are discussed in Section 7.4.2 below). Mice (NTP, 1992a) and rats (NTP, 2000) had increased incidences of multiple nasal lesions after inhalation exposure to naphthalene for two years. Exposure-related increases in the incidences of alveolar bronchiolar hyperplasia were observed in female rats (NTP, 2000) and in the incidences of chronic inflammation in the lung of male and female $B6C3F_1$ mice (NTP, 1992a). In addition, respiratory tract lesions have been observed in mice after parenteral administration of naphthalene (summarized in U.S. EPA, 1998a). The occurrence of lung lesions after non-inhalation exposure suggests that lung tissue may be especially sensitive to naphthalene or its metabolites, or that particular metabolic pathways are acting in the lung to produce high concentrations of toxic intermediates.

Several studies have found that the pattern of naphthalene-induced lesions in a mouse lung closely correlates with cytochrome P-450 activity (Warren et al., 1982; Buckpitt and Franklin, 1989). *In vitro* studies suggest the epoxides may be the key cytotoxic metabolites in mouse lung, although down-stream metabolites (the dihydrodiol and quinones) cannot be conclusively ruled out. Buckpitt et al. (1992) found that mouse lung microsomes metabolize naphthalene approximately 92 times faster than lung microsomes from Rhesus monkeys, and that the enantiomeric composition of the metabolic products was different in mice than in monkeys (U.S. EPA, 1998a). The study authors suggested that these differences at least partially explain the differences in sensitivity to lung toxicity of mice and primates. A more recent study (Buckpitt et

al., 1995) identified the rate of conversion of naphthalene to naphthalene-1R,2S oxide by cytochrome P-450 2F2 as the most important determinant of naphthalene toxicity in mouse lung.

The mode(s) of action for the other toxic effects reported in Table 7-7 are not well-understood. The decreased body weights seen in several of the subchronic studies do not appear to be related to reduced food intake, but may indicate generally depressed metabolic function. Changes in organ weights have only been observed sporadically, with different organs affected in different studies, and no specific patterns of histopathological changes in the affected organs (other than the lung). Numerous studies suggest that naphthalene is a very weak reproductive and developmental toxicant, with detectable effects occurring only at doses associated with substantial maternal toxicity or even mortality. Finally, no biochemical explanation has been put forward for the neurological effects seen in pregnant rats (BCL 1980a; NTP, 1991). However, the available studies support a clearly-defined NOAEL and LOAEL for this effect.

7.4.2 Synthesis and Evaluation of Carcinogenic Effects

The available human data are inadequate to evaluate any association between naphthalene and cancer occurrence. The available epidemiological studies (Wolf, 1976; Kup, 1978) are limited due to the size of the populations examined (n=15) and co-exposure to other potential carcinogens, such as tobacco smoke or other polycyclic aromatic hydrocarbons, such as benzo[a]pyrene. No large-scale epidemiological study has been conducted to examine the possible association between naphthalene exposure and cancer (U.S. EPA, 1998a).

Data available from animal studies are also limited. Only two inhalation studies were adequately designed to examine the carcinogenicity of lifetime naphthalene exposure. NTP (1992a) examined the carcinogenicity in mice exposed to naphthalene for 2 years by inhalation. A statistically significant increase in the incidence of alveolar/bronchiolar adenomas and carcinomas combined was reported for female $B6C3F_1$ mice, but not male mice, exposed via inhalation to 30 ppm naphthalene for 6 hours/day, 5 day/week for 2 years (NTP, 1992a). However, NTP (1992a) concluded that the study provided "*some evidence*" only of carcinogenicity in female mice, but not "*clear evidence*," because only one carcinoma was observed (U.S. EPA, 1998a). In a similar study, NTP (2000) examined tumor occurrence in F344/N rats exposed to naphthalene vapor for 2 years. Increased incidences of two types of nasal tumors were noted in naphthalene-treated animals. The incidences of adenoma of the respiratory epithelium were increased in male rats exposed to 10, 30, and 60 ppm (approximately 3.6, 10.7, and 20.1 mg/kg-day, respectively). The incidence of neuroblastoma of the olfactory epithelium was significantly increased in female rats exposed to 60 ppm (approximately 20.6 mg/kg-day). Because these tumors did not occur in control animals and because the historical incidence in NTP chamber control rats is low, the increased incidence of these tumors in naphthalene-exposed animals was considered by the study authors to be "*clear evidence*" of carcinogenic activity.

In the Adkins et al. (1986) study, A/J strain mice were exposed to 10 or 30 ppm naphthalene vapors for 6 months. Following the exposure period, excised lungs were examined for pulmonary adenomas. Histopathological study of lung tissue was limited to the examination of

the tumors. Increased numbers of adenomas were found in the lungs of naphthalene-exposed mice when compared to the control group, but the differences were not statistically significant. A significant increase in the number of alveolar adenomas per tumor-bearing lung was reported in both dose groups. However, the response did not increase with increasing dose. Limitations of this study include the less-than-lifetime exposure duration and the restricted histopathology.

Several studies have been conducted in which naphthalene was administered by routes of exposure other than inhalation or diet (Schmähl, 1955; Boyland et al., 1964; La Voie et al., 1988). However, no carcinogenic responses were observed in these studies, and each has at least one limitation that makes it inadequate for assessing the potential for lifetime naphthalene exposure to produce cancer (U.S. EPA, 1998a).

Table 7-7. Summary of Key Studies of Noncancer Toxic Effects of Naphthalene

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Hemolytic anemia								
Zuelzer and Apt (1949)	Dog	3	410 1,530 262 (average of 7 daily doses ranging from 74 to 441 mg/kg)	Diet	single dose single dose 7 days	--	262	Hemolytic anemia observed (decreased hemoglobin and hematocrit concentrations, development of Heinz bodies in erythrocytes, erythrocyte fragmentation and reticulocytosis).
BCL (1980a)	Rat (F344)	Male and Female 10/sex/dose	0 25 50 100 200 400	Gavage corn oil	13 weeks 5 days/week	400	--	No indications of hemolytic anemia observed
BCL (1980b)	Mouse ($B6CF_1$)	Male and Female 10/sex/dose	0 12.5 25 50 100 200	Gavage corn oil	90 days	200	--	No indications of hemolytic anemia observed

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Shopp et al. (1984)	Mouse (CD-1)	Male and Female 40–112	0 27 53 267	Gavage corn oil	14 days	267	--	Red cell hemolysis not observed
Shopp et al. (1984)	Mouse (CD-1)	Male and Female 40–76	0 53 133	Gavage corn oil	90 days	53	--	No indications of hemolytic anemia observed
NTP (1992a)	Mouse ($B6CF_1$)	Male and Female 75–150	0 10 30	Inhalation	2 years (6 hr/day; 5 days/wk)	30	--	No changes in hematological parameters observed after 14 days
Cataracts								
Van Heyningen and Pirie (1976)	Rabbits (Dutch, albino)	Sex not stated 39	0 1,000	Gavage oil	3–28 consecutive daily doses	--	1,000	Cataracts in 10/16 Dutch and 11/12 albino animals)
Rossa and Pau (1988)	Rabbits (Chinchilla Bastard)	Sex not stated 4	0 1,000	Oral	Single dose	--	1,000	Cataracts
	Rabbit (New Zealand)	Sex not stated 4	0 1,000	Oral	4 biweekly doses	--	1,000	Cataracts

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Orzalesi et al. (1994)	Rabbit (pigmented)	Male 31	0 1,000 duration-adjusted 500	Gavage	5 weeks	--	500	Cataracts, retinal degeneration, subretinal neovascularization
Fitzhugh and Buschke (1949)	Weanling rats (NS*)	–[a]	2,000 (estimated)	Diet	2 months (approx.)	--	2,000	Mild cataracts
Tao et al. (1991a, b)	Rat (Brown Norway)	Female 80	0 700	Gavage	102 days	--	700	Lens opacities
Koch et al. (1976)	Rats (Sprague-Dawley, Wistar, albino)	–[a]	0 1,000	Gavage	total duration not specified; cataracts appeared in 16 to 28 days. Doses administered on alternate days	--	1,000	Cataracts

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL mg/kg-day	LOAEL mg/kg-day	Effect
Xu et al. (1992a, b)	Rats (Sprague-Dawley, Wistar, Lewis, Long-Evans and Brown Norway)	Male 6–10	0 1,000	Gavage oil	28 days	--	1,000	Cataracts
Murano et al. (1993)	Rats (Brown Norway, Sprague-Dawley)	Male 6	1,000	Gavage	6 weeks (administered every other day)	--	1,000	Cataracts
Shichi et al. (1980)	Mouse (C57BL/6N and DBA/2N)	Male and Female 15/group	60 120	Diet	60 days	C57BL/6N mice: -- DBA/2N mice: 120	C57BL/6N mice: 60 DBA/2N mice: --	Cataracts observed in C57BL/6N mice (1/15) at each dose No cataracts observed in DBA/2N mice
Schmähl (1955)	Rat (in-house strain BDI, BDIII)	Male and Female 28	41	Food	2 years	Study not adequate to develop LOAEL or NOAEL	--	No cataracts observed

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
BCL (1980a)	Rat (Fisher 344)	Male and Female 10/sex/dose	0 25 50 100 200 400	Gavage corn oil	13 weeks (5 days/week)	400	--	No cataracts observed
BCL (1980b)	Mouse ($B6CF_1$)	Male and Female 10/sex/dose	0 12.5 25 50 100 200	Gavage corn oil	13 weeks (5 days/week)	200 Adjusted 143	--	No cataracts observed
Shopp et al. (1984)	Mouse (CD-1)	Male and Female 40–76	0 53 133	Gavage	90 days	133	--	No cataracts observed
Shopp et al. (1984)	Mouse (CD-1)	Male and Female 40–112	0 27 53 267	Gavage corn oil	14 days	267	--	No cataracts observed
NTP (1992a)	Mouse ($B6CF_1$)	Male and Female 75–150	0 ppm 10 ppm 30 ppm	Inhalation	2 years (6 hr/day; 5 days/wk)	30 ppm*	--	No cataract formation observed
NTP (2000)	Rat (F344/N)	Male and Female 49/sex/dose	0 3.6–3.9 10.7–11.4 20.1–20.6	Inhalation	2 years	20.1-20.6	--	No cataracts observed.

