DRAFT
TOXICOLOGICAL PROFILE FOR NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene was released in 1995. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
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Mailstop E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, N.E.
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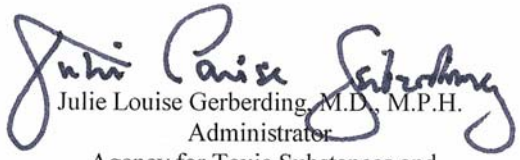
Atlanta, Georgia 30333

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0093
E-mail: atsdric@cdc.gov **Internet:** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include Reproductive and Developmental Hazards; Skin Lesions

and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—Medical Management Guidelines for Acute Chemical Exposures—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. The panel consisted of the following members:

1. Martin Alexander, Ph.D., Cornell University, Ithaca, New York;

2. Susan Borghoff, Ph.D., DABT, CIIT Centers for Health Research, Research Triangle Park, North Carolina; and

3. G.A. Shakeel Ansari, Ph.D., The University of Texas Medical Branch, Galveston, Texas.

These experts collectively have knowledge of naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene have been found in at least 647, 37, and 410, respectively, of the 1,636 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at which naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are found may increase. This information is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to substances such as naphthalene, 1-methylnaphthalene, or 2-methyl-naphthalene, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYL-NAPHTHALENE?

Naphthalene is a white solid that evaporates easily. It is also called mothballs, moth flakes, white tar, and tar camphor. When mixed with air, naphthalene vapors easily burn. Fossil fuels, such as petroleum and coal, naturally contain naphthalene. Burning tobacco or wood produces

naphthalene. The major commercial use of naphthalene is to make other chemicals used in making polyvinyl chloride (PVC) plastics. The major consumer products made from naphthalene are moth repellents, in the form of mothballs or crystals, and toilet deodorant blocks. It is also used for making dyes, resins, leather tanning agents, and the insecticide carbaryl.

Naphthalene has a strong but not unpleasant smell. Its taste is unknown, but it must not be unpleasant since children have eaten mothballs and deodorant blocks. You can smell naphthalene in the air at a concentration of 84 parts naphthalene per one billion parts (ppb) of air. You can smell it in water when 21 ppb are present.

1-Methylnaphthalene is a naphthalene-related compound that is also called alpha methylnaphthalene. It is a clear liquid. Its taste and odor have not been described, but you can smell it in water when only 7.5 ppb are present.

Another naphthalene-related compound, 2-methylnaphthalene, is also called beta methylnaphthalene. It is a solid like naphthalene. The taste and odor of 2-methylnaphthalene have not been described. Its presence can be detected at a concentration of 10 ppb in air and 10 ppb in water.

1-Methylnaphthalene and 2-methylnaphthalene are used to make other chemicals such as dyes, and resins. 2-Methylnaphthalene is also used to make vitamin K. All three chemicals are present in cigarette smoke, wood smoke, tar, asphalt, and at some hazardous waste sites.

See Chapters 4, 5, and 6 for more information on the properties and uses of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

1.2 WHAT HAPPENS TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE WHEN THEY ENTER THE ENVIRONMENT?

Naphthalene enters the environment from industrial uses, from its use as a moth repellent, from the burning of wood or tobacco, and from accidental spills. Naphthalene at hazardous waste

sites and landfills can dissolve in water and be present in drinking water. Naphthalene can become weakly attached to soil or pass through the soil particles into underground water.

Most of the naphthalene entering the environment is from the burning of woods and fossil fuels in the home. The second greatest release of naphthalene is through the use of moth repellents. Only about 10% of the naphthalene entering the environment is from coal production and distillation. Less than 1% of the naphthalene released to the atmosphere can be attributed to the losses from naphthalene production. Cigarette smoking also releases small amounts of naphthalene into the air.

Naphthalene evaporates easily. That is why you can smell mothballs. In the air, moisture and sunlight make it break down, often within 1 day. Naphthalene can change to 1-naphthol or 2-naphthol. These chemicals have some of the toxic properties of naphthalene. Some naphthalene will dissolve in water in rivers, lakes, or wells. Naphthalene in water is destroyed by bacteria or evaporates into the air. Most naphthalene will be gone from water in rivers or lakes within 2 weeks.

Naphthalene binds weakly to soils and sediments. It easily passes through sandy soils to reach underground water. In soil, some microorganisms break down naphthalene. When near the surface of the soil, naphthalene will evaporate into air. Microorganisms present in the soil will break down most of the naphthalene in 1–3 months.

Naphthalene does not accumulate in the flesh of animals and fish that you might eat. If dairy cows are exposed to naphthalene, some naphthalene will be in their milk; if laying hens are exposed, some naphthalene will be in their eggs. Naphthalene and the methylnaphthalenes have been found in very small amounts in some samples of fish and shellfish from polluted waters.

Scientists know very little about what happens to 1-methylnaphthalene and 2-methylnaphthalene in the environment. These compounds are similar to naphthalene and should act like it in air, water, or soil.

See Chapters 5 and 6 for more information on what happens to naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene in the environment.

1.3 HOW MIGHT I BE EXPOSED TO NAPHTHALENE, 1-METHYL-NAPHTHALENE, AND 2-METHYLNAPHTHALENE?

You are most likely to be exposed to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene from the air. Outdoor air contains low amounts of these chemicals. Burning of wood or fossil fuels and industrial discharges adds these chemicals to the environment. Automobile exhaust contributes naphthalene among other chemicals to air pollution in the cities. Typical air concentrations for naphthalene are low, 0.2 ppb or less. Studies of outdoor air reported concentrations of 0.09 ppb 1-methylnaphthalene and 0.011 ppb 2-methylnaphthalene. In homes or businesses where cigarettes are smoked, wood is burned, or moth repellents are used, the levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in the air are higher. Studies of indoor air typically report that average indoor air concentrations of these contaminants are less than 1 ppb.

You are not likely to be exposed to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene by eating foods or drinking beverages. These materials are unlikely to come in contact with naphthalene or methylnaphthalenes during production or processing. Naphthalene and the methylnaphthalenes are also unlikely to be present in tap water.

If you live near a hazardous waste site and have a well used for drinking water, you might be exposed to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. For this to happen, the chemicals must pass through the soil and dissolve in the underground water that supplies your well. Children might also contact these chemicals by playing in or eating the dirt near a waste site.

Work using or making moth repellents, coal tar products, dyes, or inks could expose you to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in the air. Working in the wood-preserving, leather tanning, or asphalt industries could expose you to naphthalene.

Using moth repellents containing naphthalene in your home will expose you to naphthalene vapors. Your skin can come in contact with naphthalene via the use of naphthalene-treated clothing, blankets, or coverlets. You can breathe in the naphthalene vapors that are present in clothes and linen stored with moth-balls. Smoke from cigarettes can also expose you to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. The highest airborne naphthalene concentrations in indoor air occur in the homes of cigarette smokers.

See Chapter 6 for more information on how you might be exposed to naphthalene, 1-methyl-naphthalene, or 2-methylnaphthalene.

1.4 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYL-NAPHTHALENE ENTER AND LEAVE MY BODY?

Naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene can enter your body if you breathe air that contains these chemicals, if you smoke, if you eat mothballs, if you drink water that contains these chemicals, or if they touch your skin. These chemicals are most likely to enter your body through the air you breath into your lungs. Naphthalene can also enter your body through your skin when you handle mothballs, particularly if you have used an oil-based skin lotion. You can also breathe in naphthalene vapors from clothes that have been stored in mothballs.

Once naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene enter your body, small amounts will dissolve in your blood. Your blood carries them to your liver and other organs. These organs change them so that they pass through your body, mainly into your urine. Some naphthalene, 2-methylnaphthalene, and their breakdown products can be present in your stool. Naphthalene also has been found in some samples of fatty tissue and breast milk taken from the general U.S. population, but the concentrations of naphthalene were low. Most naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene that enters your body is expected to leave quickly within 1–3 days.

See Chapter 3 for more information on how naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene enter and leave your body.

1.5 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYL-NAPHTHALENE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Exposure to a large amount of naphthalene may damage or destroy some of your red blood cells. This could cause you to have too few red blood cells until your body replaces the destroyed cells. This problem is called hemolytic anemia. People, particularly children, have developed this problem after eating naphthalene-containing mothballs or deodorant blocks. Anemia has also occurred in infants wearing diapers that have been stored in mothballs. If your ancestors were from Africa or Mediterranean countries, naphthalene may be more dangerous to you than to people of other origins. These populations have a higher incidence of problems with an enzyme that usually protects red blood cells from damage created by oxygen in the air.

Some of the symptoms that occur with hemolytic anemia are fatigue, lack of appetite, restlessness, and a pale appearance to your skin. Exposure to a large amount of naphthalene, such as by eating mothballs, may cause nausea, vomiting, diarrhea, blood in the urine, and a yellow color to the skin. If you have these symptoms, you should see a doctor quickly.

Anemia is a common condition in pregnancy that can be due to causes other than naphthalene exposure. However, if you are a pregnant woman and are anemic due to naphthalene exposure, then it is possible that your unborn child may be anemic as well. Naphthalene can move from your blood to your baby's blood. Once your baby is born, naphthalene may also be carried from your body to your baby's body through your milk. It is not completely clear if naphthalene causes reproductive effects in animals; most evidence says that it does not.

Laboratory rabbits, guinea pigs, mice, and rats sometimes develop cataracts (cloudiness) in their eyes after swallowing naphthalene at high dose levels. It is not certain whether cataracts also develop in humans exposed to naphthalene, but the possibility exists.

When mice or rats breathed in naphthalene vapors daily throughout their lives (2 years), cells in the lining of their noses or lungs were damaged. Some exposed female mice also developed lung tumors. Some exposed male and female rats developed nose tumors. When mice or rats were fed naphthalene in their food for 13 weeks, no tumors or other tissue changes were found. The only effect found was decreased body weight in rats that were fed naphthalene.

Based on these results from animal studies, the U.S. Department of Health and Human Services concluded that naphthalene is reasonably anticipated to be a human carcinogen. The International Agency for Research on Cancer (IARC) concluded that naphthalene is possibly carcinogenic to humans, because there is enough evidence that naphthalene causes cancer in animals, but not enough evidence about such an effect in humans. The EPA determined that naphthalene is not classifiable as to its carcinogenicity to humans, but has not yet looked at new studies that found nose tumors in rats that breathed in naphthalene throughout their lives.

When mice were fed food containing 1-methylnaphthalene or 2-methylnaphthalene for most of their lives (81 weeks), the gas-exchange part of the lungs of some mice became filled with an abnormal material. This type of lung injury is called pulmonary alveolar proteinosis. A few mice also had lung tumors, but the numbers of mice with lung tumors were not enough to conclude that 1-methylnaphthalene or 2-methylnaphthalene caused the tumors. Pulmonary

alveolar proteinosis has been seen in some people, but the cause of this uncommon lung disease in humans is unknown.

See Chapter 3 for more information on the effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene on your health.

1.6 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYL-NAPHTHALENE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Hospitals have reported many cases of hemolytic anemia in children, including newborns and infants, who either ate naphthalene mothballs or deodorant cakes or who were in close contact with clothing or blankets stored in naphthalene mothballs. Newborns or infants are thought to be especially susceptible to this effect on the blood, because their bodies are less able to get rid of naphthalene than adults.

Newborn mice appear to be more susceptible to lung injury than adult mice, when they are injected with naphthalene. These results suggest that children may be more susceptible to lung injury from naphthalene than adults. Scientists do not know if lung injury from breathing in naphthalene in childhood may lead to lung disease later in life.

There are no reports that prenatal or postnatal exposure to naphthalene has caused developmental problems in human offspring. When pregnant mice, rats, or rabbits were fed naphthalene during their pregnancy, the development of their offspring was normal. Normal offspring development occurred even when the amounts of naphthalene given were large enough to prevent the pregnant animals from gaining their normal amount of weight.

There are no studies in humans or animals indicating whether or not children are more susceptible to health effects from 1-methylnaphthalene or 2-methylnaphthalene.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYL-NAPHTHALENE?

If your doctor finds that you have been exposed to significant amounts of naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

The most important way that families can reduce the risk of exposure to naphthalene, 1-methyl-naphthalene, or 2-methylnaphthalene is to avoid smoking tobacco, generating smoke during cooking, or using fireplaces or heating appliances in their homes. If families use naphthalene-containing moth repellants, the material should be enclosed in containers that prevent vapors from escaping. The containers should not be accessible to young children. Blankets and clothing stored with naphthalene moth repellents should be aired outdoors to remove naphthalene odors and washed before they are used. To further minimize the risk of exposure to naphthalene, families should inform themselves of the contents of air deodorizers that are used in their homes, and refrain from using deodorizers with naphthalene.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYL-NAPHTHALENE?

Several tests determine whether you have been exposed to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. These tests include measuring naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, or their breakdown products in samples of urine, stool, blood, maternal milk, or body fat. These tests require special equipment, which is not routinely available in a doctor's office. Body fluids, urine, stool samples, or tissue samples can be sent to a special laboratory for the tests. These tests cannot determine exactly how much naphthalene, 1-methyl-naphthalene, or 2-methylnaphthalene you were exposed to or predict whether harmful effects will occur. If the samples are collected within a day or two of exposure, then the tests can show

if you were exposed to a large or small amount of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

See Chapters 3 and 7 for more information on tests for exposure to naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has developed regulations and advisories to protect individuals from the possible health effects of naphthalene in the environment. OSHA set a limit of 10 parts per million (ppm) for the level of naphthalene in workplace air over an 8-hour workday. NIOSH set a limit of 500 ppm for the level of naphthalene in workplace air expected to be immediately dangerous to life or health. Exposure to workplace air concentrations above this limit for more than 30 minutes would be expected to impair a worker's ability to escape the contaminated workplace.

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene include the following:

The federal government has developed regulations and advisories to protect individuals from the possible health effects of naphthalene in the environment. OSHA set a limit of 10 parts per

million (ppm) for the level of naphthalene in workplace air during an 8-hour workday. NIOSH considers more than 500 ppm of naphthalene in air to be immediately dangerous to life or health.

EPA recommends that children not drink water with over 0.5 ppm naphthalene for more than 10 days or over 0.4 ppm for any longer than 7 years. Adults should not drink water with more than 1 ppm for more than 7 years. For water consumed over a lifetime (70 years), EPA suggests that it contain no more than 0.1 ppm naphthalene.

Industrial releases of naphthalene into the environment of more than 100 pounds must be reported to EPA.

There are no regulations or advisories for 1-methylnaphthalene or 2-methylnaphthalene.

See Chapter 8 for more information on government regulations for naphthalene.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE IN THE UNITED STATES

Naphthalene and methylnaphthalenes occur naturally in fossil fuels such as petroleum and coal, and are produced when organic materials (e.g., fossil fuels, wood, tobacco) are burned (EPA 2002b; IARC 2002). Naphthalene is also produced commercially from either coal tar or petroleum. In 2000, estimates of commercial production of naphthalene in Japan, Western Europe, and the United States were 179, 205, and 107 thousand tonnes. Commercially produced naphthalene is predominately used in the production of phthalic anhydride, which is used as an intermediate for polyvinyl chloride plasticizers such as di(2-ethylhexyl) phthalate. In 1999, this use of naphthalene accounted for 73 and 60% of commercial demand for naphthalene in Japan and the United States, respectively. Other uses of naphthalene include production of naphthalene sulfonates (used in concrete additives and synthetic tanning agents), pesticides (e.g., carbaryl insecticides and moth repellents), and dye intermediates.