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Srivastava and Nath (1969)	Rabbits (NS*)	NS 6–8	0 2,000	Gavage	5 days	--	2,000	Cataracts in 8/8 animals
Yamauchi et al. (1986)	Rat (Wistar)	Male 4–5	0 1,000	Oral	18 days	--	1,000	Cataracts
Rathbun et al. (1990)	Rat (Black-Hooded)	NS	0 5,000	Gavage	79 days	--	5,000	Lens opacities
Rao and Pandya (1981)	Rat (NS)	Male 6	0 1,000	Gavage	10 days	1,000	--	No effects observed
Ikemoto and Iwata (1978)	Rabbits (Albino)	Male and Female NS	100	Oral	2 days	--	1,000	Cataracts
Holmen et al. (1999)	Rat (Brown Norway)	Female 3–15	0 100 500 1,000 1,500	Gavage	10 weeks 2 doses/week	100 adjusted: 29	500 adjusted: 143	First signs of ocular changes occurred within 2.5 weeks after start of treatment, leading to cataract formation
Kojima (1992)	Rat (Brown Norway)	Female 3–12	0 1,000 every second day	Gavage	4 weeks	--	1,000 adjusted: 500	Lens opacities

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Nasal Pulmonary Lesions								
Plasterer et al. (1985)	Mouse	Male and Female 33–40	250 500	Gavage	8 days	--	500	No exposure-related lesions observed in any organ system
Germansky and Jamall (1988)	Rats, weanling (Blue Spuce)	Male 24	100–750 169 mg/kg-day (TWA)		9 weeks	169	--	No effect observed on peroxidation in lung
BCL (1980b)	Mouse ($B6CF_1$)	Male and Female 10/sex/dose	0 12.5 25 50 100 200	Gavage corn oil	13 weeks (5days/week)	200		No exposure related leisons observed
Adkins et al. (1986)	Rats (A/J)	Female 30	0 ppm* 10 ppm 30 ppm	Inhalation	2 years (6 hr/day; 5 days/wk)	30 ppm		No adverse non-cancer effects reported on the lung
NTP (1992a)	Mouse ($B6CF_1$)	Male and Female 75–150	0 ppm* 10 ppm 30 ppm	Inhalation	2 years (6 hr/day; 5 days/wk)	--	10 ppm* (for chronic nasal and respiratory irritaiton)	Respiratory tract lesions (chronic lung inflammation, chronic nasal irritation with hyperplasia of the respiratory epithelium, metaplasia of the nasal epithelium)

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
NTP (2000)	Rat (F344/N)	Male and Female 49/sex/dose	0 3.6–3.9 10.7–11.4 20.1–20.6	Inhalation	2 years	--	3.6–3.9	Non-neoplastic lesions of the nose were observed.
Body Weight								
BCL (1980a)	Rat (Fisher 344)	Male and Female 10/sex/dose	0 25 50 100 200 400	Gavage corn oil	13 weeks (5 days/wk)	100	200	Reduced body weight (>10% males)
BCL (1980b)	Mouse ($B6CF_1$)	Male and Female 10/sex/dose	0 12.5 25 50 100 200	Gavage corn oil	13 weeks (5 days/wk)	200	--	No effect observed
NTP (1991)	Rat	Pregnant Female 25–26	0 50 150 450		GD 6–15	50 (for maternal toxicity)	150	Significant decrease in weight gain (150 and 450 dose groups)

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
NTP (1992b)	Rabbit (New Zealand, White)	Pregnant Female 25–27	0 20 80 120	Gavage corn oil	GD 6–19	120	--	Maternal: No consistently observed toxicity No effect on fetal body weight
NTP (2000)	Rat (F344/N)	Male and Female 49/sex/dose	0 3.6–3.9 10.7–11.4 20.1–20.6	Inhalation	2 years	20.1–20.6	--	No difference in mean body weights observed.
Shopp et al. (1984)	Mouse (CD-1)	Male and Female (40–112)	0 27 53 267	Gavage corn oil	14 days	53	267	Decreased body weight (males and females)
Germansky and Jamall (1988)	Rats, weanling (Blue Spuce)	Male 24	100–750 169 (TWA)		9 weeks	--	169	Decreased body weight (20%)
NTP (1992a)	Mouse ($B6CF_1$)	Male and Female 75–150	0 ppm* 10 ppm 30 ppm	Inhalation	2 years (6hr/day; 5 days/week)	30	--	No significant change in mean body weight
Holmen et al. (1999)	Rat (Brown Norway)	Female 3–15	0 100 500 1,000 1,500	Gavage	10 weeks 2 doses/week	500 adjusted: 143	1,000 adjusted: 285	Decreased mean body weights observed in rats administered 1000 and 1500 mg/kg.

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Shopp et al. (1984)	Mouse (CD-1)	Male and Female (40–76)	0 53 133	Gavage corn oil	90 days	133	--	No effects observed on body weight
Organ Weight								
Shopp et al. (1984)	Mouse (CD-1)	Male and Female (40–112)	0 27 53 267	Gavage corn oil	14 days	53	267	Decreased thymus weight (male) Increased spleen and lung weights (female)
Shopp et al. (1984)	Mouse (CD-1)	Male and Female (40–76)	0 53 133	Gavage corn oil	90 days	53	133	Decreased brain, liver, and spleen wts. (Female only) No effects observed on organ weights from all exposure groups (male)
Rao and Pandya (1981)	Rats (NS)	Males 6	0 1,000		10 days	--	1,000	Increased liver weight (39%)
Nervous System Depression								
BCL (1980a)	Rat (Fisher 344)	Male and Female 10/sex/dose	0 25 50 100 200 400	Gavage corn oil	13 weeks (5 days/wk)	--	400	Lethargy observed in highest dose group (400 mg/kg-day) for males and females

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
BCL (1980b)	Mouse ($B6CF_1$)	Male and Female 10/sex/dose	0 12.5 25 50 100 200	Gavage corn oil	13 weeks (5 days/wk)	--	200	Transient signs of lethargy observed in highest dose groups during weeks 3 and 5
PRI (1986)	Rabbit (New Zealand White)	Female 18	0 40 200 400	Gavage Methyl-cellulose	GD 6–18	40	200	Treatment related signs of labored breathing, body drop, decreased activity and salivation were observed.
NTP (1991)	Rat (Sprague-Dawley)	Pregnant Females 25–26	0 50 150 450	Gavage	10 days (GD 6–15)	--	50	Neurotoxic effects observed in all dose groups (lethargy, slow respiration, periods of apnea, apparent inability to move after dosing). Effects were transient, and diminished with continued exposure.

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
NTP (1992a)	Mice	Male	0ppm* 10 ppm 30 ppm	Inhalation	2 years	--	--	Increased huddling behavior during exposure and reduced inclination to fight (may indicate neurological effects, although basis for behavioral changes were not speculated on by authors). No additional signs of neurotoxicity reported.
BCL (1980a)	Rats (Fisher 344)	Male and Female 10/sex/dose	0 25 50 100 200 400	Gavage corn oil	13 weeks (5 days/wk)	400	--	No neurological effects found.
BCL (1980b)	Mice ($B6C3F_1$)	Male and Female 10/sex/dose	0 12.5 25 50 100 200	Gavage corn oil	13 weeks (5 days/wk)	200	--	No neurological effects found.