Naphthalene is frequently present in industrial and automobile emissions and effluents and in various media in the general environment due to its natural occurrence in coal and petroleum products and emissions, its use as an intermediate in the production of plasticizers, resins, and insecticides, and its use in a variety of consumer products such as moth repellants. In 2001, environmental releases of naphthalene reported under the EPA Toxics Release Inventory (TRI) program were about 2.0 million pounds in air emissions, 0.04 million pounds in surface water discharges, 0.16 million pounds in underground injection discharges, and 0.04 million pounds in releases to land. These figures reflect estimates that most naphthalene entering the environment is discharged to the air, with the largest releases associated with the combustion of plant material and fossil fuels and volatilization from naphthalene-containing consumer products.

Monitoring studies of outdoor ambient air levels of naphthalene have reported concentrations in the range of about 0.4–170 $\mu g/m^3$, with a median naphthalene concentration of 0.94 $\mu g/m^3$ (0.0002 ppm) reported for urban/suburban air samples collected from 11 U.S. cities. The highest outdoor air concentrations have been found in the immediate vicinity of certain industrial sources and hazardous waste sites. For example, average concentrations of naphthalene in ambient air at five hazardous waste sites and one landfill in New Jersey ranged from 0.42 to 4.6 $\mu g/m^3$ (0.00008–0.0009 ppm). In indoor air, emissions

from cooking, tobacco smoking, or moth repellants are expected to be the predominant sources of naphthalene. Indoor air concentrations of naphthalene in homes with smoking residents and homes without smoking residents were reported to be 2.2 μg/m^3 (0.0004 ppm) and 1.0 μg/m^3 (0.0002 ppm), respectively. A study of indoor and outdoor air in 24 low-income homes in North Carolina found naphthalene levels ranging from 0.33–9.7 μg/m^3 and 0.57–1.82 μg/m^3 respectively. Methylnaphthalenes have also been detected in ambient outdoor and indoor air. For example, average concentrations of 1-methylnaphthalene and 2-methylnaphthalene in ambient outdoor air samples were reported to be 0.51 and 0.065 μg/m^3, respectively, whereas 2-methylnaphthalene in indoor air samples showed an average concentration of 1.5 μg/m^3 (0.0003 ppm). Based on a median concentration of 0.95 μg/m^3 (0.0002 ppm) naphthalene in urban and suburban air samples and an inhalation rate of 20 m^3/day, the average daily intake of naphthalene from ambient air is estimated at 19 μg/day, or 0.3 μg/kg/day assuming 70-kg body weight.

Levels of naphthalene (and methylnaphthalenes), when detected in water, sediments, and soil tend to be low: usually <10 μg/L in surface water or groundwater, <500 μg/kg in sediments, and 0–3 μg/kg in untreated agricultural soils. However, in the immediate vicinity of point sources of release, such as chemical waste sites, concentrations can be higher. For example, concentrations of 6.1 and 2.9 mg/kg were reported for naphthalene and methylnaphthalene, respectively, in soil samples contaminated with coal tar.

2.2 SUMMARY OF HEALTH EFFECTS

Reports that establish associations between naphthalene exposure and health effects in humans are restricted to numerous reports of hemolytic anemia or cataracts following acute exposure or occupational exposure to naphthalene, either by ingestion or by inhalation of naphthalene vapors, but these reports have not identified exposure levels associated with these effects. A relationship appears to exist between an inherited deficiency in the enzyme, glucose 6-phosphate dehydrogenase (G6PD), and susceptibility to naphthalene-induced hemolysis. Newborn infants also appear to be susceptible to naphthalene-induced hemolysis presumably due to a decreased ability to conjugate and excrete naphthalene metabolites. The only studies of cancer in humans exposed to naphthalene are two case series reports of cancer; one report of four laryngeal cancer cases (all of whom were smokers) among workers in a naphthalene purification plant in East Germany, and another report of 23 cases of colorectal carcinoma admitted to a hospital in Nigeria. NTP, EPA, and IARC concur that these studies provide inadequate evidence of naphthalene carcinogenicity in humans. No cohort mortality or morbidity studies or case-control studies examining

possible associations between naphthalene exposure and increased risk of cancer (or other health effects) are available.

Epidemiology studies, case reports, or controlled-exposure studies examining the potential health effects of human exposure to 1-methylnaphthalene or 2-methylnaphthalene by any route of exposure are not available.

Results from animal studies exposed to naphthalene by oral administration, by inhalation exposure, or by parenteral administration identify several health effects of potential concern for humans, including maternal toxicity during pregnancy with acute oral exposure, decreased body weight (without lesions developing in any tissues or organs) with intermediate oral exposure, and increased incidence of nonneoplastic and neoplastic lesions in the nose (in rats and mice) and the lung (in mice only) with chronic inhalation exposure.

Hemolytic and Ocular Effects of Naphthalene in Animals. Rats and mice do not appear to be susceptible to the hemolytic effects of naphthalene as hematological end points have not been affected in acute or intermediate duration oral studies or in acute 14-day inhalation studies. There is one report of hemolytic anemia in a few dogs orally exposed to naphthalene, but the data are inadequate to describe dose-response relationships that can be reliably extrapolated to human exposure scenarios. Naphthalene-induced cataracts or lens opacities are well studied in rats and rabbits and appear to occur at acute- or intermediate-duration oral exposure levels >500 mg/kg/day. Naphthalene-induced cataracts were not found with intermediate-duration (i.e., 13 weeks) oral exposure at lower dose levels up to 200 mg/kg/day in mice or 400 mg/kg/day in rats.

Maternal and Developmental Toxicity of Naphthalene in Animals. Acute oral exposure of pregnant rats to naphthalene doses of 150 or 450 mg/kg/day (but not 50 mg/kg/day) during gestation has produced maternal toxicity including clinical signs of neurological impairment (lethargy and prone position) and marked decreases in body weight gain, but clear effects on the developing fetus have not been found at maternal oral doses as high as 450 mg/kg/day in rats, 300 mg/kg/day in mice, or 120 or 400 mg/kg/day in rabbits. Reduced numbers of mouse pups per litter were observed when naphthalene (300 mg/kg/day) in corn oil was orally administered to pregnant mice; however, no fetotoxic effects were seen when pregnant rabbits were orally administered naphthalene at even higher doses (400 mg/kg/day) but delivered in methylcellulose rather than in an oil vehicle. It is unclear if these differences are due to species differences in sensitivity or to the vehicle used to deliver naphthalene. The finding of maternal toxicity in

orally exposed pregnant rats serves as the basis of the acute oral MRL for naphthalene (see Section 2.3). Dermal or inhalation developmental toxicity studies in animals are not available.

Body Weight Effects of Naphthalene in Animals. Comprehensive intermediate-duration (13 weeks) oral toxicity studies found no evidence for naphthalene-induced lesions in any tissue or organs in male or female Fischer 344 rats exposed to doses as high as 400 mg/kg/day or in male or female B6C3F1 mice exposed to doses as high as 200 mg/kg/day. The only biologically significant effects found in these studies were decreases in rat terminal body weights compared with controls at dose levels of 200 mg/kg/day (12% decrease in male rats) and 400 mg/kg/day (28 and 23% decreases in male and female rats, respectively). No effect on food consumption was observed in exposed rats. Exposed male mice had higher body weights than controls, and exposed female mice had lower body weights than controls, but mean body weights were not decreased by more than 5%. In another intermediate-duration oral study with CD-1 mice that focused on a battery of immunologic tests (but did not include comprehensive histopathologic examination of tissues), no biologically significant effects were found except for decreases in weights of several organs (brain, liver, and spleen) in mice exposed to 133 mg/kg/day, but not to 53 or 5.3 mg/kg/day. The lack of naphthalene-induced lesions in these organs suggests that the brain, liver, and spleen are not sensitive targets of naphthalene following intermediate oral exposure. Body weight changes in rats were the most sensitive, biologically relevant effects observed in the available toxicity studies in animals orally exposed for intermediate durations. These effects were considered in deriving the intermediate-duration oral MRL for naphthalene (see Section 2.3). Chronic-duration oral toxicity studies with naphthalene in animals are not available.

Cancer and Respiratory Effects of Naphthalene in Animals. Chronic inhalation studies found increased incidences of nonneoplastic and neoplastic lesions in the nose of rats, nonneoplastic lesions in the nose of mice, and neoplastic and nonneoplastic lesions in the lungs of mice. In mice of both sexes, chronic inhalation of 10 or 30 ppm naphthalene induced inflammation of the nose and lung, metaplasia of the olfactory epithelium, and hyperplasia of the nasal respiratory epithelium. In female mice (but not male mice), exposure to 30 ppm (but not 10 ppm) increased the incidence of benign lung tumors (alveolar/bronchiolar adenomas) compared with controls. One other female mouse exposed to 30 ppm showed a malignant lung tumor (alveolar/bronchiolar carcinoma). In rats of both sexes, inhalation of 10, 30, or 60 ppm naphthalene induced nonneoplastic and neoplastic lesions only in the nasal cavity. Nonneoplastic nasal lesions included (1) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium and (2) hyperplasia, metaplasia or degeneration of the respiratory epithelium or glands. Neoplastic lesions associated with naphthalene exposure in rats were olfactory epithelial neuro-

blastoma (a rare malignant tumor) and respiratory epithelial adenoma. The chronic inhalation MRL for naphthalene is based on the LOAEL of 10 ppm for nonneoplastic lesions in the olfactory epithelium and respiratory epithelium of the nose of rats (see Section 2.3).

The mechanisms by which naphthalene causes nonneoplastic or neoplastic lesions are incompletely understood, but are thought to involve reactive metabolites of naphthalene, including 1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and possibly 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetra-hydronaphthalene(see Sections 3.4.3. and 3.5).

Comparison of species susceptibility to naphthalene-induced nonneoplastic lung damage suggests that mice are much more sensitive than rats (e.g., nonneoplastic or neoplastic lung lesions were not found in chronically exposed rats in the NTP study) and that differences in rates and stereoselectivity of naphthalene metabolism to epoxide intermediates may be involved in this species difference. Acute (4-hour) inhalation exposure of mice to naphthalene concentrations as low as 2–10 ppm induced lung injury, whereas rats exposed to naphthalene concentrations as high as 110 ppm showed no signs of lung injury. Some evidence has been reported that rates and stereoselectivity of naphthalene metabolism in primate lung tissue may be more like rats than mice. In *in vitro* studies with microsomes from lymphoblastoid cells, which expressed recombinant human CYP2F1, metabolism of naphthalene to epoxide intermediates was demonstrated, but the predominant enantiomeric form produced (1*S*,2*R*-oxide) was different from the form (1*R*,2*S*-oxide) produced by mouse CYP2F2. Although these observations on epoxide formation may suggest that mice may be more sensitive than humans to acute naphthalene lung toxicity from epoxide intermediates, the possible role of other potentially reactive metabolites of naphthalene (e.g., the naphthoquinone metabolites) is unknown with chronic exposure scenarios. To date, mechanistic understanding of species differences in naphthalene bioactivation in the lung is too incomplete to definitively rule out the possible human relevance of naphthalene-induced lung lesions in mice (see Section 3.5).

In contrast, the olfactory epithelium and respiratory epithelium of the nose of rats and mice do not appear to differ in sensitivity to naphthalene toxicity from chronic inhalation exposure. Nonneoplastic nasal lesions were found in nearly all exposed animals of both species at the lowest exposure level, 10 ppm, in both chronic studies. CYP monooxygenases, which might be involved in naphthalene metabolism and bioactivation, have been demonstrated to exist in nasal respiratory epithelial and olfactory epithelial tissue from rodents and humans. Studies designed to specifically characterize metabolism of naphthalene in nasal tissue, however, have not been conducted, with the exception of a single study, which examined *in*

vitro rates of metabolism of naphthalene to naphthalene oxides in postmitochondrial supernatants from mouse, rat, and hamster olfactory tissue. Metabolic rates (units of nmol/min/mg protein) showed the following order: mouse (87.1) > rat (43.5) > hamster (3.9). This order did not correspond with species differences in sensitivity to single intraperitoneal injections of naphthalene in a companion study. The lowest dose levels producing substantial necrosis and exfoliation in olfactory epithelium were 200 mg/kg in rats and 400 mg/kg in mice and hamsters.

It is unknown whether the naphthalene-induced neoplastic lesions found in mice (lung adenomas) and rats (nose respiratory epithelial adenomas and olfactory epithelial neuroblastomas) are produced via a genotoxic mode of action or a nongenotoxic mode requiring tissue damage and regenerative responses as precursor events. Results from genotoxicity tests for naphthalene have been predominately (but not completely) negative (see Section 3.3), and the general sites of neoplastic lesions, the nose in rats and the lungs in mice, show some correspondence (but not complete) with the general sites of nonneoplastic lesions. However, mechanistic understanding of naphthalene's carcinogenic mode of action is too incomplete to rule out the possibility of a genotoxic mode of action. Key issues that remain unexplained or unstudied include:

(1) the possible significance of the few positive genotoxicity results that have been obtained, including: reverse mutations in *Salmonella typhimurium* by 1,2-naphthoquinone; *in vitro* formation of N-7 guanine adducts of DNA by 1,2-naphtoquinone; reverse mutations for luminescence in the marine bacteria, *Vibrio fischeri*, by naphthalene; induction of sister chromatid exchanges in Chinese hamster ovary cells by naphthalene and in human mononuclear leukocytes by 1,2- or 1,4-naphtho-quinone; induction of chromosomal aberrations in Chinese hamster ovaries and preimplantation mouse embryos by naphthalene; induction of somatic mutations and recombination in *Drosophila melanogaster* by naphthalene; and weak (about 2-fold) induction of micronuclei in red blood cells from *Pleurodeles waltl* larvae by naphthalene.

(2) the lack of a mechanistic explanation of why nearly all rats and mice develop nasal nonneoplastic lesions following chronic exposure to naphthalene at concentrations ≥10 ppm, but only some rats develop nasal tumors;

(3) the lack of a mechanistic explanation of why both male and female mice exposed to naphthalene show similar incidences of chronic lung inflammation following chronic exposure to 10 or 30 ppm, but only female mice showed statistically significant increased incidence of lung tumors;

(4) the lack of *in vivo* genotoxicity assays involving target tissues of naphthalene carcinogenicity (nose and lung); and

(5) the lack of information on the possible threshold exposure levels for nonneoplastic nasal lesions in rats and mice at air concentrations <10 ppm.

The National Toxicology Program *10th Report on Carcinogens* does not include naphthalene in its list of chemicals *known to be human carcinogens* or *reasonably anticipated to be human carcinogens*, but the NTP is currently in the process of considering naphthalene carcinogenicity for the 11th Report on Carcinogens. In this process, the National Institute of Environmental Health Sciences (NIEHS) Review Committee for the Report on Carcinogens (RG1) passed a motion to list naphthalene as reasonably anticipated to be a human carcinogen by a vote of 6 to 1. Next, the NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2) could not reach a majority recommendation for either listing or not listing naphthalene in the *11th Report on Carcinogens*. Finally, the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee (the External Peer Review Group) passed a motion, by unanimous vote (9–0), to list naphthalene as reasonably anticipated to be a human carcinogen. The final evaluation is in a period of collecting and responding to public comments.

International Agency for Research on Cancer concluded that naphthalene is *possibly carcinogenic to humans* (Group 2B) based on specific evaluations that there is inadequate evidence in humans and sufficient evidence in animals for the carcinogenicity of naphthalene. IARC considered the findings for nasal tumors in male and female rats and lung tumors in female mice in the NTP bioassays as sufficient evidence, noting that both nasal tumor types (olfactory epithelial neuroblastomas and respiratory epithelial adenomas) are rare in untreated rats.

EPA last assessed the carcinogenicity of naphthalene before the availability of the results from the chronic rat bioassay. In the EPA *Toxicological Review on Naphthalene,* it was concluded that there was inadequate evidence in humans and limited evidence in animals of naphthalene carcinogenicity (increased incidence of lung tumors in female mice). Under the EPA cancer guidelines, naphthalene was assigned to Group C – *possible human carcinogen*. Under the EPA proposed cancer guidelines, it was judged that the human carcinogenic potential of naphthalene via the oral or inhalation routes “cannot be determined”, but it was noted that there was suggestive evidence of potential human carcinogenicity based on increased

lung tumors in female mice. Currently, the EPA Integrated Risk Information System (IRIS) Office is reassessing the inhalation carcinogenicity of naphthalene.

Cancer and Respiratory Effects of 1- and 2-Methylaphthalene in Animals. Increased incidences of pulmonary alveolar proteinosis have been observed in mice of both sexes exposed to 1-methylnaphthalene in the diet for 81 weeks at approximate dose levels of 72–75 and 140–144 mg/kg/day and 2-methylnaphthalene in the diet at doses of 50–54 and 108–114 mg/kg/day. Histologic examination of major tissues and organs in these studies showed no other exposure-related nonneoplastic or neoplastic lesions at other sites (including the bronchiolar regions of the lung). Mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene (a mixture of 1- and 2-methylnaphthalene) for 30–61 weeks also showed increased incidence of pulmonary alveolar proteinosis. The chronic studies with mice exposed to 1- or 2-methylnaphthalene in the diet provide the basis for the chronic oral minimal risk levels (MRLs) for these substances (see Section 2.3).

Pulmonary alveolar proteinosis is characterized by an accumulation in the alveolar lumen of foamy cells, cholesterol crystals, and proteinaceous materials rich in lipids. The condition is rare in humans and has not been associated with human exposure to 2-methylnaphthalene or 1-methylnaphthalene. Human subjects with this condition can display pulmonary function deficits. The absence of pulmonary alveolar proteinosis in a 13-week range-finding study that exposed B6C3F1 mice to dietary doses as high as 2,500 mg/kg/day suggests that the development of this lesion requires chronic-duration exposure.

The mechanisms by which 1- or 2-methylnaphthalene may cause pulmonary alveolar proteinosis are poorly understood, but light and electron microscopic observations of lung tissues from mice repeatedly exposed to dermal doses of methylnaphthalene indicate that type II pneumocytes are a specific cellular target. It has been hypothesized that, in response to 1- or 2-methylnaphthalene, type II pneumocytes produce increased amounts of lamellar bodies due to hyperplasia and hypertrophy, and eventually transform into balloon cells. The rupture of balloon cells is hypothesized to lead to the accumulation of proteinaceous materials rich in lipids in the alveolar lumen. It is unknown whether the methylnaphthalenes themselves or their metabolites are responsible for the development of pulmonary alveolar proteinosis.

The chronic dietary studies with 1- or 2-methylnaphthalene provide limited evidence for the carcinogenicity of these chemicals. In the 1-methylnaphthalene study, respective incidences of mice with lung adenomas or carcinomas were 5/50, 2/50, and 5/50 for control through high-dose females, and 2/49,

13/50, and 15/50 for males. With 2-methylnaphthalene, incidences for lung adenomas or carcinomas were 5/50, 4/49, and 6/48 for females and 2/49, 10/49, and 6/49 for males. The tumorigenic response was predominantly benign and was only consistently seen in male mice exposed to 1-methylnaphthalene. The available data on the methylnaphthalenes appear inadequate to determine their carcinogenicity potential in humans, given the lack of any human studies on the potential carcinogenicity of the methylnaphthalenes and the limited evidence of carcinogenicity in animals.

The NTP *10th Report on Carcinogens* does not include 1-methylnaphthalene or 2-methylnaphthalene on its list of chemicals *known to be human carcinogens* or *reasonably anticipated to be human carcinogens*. IARC has not assessed the carcinogenicity potential of the methylnaphthalenes. The EPA IRIS office is in the process of preparing a Toxicological Review on 2-methylnaphthalene in which the carcinogenicity of 2-methylnaphthalene is assessed.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

- An MRL of 0.0007 ppm was derived for chronic inhalation exposure to naphthalene.

The MRL was derived from two chronic inhalation toxicity and carcinogenicity studies with mice (NTP 1992a) and rats (Abdo et al. 2001; NTP 2000). In one study, groups of 75 B6C3F1 mice of each sex were exposed by inhalation at concentrations of 0, 10, or 30 ppm, 6 hours/day, 5 days/week for 104 weeks. In the other study, groups of 49 male and 49 female F344/N rats were exposed to naphthalene at concentrations of 0, 10, 30, or 60 ppm, 6 hours/day, 5 days/week for 105 weeks. The lowest exposure level in both studies, 10 ppm, was a lowest-observed-adverse-effect level (LOAEL) in both sexes of both species for nonneoplastic lesions in nasal olfactory epithelium (metaplasia in mice, and hyperplasia, atrophy, and chronic inflammation in rats) and respiratory epithelium (hyperplasia in mice, and hyperplasia, metaplasia, hyaline degeneration, or gland hyperplasia in rats). At 10 ppm, nearly all of the animals showed nasal lesions. Exposed rats also showed increased incidences of nasal tumors (respiratory epithelial adenomas and olfactory epithelial neuroblastomas), but mice did not develop nose tumors. Exposed mice also showed an increased incidence of chronic lung inflammation at both exposure levels and an increased incidence of lung tumors in females exposed to 30 ppm. Lung lesions did not occur in exposed rats.

Following EPA (1994b) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry,* equations for a category 1 gas producing nasal effects were used to derive human equivalent concentrations of 0.2 ppm based on the rat data and 0.3 ppm based on the mouse data (see Appendix B). Using public health protection reasoning, the $LOAEL_{HEC}$ based on the rat data, 0.2 ppm, was selected as the point of departure for the chronic inhalation MRL, which was divided by a total uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustment, and 10 for human variability) to derive the MRL of 0.0007 ppm ($3x10^{-3}$ mg/m^3).

No appropriate data were located on effects of acute- and intermediate-duration inhalation exposure in humans or animals that could be used to derive acute and intermediate MRLs for inhalation exposure to naphthalene.

No appropriate data were located for deriving inhalation MRLs for 1-methylnaphthalene or 2-methyl-naphthalene.

Oral MRLs

- An MRL of 0.6 mg/kg/day was derived for acute oral exposure to naphthalene.

A rat developmental toxicity study involving exposure of Sprague-Dawley rats to gavage doses of 50, 150, or 450 mg/kg/day naphthalene on gestation days 6-15 was selected as the basis of the acute oral MRL (NTP 1991a). The only maternal or fetal effects observed at the lowest dose level were slow respiration, lethargy, or prone body posture in most dams following dose administration on the first and second day of dosing. These effects did not occur on subsequent days of dosing at this dose level. Because of this transient behavior and the lack of any other effect, 50 mg/kg/day was judged to be a minimal lowest-observed-adverse-effect level (LOAEL) for clinical signs of neurotoxicity. At 150 and 450 mg/kg/day, these clinical signs of neurotoxicity were more persistent and were accompanied with marked decreases in body weight gain during the exposure period (31 and 53%, respectively, compared with controls). No exposure-related fetal effects were found in any of the exposure groups compared with the controls in this study.

The MRL was calculated from the minimal LOAEL of 50 mg/kg/day using an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability) to derive the MRL of 0.6 mg/kg/day (see Appendix A). An uncertainty factor of 3 was used

for human variability because the critical effect is based on effects in a sensitive animal subpopulation. Pregnant rats appear to be more sensitive for the effects observed (clinical signs of neurotoxicity in response to gavage exposure and decreased body weight gain) than nonpregnant rats. In 13-week gavage studies with nonpregnant rats (NTP 1980b), similar persistent neurologic symptoms were not observed following administration of doses as high as 200 mg/kg/day, but were observed at 400 mg/kg/day. In nonpregnant rats exposed for 13 weeks, significant body weight decreases occurred at 200 mg/kg/day throughout exposure, but not at 100 mg/kg/day (NTP 1980b) or in nonpregnant mice exposed for 13 weeks to 133 mg/kg/day (Shopp et al. 1984) or 200 mg/kg/day (NTP 1980a). Mice in the NTP (1980a) study showed transient signs of toxicity (lethargy, rough hair coats, and decreased food consumption), but these only occurred between weeks 3 and 5 in the 200-mg/kg/day group.

- The acute-duration oral MRL of 0.6 mg/kg/day is adopted as the intermediate-duration oral MRL for naphthalene.

There are three intermediate-duration oral toxicity studies in laboratory animals that were considered for deriving the intermediate-duration oral MRL for naphthalene. A 13-week comprehensive oral toxicity study in Fischer 344 rats found no adverse exposure-related effects other than decreased body weight (NTP 1980b). This study identified 100 mg/kg/day as a no-observed-adverse-effect level (NOAEL) and 200 mg/kg/day as a LOAEL for decreased body weight in male and female rats. Another 13-week comprehensive oral toxicity study in B6C3F1 mice found no adverse effects in mice exposed to doses as high as 200 mg/kg/day (NTP 1980a). Another 90-day gavage study in CD-1 mice focused on immune system variables and other toxicity variables (e.g., body weight, organ weight, haematological parameters) and identified 133 mg/kg/day as a LOAEL and 53 mg/kg/day as a NOAEL for weight decreases in several organs (brain, liver, and spleen), but found no biologically significant exposure-related changes in other end points evaluated (Shopp et al. 1984). This study, however, did not include histopathological examination of tissues.

The findings from the three intermediate-duration oral toxicity studies do not collectively identify a clear, biologically significant target of toxicity other than body weight changes in rats (see Appendix A for comprehensive descriptions of the design and results of these studies). Consideration was given to basing the MRL on the NOAEL of 53 mg/kg/day and LOAEL of 133 mg/kg/day for decreases in absolute weight of brain, liver, and spleen, and in relative weight of spleen, in female mice (Shopp et al. 1984). However, the biological significance of these effects is uncertain because (1) the effects were only observed in females, and (2) histological effects in the affected organs were not observed in the other 13-week oral studies with rats and mice.

As discussed in Appendix A, a potential intermediate-duration MRL of 0.7 mg/kg/day was derived based on the duration-adjusted NOAEL of 71 mg/kg/day for decreased body weight in male and female rats exposed by gavage to naphthalene 5 days/week for 13 weeks (NTP 1980b) and a total uncertainty factor of 100 (10 for extrapolating from rats to humans and 10 for human variability). Because the value of 0.7 mg/kg/day is slightly larger than the acute-duration oral MRL of 0.6 mg/kg/day, the acute MRL is expected to be protective for intermediate-duration exposure scenarios and was adopted as the intermediate-duration oral MRL.

No appropriate studies were located for deriving an MRL for chronic oral exposure to naphthalene. One chronic study was located that examined the toxicity of naphthalene in rats (Schmahl 1955). No treatment-related effects were reported at a dose level of 41 mg/kg/day for 700 days. The study was not suitable as the basis for deriving a chronic MRL because only one dose level was evaluated, histopathological examination was limited, and dosing was not precisely controlled.

- An MRL of 0.07 mg/kg/day was derived for chronic oral exposure to 1-methylnaphthalene.

The MRL for 1-methylnaphthalene was derived from an 81-week study in groups of 50 male and 50 female mice using diets containing 0, 71.6 (males), 75.1 (females), 140.2 (males), or 143.7 (females) mg/kg/day (Murata et al. 1993). Food intake, clinical signs, and body weight were determined throughout the study. At the end of 81 weeks, peripheral blood samples were collected and the animals were sacrificed. Organ weights were determined and the tissues examined histologically; tumors were identified and characterized. Hematological parameters and biochemical indices were evaluated in the blood samples.

Male and female mice in both exposure groups showed increased incidences of pulmonary alveolar proteinosis. In males, there was also a significant increase in pulmonary adenomas. The alveolar nodules were filled with an amorphous acidophilic material, cholesterol crystals, and foamy cells. They were not accompanied by inflammation, edema, or fibrosis. The LOAEL of 71.6 mg/kg/day for 1-methyl-naphthalene in female mice was used for the derivation of the MRL, employing an uncertainty factor of 1,000 (10 for using a LOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

- An MRL of 0.05 mg/kg/day was derived for chronic oral exposure to 2-methylnaphthalene.

The chronic MRL is based on a study in which groups of 50 male and 50 female B6C3F1 mice were exposed to dietary levels of 0, 0.075, or 0.15% 2-methylnaphthalene (Murata et al. 1997). Average intakes were reported as 0, 54.3, or 113.8 mg/kg/day for males and 0, 50.3, or 107.6 mg/kg/day for females. Survival and food consumption were not affected by exposure. Mean final body weights were decreased by 7.5 and 4.5% in high-dose males and females, respectively; these changes are not considered to be biologically significant. Histopathology only found exposure-related changes in the lung. Tissues examined were brain, heart, kidney, liver, lung, pancreas, salivary glands, spleen, testis, adrenals, bone, eye, Harderian glands, mammary gland, ovary, seminal vesicle, skeletal muscle, skin, small and large intestine, spinal cord, stomach, trachea, uterus, and vagina. No evidence of bronchiolar Clara cell necrosis or sloughing was found. Females showed statistically significantly decreased differential counts of stab and segmented form neutrophils and increased lymphocytes compared to controls, but the biological significance of these changes is not clear due to a lack of reporting of the data (i.e., the report did not specify the response magnitudes or the dose levels at which they occurred). Incidences for mice with pulmonary alveolar proteinosis were (control through high-dose groups): 5/50, 27/49, and 22/49 for females, and 4/49, 21/49, and 23/49 for males. Incidences for mice with lung adenomas were: 4/50, 4/49, and 5/48 in females, and 2/49, 9/49, and 5/49 in males. Only the lung adenoma incidence in the male 54.3-mg/kg/day groups was significantly different from the control incidence. Combined incidences for lung adenomas or adenocarcinomas were: 5/50, 4/49, and 6/48 for females, and 2/49, 10/49, and 6/49 for males.

Support for pulmonary alveolar proteinosis as the critical effect for the chronic oral MRL for 2-methylnaphthalene comes from chronic duration studies with the isomer, 1-methylnaphthalene, and methylnaphthalene (a mixture of 1- and 2-methylnaphthalene). Increased incidence of pulmonary alveolar proteinosis was reported in B6C3F1 mice exposed to 1-methylnaphthalene in the diet for 81 weeks at dose levels as low as 71.6 mg/kg/day (Murata et al. 1993), and in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (a mixture of 1- and 2-methylnaphthalene) (Emi and Konishi 1985; Murata et al. 1992).

The LOAEL of 50.3 mg/kg/day for pulmonary alveolar proteinosis in mice (Murata et al. 1997) was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) to derive the chronic oral MRL of 0.05 mg/kg/day for 2-methylnaphthalene.

2. RELEVANCE TO PUBLIC HEALTH

No appropriate studies were located for deriving acute or intermediate-duration oral MRLs for 1-methylnaphthalene or 2-methylnaphthalene.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of naphthalene are indicated in Tables 3-1 and 3-2, and Figures 3-1 and 3-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Two Greek infants died as a consequence of acute hemolysis that resulted from exposure to naphthalene-treated materials (clothing, diapers, blankets, rugs, etc.). Both infants exhibited a severe form of jaundice (kernicterus), which often causes brain damage (Valaes et al. 1963). Exposure levels experienced by these children are unknown. One infant suffered from a glucose-6-phosphate dehydrogenase (G6PD) deficiency. The other infant was apparently heterozygous for this trait. Individuals with a G6PD genetic defect are prone to hemolysis after exposure to a variety of chemical oxidizing agents including nitrates, nitrites, aniline, phenols (Dean et al. 1992), and naphthalene.