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
Developmental Toxicity								
Plasterer et al. (1985)	Mouse (CD-1)	Female 33–40	0 300	Gavage corn oil	GD 7–14	--	300 (FEL)	Maternal: Reduced wt. gain; reduced survival Fetal: Reduced no. of pups/litter; no abnormalities in surviving pups
PRI (1985)	Rabbit (New Zealand White)	Female 4	0 50 250 630 1,000	Gavage Methyl-cellulose	GD 6–18	Maternal 250 Fetal 250	Maternal 630 (FEL) Fetal 630 (abortion)	Maternal: Mortality and decreased wt. gain at 630 mg/kg-day Fetal: Aborted at 630 mg/kg-day
PRI (1986)	Rabbit (New Zealand White)	Female 18	0 40 200 400	Gavage Methyl-cellulose	GD 6–18	Maternal 400 Fetal 400	Maternal - Fetal -	Maternal: survival, body wt. and body wt. gain unaffected Fetal: No effect on reproduction or development of fetus

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
NTP (1991)	Rat (Sprague-Dawley CD)	Female 25–26	0 50 150 450	Gavage	GD 6–15	Maternal – Fetal 450	Maternal 50 (central nervous system depression) Fetal --	Maternal: Central nervous system depression manifested as lethargy, slow breathing, prone body posture, and increased rooting Decreased weight gain (150 and 450 mg/kg-day) Fetal: no finding of fetal toxicity or embryo toxicity
NTP (1992b)	Rabbit (New Zealand, White)	Female 25–27	0 20 80 120	Gavage oil	GD 6–19	Maternal 120 Fetal 120	Maternal -- Fetal --	Maternal: Two deaths in low-dose group Fetal: No effect on reproduction or development of fetus
Shopp et al. (1984)	Mouse (CD-1)	Male 76–112	0 27 53 267	Gavage oil	14	267	--	No effect on testicular weight
		Male 76–96	53 133	Gavage oil	90	133	--	No effect on testicular weight

Table 7-7 (continued)

Study	Species (Strain)	Sex n	Doses mg/kg-day	Route	Duration	NOAEL	LOAEL	Effect
						mg/kg-day		
BCL (1980a)	Rat (F344)	Male 10/dose	0 25 50 100 200 400	Gavage corn oil	13 weeks 5 days/week	400	--	Absence of gross testicular lesions
BCL (1980b)	Mouse ($B6C3F_1$)	Male 10/dose	0 12.5 25 50 100 200	Gavage corn oil	90 days	200	--	Absence of gross testicular lesions

* Dose conversion not provided in study or secondary source material
NS Not stated

7.4.3 Mode of Action and Implications in Cancer Assessment

Data are not available to clearly identify a mode of action that would contribute to the carcinogenic potential of naphthalene. Buckpitt and Franklin (1989) hypothesized that oxygenated reactive metabolites of naphthalene produced via the cytochrome P-450 monooxygenase system mediate the development of benign respiratory tract tumors and cytotoxic effects by reaction with cellular macromolecules. Because the majority of the genotoxicity tests are negative, it appears unlikely that naphthalene represents a genotoxic hazard (U.S. EPA, 1998a). The development of benign and malignant respiratory tract tumors in mice (NTP, 1992a) and rats (NTP, 2000) may alternatively be explained by the hyperplasia seen in the epithelia of the respiratory tract (ATSDR, 1995). Rapid cell division in response to tissue injury may lead to tumorigenesis when precancerous cells that are present in the tissue are stimulated to divide (Ames and Gold, 1990).

7.4.4 Weight of Evidence Evaluation for Carcinogenicity

Applying the criteria described in U.S. EPA's guidelines for the assessment of carcinogenic risk (U.S. EPA, 1986a), IRIS classified naphthalene as Group C: possible human carcinogen. This classification was based on inadequate human data following exposure to naphthalene via the oral and inhalation routes, and on evidence of carcinogenicity in animals following exposure via the inhalation route (U.S. EPA, 1998b). Using the 1996 Proposed Guidelines for Carcinogen Risk Assessment, the human carcinogenic potential of naphthalene via the oral or inhalation routes is classified in IRIS as "cannot be determined."

At the time of the IRIS review, only one animal (mouse) bioassay had been conducted for naphthalene (NTP, 1992). The bioassay in mice showed no evidence for carcinogenicity in males and some evidence in females. All tumors were in the respiratory track. In the recent (NTP, 2000) bioassay in rats, there was clear evidence of carcinogenicity within the nasal cavity for males and females. Accordingly, carcinogenicity via the inhalation route may need to be reevaluated. The observed effects appear to be route specific since tumors were only identified in the respiratory tract in both studies.

When considering the naphthalene tumorigenicity data in the light of the new NTP study, there is a need to reevaluate the cancer classification for the inhalation route of exposure. By the oral route, data are inadequate to support a judgment and, thus, naphthalene would be classified as Group D (not classifiable). Most of the studies of naphthalene genotoxicity are negative and indicate a weak potential to affect DNA; naphthalene does not appear to be mutagenic. Hyperplastic response to inflammation and irritation of the respiratory epithelium appear to be related to the development of tumors in the nasal cavity and lungs.

7.4.5 Potentially Sensitive Populations

Glucose-6-phosphate dehydrogenase (G6PD)-Deficient Populations

Increased sensitivity to naphthalene-induced hemolysis has been associated with reduced levels of glucose-6-phosphate dehydrogenase (G6PD). This enzyme helps to protect red blood cells from oxidative damage, and G6PD enzyme deficiency makes the cells more sensitive to a wide variety of toxicants, including naphthalene. Higher rates of inherited G6PD deficiencies are found more often in defined subpopulations of males from Asian, Arab, Caucasian (of Latin ancestry), African, and African-American ancestry than in other groups (U.S. EPA, 1987b). Multiple forms of G6PD deficiency have been identified in these subpopulations. The mildest forms are totally asymptomatic, while moderate forms are associated with an adverse response to chemical stressors, including naphthalene. The most severe forms of G6PD deficiency are associated with hemolytic anemia, even in the absence of external stressors (Beutler, 1991). The overall prevalence of G6PD-deficiency in the United States is reported to be 5.2 to 11.5% (Luzzatto and Mehta, 1989).

One of the most common forms of G6PD deficiency is the G6PDA-variant. This form is relatively mild and is common in African populations. It also occurs in southern European populations. The other major form of G6PD deficiency is the more severe "Mediterranean" form, which is most prevalent in southern European and Indian populations. There are many variants (corresponding to specific point mutations) within each major class of G6PD deficiency.

There is very little information related to the precise types of G6PD variants and genotypes that are most likely to be associated with adverse effects from naphthalene. Owa (1989) found that the incidence of neonatal jaundice among G6PD-deficient African neonates was positively correlated with exposure to naphthalene, while there was no correlation in infants with normal G6PD levels. In this study, G6PD levels were measured using an enzyme screening test, but the genotype and severity of the deficiencies were not indicated. Valaes et al. (1963) reported adverse effects in 21 Greek infants exposed to naphthalene from clothing, diapers, blankets, and other items that had been stored in contact with mothballs. Ten of the 21 anemic children and 1 of the 2 infants that died from naphthalene exposure had a genetic polymorphism that resulted in a deficiency in G6PD. The genotype of this polymorphism was not reported in the sources reviewed for this document.

Santucci and Shah (2000) conducted a 10-year retrospective chart review at an inner-city hospital to determine the prevalence and severity of naphthalene-associated hemolysis in G6PD-deficient children aged 2 to 18 years. The sample population was predominately (>90%) African-American. Twenty-four children were identified by chart review as having experienced an acute hemolytic crisis. Of this group, 14 had documented exposures to naphthalene-containing products. Six children ingested mothballs, one ate naphthalene flakes, five had played in a room where naphthalene-containing products were available, and two were wearing clothing stored in a closet with a naphthalene-containing product. The remaining cases of hemolytic anemia were attributed to infectious causes. When a quantitative test was administered for G6PD deficiency at

admission, 58% of the naphthalene group had results within the normal range. However, when retested after recovery, all patients had uniformly deficient levels of G6PD. The study authors noted that "normal" levels of G6PD are to be expected in cases with severe anemia in the presence of normally functioning bone marrow. In this case, reticulocytosis will give a normal result for the G6PD analysis because of the presence of immature blood cells which have adequate G6PD stores. A cross-sectional survey was conducted in parallel to the chart review to document use of mothballs in the study population. About 25% of the study population used mothballs compared to 15% of the population in a more culturally diverse suburban population sample. An unexpected finding was that mothballs were used for previously unrecognized reasons, including air-freshening and as a roach repellant in the inner city.

Potential Gender Sensitivity

Most forms of G6PD deficiency arise from X-linked somatic mutations (Beutler, 1991), which means that males, having only one X-chromosome, cannot be heterozygous for the trait. In contrast, females that are heterozygous for G6PD deficiency are "mosaic," and usually have two distinct populations of red blood cells, one with normal G6PD, and the other with the aberrant form of the enzyme.

There is evidence from two studies to suggest that in humans, males are more sensitive to naphthalene than females. Owa et al. (1993) examined the relationship between neonatal anemia and naphthalene exposure and reported a sex ratio of 7:3 (males to females) in the affected infants. This finding is consistent with a higher susceptibility to red cell damage in homozygous males.

Valaes et al. (1963) also reported a high male-to-female ratio (16:5) among infants with neonatal hemolysis who had been exposed to naphthalene. Using a semi-quantitative enzyme assay, this research group classified ten of the affected infants as G6PD "deficient," two as "intermediate," and nine as "normal." All of the affected females were classified as having normal G6PD levels, but the study authors noted that the possibility of heterozygosity cannot be ruled out in this group. Being identified as G6PD-deficient was positively correlated with the occurrence of severe adverse outcomes including kernicterus and death. All of the severe outcomes (including two deaths) were seen in males.

U.S. EPA (1998a) summarized information on potential gender sensitivity in animals. Consistent gender differences in susceptibility have not been identified across animal studies of naphthalene. Males and female mice displayed similar incidences of non-tumor nasal and pulmonary tract lesions when exposed to naphthalene by inhalation for 2 years (NTP, 1992a). In the same study, the incidence of alveolar/bronchiolar adenomas was significantly increased in females, but not males. Male and female rats both exhibited dose-dependent decreases in body weight gain and terminal body weight following subchronic oral exposure (BCL, 1980a). However, the effect reached statistical significance at a lower dose in males (200 mg/kg-day vs. 400 mg/kg-day).

Neonates, Infants, and Fetuses

Neonates and infants in general are thought to be more susceptible to the adverse effects of naphthalene exposure than adults because the liver enzyme systems that conjugate naphthalene metabolites are not well-developed (U.S. EPA, 1987b). Fetuses may also experience greater susceptibility for the same reason. In addition, the activity of methemoglobin reductase is low in infants. This enzyme catalyzes the reduction of methemoglobin, a chemically-oxidized form of hemoglobin that is formed in association with naphthalene-induced hemolytic anemia. Low levels of this enzyme prevent regeneration and may prolong and/or compound the effects of hemolytic anemia.