No studies were located that documented lethal effects in humans after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Exposure to 78 ppm naphthalene for 4 hours did not cause any deaths in rats. In addition, no definitive adverse clinical signs were observed during the 14 days after exposure, and no gross pathologic lesions were observed at necropsy (Fait and Nachreiner 1985). A high background mortality in the male control group precluded drawing conclusions regarding the effects of lifetime exposures to 10 and 30 ppm naphthalene (6 hours/day, 5 days/week) on lifetime mortality; no apparent effects on mortality occurred in the females (NTP 1992a). Similarly, exposure of male and female rats to 10, 30, or 60 ppm naphthalene (6 hours/day, 5 days/week) for 2 years did not affect survival, compared to controls (Abdo et al. 2001; NTP 2000).

No studies were located that documented lethal effects in animals after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

3.2.1.2 Systemic Effects

No studies were located that documented dermal effects in humans or animals after inhalation exposure to naphthalene. Most of the human data come from occupational and domestic settings where mothballs were the source of the naphthalene vapors. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. No studies were located that documented systemic effects in humans after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene. In animals, one study evaluated hematological end points in dogs following acute inhalation exposure to undetermined air concentrations of 1-methylnaphthalene or 2-methylnaphthalene (Lorber 1972). This study, however, did not identify reliable NOAEL or LOAEL values, and the results are not included in Table 3-1 or Figure 3-1.

Respiratory Effects. No studies were located that documented respiratory effects in humans after inhalation exposure to naphthalene.

The nose is the most sensitive toxicity target in rats and mice following chronic inhalation exposure to naphthalene. Chronic inhalation exposure resulted in increased incidences of nonneoplastic and neoplastic lesions in the nose of rats (Abdo et al. 2001; NTP 2000), nonneoplastic lesions in the nose of mice (NTP 1992a), and neoplastic and nonneoplastic lesions in the lungs of mice (NTP 1992a). No exposure-related lesions were found in other tissues or organs in these studies, which included comprehensive histopathological examinations of major tissues and organs. Nearly all mice of both sexes (>95%) exposed to naphthalene vapors for 2 years (10 or 30 ppm) showed chronic inflammation and metaplasia of the olfactory epithelium and hyperplasia of the nasal respiratory epithelium (NTP 1992a). Chronic lung inflammation was also observed in exposed mice, but at lower incidences than incidences for nasal lesions. Incidences for chronic lung inflammation were 0/70, 21/69, and 56/135 for male mice and 3/69, 13/65, and 52/135 for female mice exposed to 0, 10, or 30 ppm. In addition, exposure to 30 ppm (but not 10 ppm) increased the incidence of benign lung tumors (alveolar/bronchiolar adenomas) in female mice, compared with controls. One other female mouse exposed to 30 ppm showed a malignant lung tumor (alveolar/bronchiolar carcinoma). In rats of both sexes, inhalation of 10, 30, or 60 ppm naphthalene induced nonneoplastic and neoplastic lesions only in the nasal cavity (Abdo et al. 2001; NTP 2000). Nearly all rats in each exposure group (>95%) showed nonneoplastic nasal lesions. Nonneoplastic nasal lesions in exposed rats included (1) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium and (2) hyperplasia, metaplasia, or degeneration of the

Table 3-1 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
	ACUTE EXPOSURE								
	Systemic								
1	Rat (Sprague-Dawley)	4 h	Resp	100					West et al. 2001
2	Mouse B6C3F1	14 d 5 d/wk 6 hr/d	Hemato	30					NTP 1992a
3	Mouse (Swiss-Webster)	4 h	Resp	2	10	(Clara cell necrosis and decreased Clara cell mass [volume/surface area] in proximal airways)	75	(Proximal and terminal epithelium devoid of Clara cells)	West et al. 2001
	Neurological								
4	Rat (Wistar)	4 h		26	44	(increased latency of paw lick response to being placed on a hot surface [decreased pain sensitivity]; no change in rotarod performance)			Korsak et al. 1998 1-MN
5	Rat (Wistar)	4 h		39	61	(increased latency of paw lick response to being placed on a hot surface [decreased pain sensitivity]; no change in rotarod performance)			Korsak et al. 1998 2-MN

Table 3-1 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
6	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d vapor	Resp		10[b] (inflammation of the nose; olfactory epithelium: atypical hyperplasia, atrophy, degeneration; nasal respiratory epithelium: hyperplasia, squamous metaplasia, degeneration; Bowman's glands: hyperplasia)		NTP 2000 (Abdo et al. 2001)
			Cardio	10			
			Gastro	10			
			Musc/skel	10			
			Hepatic	10			
			Renal	10			
			Endocr	10			
			Ocular	10			
			Bd Wt	10			

Table 3-1 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
7	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d	Resp		10 (inflammation of the nose and lung, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium)		NTP 1992a
			Cardio	30			
			Gastro	30			
			Hepatic	30			
			Renal	30			
			Dermal	30			
	Neurological						
8	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d vapor		60			NTP 2000 (Abdo et al. 2001)
9	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d		30			NTP 1992a
	Reproductive						
10	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d vapor		60			NTP 2000 (Abdo et al. 2001)

Table 3-1 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
11	Mouse B6C3F1	104 wk 5d/wk 6 hr/d		30				NTP 1992a
	Cancer							
12	Rat (Fischer- 344)	105 wk 5d/wk 6hr/d vapor				10	(CEL: nasal respiratory epithelial adenomas in males & in females at higher concentrations; olfactory epithelial neuroblastomas in both sexes at higher concentrations)	NTP 2000 (Abdo et al. 2001)
13	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d				30	(CEL: pulmonary alveolar adenomas in females)	NTP 1992a

a The number corresponds to the entries in Figure 3-1.

b Used to derive a chronic-duration Minimal Risk Level (MRL) of 0.0007 ppm; based on a human equivalent concentration LOAEL of 0.2 ppm which was divided by an uncertainty factor of 300 (10 for the use of LOAEL, 3 for extrapolating from rodents to humans with interspecies dosimetric adjustment, and 10 for human variability).

Cardio = cardiovascular; d = day(s); Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-MN Or 2-MN)- Inhalation

Acute (≤14 days)

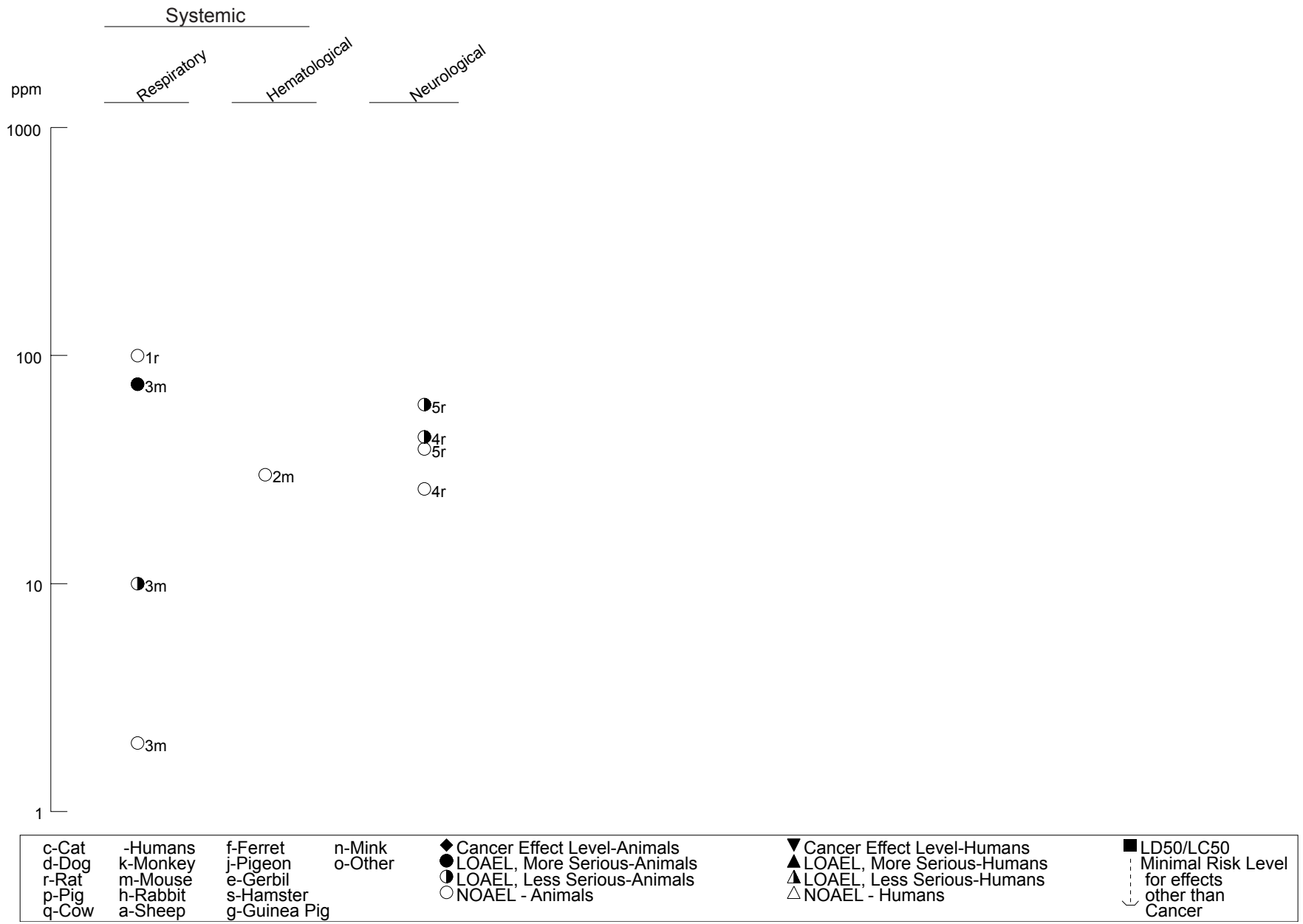
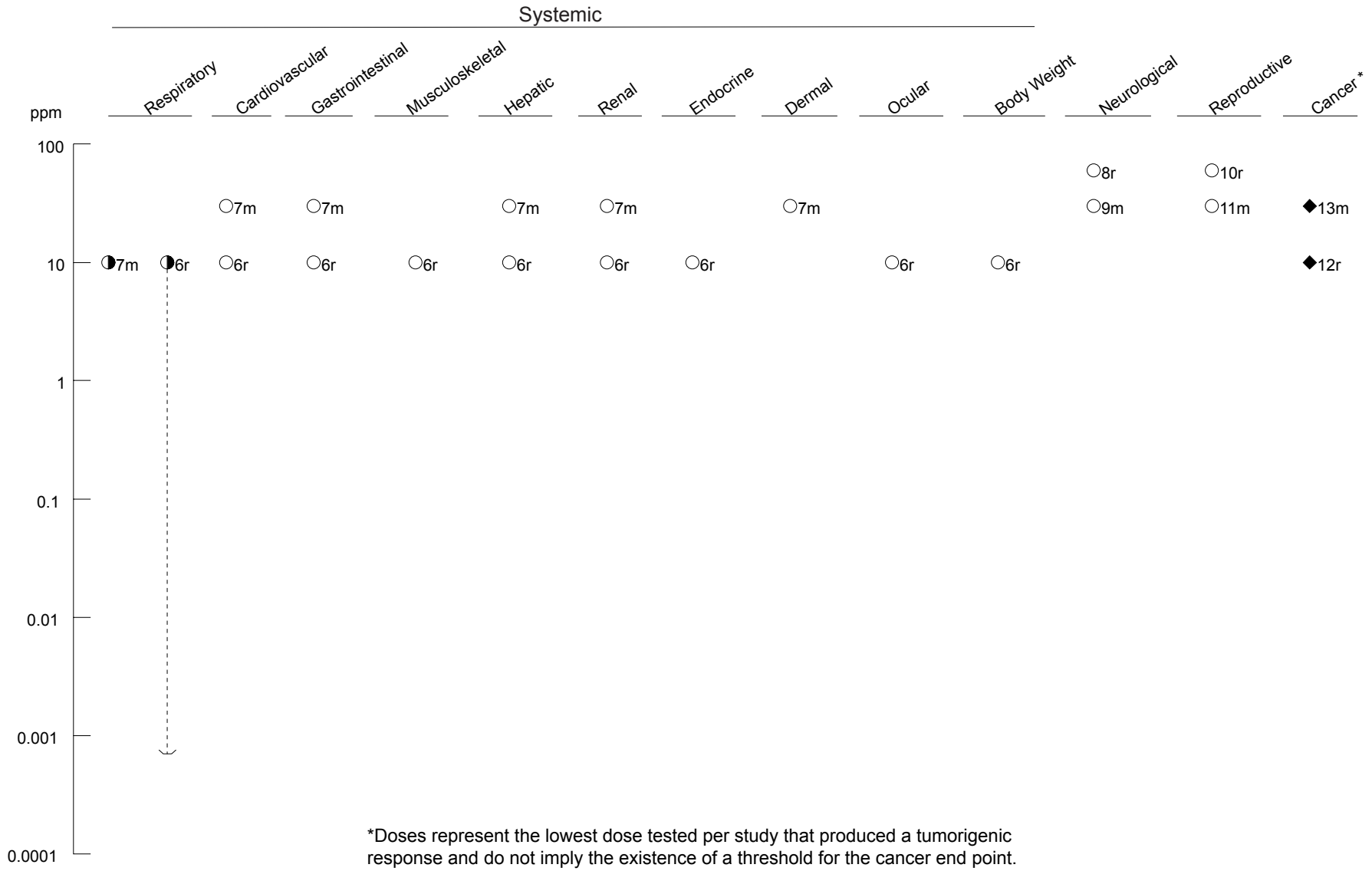


Figure 3-1. Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-MN Or 2-MN) - Inhalation (*Continued*)

Chronic (≥365 days)



respiratory epithelium or glands. Neoplastic lesions associated with naphthalene exposure in rats were olfactory epithelial neuroblastoma (a rare malignant tumor) and respiratory epithelial adenoma.

The chronic inhalation MRL for naphthalene, 0.0007 ppm, is based on the LOAEL of 10 ppm for nonneoplastic lesions in the olfactory epithelium and respiratory epithelium of the nose of rats (NTP 2000; see Table 3-1; Figure 3-1; Appendix A; and Section 2.3). To derive the chronic MRL, the rat LOAEL was converted to a human equivalent concentration of 0.2 ppm for continuous exposure using EPA (1994b) equations for a category 1 gas producing nasal effects and divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustment, and 10 for human variability). Naphthalene-induced damage to the nasal tissue is thought to be due to reactive metabolites formed in the nasal tissues (Buckpitt et al. 2002). Sections 3.4.3 and 3.5 discuss current mechanistic hypotheses in more detail.

Acute (4-hour) inhalation exposure to naphthalene induced necrosis of Clara cells in the epithelium of the proximal airways of the lungs of mice at exposure levels as low as 10 ppm, but did not affect lung tissue in rats at concentrations as high as 100 ppm (West et al. 2001). These results, and those from the chronic inhalation studies, show that mice are more susceptible than rats to lung damage from inhaled naphthalene. However, there are no studies that have examined nasal tissues for the development of lesions following acute inhalation exposure. No acute inhalation MRL was derived for naphthalene, due to the lack of such data and the results of the chronic studies indicating that nasal tissues are the critical toxicity targets of inhaled naphthalene in both rats and mice.