8.0 DOSE-RESPONSE ASSESSMENT

8.1 Dose-Response for Noncancer Effects

The derivations of the reference dose (RfD) and reference concentration (RfC) for naphthalene are described below. The RfD is an estimate of the daily oral exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime. The RfC is an estimate of the daily inhalation exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime.

8.1.1 RfD Determination

The RfD typically is derived from the NOAEL (or LOAEL) identified from a chronic (or subchronic) study. Alternatively, the RfD may be derived using a benchmark dose modeling approach (U.S. EPA, 1995).

U.S. EPA (1998a, b) extensively evaluated the toxicity data for naphthalene, and developed the existing RfD using a conventional NOAEL/LOAEL approach. Because there are no adequate data for chronic effects in humans or animals, the RfD for naphthalene is based on the subchronic rat study conducted by BCL (1980a). In this study, naphthalene (>99% pure, in corn oil) was administered to groups of Fischer 344 rats (10/dose/sex), 5 days per week for 13 weeks. Unadjusted daily dose levels were 0, 25, 50, 100, 200, or 400 mg/kg-day. Weekly food consumption and body weights were measured, and rats were examined twice daily for clinical signs of adverse effects. Hematological parameters (hemoglobin, hematocrit, total and differential white cell count, red blood cell count, mean cell volume, and mean cell hemoglobin) were measured in all animals. All rats were necropsied, and detailed histopathological examinations were performed on 27 tissues from all rats in the control and 400 mg/kg-day groups. The tissues examined included eyes, stomach, liver, reproductive organs, thymus, and kidneys. In the 100-mg/kg-day group, the kidneys of males and thymus of females were subject to detailed histopathological examinations. Male and female rats in the 400 mg/kg-day dose group exhibited diarrhea, lethargy, hunched posture, and rough coats during the study, and one high-dose male rat died during the last week of exposure. Food consumption was not affected in any dose group, but body weights were markedly decreased (by at least10%) both in males at 200 mg/kg-day and in females receiving 400 mg/kg-day. NOAEL and LOAEL values of 100 mg/kg-day and 200 mg/kg-day were identified from this study based on body weight reduction in male rats. The corresponding duration-adjusted NOAEL and LOAEL values are 71 mg/kg-day and 143 mg/kg-day, respectively.

A composite UF of 3,000 was used to estimate a chronic RfD from the duration-adjusted NOAEL of 71 mg/kg-day. The composite UF included a factor of 10 to extrapolate from rats to humans, a factor of 10 to account for the protection of sensitive human populations, a factor of 10 to extrapolate from subchronic to chronic exposures, and a factor of 3 for database deficiencies (U.S. EPA, 1998a). Dividing the NOAEL by 3,000 results in an RfD value of 2×10^{-2} mg/kg-day.

$$RfD = \frac{71 \text{ mg/kg-day}}{3000} = 0.02 \text{ mg/kg/day}$$

A benchmark dose modeling approach was also explored for derivation of the naphthalene RfD (U.S. EPA, 1998a). Modeling of terminal body weight decrease resulted in benchmark doses of 130 and 135 mg/kg-day. Following adjustment of these doses for a five day/week dosing regimen and division by a composite UF of 3,000 (determined as for the NOAEL/LOAEL approach above), an RfD of 3×10^{-2} mg/kg-day was obtained. This value is very similar to the value of 2×10^{-2} mg/kg-day derived using the conventional NOAEL/LOAEL approach.

8.1.2 RfC Determination

U.S. EPA (1998a, b) derived an inhalation pathway Reference Concentration (RfC) for naphthalene exposure. This value may have some relevance to naphthalene exposure from drinking water, since a potential exists for indoor air release during water use. An overview of the RfC calculations are provided below.

The RfC was derived using data from the NTP (1992a) study of adverse effects from chronic naphthalene inhalation on mice at 10 and 30 ppm using the conventional NOAEL/LOAEL approach. The nasal effects from naphthalene were considered to be extrarespiratory effects of a category 3 gas, as defined in U.S. EPA (1994b). Following the guidance provided by U.S. EPA (1994b), experimental concentrations were converted to mg/m^3 (0, 52, and 28 mg/m^3) and converted to a continuous exposure basis ($mg/m^3 \times 6$ hours/24 hours $\times$ 5 days/7days). The resulting values were converted to human equivalent concentrations (HECs) by multiplying the adjusted concentrations by the ratio of mouse:human blood/gas partition coefficients. Because blood/gas coefficients were not available for naphthalene, the default ratio of one was used.

The adjusted LOAEL (HEC) for nasal effects (hyperplasia in respiratory epithelium and metaplasia in olfactory epithelium) was divided by an UF of 3,000. The UF value included a factor of 10 to extrapolate from mice to humans, a factor of 10 to account for protection of sensitive human populations, a factor of 10 to extrapolate from a LOAEL to a NOAEL, and a factor of 3 to account for deficiencies in the database. The resulting chronic RfC value is 3×10^{-3} mg/m^3.

8.2 Dose-Response for Cancer Effects

Because chronic oral data are lacking and because evidence is weak that naphthalene may be carcinogenic in humans, no quantitative cancer dose-response assessment for naphthalene has been conducted. The available human data are inadequate to evaluate a plausible association with cancer. Although statistically significant increases in the incidences of respiratory system tumors were reported in mice (lung) and rats (nasal cavity) exposed to naphthalene via inhalation for 2

years (NTP, 1992a, 2000), this evidence is considered insufficient to assess the carcinogenic potential of naphthalene in humans exposed via the oral route (U.S. EPA, 1998a).

9.0 REGULATORY DETERMINATION AND CHARACTERIZATION OF RISK FROM DRINKING WATER

9.1 Regulatory Determination for Chemicals on the CCL

The Safe Drinking Water Act (SDWA), as amended in 1996, required the Environmental Protection Agency (EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. EPA published a draft of the first Contaminant Candidate List (CCL) on October 6, 1997 (62 FR 52193, U.S. EPA, 1997). After review of and response to comments, the final CCL was published on March 2, 1998 (63 FR 10273, U.S. EPA, 1998). The CCL grouped contaminants into three major categories as follows:

Regulatory Determination Priorities - Chemicals or microbes with adequate data to support a regulatory determination,

Research Priorities - Chemicals or microbes requiring research for health effects, analytical methods, and/or treatment technologies,

Occurrence Priorities - Chemicals or microbes requiring additional data on occurrence in drinking water.

The March 2, 1998 CCL included one microbe and 19 chemicals in the regulatory determination priority category. More detailed assessments of the completeness of the health, treatment, occurrence, and analytical method data led to a subsequent reduction of the regulatory determination priority chemicals to a list of 12 (one microbe and 11 chemicals) which was distributed to stakeholders in November 1999.

SDWA requires EPA to make regulatory determinations for no fewer than five contaminants in the regulatory determination priority category by August, 2001. In cases where the Agency determines that a regulation is necessary, the regulation should be proposed by August 2003 and promulgated by February 2005. The Agency is given the freedom to also determine that there is no need for a regulation if a chemical on the CCL fails to meet one of three criteria established by SDWA and described in section 9.1.1.

9.1.1 Criteria for Regulatory Determination

These are the three criteria used to determine whether or not to regulate a chemical on the CCL:

The contaminant may have an adverse effect on the health of persons,

The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern,

In the sole judgment of the administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The findings for all criteria are used in making a determination to regulate a contaminant. As required by the SDWA, a decision to regulate commits the EPA to publication of a Maximum Contaminant Level Goal (MCLG) and promulgation of a National Primary Drinking Water Regulation (NPDWR) for that contaminant. The agency may determine that there is no need for a regulation when a contaminant fails to meet one of the criteria. A decision not to regulate is considered a final Agency action and is subject to judicial review. The Agency can choose to publish a Health Advisory (a nonregulatory action) or other guidance for any contaminant on the CCL independent of the regulatory determination.

9.1.2 National Drinking Water Advisory Council Recommendations

In March 2000, the EPA convened a Working Group under the National Drinking Water Advisory Council (NDWAC) to help develop an approach for making regulatory determinations. The Working Group developed a protocol for analyzing and presenting the available scientific data and recommended methods to identify and document the rationale supporting a regulatory determination decision. The NDWAC Working Group report was presented to and accepted by the entire NDWAC in July 2000.

Because of the intrinsic difference between microbial and chemical contaminants, the Working Group developed separate but similar protocols for microorganisms and chemicals. The approach for chemicals was based on an assessment of the impact of acute, chronic, and lifetime exposures, as well as a risk assessment that includes evaluation of occurrence, fate, and dose-response. The NDWAC protocol for chemicals is a semi-quantitative tool for addressing each of the three CCL criteria. The NDWAC requested that the Agency use good judgment in balancing the many factors that need to be considered in making a regulatory determination.

The EPA modified the semi-quantitative NDWAC suggestions for evaluating chemicals against the regulatory determination criteria and applied them in decision-making. The quantitative and qualitative factors for naphthalene that were considered for each of the three criteria are presented in the sections that follow.

9.2 Health Effects

The first criterion asks if the contaminant may have an adverse effect on the health of persons. Because all chemicals have adverse effects at some level of exposure, the challenge is to define the dose at which adverse health effects are likely to occur, and estimate a dose at which adverse health effects are either not likely to occur (threshold toxicant), or have a low probability for occurrence (non-threshold toxicant). The key elements that must be considered in evaluating the first criterion are the mode of action, the critical effect(s), the dose-response for critical effect(s), the RfD for threshold effects, and the slope factor for nonthreshold effects.

A full description of the health effects associated with exposure to naphthalene is presented in Chapter 7 of this document and summarized below in Section 9.2.2 Chapter 8 and Section 9.2.3 present dose-response information.

9.2.1 Health Criterion Conclusion

The available toxicological data indicate that naphthalene has the potential to cause adverse health effects in humans and animals. In humans, hemolytic anemia is the most common manifestation of naphthalene toxicity. The dose-response relationship for hemolytic anemia is not well-characterized in animals or humans, but in one instance occurred following a single oral dose of approximately 109 mg/kg (Gidron and Leurer, 1956). Indications of naphthalene toxicity in rats and mice include reduced body weight, changes in organ weight, signs of neurotoxicity, and, at high doses, cataracts. Hemolytic anemia has been observed in dogs administered naphthalene. Review of animal dose-response data indicates that short-term and subchronic LOAEL values for naphthalene toxicity are in the range of 50 to 267 mg/kg-day. The RfD for naphthalene is 2×10^{-2} mg/kg-day. Naphthalene does not appear to be a carcinogen by the oral route of exposure. Based on these considerations, the evaluation of the first criterion for naphthalene is positive: naphthalene may have an adverse effect on human health.

9.2.2 Hazard Characterization and Mode of Action Implications

Data for the human health effects of naphthalene are limited. Medical case reports of accidental and intentional ingestion identify hemolytic anemia and cataracts as significant outcomes of oral exposure in humans. Case reports of individuals (primarily infants) exposed to naphthalene via dermal contact, inhalation, or a combination of both exposure routes point to hemolytic anemia and its sequelae as the most commonly manifested toxic effects in humans following exposure at concentrations that exceed average environmental levels. There are no reliable human toxicity data for subchronic or chronic exposure to naphthalene.

In animals, acute or subchronic exposure to relatively high oral doses (200 to 700 mg/kg or greater) of naphthalene resulted in hemolytic anemia (dogs only) and cataracts (rats and rabbits). Lower oral doses of naphthalene (less than 200 to 400 mg/kg) administered to rats and mice in three subchronic studies resulted in decreased body weight, central nervous system depression, and altered organ weights, but did not result in hemolytic anemia or cataracts. No treatment-related lesions were observed in studies reporting histopathology. A limitation of the health effects database for naphthalene is the lack of adequately designed chronic oral exposure studies in animals.

There is no evidence of developmental effects in animals after exposure to naphthalene doses of 120 mg/kg or less. Developmental studies at higher doses produced inconsistent results with regard to maternal and fetal effects.

The available data for mode of action indicate that oxidative metabolism of naphthalene following oral or inhalation exposure produces a variety of reactive metabolites. These metabolites subsequently react with cellular macromolecules to elicit toxicity in target tissues such as the blood, eye, and (in animal inhalation studies) nose and lung. Direct exposure of the cells lining the respiratory track causes inflammation, tissue damage and hyperplasia. Although naphthalene does not appear to be directly genotoxic, long-term inhalation exposure of mice and rats has caused development of adenomas and carcinomas in the nasal cavity (rats) and lungs (female mice). Naphthalene does not appear to be carcinogenic by the oral route.

Individuals with impaired cellular defense capabilities may be more susceptible to naphthalene toxicity. The finding that individuals deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) are more likely to develop hemolytic anemia following exposure to naphthalene confirms this prediction and identifies this group as a potentially susceptible population. Individuals with this deficiency have lower erythrocyte levels of reduced glutathione, a compound that normally protects red blood cells against oxidative damage. G6PD-deficient neonates, infants, and the fetus are particularly sensitive to naphthalene toxicity because the metabolic pathways responsible for conjugation of toxic metabolites (a prerequisite for excretion) are not yet well developed in these groups. In addition, these groups have low levels of methemoglobin reductase, the enzyme that catalyzes the reduction of methemoglobin, increasing vulnerability in the period immediately after birth.

9.2.3 Dose-Response Characterization and Implications in Risk Assessment

Information on the human health effects of naphthalene has been obtained from medical case reports of intentional or accidental ingestion. The usefulness of case study data for assessing risk from drinking water ingestion is limited by one or more of the following factors: quantitative exposure data are not available in most case reports; the toxicokinetics of a single bolus dose may differ from that of chronic low-level exposure; and the low aqueous solubility of naphthalene may prevent the occurrence of concentrations in drinking water that are comparable to the doses that require medical attention. The limited human exposure data that are available from case reports suggest that cataracts occurred following a single dose of approximately 71 mg/kg consumed over 13 hours (Lezenius, 1902). Indications of hemolytic anemia resulted after a single oral dose of approximately 109 mg/kg (Gidron and Leurer, 1956).

All available dose-response information for naphthalene toxicity in animals is extensively summarized in Table 7-7. Five key studies are summarized in Table 9-1 below. These five studies currently provide the most reliable information on threshold levels for naphthalene toxicity in animals exposed via the oral route. Included in this group are two short-term studies and three subchronic studies. There are presently no adequately designed chronic oral exposure studies.

In short-term studies, a LOAEL of 50 mg/kg-day (the lowest dose tested) was identified for transient signs of neurotoxicity in pregnant Sprague-Dawley rats administered naphthalene by gavage on gestation days 6–15 (NTP, 1991). NOAEL and LOAEL values of 53 mg/kg-day and 267 mg/kg-day, respectively, were identified for effects on body weight and organ weight

observed in a 14-day corn oil gavage study conducted in CD-1 mice (Shopp et al., 1984). In subchronic studies, NOAEL and LOAEL values of 100 mg/kg-day and 200 mg/kg-day, respectively, were identified in 13-week gavage studies conducted in Fischer 344 rats and B6C3F$_1$ mice (BCL, 1980a, b). The corresponding duration-adjusted values are 71 mg/kg-day and 143 mg/kg-day, respectively. The LOAEL in rats was identified on the basis of decreased terminal body weight, while the LOAEL in mice was identified on the basis of transient clinical signs of toxicity observed during weeks 3 to 5 of the study. In the third subchronic study, NOAEL and LOAEL values of 53 mg/kg-day and 133 mg/kg-day, respectively, were identified on the basis of changes in organ weights and data suggestive of changes in enzyme activity observed in CD-1 mice administered naphthalene by gavage in corn oil for 90 days (Shopp et al., 1984).

For hemolytic anemia and cataracts (the endpoints of greatest relevance to humans), the available animal data are limited by deficiencies in study design, including the use of a single high dose (typically 500 to 2,000 mg/kg-day) and/or an inadequate number of test animals. NOAEL and LOAEL values, therefore, cannot be identified in these studies. Holmen et al. (1999) identified a LOAEL of 500 mg/kg-day for ocular changes in a multidose study where rats were dosed by gavage twice weekly for 10 weeks.

To place short-term and subchronic dose-response information in perspective, a high-end estimate of naphthalene intake can be calculated. The solubility of naphthalene in water is 31 mg/L. Assuming that naphthalene is present at the limit of solubility, the dose to a 70 kg adult consuming 2 L of drinking water per day would be 0.9 mg/kg-day. The dose to a 10 kg child consuming 1 L of drinking water per day would be 3.1 mg/kg-day. Comparison of these doses to the threshold levels for naphthalene toxicity indicates that the human LOAEL values are at least an order of magnitude greater than the estimated high-end dose.

The Reference Dose (RfD) for naphthalene is 2×10^{-2} mg/kg-day (U.S. EPA, 1998a). The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Because there are no adequate chronic oral exposure studies for naphthalene, the RfD is based on a NOAEL of 71 mg/kg-day identified in a subchronic (13-week) oral exposure study in which no effect on terminal body weight in male rats was observed (BCL, 1980a). An uncertainty factor of 3,000 was used in the derivation of the RfD to account for use of a subchronic study (factor of 10), extrapolation from animals to humans (factor of 10), variability in human populations (factor of 10), and lack of multidose studies in species that are sensitive to hemolytic anemia and cataracts (factor of 3).

The Reference Concentration (RfC) for naphthalene is 3×10^{-3} mg/m^3 (U.S. EPA, 1998a). The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation dose to the human population (including sensitive subgroups) that is likely to be without appreciable risk of adverse effects over a lifetime of exposure. The RfC for naphthalene is based on lesions of the nose observed in a chronic inhalation study of naphthalene in B6C3F$_1$ mice (NTP, 1992a). Details of the RfC derivation are provided in Section 8.1.2 of this document. Comparison of inhalation doses to the RfC can be useful in the risk assessment of contaminants

Table 9-1. Dose-Response Information from Five Key Studies of Naphthalene Toxicity

Study	Species	No. Sex	Doses mg/kg-day	Duration	NOAEL mg/kg-day	LOAEL mg/kg-day	Effects
Short-term Studies							
Shopp et al. (1984)	Mouse CD-1	76–112 M 40–76 F	0 27 53 267	14 days	53	267	Increased mortality, decreased terminal body wt.; altered organ wts.
NTP (1991)	Rat Sprague-Dawley	25–26 F	0 50 150 450	Gestation Days 6–15	Maternal -- Fetal 450	Maternal 50 Fetal --	Maternal: Signs of neurotoxicity lethargy, slow respiration and apnea; signs transient at low dose
Subchronic Studies							
BCL (1980a)	Rat F344	10 M 10 F	0 25 50 100 200 400	13 weeks (5 days/wk)	100 Duration adj. dose: 71	200 Duration adj. dose: 143	Greater than 10% reduction in body weight
BCL (1980b)	Mouse $B6C3F_1$	10 M 10 F	0 12.5 25 50 100 200	13 weeks (5 days/wk)	100 Duration adj. dose: 71	200 Duration adj. dose: 143	Transient signs of toxicity (lethargy, rough coats, decreased food consumption) during weeks 3 -5
Shopp et al. (1984)	Mouse CD-1	76–112 M 40–76 F	5.3 53 133	90 days	53	133	Decreased organ weights; liver enzyme activity

M = male
F = female
wt. = weight
adj. = adjusted
-- = no data

that readily volatilize from drinking water during household activities. In the case of naphthalene, volatilization from water is expected to be minimal.