A change to mouth breathing occurred in rats during exposure to 78 ppm naphthalene, but no other effects on respiration were noted (Fait and Nachreiner 1985).

Cardiovascular Effects. No studies were located that documented cardiovascular effects in humans after inhalation exposure to naphthalene.

No histological changes were seen in the hearts of mice (30 ppm) or rats (60 ppm) that were exposed to naphthalene for 2 years (Abdo et al. 2001; NTP 1992a, 2000).

Gastrointestinal Effects. Nausea, vomiting, and abdominal pain were reported in eight adults and one child exposed to naphthalene vapors from large numbers of mothballs (300–500) scattered throughout their homes for odor and pest control (Linick 1983). Air samples collected in one home contained

naphthalene at 20 ppb; concentrations could have been higher when the mothballs were fresh. Gastrointestinal symptoms disappeared after the mothballs were removed. Few location-specific background data to support this air concentration were reported.

There were no histopathological changes in the stomach or intestines of mice (30 ppm) or rats (60 ppm) exposed to naphthalene for 2 years (Abdo et al. 2001; NTP 1992a, 2000).

Hematological Effects. Hemolytic anemia is the most frequently reported manifestation of naphthalene exposure in humans. Acute hemolytic anemia was observed in 21 infants exposed to naphthalene via mothball-treated blankets, woolen clothes, or materials in the infants' rooms (Valaes et al. 1963). Ten of these children had a G6PD genetic defect that increased their sensitivity to hemolysis from a variety of chemicals, including naphthalene. Clinical observations included high serum bilirubin values, methemoglobin, Heinz bodies, and fragmented red blood cells. Inhalation appeared to be the primary route of exposure because in all children but two, the naphthalene-treated material was not worn next to the skin. One of the exceptions was an infant who wore diapers that had been stored in naphthalene.

Anemia was reported in nine individuals exposed to large numbers of mothballs distributed throughout their homes (Linick 1983). The nature of the anemia and specific levels of naphthalene exposure were not identified. In one home, the naphthalene concentration was determined to be 20 ppb at the time of testing, but could have been higher when the mothballs were first distributed.

In another study, a woman who was exposed to reportedly high (but unmeasured) concentrations of a combination of naphthalene and paradichlorobenzene for several weeks in a hot, poorly ventilated work area developed aplastic anemia (Harden and Baetjer 1978). It is difficult to determine the contribution of naphthalene to the aplastic anemia since there was simultaneous exposure to paradichlorobenzene.

In animals, no treatment-related effects on hematologic parameters (hematocrit, hemoglobin concentration, erythrocyte counts, mean cell volume, reticulocytes, and leucocytes) were observed among mice exposed to 10 and 30 ppm naphthalene for 14 days (NTP 1992a). Due to high mortality in the control males, hematology measurements were not continued beyond 14 days.

The effects of 1-methylnaphthalene (pure and practical grade) and 2-methylnaphthalene (pure and practical grade) on the hematocrit values, total and differential white blood cell counts, and reticulocyte counts were determined in intact and splenectomized dogs. Each compound was dispersed in the

atmosphere in a refined kerosene base using a fogger. Exposures occurred on four consecutive mornings (Lorber 1972). Based on the information presented, it was not possible to determine the exposure concentration.

Pure 1-methylnaphthalene increased the reticulocyte counts in the splenectomized dogs but not the intact dogs. Reticulocyte values remained elevated for 10 days after the fogging ceased. Practical grade 1-methylnaphthalene increased leukocyte counts in intact and splenectomized dogs and neutrophil counts in intact dogs, but pure 1-methylnaphthalene had no effect on these parameters. 2-Methylnaphthalene had no effect on any of the parameters monitored (Lorber 1972).

Neither 1-methylnaphthalene nor 2-methylnaphthalene had an effect on hematocrit values, suggesting that these compounds do not cause hemolysis under the conditions of the study. Since the increased reticulocyte counts were seen only in splenectomized dogs, it is difficult to interpret whether or not this change signifies increased hematopoiesis in response to 1-methylnaphthalene exposure (Lorber 1972).

Musculoskeletal Effects. No studies were located that documented musculoskeletal effects in humans after inhalation exposure to naphthalene.

Histological examination of the femur did not reveal compound-related effects in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively.

Hepatic Effects. Jaundice has been reported in infants and adults after exposure to naphthalene (Linick 1983; Valaes et al. 1963). However, the jaundice is a consequence of hemolysis rather than a direct effect of naphthalene on the liver. Infant exposures lasted 1–7 days (Valaes et al. 1963); adult exposure durations were not provided (Linick 1983). Dose was not determined in either instance, although a concentration of 20 ppb was measured in the home of one affected individual (Linick 1983).

In animals, no treatment-related gross or histopathological lesions of the liver were reported in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively.

Renal Effects. Renal disease was reported in nine individuals (details not specified) exposed to large numbers of mothballs in their homes, but symptoms were not described and dose could not be determined (Linick 1983).

In animals, no treatment-related gross or histopathological lesions of the kidneys were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively.

Ocular Effects. Twenty-one workers exposed to naphthalene for up to 5 years in a plant that manufactured dye intermediates were examined for eye problems (Ghetti and Mariani 1956). During the period of exposure, plant conditions were primitive, involving heating of naphthalene in open vats and considerable worker contact with the naphthalene. Eight of the 21 workers developed multiple pin-point lens opacities that had no correlation with the age of the workers. These effects were not overtly noticeable and apparently had no effect on vision. They were judged to be a consequence of naphthalene exposure on the basis of their location in the crystalline lens and the fact that occurrence did not correlate with age. Exposure involved long-term inhalation of vapors and direct contact of vapors with the eyes and skin.

Retinal bleeding and the beginnings of a cataract were identified in a worker from a naphthalene storage area who was most likely exposed to naphthalene through inhalation and dermal/ocular contact (van der Hoeve 1906). The duration of exposure prior to seeking medical attention for eye irritation and problems with vision was not identified.

In animals, no treatment-related gross or histopathological lesions of the eyes were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively. However, during a 4-hour exposure of rats to a concentration of 78 ppm, irritation to the eyes was evidenced through lacrimation (Fait and Nachreiner 1985).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located that examined immunological or lymphoreticular end points in humans or animals after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

3.2.1.4 Neurological Effects

Infants are prone to permanent neurological damage (kernicterus) as a consequence of the jaundice that results from naphthalene-induced hemolysis. Bilirubin is absorbed by vulnerable brain cells and this leads to convulsions and sometimes death. Survivors often suffer from motor disturbances and mental retardation (McMurray 1977). Kernicterus was diagnosed in 8 of 21 Greek infants that experienced hemolysis as a result of naphthalene exposure (Valaes et al. 1963). Two of the eight died. One of the infants that died had no G6PD enzyme activity and the other had intermediate activity. Two of the infants were normal with regard to the G6PD trait. Of the remaining infants, three had no G6PD activity and the fourth had intermediate activity. Brain damage seldom occurs in adults as a consequence of jaundice (McMurray 1977).

Nausea, headache, malaise, and confusion were reported in several individuals (children and adults) exposed to large numbers of mothballs in their homes (Linick 1983). Actual levels and duration of exposure were unknown, although a concentration of 20 ppb was measured in one of the affected residences.

In animals, no treatment-related gross or histopathological lesions of the brain were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively. Clinical observations (made twice daily in these studies) revealed no gross behavioral changes except that exposed mice tended to huddle together in cage corners during exposure periods.

No studies were located that documented neurological effects in humans after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

In male Wistar rats, decreased sensitivity to pain occurred after 4-hour inhalation exposures to 253 or 407 mg/m^3 1-methylnaphthalene (44 or 70 ppm), or 352 or 525 mg/m^3 2-methylnaphthalene (61 or 90 ppm), but not after exposure to 152 mg/m^3 (26 ppm) 1-methylnaphthalene or 229 mg/m^3 (39 ppm) 2-methylnaphthalene (Korsak et al. 1998). Decreased sensitivity to pain was measured as a decreased time to begin licking of the paws after being placed on a hot plate at 54.5 °C. The ability of exposed rats to balance on a rotating rod (rotarod performance), however, was not affected by any of these exposure conditions (Korsak et al. 1998). NOAEL and LOAEL values for decreased pain sensitivity from this study are included in Table 3-1 and Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located that documented reproductive effects in humans after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

In animals, histological examination did not reveal damage to male or female reproductive organs in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to 30 or 60 ppm, respectively.

No studies were located that documented reproductive effects in animals after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

3.2.1.6 Developmental Effects

No studies were located that examined developmental end points in humans or animals after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

3.2.1.7 Cancer

No studies were located that documented carcinogenic effects in humans after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

In animals, inhalation exposure to naphthalene (6 hours/day) has been associated with: (1) increased incidences of F344/N rats of both sexes with nasal tumors following 2 years of exposure (Abdo et al. 2001; NTP 2000); (2) increased incidences of female B6C3F1 mice, but not male mice, with lung tumors following 2 years of exposure (NTP 1992a); and (3) increased number of tumors per tumor-bearing A/J strain mice following 6 months of exposure (Adkins et al. 1986).

In F344/N rats, incidences of nasal respiratory epithelial adenomas were statistically significantly elevated, compared with controls, in males exposed to 0, 10, 30, or 60 ppm naphthalene (0/49, 6/49, 8/48, or 15/48), but not in females (0/49, 0/49, 4/49, 2/49) (Abdo et al. 2001; NTP 2000). Incidences for olfactory epithelial neuroblastoma were 0/49, 0/49, 4/48, and 3/48 in male rats, and 0/49, 2/49, 4/48, and 12/49 in female rats. Both tumor types are rare in NTP control F344/N rats (NTP 2000). For example,

neither tumor type was observed in 299 control male rats given NTP-2000 feed or 1,048 control male rats given NIH-07 feed. NTP (2000) concluded that there was clear evidence of carcinogenic activity of naphthalene in male and female F344/N rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose. Nearly all rats in all exposure groups showed nonneoplastic nasal lesions in both olfactory and respiratory epithelia, including atypical hyperplasia in olfactory epithelium, hyaline degeneration in olfactory and respiratory epithelia, and Bowman's gland hyperplasia.

In B6C3F1 mice, statistically significant increased incidence of alveolar/bronchiolar adenomas and carcinoma was found in 30-ppm females, but not in 10-ppm females or in males (females: 5/69, 2/65, 29/135; males: 7/70, 17/69, and 31/135) (NTP 1992a). Although Fisher Exact tests indicated that incidences in both exposed male groups and the high-dose female group were significantly increased compared with control groups, logistic regression analysis, which modeled tumor incidence as a function of dose and exposure time, indicated that only the incidence in the 30-ppm female group was elevated compared with controls. The response was predominantly benign; only one female mouse in the 30-ppm group developed a carcinoma. Exposed mice of both sexes also showed increased incidences of chronic lung inflammation (males: 0/70, 21/69, 56/135; females: 3/69, 13/65, 52/135). Nonneoplastic nasal lesions were found in nearly all exposed mice, but no nasal tumors developed. On the basis of this analysis, NTP (1992a) determined that there was some evidence of naphthalene carcinogenicity in female mice, but no evidence of carcinogenicity in male mice in this study.

In a 6-month study, there was a statistically significant increase in the number of tumors per tumor-bearing mouse, but not in the number of mice with pulmonary adenomas after exposure to 10 or 30 ppm naphthalene vapors (Adkins et al. 1986). However, the incidence of adenomas in the control group for this experiment was significantly lower than the pooled incidence observed in the control groups of eight concurrently conducted 6-month studies, and the difference in tumor incidence was not significantly greater than that of the historic controls.

No studies were located that documented carcinogenic effects in animals after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

3.2.2 Oral Exposure

3.2.2.1 Death

Death has been documented in humans who intentionally ingested naphthalene. A 17-year-old male died 5 days after the ingestion of an unknown quantity of naphthalene mothballs. Death was preceded by vomiting, evidence of gastrointestinal bleeding, blood-tinged urine, and coma (Gupta et al. 1979). A 30-year-old female died following similar sequelae 5 days after reportedly swallowing 40 mothballs (25 were recovered intact from the stomach upon autopsy) (Kurz 1987). No studies were located that documented lethal effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Several animal studies have been conducted to estimate lethal doses of naphthalene. Mice appear to be more sensitive than rats or rabbits. The LD_{50} values in male and female mice were 533 and 710 mg/kg, respectively (Shopp et al. 1984). An LD_{50} of 354 mg/kg was estimated in female mice treated with naphthalene once daily by gavage for 8 consecutive days (Plasterer et al. 1985). The dose response curve appeared to be very steep because no deaths occurred at 250 mg/kg/day, but all animals died with a dose of 500 mg/kg/day. At the 300 mg/kg/day dose, mortality was approximately 15%. In a different study with a 14-day dosing period, 10% of the males and 5% of the females died at a dose of 267 mg/kg/day, but none were affected by doses of 27 and 53 mg/kg/day (Shopp et al. 1984).

The oral LD_{50} values in male and female rats were 2,200 and 2,400 mg/kg, respectively, in one study (Gaines 1969), and 2,600 in a second study that did not differentiate by sex (Papciak and Mallory 1990). Male rats tolerated daily doses of 1,000 mg/kg without lethality, even after 18 days of administration (Yamauchi et al. 1986). In an increasing dose study, Germansky and Jamall (1988) treated male rats with naphthalene at doses beginning at 100 mg/kg/day and raised the dose weekly to a final level of 750 mg/kg/day over 6 weeks. Doses were then kept constant for an additional 3 weeks. The animals tolerated 750 mg/kg/day with no mortalities. No increase in mortality was observed in rats administered naphthalene at 41 mg/kg/day in a 2-year feeding study (Schmahl 1955).

Although few data are available, rabbits appear to tolerate naphthalene in doses similar to those administered to rats. Two different rabbit strains were administered 1,000 mg/kg twice per week for 12 weeks without lethality (Rossa and Pau 1988).

Male and female mice survived oral exposure to concentrations of 71.6–143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). No studies were located that documented lethal effects in animals after ingestion of 1-methylnaphthalene.

All LOAEL values for lethality in each species after acute exposure to naphthalene are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located that documented musculoskeletal or dermal effects in humans or animals after oral exposure to naphthalene; data were available for all other systems. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

No studies were located that documented systemic effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene. In animals, data are restricted to two studies with B6C3F1 mice exposed to 1-methylnaphthalene (Murata et al. 1993) or 2-methylnaphthalene (Murata et al. 1997) in the diet for 81 weeks. The highest chronic NOAEL values and the lowest LOAEL value for systemic effects in mice are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. No reports have been located to indicate that there are direct effects of oral exposure to naphthalene on the respiratory system in humans. In situations where respiratory effects such as hypoxia or pulmonary edema were noted, the respiratory effects appear to be secondary to hemolysis and the events leading to general multiple organ failure (Gupta et al. 1979; Kurz 1987). On hospital admission, one male infant was described as experiencing labored breathing after presumably chewing a naphthalene-containing diaper pail deodorant block (Haggerty 1956). This may have been a reflection of the reduced oxygen carrying capacity of the blood due to hemolysis.

Lesions of the lungs were seen in rats that died after being given a single large dose of naphthalene (1,000–4,000 mg/kg) during an LD_{50} study (Papciak and Mallory 1990). On the other hand, no significant respiratory toxicity was seen in rats following oral administration of naphthalene at time-weighted average doses of 169 mg/kg/day for 9 weeks (Germansky and Jamall 1988). Dosages were increased from 100 to 750 mg/kg/day over a 6-week period and held constant at 750 mg/kg/day for the last 3 weeks of the 9-week exposure period.