9.3 Occurrence in Public Water Systems

The second criterion asks if the contaminant is known to occur or if there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern. In order to address this question the following information was considered:

- Monitoring data from public water systems
- Ambient water concentrations and releases to the environment
- Environmental fate

Data on the occurrence of naphthalene in public drinking water systems were the most important determinants in evaluating the second criterion. EPA looked at the total number of systems that reported detections of naphthalene, as well those that reported concentrations of naphthalene above an estimated drinking-water health reference level (HRL). For noncarcinogens, the estimated HRL level was calculated from the RfD assuming that 20% of the total exposure would come from drinking water. For carcinogens, the HRL was the 10^{-6} risk level. The HRLs are benchmark values that were used in evaluating the occurrence data while the risk assessments for the contaminants were being developed.

The available monitoring data, including indications of whether or not the contamination is a national or a regional problem, are included in Chapter 4 of this document and summarized below. Additional information on production, use, and fate are found in Chapters 2 and 3.

9.3.1 Occurrence Criterion Conclusion

The available data for naphthalene production and use are consistent with a downward trend for both. The ten-year pattern of TRI releases to surface water is variable within the range of 2.2 to 6.7 million pounds. The physiochemical properties of naphthalene and the available data for environmental fate indicate that naphthalene in surface water is likely to be rapidly degraded by biotic and abiotic processes and that it has little potential for bioaccumulation. Monitoring data indicate that naphthalene is infrequently detected in public water supplies. When naphthalene is detected, it very rarely exceeds the HRL or a value of one-half of the HRL. Chemical treatment of drinking water and leaching from drinking water surfaces are not expected to contribute to significantly elevated levels of naphthalene in drinking water. Based on these data, it is unlikely that naphthalene will occur in public water systems at frequencies or concentration levels that are of public health concern. Thus, the evaluation for the second criterion is negative.

9.3.2 Monitoring Data

Drinking Water

Naphthalene has been detected in public water supply (PWS) samples collected under the authority of the Safe Drinking Water Act. Data from two monitoring periods were available for analysis. Data from Round 1 were collected during the period 1988 to 1992. Data from Round 2 were collected during the period 1993 to 1998. Round 1 and 2 monitoring detected naphthalene in only 0.43% and 0.24% of all samples analyzed, respectively. When data are expressed on a PWS basis, Round 1 and Round 2 monitoring detected naphthalene at least once in 1.2% (769 systems) and 0.8% (491 systems) of the tested water supplies, respectively.

The median and 99th percentile concentrations for all samples (i.e., samples with and without detectable levels of naphthalene) were below the minimum reporting level (MRL). When subsets of the data containing only samples with detectable levels of naphthalene were analyzed, the median and 99th percentile concentrations for Round 1 were 1.0 µg/L and 900 µg/L, respectively. The median and 99th percentile for Round 2 detections were 0.74 µg/L and 73 µg/L, respectively. There are indications that the high concentrations reflected in the 99th percentile value for the Round 1 detections are outlier values from two ground water systems in one cross-section state (Appendix B). No other State that contributed monitoring data had any detections that exceeded the HRL.

PWSs with detected levels of naphthalene were widely distributed throughout the United States (see Figures 4-2 and 4-3 in this document) and no clear patterns of regional geographic occurrence associated with geology or other factors were evident.

Ambient Water

Naphthalene has been detected in ambient ground water samples reviewed and/or analyzed by the U.S. Geological Survey National Ambient Water Quality Assessment (NAWQA) program. The first round of intensive monitoring in the ongoing NAWQA was conducted from 1991 to 1996 and targeted 20 watersheds. Data from each NAWQA study unit were augmented by additional data from local, state, and federal agencies that met specified criteria (see Section 4.2.1). The data were stratified by population density into rural and urban areas.

The results for ambient water quality monitoring (summarized in Table 4-1 of this document) indicate that detection frequencies were low (3.0% and 0.2% for urban and rural areas, respectively). The median concentrations for detections in urban and rural areas were 3.9 µg/L and 0.4 µg/L, respectively. Because the proportion of detections in the sample database is low and nondetect samples are not considered, these concentrations overestimate the actual concentrations of naphthalene in ambient water and thus are conservative approximations for risk assessment purposes. At the time the data were collected and evaluated, the EPA lifetime Health Advisory for naphthalene was 20 µg/L. This value was exceeded in 0.4% and 1% of urban and

rural wells, respectively. None of the drinking water wells that were tested exceeded the present Health Advisory value (100 μg/L).

Naphthalene concentrations were examined in two studies of urban and highway runoff. The maximum concentrations of naphthalene observed in these studies were well below the HRL.

9.3.3 Use and Fate Data

Naphthalene is a natural constituent of coal tar and crude oil. Commercial quantities of naphthalene are produced from these materials by fractional distillation. Naphthalene production in the United States decreased from 900 million pounds per year in 1968 to 354 million pounds per year in 1982. U.S. manufacturers produced an estimated 1.09×10^5 metric tons (approximately 240 million pounds) of naphthalene in 1996 (CEH, 2000). Thus, naphthalene production has generally declined over the last 32 years. Approximately 7 million pounds of naphthalene were imported and 9 million pounds were exported in 1978. In 1989, approximately 4 million pounds of naphthalene were imported and 21 million pounds were exported. These limited import and export data suggest a decreasing trend in the amount of naphthalene available for consumption in the U.S.

Naphthalene consumption was reported to be 1.08×10^5 metric tons (approximately 238 million pounds) in 1996 (CEH, 2000). Most consumers use naphthalene as a moth repellent (moth balls) or a solid block deodorant for diaper pails. A recent survey of naphthalene use at an inner-city location indicated that naphthalene was used for unexpected purposes, including air freshening and as a roach repellant (Santucci and Shah, 2000). Most industrial naphthalene consumption in the United States occurs in the production of phthalate plasticizers, resins, phthaleins, and dyes (ATSDR, 2000). Other manufacturing uses include the production of carbaryl insecticide, synthetic tanning agents, and surface active agents.

Direct releases to the air constitute more than 90% of the naphthalene entering environmental media (ATSDR, 1995). In contrast, only about 5% of environmental naphthalene is released to water (ATSDR, 1995). Examination of data from the Toxic Release Inventory (TRI) (EPA, 2000b), shown in Table 3-1 of this document, indicates that releases to water varied from 2.2 to 6.7 million pounds for the period 1988 to 1998. No apparent trend (increasing or decreasing) was evident over the reported interval.

Naphthalene is lost from surface water via several mechanisms. The most important route of loss is volatilization. Published volatilization half-lives for naphthalene in surface water range from 4.3 to 7.2 hours (Southworth, 1979; Rodgers et al., 1983). Naphthalene has a log K_{OC} of 2.97. Therefore, a fraction of naphthalene in water will be associated with organic particulate matter and will settle into sediments. For naphthalene, this fraction is expected to be less than 10% (ATSDR, 1995). Naphthalene remaining in surface water is degraded by photolysis and biodegradation processes. Naphthalene undergoing photolysis has an estimated half-life of 71 hours (ATSDR, 1995). Biodegradation also occurs quite rapidly, although the rate of degradation will vary with naphthalene concentration, water temperature and the availability of

nutrients. Naphthalene has a log octanol:water partition coefficient (K_{ow}) of 3.29. Based on this value, significant bioaccumulation of naphthalene in the food-chain is not expected to occur (ATSDR, 1995).

Naphthalene is not used as a drinking water treatment chemical. Although it is possible that residual naphthalene may leach from some materials (i.e., from low density polyethylene; Lau et al., 1994), no data were identified in the materials reviewed for this document that indicate naphthalene is likely to be a leachate from drinking water contact surfaces. Therefore, these factors are not expected to contribute to elevated levels of naphthalene in drinking water.

9.4 Risk Reduction

The third criterion asks if, in the sole judgment of the Administrator, regulation presents a meaningful opportunity for health risk reduction for persons served by public water systems. In evaluating this criterion, EPA looked at the total exposed population, as well as the population exposed to levels above the estimated HRL. Estimates of the populations exposed and the levels to which they are exposed were derived from the monitoring results. These estimates are included in Chapter 4 of this document and summarized in section 9.4.2 below.

In order to evaluate risk from exposure through drinking water, EPA considered the net environmental exposure in comparison to the exposure through drinking water. For example, if exposure to a contaminant occurs primarily through ambient air, regulation of emissions to air provides a more meaningful opportunity for EPA to reduce risk than does regulation of the contaminant in drinking water. In making the regulatory determination, the available information on exposure through drinking water (Chapter 4) and information on exposure through other media (Chapter 5) were used to estimate the fraction that drinking water contributes to the total exposure. The EPA findings are discussed in Section 9.4.3 below.

In making its regulatory determination, EPA also evaluated effects on potentially sensitive populations, including the fetus, infants and children. Sensitive population considerations are included in section 9.4.4.

9.4.1 Risk Criterion Conclusion

Approximately 6 to 10 million people are served by systems with detections greater than the MRL. An estimated 5,000 of these individuals may be served by systems with detections greater than one-half the HRL, based on Round 2 monitoring data, but exposures above the HRL would be rare and localized. Prevalence data for G6PD deficiency in the United States indicate that 5.2 to 11.5% of the exposed individuals may have reduced activity of G6PD, and thus may have an increased risk for methemoglobinemia and possibly hemolytic anemia if exposed to moderate-to-high doses of naphthalene. Methemoglobinemia is the consequence of oxidation of the iron in hemoglobin and is a precursor event to hemolysis induced by naphthalene, as well as by a variety of other chemical agents. Hemolytic anemia is an acute effect that is precipitated when the oxidative damage to the red blood cell is sufficient to cause lysis of the cell membrane.

Neonates and infants have reduced protection against methemoglobinemia due to developmental delays in the activity of methemoglobin reductase, a protective enzyme.

Hemolytic anemia is an acute effect that occurs at moderate-to-high doses of naphthalene. When average daily intakes from drinking water are compared with intakes from food, air and soil, drinking water accounts for a relatively small proportion of total naphthalene intake. On the basis of these observations, the impact of regulating naphthalene concentrations in drinking water on health risk reduction is likely to be small. Thus the evaluation of the third criterion is negative.

9.4.2 Exposed Population Estimates

National population estimates for naphthalene exposure were derived using summary statistics for Round 1 and Round 2 PWS cross-sectional data (see Table 4-3 of this document) and population data from the *Water Industry Baseline Handbook* (U.S. EPA, 2000f). Summary data are provided in Table 9-2 below. An estimated 6 to 10 million people are served by PWSs with detections of naphthalene greater than the MRL. Approximately 5,000 people are served by PWSs with detected naphthalene concentrations greater than one-half the HRL. These estimates are based on data from Round 2 sampling. Based on the data from Round 1 monitoring, a total of 16,000 persons were estimated to be exposed to concentrations of naphthalene that exceed both the HRL and one-half the HRL. However, as mentioned in Section 9.3.2, this estimate was heavily influenced by the results from samples collected at two ground water systems in one of the cross-section states which can be considered to be outlier values. The Round 2-based estimate of 5,000 individuals exposed to concentrations greater than one-half the HRL, with no exposures at concentrations greater than the HRL, appears to be a better estimate of possible national exposure. These estimates are conservative (i.e., may somewhat overestimate the actual number of persons exposed), since more than 98% of the systems tested did not have detectable levels of naphthalene.

Table 9-2. National Population Estimates for Naphthalene Exposure via Drinking Water

Population of Concern	Round 1	Round 2
Served by PWS with detections	6,198,000	10,204,000
Served by PWSs with detections > (1/2 HRL)	16,000*	5,000
Served by PWSs with detections > HRL	16,000*	0

Source: Data taken from Table 4-4 of this document.
HRL = Health Reference Level
* Probable outlier values

9.4.3 Relative Source Contribution

Relative source contribution analysis compares the magnitude of exposure expected via drinking water to the magnitude of exposure from intake of naphthalene in other media, such as food, air, and soil. To perform this analysis, intake of naphthalene from drinking water must be estimated. Occurrence data for naphthalene are presented in Chapter 4 of this document. As indicated in Table 9-2, the median and 99th percentile concentrations for naphthalene were below the MRL when all samples (i.e., those with detectable and nondetectable levels of naphthalene) from either Round 1 or Round 2 were analyzed.

As a simplifying assumption, a value of one-half of the MRL is often used as an estimate of the concentration of a contaminant when the results are less than the MRL. Because a single estimate of the MRL for naphthalene was unavailable (see Section 4.4.1), two alternative approaches were used to estimate average daily intakes from drinking water. The reported detection limits for naphthalene range from 0.01 µg/L for the most sensitive to 3.3 µg/L for the least sensitive methods (ATSDR, 1995). If a value of one-half the detection limit is used as a rough estimate of the concentration of naphthalene, this equates to a range of 0.005 to 1.65 µg/L. Assuming intake of 2 L/day of drinking water by a 70 kg adult, the average daily dose would be 1.4×10^{-3} to 47.1×10^{-3} µg/kg-day (1.4 to 47.1 ng/kg-day). The corresponding dose for a 10 kg child consuming 1 L/day of drinking water would be 0.5×10^{-3} to 165×10^{-3} µg/kg-day (0.5 to 165 ng/kg-day). Alternatively, if the median concentration for naphthalene in samples with detectable levels (approximately 1 µg/L) is used, the average daily doses to an adult and child would be 28.6×10^{-3} and 100×10^{-3} µg/kg-day (28.6 and 100 ng/kg-day), respectively.

Collectively, available data data indicate that intake from drinking water will often be relatively low when compared to intake from other media. The estimated average daily intakes of naphthalene from drinking water (based on median detected concentrations) and other media are shown in Table 9-3. These intakes were used to calculate estimated ratios of the exposure from each medium to the exposure from water (Table 9-4). The estimated food:drinking water exposure ratio ranges from 1 to 8 for an adult and from 2 to 9 for a child. The estimated air:drinking water exposure ratio is 39 for an adult and 45 for a child. The range of estimated naphthalene intake from soil is very broad for both children and adults; thus the soil:drinking water intake ratio will be highly scenario-dependent. For an adult, the estimated soil:drinking water exposure ratio ranges from less than 1 to 103. For a child, the estimated soil:drinking water exposure ratio ranges from 2 to 430.

The data indicate that, with the exception of locations with highly contaminated soils, most naphthalene exposure occurs through ambient air, especially near source-dominated locations. Indoor air concentrations tend to have higher concentrations of naphthalene if cigarette smoking is permitted.

Table 9-3. Comparison of Average Daily Intakes from Drinking Water and Other Media[a]

Medium	Adult (ng/kg-day)	Child (ng/kg-day)
Drinking Water[b]	29[c]	100
Food	41[c]–237	204–940
Air	1,127	4,515
Soil[d]	10–3,000	200–43,000

[a] See Chapter 5 for derivation of intakes from media other than water
[b] Based on the median values for detected naphthalene concentrations in Round 1 and Round 2 (data for Round 2 rounded to 1 µg/L)
[c] Rounded values
[d] Includes household dust

Table 9-4. Ratios of Exposures from Various Media to Exposures from Drinking Water[a]

Exposure Ratio	Adult	Child
Food:Drinking Water	1–8	2–9
Air:Drinking Water	39	45
Soil:Drinking Water	< 1–103	2–430

[a] Calculated from estimated daily intakes in Table 9-2.

9.4.4 Sensitive Populations

The sensitive populations identified for naphthalene include individuals (including infants, neonates and the fetus) deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). This enzyme helps protect red blood cells from oxidative damage; deficiency makes red blood cells more sensitive to a variety of toxicants, including naphthalene. The hemolytic response to naphthalene is enhanced in G6PD-deficient individuals. Higher rates of inherited G6PD deficiency are found among the people of Asia, Greece, Italy, the Middle East, and Africa. In the United States, an estimated 5.2 to 11.5% of the population has an inherited G6PD deficiency (Luzzato and Mehta, 1989). Because this defect is linked to the X-chromosome, males are more likely to be affected than females.

Newborn infants are generally considered to be more sensitive to naphthalene toxicity because the metabolic pathways for conjugation of naphthalene are not well-developed. Newborn infants also have low levels of methemoglobin reductase, a result of which may be to compound and prolong some effects of hemolytic anemia.

Calculation of medium-specific exposure ratios (Table 9-4) indicates that naphthalene intake from air is about 40-fold greater than intake from water. Therefore, regulation of naphthalene in drinking water would be unlikely to significantly reduce the risk to sensitive populations.

9.5 Regulatory Determination Decision

As stated in Section 9.1.1, a positive finding for all three criteria is required in order to make a determination to regulate a contaminant. For naphthalene, negative findings were obtained for two of the three criteria. While there is evidence that naphthalene may have adverse health effects in humans at moderate-to-high doses, it is unlikely that: 1) this contaminant will occur in drinking water with a frequency or at concentrations that are of public health concern; or 2) regulation of this contaminant represents a meaningful basis for health risk reduction in persons served by public water systems.