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat Sherman	once (GO)				2200 (LD50 - male) 2400 (LD50 - female)	Gaines 1969
2	Rat Sprague-Dawley	once (GO)				2600 LD50	Papciak and Mallory 1990
3	Mouse CD-1	8 d 1x/d (GO)				300 (5/33 died)	Plasterer et al. 1985
4	Mouse CD-1	once (GO)				710 (LD50) 533 (LD50)	Shopp et al. 1984
5	Mouse CD-1	14 d 1x/d (GO)				267 (10/96 male, 3/60 female)	Shopp et al. 1984
	Systemic						
6	Human	once	Gastro		109 (adbominal pain)		Gidron and Leurer 1956
			Hemato			109 (hemolytic anemia)	
			Other			109 (106 degree F fever)	
7	Rat Sprague-Dawley	9 d Gd 6-15 (GO)	Bd Wt	50		150 (31% decrease in maternal body weight gain)	NTP 1991a

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
8	Rat Sprague-Dawley	once (GO)	Resp		1000 lung lesions		Papciak and Mallory 1990
9	Rat Sprague-Dawley	once (GO)	Gastro		1000 stomach lesions		Papciak and Mallory 1990
10	Rat NS	10 d 1x/d (G)	Hepatic		1000 (39% increase in liver weight; increased lipid peroxidation, aniline hydroxylase activity)		Rao and Pandya 1981
			Renal	1000			
			Ocular	1000			
11	Mouse CD-1	14 d 1x/d (GO)	Resp	267 M 53 F	267 F (increase in lung weight)		Shopp et al. 1984
			Hemato	267			
			Hepatic	267			
			Renal	267			
			Bd Wt	53	267 (6% (female) or 13% (male) decreased final body weight)		
12	Dog NS	once (F)	Hemato			1525 (hemolysis)	Zuelzer and Apt 1949

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
13	Rabbit NS	5 d (F)	Hepatic	2000					Srivastava and Nath 1969
			Ocular				2000	(cataracts)	
14	Rabbit NS	10 d 1x/d (GO)	Ocular				1000	(lens opacities, decreased ascorbic acid in aqueous humor)	van Heyningen and Pirie 1967
	Immuno/ Lymphoret								
15	Mouse CD-1	14 d 1x/d (GO)		53	267	(30% decrease in thymus weight in males; 18% decrease in spleen weight in females)			Shopp et al. 1984
	Neurological								
16	Rat Sprague-Dawley	9d Gd 6-15 (GO)			50[b]	(transient clinical signs of neurotoxicity in dams; at higher exposure levels, signs were more persistent and accompanied by decreases in body weight gain)			NTP 1991a
17	Mouse CD-1	14 d (GO)		267					Shopp et al. 1984
	Reproductive								
18	Rat Sprague-Dawley	9 d Gd 6-19 (GO)		450					NTP 1991a
19	Mouse CD-1	8d Gd 7-14 (GO)					300	(>10% maternal mortality)	Plasterer et al. 1985

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Rabbit New Zealand white	14 d Gd 6-19 (GO)		120			NTP 1992b
	Developmental						
21	Rat Sprague-Dawley	9 d Gd 6-15 (GO)		50			NTP 1991a
						150 (decreased maternal weight gain >20%; no fetotoxic or teratogenic effects at 150 or 450 mg/kg/day)	
22	Mouse CD-1	8d Gd 7-14 (GO)		300			Plasterer et al. 1985
23	Rabbit New Zealand white	14 d Gd 6-19 (GO)		120			NTP 1992b
24	Rabbit New Zealand white	13 d 1x/d Gd 6-18 (G)		40	200 (maternal dyspnea, cyanosis, body drop, hypoactivity with no pathological aberrations)		PRI 1985, 1986
	INTERMEDIATE EXPOSURE						
	Systemic						
25	Rat blue spruce	9 wk 3.5d/wk (GO)	Resp	169			Germansky and Jamall 1988
			Hepatic		169 (elevated lipid peroxides)		
			Bd Wt			169 (20% decreased body weight gain)	

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Rat Brown-Norway	4 wk 3.5d/wk (GO)	Ocular			500 (lens opacity)	Kojima 1992
27	Rat Sprague-Dawley Brown-Norway	6 wk	Ocular			500 (cataract formation)	Murano et al. 1993
28	Rat Fischer 344	13 wk 5x/wk (GO)	Resp	400			NTP 1980b
			Cardio	400			
			Gastro		400 (intermittent diarrhea)		
			Hemato	400			
			Hepatic	400			
			Renal	200 M 400 F	400 M (10% had cortical tubular degeneration)		
			Ocular	400			
			Bd Wt	100	200 (decreased terminal body weight: 12% male & 6% female)	400	
29	Rat black-hooded	79 d (GO)	Ocular			5000 (lens opacity)	Rathbun et al. 1990

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
30	Rat Brown-Norway	102 d NS (GO)	Ocular			700 (lens opacity)	Tao et al. 1991
31	Rat 5 strains	4-6 wk (GO)	Ocular			1000 (lens opacity)	Xu et al. 1992b
32	Rat Wistar	18 d 1x/d (G)	Hepatic		1000 (elevated lipid peroxides)		Yamauchi et al. 1986
			Ocular			1000 (cataracts)	
33	Mouse B6C3F1	13 wk 5x/wk 1x/d (GO)	Resp	200			NTP 1980a
			Cardio	200			
			Gastro	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Ocular	200			
			Bd Wt	200			

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
34	Mouse CD-1	90 d 7d/wk 1x/d (GO)	Resp	133					Shopp et al. 1984
			Hemato	133					
			Hepatic	133					
			Renal	133					
			Bd Wt	133					
			Other	53	133	(decreases in absolute weights of brain (9%), liver (18%), and spleen (28%) and relative weight of spleen (24%) in females only)			
35	Rabbit NS	5 wk	Ocular				500	(destruction of retinal photoreceptors and vascularization of the retinal area)	Orzalesi et al. 1994
36	Rabbit Chinchilla Bastard New Zealand white	12 wk 2d/wk 1x/d (GO)	Ocular				1000	(cataracts)	Rossa and Pau 1988
37	Rabbit NS	4 wk 1x/d (GO)	Ocular		1000	(increased ascorbic acid in lens)			van Heyningen 1970

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rabbit NS	4 wk 1x/d (GO)	Ocular			1000 (lens opacities, retinal damage)	van Heyningen and Pirie 1967
	Immuno/ Lymphoret						
39	Rat Fischer 344	13 wk 5d/wk 1x/d (GO)		200	400 (lymphoid depletion of thymus in 2/10 females)		NTP 1980b
40	Mouse CD-1	90 d (GO)		133			Shopp et al. 1984
	Neurological						
41	Rat Fischer 344	13 wk 5x/wk (GO)			400 (hunched posture and lethargy)		NTP 1980b
42	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)		200			NTP 1980a
43	Mouse CD-1	90 d (GO)		133			Shopp et al. 1984
	Reproductive						
44	Rat Fischer 344	13 wk 5x/wk (GO)		400			NTP 1980b

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
45	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)		200			NTP 1980a
	CHRONIC EXPOSURE						
	Systemic						
46	Mouse B6C3F1	81 wk (F)	Resp		71.6[c]	(increased incidence of pulmonary alveolar proteinosis in males and females)	Murata et al. 1993 1-MN
			Cardio	143.7			
			Gastro	143.7			
			Hemato	143.7			
			Hepatic	143.7			
			Renal	143.7			
			Endocr	143.7			
			Bd Wt	143.7			

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
47	Mouse (B6C3F1)	81 wk (F)	Resp		50.3[d] (increased incidence of pulmonary alveolar proteinosis in males and females)		Murata et al. 1997 2-MN
			Cardio	113.8			
			Gastro	113.8			
			Hemato	113.8			
			Musc/skel	113.8			
			Hepatic	113.8			
			Renal	113.8			
			Dermal	113.8			
			Ocular	113.8			
			Bd Wt	113.8			
	Immuno/ Lymphoret						
48	Mouse B6C3F1	81 wk 1x/d (F)		143.7			Murata et al. 1993 1-MN

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
49	Mouse (B6C3F1)	81 wk (F)		113.8				Murata et al. 1997 2-MN
	Neurological							
50	Mouse B6C3F1	81 wk 1x/d (F)		143.7				Murata et al. 1993 1-MN
51	Mouse (B6C3F1)	81 wk (F)		113.8				Murata et al. 1997 2-MN
	Reproductive							
52	Mouse B6C3F1	81 wk 1x/d (F)		143.7 F				Murata et al. 1993 1-MN
53	Mouse (B6C3F1)	81 wk (F)		113.8				Murata et al. 1997 2-MN
	Cancer							
54	Mouse B6C3F1	81 wk 1x/d (F)				71.6	(CEL: increased incidence of lung adenomas in males only)	Murata et al. 1993 1-MN

Table 3-2 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
55	Mouse (B6C3F1)	81 wk (F)				54.3	(CEL: increased incidence of lung adenomas in males only; not at higher exposure level in males or in females at either exposure level)	Murata et al. 1997 2-MN

a The number corresponds to the entries in Figure 3-2

b Used to derive an acute-duration Minimal Risk Level (MRL) of 0.6mg/kg/day; based on a minimal LOAEL of 50 mg/kg/day for transient clinical signs of neurotoxicity in pregnant rats, which was divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability). Based on an analysis of results from the three available intermediate-duration oral toxicity studies in animals (NTP 1980a,b; Shopp et al. 1984), the acute-duration MRL is expected to be applicable to and protective for intermediate-duration exposure scenarios (see Section 2.3 and Appendix A).

c Used to derive a chronic-duration Minimal Risk Level (MRL) of 0.07 mg/kg/day for 1-MN; based on a LOAEL of 71.6 mg/kg/day which was divided by an uncertainty factor of 1000 (10 for use the use of a LOAEL, 10 for extrapolation from animals to humans; and 10 for human variability)

d Used to derive a chronic-duration Minimal Risk Level (MRL) of 0.05 mg/kg/day for 2-MN; based on a LOAEL of 50.3 mg/kg/day which was divided by an uncertainty factor of 1000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = females; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (G) = gavage in oil; Hemato = hematological; hr = hour(s); Immuno = immunological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s); 1-Mn = 1-methylnaphthalene; 2-Mn = 2-methylnaphthalene.

Figure 3-2. Levels of Significant Exposure to Naphthalene or Methylnaphthalene (1-MN or 2-MN) - Oral

Acute (≤14 days)

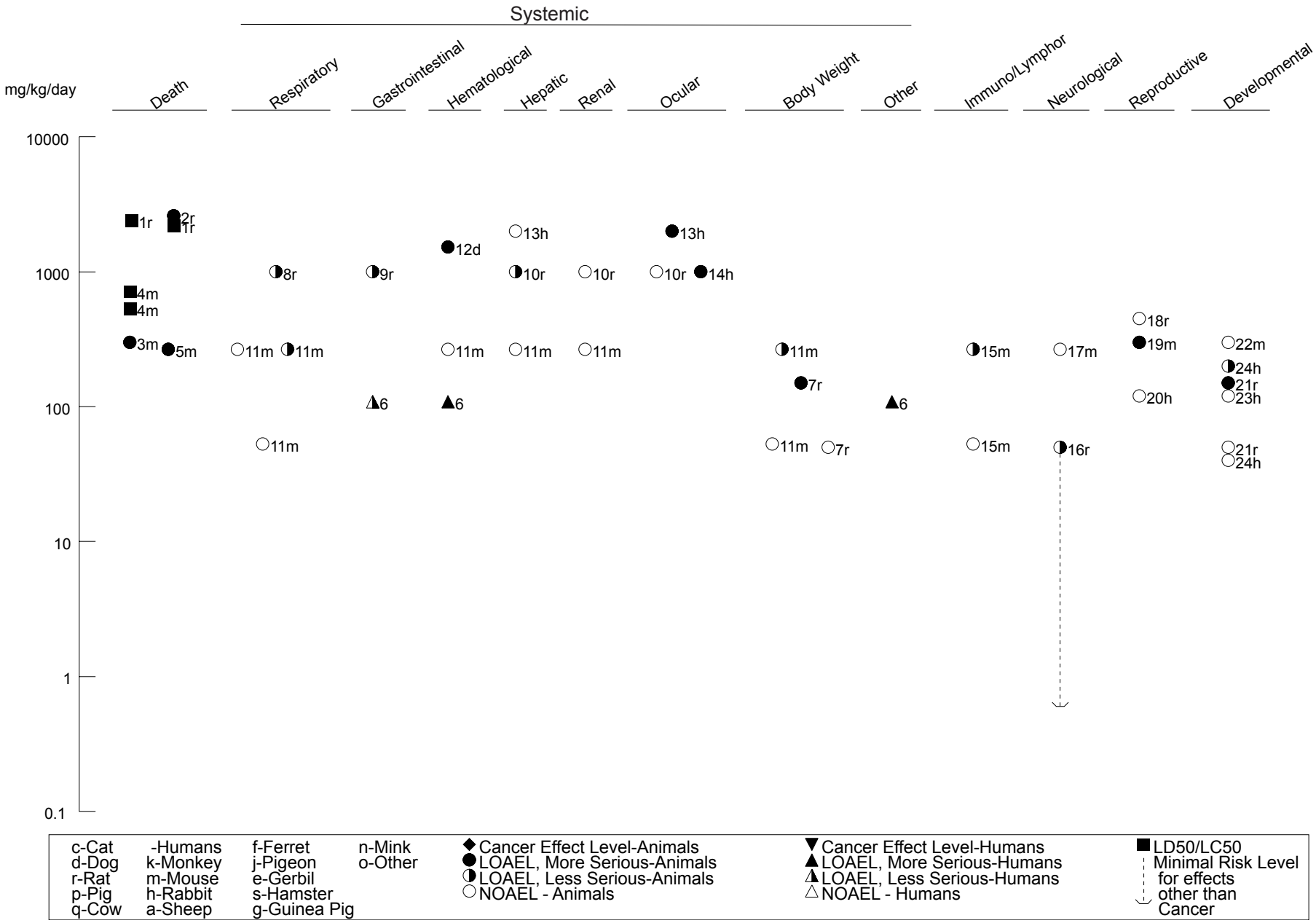


Figure 3-2. Levels of Significant Exposure to Naphthalene or Methylnaphthalene (1-MN or 2-MN) - Oral (*Continued*)

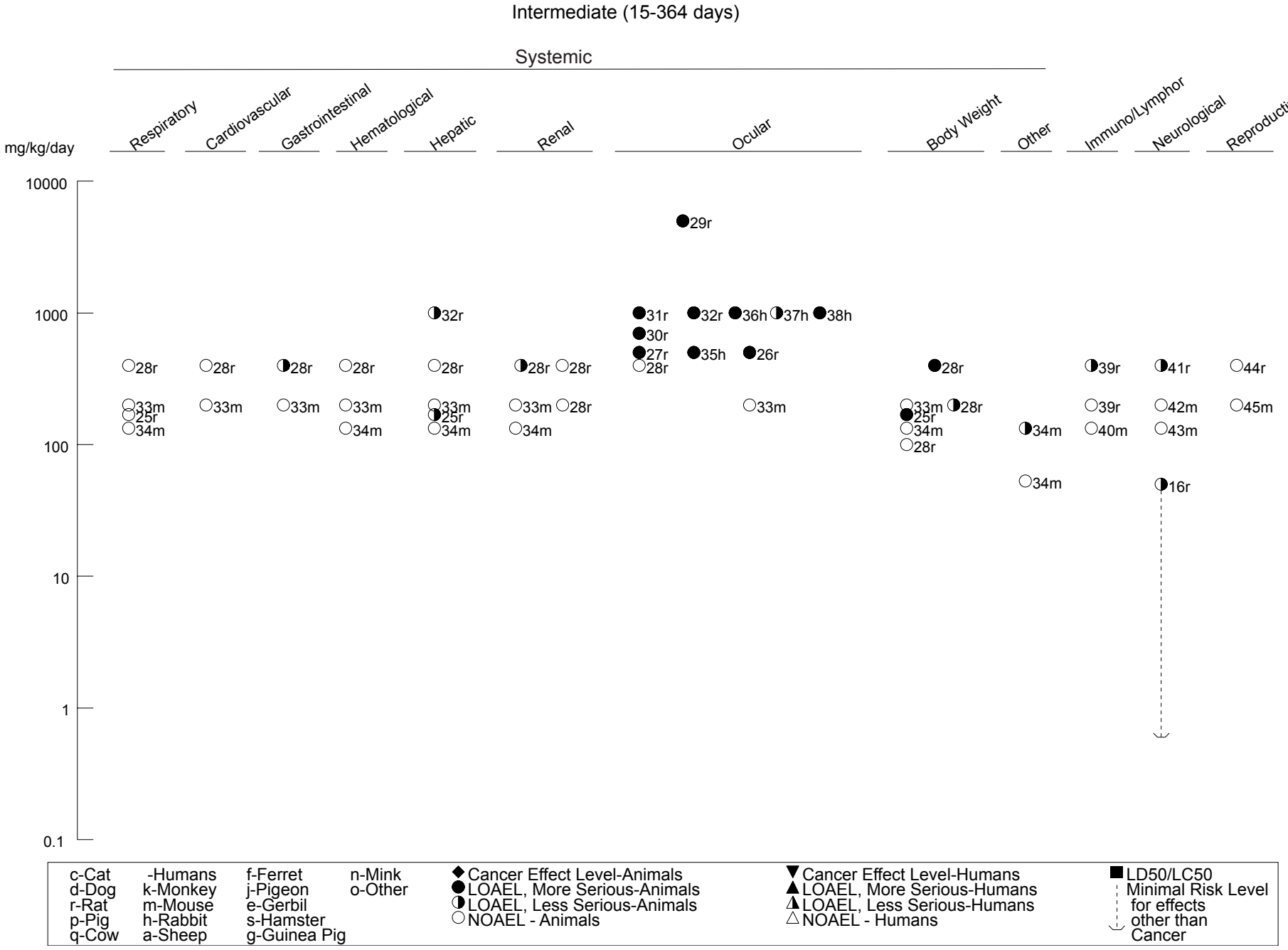
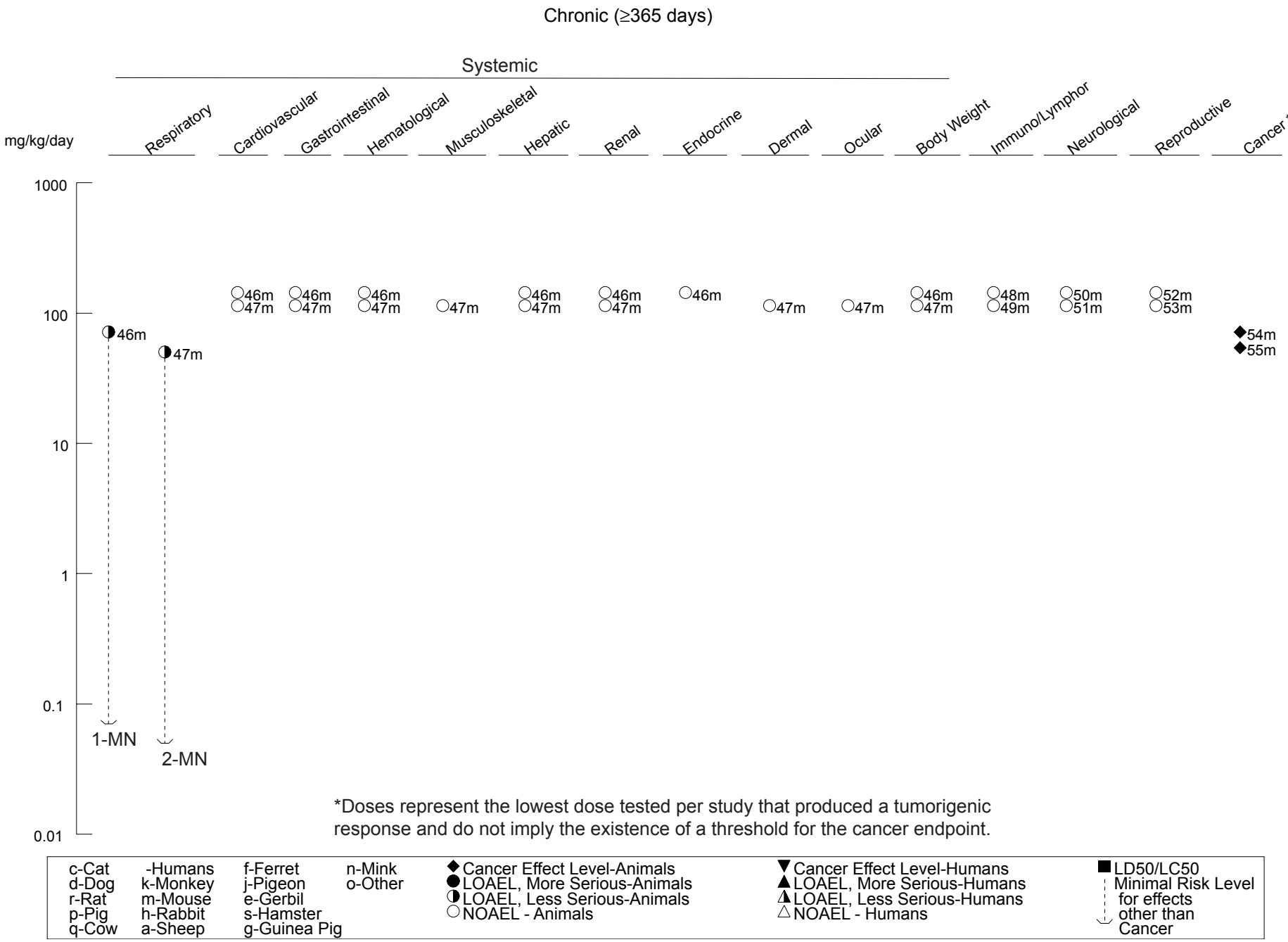


Figure 3-2. Levels of Significant Exposure to Naphthalene or Methylnaphthalene (1-MN or 2-MN) - Oral (*Continued*)



Lung weights were increased in female mice administered naphthalene at 267 mg/kg/day for 14 days; however, these effects were not seen in either sex at 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the lungs were noted in mice at doses up to 200 mg/kg/day (NTP 1980a) or in rats at doses of 400 mg/kg/day (NTP 1980b) after 13 weeks of exposure.

There was a significantly increased incidence of pulmonary alveolar proteinosis in male and female B6C3F1 mice fed diets containing 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The lesions contained acidophilic amorphous material, foam cells, and cholesterol crystals. There was no apparent inflammation, edema, or fibrosis of the tissues. Average administered doses were 0, 71.6, or 140.2 mg/kg/day for males and 0, 75.1, or 143.7 mg/kg/day for females. Respective incidences for pulmonary alveolar proteinosis in the control, low-, and high-dose groups were 4/49, 23/50, and 19/49 for males and 5/50, 23/50, and 17/49 for females. Histopathological examination of major organs and tissues only found exposure-related lesions in the lung. This effect was used as the basis of the chronic-duration oral MRL (0.07 mg/kg/day) for 1-methylnaphthalene.

Pulmonary alveolar proteinosis is characterized by the accumulation of surfactant material in the alveolar lumen, and has been hypothesized to be caused by either excessive secretion of surfactant by type II pneumocytes, or disruption of surfactant clearance by macrophages (Lee et al. 1997; Mazzone et al. 2001; Wang et al. 1997). Electron microscopic examination of lungs of mice exposed dermally to a mixture of 1-methylnaphthalene and 2-methylnaphthalene showed that alveolar spaces were filled with numerous myelinoid structures resembling lamellar bodies of type II pneumocytes (Murata et al. 1992).

In a companion study, pulmonary alveolar proteinosis was the only exposure-related lesion found in B6C3F1 mice of both sexes exposed to 2-methylnaphthalene in the diet at doses as low as 50.3 mg/kg/day (Murata et al. 1997). Average administered doses were 0, 54.3, or 113.8 mg/kg/day for males and 0, 50.3, or 107.6 mg/kg/day for females. Respective incidences for pulmonary alveolar proteinosis in the control, low-, and high-dose groups were 4/49, 21/49, and 23/49 for males and 5/50, 27/49, and 22/49 for females. This effect was used as the basis of the chronic-duration oral MRL (0.05 mg/kg/day) for 2-methyl-naphthalene.

Cardiovascular Effects. No studies were located that demonstrate any direct effects of naphthalene ingestion on the cardiovascular system. In those reports where cardiovascular effects such as increased heart rate and decreased blood pressure were noted in humans, the cardiovascular effects appeared to be

secondary to the hemolytic effects and the events leading to general multiple organ failure (Gupta et al. 1979; Kurz 1987).

No gross or histopathological lesions of the heart were noted in mice at doses up to 200 mg/kg/day (NTP 1980a) or in rats at doses of 400 mg/kg/day (NTP 1980b) after 13 weeks of exposure.

Heart weights were significantly decreased (6–7%) in male and female mice that were fed 1-methylnaphthalene for 81 weeks in their diet. However, the changes in heart weight were not dose-related and there were no accompanying tissue abnormalities (Murata et al. 1993). Histopathological examination revealed no lesions in the hearts of mice fed 1-methylnaphthalene at doses as high as 143.7 mg/kg/day (Murata et al. 1993) or 2-methylnaphthalene at doses as high as 113.8 mg/kg/day (Murata et al. 1997).

Gastrointestinal Effects. Gastrointestinal disorders are common following naphthalene ingestion by humans. These effects have been attributed to the irritant properties of naphthalene (Kurz 1987). Nausea, vomiting, abdominal pain, and diarrhea (occasionally containing blood) have been reported (Bregman 1954; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). While the presence of blood in the stool is indicative of intestinal bleeding, only a few areas of mucosal hemorrhage were noted in postmortem examination of the intestines (Kurz 1987). These areas were restricted to the small bowel and colon. No frank erosions or perforations were noted anywhere in the gastrointestinal tract.

A single dose of 1,000–4,000 mg/kg was associated with stomach lesions and discoloration of the intestines in rats that died during an LD_{50} study. The survivors were not affected (Papciak and Mallory 1990). No gross or histopathological lesions of the stomach, small intestine, and colon were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b). There was some intermittent diarrhea in the rats, but this may not have been treatment related.

No histopathological lesions were seen in the stomach or intestines of mice fed 71.6–143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993) or 50.3–113.8 mg/kg/day 2-methylnaphthalene for 81 weeks (Murata et al. 1997).

Hematological Effects. The most commonly reported hematologic effect in humans following the ingestion of naphthalene is hemolytic anemia (Dawson et al. 1958; Gidron and Leurer 1956; Gupta et al.

1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Mackell et al. 1951; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Shannon and Buchanan 1982). Changes observed in hematology and blood chemistry are consistent with this effect: hemolysis, decreased hemoglobin and hematocrit values, increased reticulocyte counts, serum bilirubin levels, and Heinz bodies. This was caused by hemolysis. Most of the reported case studies provide no information on dose. However, in one case report, a 16-year-old girl swallowed 6 g of naphthalene before exhibiting hemolytic anemia (Gidron and Leurer 1956). This is a dose of 109 mg/kg (assuming a 55-kg body weight). The hematological condition of this individual, who was an immigrant from Kurdistan, was not provided.

As mentioned previously, there is an association between G6PD deficiency and the hemolytic effects of naphthalene (Dawson et al. 1958; Melzer-Lange and Walsh-Kelly 1989; Shannon and Buchanan 1982). Individuals with a genetic defect for this enzyme show an increased susceptibility to hemolysis from naphthalene exposure.

Few hematologic changes have been reported in animals. Standard laboratory animals do not appear to be sensitive to the hemolytic effects of naphthalene. In CD-1 mice, naphthalene at doses up to 267 mg/kg/day for 14 days or up to 133 mg/kg/day for 90 days did not result in hemolytic anemia (Shopp et al. 1984). However there was an increase in eosinophils in the 14- and 90-day studies. There was an increase in prothrombin time at 14 days. The clinical significance of these observations is not clear; the effects are not considered to be adverse.

There were no pronounced changes in red cell related hematological parameters in mice following 13-week exposures to doses of up to 200 mg/kg/day (NTP 1980a) and up to 400 mg/kg/day in rats (NTP 1980b). In male mice exposed to 200 mg/kg/day for 13 weeks, there was a decrease in segmented neutrophils and an increase in lymphocytes, but in male rats given 400 mg/kg/day, there were increased neutrophils and decreased lymphocytes. These effects are not considered to be biologically significant or adverse.

Hemolytic anemia was reported by Zuelzer and Apt (1949) in a dog receiving a single 1,525 mg/kg dose of naphthalene in food and in another dog receiving approximately 263 mg/kg/day for 7 days in food. Dogs are more susceptible to chemically induced hemolysis than are rats and mice.

Exposure to 75.1 or 143.7 mg/kg/day 1-methylnaphthalene for 81 weeks was associated with a slight but statistically significant increase in the hemoglobin concentration, mean corpuscular hemoglobin, and

mean corpuscular hemoglobin concentration in female mice (Murata et al. 1993). Corresponding changes were not observed in male mice given comparable doses of 1-methylnaphthalene, or in male or female mice exposed to 2-methylnaphthalene doses as high as 113.8 mg/kg/day (Murata et al. 1997). Consistent exposure-related changes were not found in differential white blood cell counts or several serum biochemical parameters in male and female mice exposed to 1-methylnaphthalene or 2-methyl-naphthalene in these studies. The results from these studies do not provide consistent evidence that hematological parameters are consistent toxicity targets of chronic oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Hepatic Effects. Evidence of hepatotoxicity following oral exposure to naphthalene has been reported in humans, based on elevated plasma levels of hepatic enzymes (such as aspartate aminotransferase and lactic acid dehydrogenase) (Kurz 1987; Ojwang et al. 1985) and liver enlargement (Gupta et al. 1979; MacGregor 1954). The relationship between liver enlargement and potential naphthalene-induced hemolysis is unknown.

There is limited evidence of hepatic effects in laboratory animals, but the liver does not appear to be a critical toxicity target of orally administered naphthalene. A 39% increase in liver weight, a modest elevation in activity of aniline hydroxylase, and evidence of lipid peroxidation were observed in male rats treated with naphthalene at 1,000 mg/kg/day for 10 days (Rao and Pandya 1981). Male rats demonstrated an elevation in hepatic lipid peroxides at naphthalene doses of 1,000 mg/kg/day for 18 days (Yamauchi et al. 1986). In rats administered increasing doses of naphthalene up to 750 mg/kg/day (time-weighted average of 169 mg/kg/day), hepatic lipid peroxides were doubled at the end of 9 weeks of treatment (Germansky and Jamall 1988).