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APPENDIX A: Abbreviations and Acronyms

ACGIH	- American Conference of Governmental Industrial Hygienists
ATSDR	- Agency for Toxic Substances and Disease Registry
CAS	- Chemical Abstract Service
CCL	- Contaminant Candidate List
CERCLA	- Comprehensive Environmental Response, Compensation & Liability Act
CMR	- Chemical Monitoring Reform
CWS	- Community Water System
DWEL	- Drinking Water Equivalent Level
EPA	- Environmental Protection Agency
EPCRA	- Emergency Planning and Community Right-to-Know Act
GW	- ground water
HA	- Health Advisory
HAL	- Health Advisory Level
HazDat	- Hazardous Substance Release and Health Effect Database
HRL	- Health Reference Level
IOC	- inorganic compound
IRIS	- Integrated Risk Information System
MRL	- Minimum Reporting Level
NAWQA	- National Ambient Water Quality Assessment
NCOD	- National Drinking Water Contaminant Occurrence Database
NIOSH	- National Institute for Occupational Safety and Health
NPDES	- National Pollution Discharge Elimination System
NPDWR	- National Primary Drinking Water Regulation
NTIS	- National Technical Information Service
NTNCWS	- Non-Transient Non-Community Water System
ppm	- part per million
PWS	- Public Water System
RCRA	- Resource Conservation and Recovery Act
SARA Title III	- Superfund Amendments and Reauthorization Act
SDWA	- Safe Drinking Water Act
SDWIS	- Safe Drinking Water Information System
SDWIS/FED	- the Federal Safe Drinking Water Information System
SOC	- synthetic organic compound
STORET	- Storage and Retrieval System
SW	- surface water
TRI	- Toxic Release Inventory
UCM	- Unregulated Contaminant Monitoring
UCMR	- Unregulated Contaminant Monitoring Regulation/Rule
URCIS	- Unregulated Contaminant Monitoring Information System
U.S. EPA	- United States Environmental Protection Agency
USGS	- United States Geological Survey

VOC	- volatile organic compound
µg/L	- micrograms per liter
mg/L	- milligrams per liter
> MCL	- percentage of systems with exceedances
> MRL	- percentage of systems with detections

APPENDIX B: Naphthalene Occurrence Data for Public Water Systems (Round 1 and Round 2)

Napthalene Occurrence in Public Water Systems in Round 1, UCM (1987) results

STATE	TOTAL UNIQUE PWS	# GW PWS	# SW PWS	% PWS > MRL	% GW PWS > MRL	% SW PWS > MRL	% PWS > HRL	% GW PWS > HRL	% SW PWS > HRL	99% VALUE (µµg/L)
AK	669	543	131	4.78%	5.52%	1.53%	0.00%	0.00%	0.00%	0.80
AL	131	93	42	28.24%	32.26%	16.67%	1.53%	2.15%	0.00%	8.20
AR										
AZ	448	407	47	1.12%	0.98%	2.13%	0.00%	0.00%	0.00%	<5.00
CA	609	592	27	1.15%	1.18%	0.00%	0.00%	0.00%	0.00%	<10.00
CO	7	3	5	14.29%	0.00%	20.00%	0.00%	0.00%	0.00%	4.62
DC	1	0	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
DE	10	8	2	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.60
FL	114	8	106	7.02%	0.00%	7.55%	0.00%	0.00%	0.00%	8.00
GA	1,161	1,052	109	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
HI	127	112	16	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.30
IA										
IL	214	150	64	1.87%	2.00%	1.56%	0.00%	0.00%	0.00%	<2.00
IN	357	321	37	0.28%	0.31%	0.00%	0.00%	0.00%	0.00%	<2.00
KY	524	291	233	1.15%	1.03%	1.29%	0.00%	0.00%	0.00%	<1.00
LA	13	9	4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
MA	2	1	1	100.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.80
MD	983	936	50	0.51%	0.53%	0.00%	0.00%	0.00%	0.00%	<0.50
MI										
MN	1,553	1,529	26	0.06%	0.07%	0.00%	0.00%	0.00%	0.00%	<0.50
MO	85	71	14	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<50.00
MS	2	2	0	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	14.80
MT										
NC	297	264	44	0.34%	0.39%	0.00%	0.00%	0.00%	0.00%	<0.50
NE	9	9	0	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	10.60
NH	1	1	0	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	0.97
NJ	783	772	11	1.02%	1.04%	0.00%	0.00%	0.00%	0.00%	<2.00
NM	590	555	35	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<1.00
NV	8	7	2	12.50%	14.29%	0.00%	0.00%	0.00%	0.00%	<0.20
NY	261	187	85	0.38%	0.00%	1.18%	0.00%	0.00%	0.00%	<5.00
OH	2,661	2,489	166	0.68%	0.68%	0.60%	0.00%	0.00%	0.00%	<2.00
SD	335	306	29	2.39%	2.29%	3.45%	0.00%	0.00%	0.00%	0.18
TN	303	156	147	0.99%	0.64%	1.36%	0.00%	0.00%	0.00%	<0.50
TX	3	2	1	100.00%	100.00%	100.00%	0.00%	0.00%	0.00%	18.00
UT	409	389	34	1.96%	1.80%	2.94%	0.00%	0.00%	0.00%	<10.00
VI	3	0	3	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<1.00
VT										
WA	992	937	77	0.20%	0.21%	0.00%	0.00%	0.00%	0.00%	<0.50
WV	57	26	31	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<4.00
WY	145	116	38	3.45%	2.59%	5.26%	0.00%	0.00%	0.00%	0.80
TOTAL	13,857	12,334	1,620	1.29%	1.18%	2.04%	0.01%	0.02%	0.00%	<5.00
24 STATES	13,452	12,034	1,502	1.18%	1.08%	1.93%	0.01%	0.02%	0.00%	<5.00

PWS= Public Water Systems; GW= Ground Water (PWS Source Water Type); SW= Surface Water (PWS Source Water Type);
MRL=Minimum Reporting Limit (for laboratory analyses)
The Health Reference Level (HRL) is the estimated health effect level as provided by EPA for preliminary assessment for this work assignment.
"% > HRL" indicates the proportion of systems with any analytical results exceeding the concentration value of the HRL.

Appendix B, Round 1 Data (continued)
The Health Reference Level (HRL) used for Naphthalene is 140 µg/L. This is a draft value for working review only.
The highlighted States are part of the URCIS 24 20 State Cross-Section.

Naphthalene Occurrence in Public Water Systems in Round 2, UCM (1993) results

STATE	TOTAL UNIQUE PWS	# GW PWS	# SW PWS	% PWS > MRL	% GW PWS > MRL	% SW PWS > MRL	% PWS > HRL	% GW PWS > HRL	% SW PWS > HRL	99% VALUE (µg/L)
Tribes (06)	22	21	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<10.00
AK	625	481	144	4.48%	3.53%	7.64%	0.00%	0.00%	0.00%	<0.00
AL	2	2		100.00%	100.00%	0.00%	0.00%	0.00%		1.40
AR	517	423	94	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.00
AZ	68	60	8	1.47%	1.67%	0.00%	0.00%	0.00%	0.00%	<1.00
CA	15	12	3	6.67%	8.33%	0.00%	0.00%	0.00%	0.00%	1.00
CO	831	619	212	3.97%	2.75%	7.55%	0.00%	0.00%	0.00%	0.42
CT	84	43	41	1.19%	2.33%	0.00%	0.00%	0.00%	0.00%	<0.00
IN	117	107	10	0.85%	0.93%	0.00%	0.00%	0.00%	0.00%	<2.00
KY	212	103	109	0.47%	0.00%	0.92%	0.00%	0.00%	0.00%	<2.50
LA	1,310	1,241	69	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
MA	418	344	74	1.20%	0.58%	4.05%	0.00%	0.00%	0.00%	<0.50
MD	976	920	56	0.51%	0.11%	7.14%	0.00%	0.00%	0.00%	<0.50
ME	744	676	68	0.54%	0.59%	0.00%	0.00%	0.00%	0.00%	<0.00
MI	2,737	2,645	92	0.33%	0.34%	0.00%	0.00%	0.00%	0.00%	<0.00
MN	1,558	1,528	30	0.58%	0.46%	6.67%	0.00%	0.00%	0.00%	<0.50
MO	1,412	1,297	115	0.07%	0.08%	0.00%	0.00%	0.00%	0.00%	<2.00
MS										
NC	1,776	1,586	190	1.18%	1.20%	1.05%	0.00%	0.00%	0.00%	<0.00
ND	296	258	38	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
NH	3	1	2	100.00%	100.00%	100.00%	0.00%	0.00%	0.00%	3.40
NJ	7	7		0.00%	0.00%		0.00%	0.00%		<1.00
NM	714	689	25	0.56%	0.44%	4.00%	0.00%	0.00%	0.00%	<1.00
OH	2,232	2,050	182	1.39%	1.51%	0.00%	0.00%	0.00%	0.00%	<0.50
OK	792	541	251	0.76%	0.92%	0.40%	0.00%	0.00%	0.00%	<0.00
OR	17	15	2	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.00
PA										
RI	100	89	11	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<1.00
SC	237	216	21	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
SD	27	19	8	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.50
TN										
TX	4,412	3,825	587	0.18%	0.16%	0.34%	0.00%	0.00%	0.00%	<1.00
VT										
WA	2,564	2,436	119	0.31%	0.21%	2.52%	0.00%	0.00%	0.00%	<0.00
WI	191	188	3	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<0.30
TOTAL	25,006	22,441	2,565	0.73%	0.60%	1.87%	0.00%	0.00%	0.00%	<2.00
20 STATES	22,926	20,525	2,401	0.77%	0.62%	2.00%	0.00%	0.00%	0.00%	<2.00
19 STATES	22,923	20,524	2,399	0.75%	0.62%	1.92%	0.00%	0.00%	0.00%	<2.00

PWS= Public Water Systems; GW= Ground Water (PWS Source Water Type); SW= Surface Water (PWS Source Water Type);
MRL=Minimum Reporting Limit (for laboratory analyses)
The Health Reference Level (HRL) is the estimated health effect level as provided by EPA for preliminary assessment for this work assignment.
"% > HRL" indicates the proportion of systems with any analytical results exceeding the concentration value of the HRL.
The Health Reference Level (HRL) used for Naphthalene is 140 µg/L. This is a draft value for working review only.
The highlighted States are part of the SDWIS/FED 20 State Cross-Section.