No effects on liver weight were observed in male or female mice receiving naphthalene at doses up to 267 mg/kg/day for 14 days or male mice receiving 133 mg/kg/day for 90 days (Shopp et al. 1984). Absolute liver weight was statistically significantly decreased, compared with the control value (by about 18%), in female mice receiving 133 mg/kg/day naphthalene for 90 days, but the biological significance of this change is unclear. Relative liver weight in exposed females was not changed to a statistically significant degree, and several serum biochemical end points indicative of liver damage (e.g., lactate dehydrogenase, SGPT, SGOT, and alkaline phosphatase) were unaffected in male and female mice exposed to doses up to 133 mg/kg/day for 90 days (Shopp et al. 1984). No other consistent biologically relevant exposure-related changes in serum chemistry end points were found. Activities of two hepatic microsomal mixed function oxidases (aniline hydroxylase, aminopyrine N-demethylase) were unchanged

in exposed mice, although hepatic activities of benzo[a]pyrene hydroxylase were statistically significantly decreased in exposed mice (Shopp et al. 1984). The biological significance of this change is unclear. Supporting the concept that the liver is not a critical toxicity target of oral exposure to naphthalene, no gross or histopathological lesions of the liver were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b).

There were no changes in liver weights or tissue histopathology in male or female mice that consumed 71.6–143.7 mg/kg/day 1-methylnaphthalene in the diet for 81 weeks (Murata et al. 1993) or 50.3–113.8 mg/kg/day 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1997).

Renal Effects. Renal toxicity has been reported in case studies of humans who ingested naphthalene. Frequent findings include the elevation of creatinine and blood urea nitrogen and the presence of proteinuria and hemoglobinuria (Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985; Zuelzer and Apt 1949). The presence of blood in the urine and increased concentrations of urobilinogen are a consequence of acute hemolysis and do not reflect any direct action of naphthalene on the kidney. Oliguria (Kurz 1987) and anuria (Gupta et al. 1979) were noted in two case reports, although urine output was normal in a third (Ojwang et al. 1985). Painful urination with swelling of the urethral orifice was also associated with medicinal naphthalene ingestion (Lezenius 1902). Proximal tubule damage and general tubular necrosis were found in postmortem examinations of two individuals who died following naphthalene ingestion (Gupta et al. 1979; Kurz 1987).

Renal effects were not consistently observed in animals exposed orally to naphthalene. Following 10 days of exposure of rats to naphthalene at 1,000 mg/kg/day, no changes were noted in kidney weight, lipid peroxidation, or in the activity of alkaline phosphatase and aniline hydroxylase (Rao and Pandya 1981). No changes were observed in the kidney weights of mice administered naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the kidney were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 200 mg/kg/day after 13 weeks of exposure (NTP 1980b). In the male rats, 10% showed cortical tubular degeneration that may have been compound-related at a dose of 400 mg/kg/day (NTP 1980b).

Relative kidney weights were increased slightly in male mice fed diets containing 71.6 or 140.2 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The females were not affected, and there were no histopathological lesions in the males or females. There were no changes in kidney

weights or tissue histopathology in male or female mice consuming 50.3–113.8 mg/kg/day 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1997).

Ocular Effects. In an early report of naphthalene toxicity, a 36-year-old pharmacist who ingested an unspecified amount of unpurified naphthalene in a castor oil emulsion over a 13-hour period as treatment of an intestinal disorder became nearly blind 8 or 9 hours later (Lezenius 1902). A medical examination the following month revealed constricted visual fields associated with optic atrophy and bilateral zonular cataracts. At 1.5 meters, the patient's vision was limited to finger counting.

Several animal studies have demonstrated ocular changes following oral naphthalene exposure. Within 1 week following exposure to naphthalene (500 or 1,000 mg/kg/day), lens densities were increased in rats and cataracts developed within 4 weeks (Kojima 1992; Murano et al. 1993; Yamauchi et al. 1986). Eight rabbits (strain not identified) developed cataracts during oral administration of naphthalene at 2,000 mg/kg/day for 5 days (Srivastava and Nath 1969). Cataracts began to develop by the first day after a single 1,000 mg/kg naphthalene dose in three Chinchilla Bastard rabbits (Rossa and Pau 1988). In the solitary New Zealand white rabbit tested, cataracts began to develop after administration of four 1,000 mg/kg doses (dosing 2 times/week) and maximized after 12 weeks (Rossa and Pau 1988).

When naphthalene was administered orally at 1,000 mg/kg/day for up to 28 days, cataracts developed in 10 of 16 Dutch (pigmented) rabbits and in 11 of 12 albino rabbits (Van Heyningen and Pirie 1976). Lens changes were seen as early as day 2 of exposure. The authors noted that albino strains were more likely to develop cataracts over a 4-week course of treatment at 1,000 mg/kg/day than pigmented strains such as the Dutch rabbit.

In contrast, administration of a time-weighted-average 500-mg/kg/day dose of naphthalene in corn oil by gavage for 6 weeks resulted in more rapid development of cataracts in pigmented Brown-Norway rats than in nonpigmented Sprague-Dawley rats (Murano et al. 1993). Cataracts developed in three distinct phases. In the first phase, water clefts formed in the anterior subcapsular region of the eye. The second stage was the development of a semicircular opaque area in the lens, and the last stage was the appearance of a wedge-shaped opacity that could be seen with retroillumination and a wide, zonular-ring opacity that was seen with slit imaging. Each stage occurred about 1 week earlier in the Brown-Norway rats than in the Sprague Dawley rats. The first stage began 1 week after treatment was initiated in the Brown-Norway rats, and stage three cataracts were seen in all animals by the end of the 6 weeks. Progressive

development of lens opacities was also reported in rats that were exposed to 700 or 5,000 mg/kg/day naphthalene by gavage for 79–102 days (Rathburn et al. 1990; Tao et al. 1991).

Damage to the eyes with continued exposure to naphthalene is not limited to lens opacification (Orzalesi et al. 1994). Retinal damage was noted in pigmented rabbits given time-weighted-average doses of 500 mg/kg/day naphthalene in corn oil by gavage for 5 weeks. The first changes to the retina occurred at about 3 weeks with degeneration of the photoreceptors. There was a subsequent increase in the retinal pigment epithelium as these cells phagocytized the debris from the photoreceptors. By the end of 6 weeks, the photoreceptor layer had almost entirely disappeared and was replaced with fibroglial tissue. As damage progressed, there was dense subretinal neovascularization of the area.

A number of biochemical changes were seen in the eyes after acute- and intermediate-duration naphthalene exposures. After 1 week of treatment with 1,000 mg/kg/day, glutathione levels in the lens were decreased in rats (Xu et al. 1992b; Yamauchi et al. 1986). After 30 days of treatment with doses of 5,000 mg/kg/day, total glutathione levels were reduced by 20% (Rathbun et al. 1990), and there was a 22% reduction at 60 days with a dose of 700 mg/kg/day (Tao et al. 1991). At 60 days, glutathione peroxidase activity in the lens was decreased by up to 45% and there was a 20–30% decrease in glutathione reductase activity (Rathbun et al. 1990). Comparable decreases in the activities of both enzymes were seen at 102 days with lower naphthalene doses (Tao et al. 1991). No changes were observed in the activity of glutathione synthetase or gamma-glutamyl cysteine synthetase (Rathbun et al. 1990). After 4 weeks of compound treatment (500 mg/kg/day), the activities of aldose reductase, sorbitol dehydrogenase, lactic dehydrogenase, and glutathione reductase were lower than in controls (Kojima 1992). No changes in ocular lipid peroxides were reported when male Blue Spruce pigmented rats were administered incremental doses of naphthalene that peaked at 750 mg/kg/day for 9 weeks (Germansky and Jamall 1988). Lens and capsule LDH activities were greatly reduced in rabbits while o-diphenyl oxidase activity was elevated with a dose of 2,000 mg/kg/day for 5 days (Srivastava and Nath 1969).

In 13-week studies, histopathologic examination revealed no ocular lesions in F344/N rats or B6C3F1 mice exposed to doses as high as 400 or 200 mg/kg/day, respectively (NTP 1980a, 1980b). In a 2-year rat feeding study, no eye damage was seen at a naphthalene dosage of 41 mg/kg/day (Schmahl 1955). The details of the eye examination were not provided.

There were no changes in eye tissue histopathology in male or female mice that consumed 71.6–143.7 mg/kg/day 1-methylnaphthalene in the diet for 81 weeks (Murata et al. 1993) or 50.3–113.8 mg/kg/day 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1997).

Body Weight Effects. No studies were located that documented effects on body weight in humans after oral exposure to naphthalene.

In pregnant Sprague-Dawley rats exposed to 50, 150, or 450 mg/kg/day on gestation days 6–15, body weight gains were depressed by 31 and 53% at 150 and 450 mg/kg/day, respectively, but were unaffected at 50 mg/kg/day. The decreased body weight gains were accompanied by persistent signs of neurological impairment (slow respiration, lethargy, or prone position) at the 150 and 450 mg/kg/day dose levels, but these signs were only apparent at the 50-mg/kg/day level during the first 2 days of dosing. The minimal LOAEL of 50 mg/kg/day for transient clinical signs of neurotoxicity and the LOAEL of 150 mg/kg/day for clinical signs associated with decreased body weight gains in pregnant rats are the basis of the acute oral MRL (0.6 mg/kg/day) for naphthalene (see Section 2.3 and Appendix A).

In animals, body weight effects appear to be the critical effect associated with intermediate-duration oral exposure to naphthalene. After 13 weeks of exposure to naphthalene, mean terminal body weights in F344/N rats exposed to gavage doses ≥200 mg/kg/day were decreased by more than 10% relative to control values (NTP 1980b). Body weights were decreased by 12 and 28% in 200- and 400-mg/kg/day male rats, and by 23% in 400-mg/kg/day female rats. Food consumption was not affected by exposure. In B6C3F1 mice exposed to naphthalene doses up to 200 mg/kg/day for 13 weeks, exposed males gained more weight than controls during exposure, whereas exposed females gained less weight than controls (NTP 1980a). However, terminal body weights in exposed female mice were within 95% of control values, indicating that the naphthalene-induced changes were not biologically significant. In male and female CD-1 mice exposed to doses as high as 133 mg/kg/day for 90 days, average terminal body weight in exposed groups were within 90% of control values (Shopp et al. 1984). Mice exposed to 267 mg/kg/day naphthalene for 14 days showed a decreased body weight gain; terminal body weights were decreased by 6% in females and 13% in males compared with control values (Shopp et al. 1984).

As discussed in Section 2.3 and Appendix A, the NOAEL of 100 mg/kg/day and the LOAEL of 200 mg/kg/day for decreased body weights in rats exposed by gavage to naphthalene 5 days/week for 13 weeks (NTP 1980b) provide the best available basis for MRL derivation among the findings from the studies in animals orally exposed to naphthalene for intermediate-durations. However, because an

intermediate-duration oral MRL based on these data is slightly larger than the acute-duration oral MRL for naphthalene, the acute MRL was adopted as the intermediate-duration oral MRL for naphthalene (as indicated in Figure 3-2 and discussed in Section 2.3).

There was no significant difference between body weights of mice that were given up to 143.7 mg/kg/day 1-methylnaphthalene in their diets and those of the control animals throughout an 81-week exposure period (Murata et al. 1993). In mice exposed to 2-methylnaphthalene doses as high as 113.8 mg/kg/day in the diet for up to 81 weeks, average body weights were within 10% of control values (Murata et al. 1997).

Other Systemic Effects. Several humans who consumed naphthalene experienced elevated body temperatures which may have been related to their hemolytic crisis (Chusid and Fried 1955; Gidron and Leurer 1956; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). However, in some situations, bacterial infections rather than hemolysis may have been the cause of the fever (Kurz 1987; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Zuelzer and Apt 1949).

No studies were located that documented other systemic effects in animals after oral exposure to naphthalene.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located that documented immunological or lymphoreticular effects in humans after oral exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. However, an enlarged spleen is a frequent consequence of hemolysis and was noted in the postmortem examination of one human subject who died after ingesting a large quantity of naphthalene (Kurz 1987).

Mice treated with naphthalene at oral doses as high as 267 mg/kg/day for 14 days showed no effects on humoral immune responses, delayed hypersensitivity responses, bone marrow stem cell number, or bone marrow DNA synthesis (Shopp et al. 1984). Mitogenic responses to concanavalin A (but not to lipopolysaccharide) were reduced in high dose females only. None of these effects were noted at doses of 27 or 53 mg/kg/day. At naphthalene doses of 133 mg/kg/day for 13 weeks, naphthalene had no effect on immune function (Shopp et al. 1984). After 14 days, thymus weights were reduced approximately 30% in male mice, but no differences were seen with a dose of 133 mg/kg/day at 13 weeks (Shopp et al. 1984). There was lymphoid depletion of the thymus in 2 of 10 female rats exposed to 400 mg/kg/day naphthalene for 13 weeks (NTP 1980b).

Spleen weights were reduced approximately 20% in female mice exposed to 267 mg/kg/day naphthalene for 14 days and 25% in females exposed to 133 mg/kg/day for 13 weeks (Shopp et al. 1984).

Monocyte concentrations were significantly elevated in male and female mice exposed to 71.6–143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The increase in monocyte counts appeared to be dose related. The authors hypothesized that these changes may have been a physiological response to the pulmonary alveolar proteinosis seen in the exposed animals. There were no changes in spleen or thymus weights and the histopathology of these tissues was normal. With 81 weeks of exposure of male and female B6C3F1 mice to 2-methylnaphthalene, neutrophils were reported to be decreased, and lymphocytes increased, compared with control values, but neither the magnitude of these changes, or the dose groups in which they occurred, were specified in the study report (Murata et al. 1997). As with 1-methylnaphthalene, histologic examination revealed no exposure-related lesions in the spleen or thymus.

The highest NOAEL values and all LOAEL values from each reliable naphthalene study for immunological/lymphoreticular effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. The highest NOAEL values from the 1-methylnaphthalene and 2-methyl-naphthalene studies for immunological/lymphoreticular effects are also recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

The neurologic symptoms of naphthalene ingestion reported in human case studies include confusion (Ojwang et al. 1985), altered sensorium (Gupta et al. 1979), listlessness and lethargy (Bregman 1954; Chusid and Fried 1955; Kurz 1987; MacGregor 1954; Zuelzer and Apt 1949), and vertigo (Gidron and Leurer 1956). Muscle twitching, convulsions (Kurz 1987; Zuelzer and Apt 1949), decreased responses to painful stimuli, and coma occurred prior to death in individuals who ingested naphthalene (Gupta et al. 1979; Kurz 1987). At autopsy, the brain has appeared edematous (Gupta et al. 1979; Kurz 1987), with separation of neural fibers and swelling of myelin sheaths being noted histologically (Gupta et al. 1979). The neurologic symptomatology could result from the cerebral edema, which was probably secondary to acute hemolysis.

No studies were located that documented neurological effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Dose-related clinical signs of neurotoxicity were apparent in female Sprague-Dawley rats exposed to doses of 50, 150, or 450 mg/kg/day naphthalene for 10 days during organogenesis. Slow respiration and lethargy were observed in a large percentage of the exposed animals. Some rats were dazed, had periods of apnea, or were unable to move after exposure. In the lowest dose group, 73% of the animals were affected on the first day of dosing. In the two higher dose groups, over 90% of the rats were affected (NTP 1991a).

The animals in the 50-mg/kg/day group acclimatized quickly. Symptoms were only apparent during the first 2 days of dosing. Signs of neurotoxicity persisted for longer periods in the higher dose groups, and were accompanied by decreased body weight gains (31 and 53% decreased at 150 and 450 mg/kg/day, respectively compared with control). Comparable neurological effects were not observed in F344/N rats exposed to doses of up to 400 mg/kg/day for 13 weeks or in B6C3F1 mice at doses of up to 200 mg/kg/day (NTP 1980a, 1980b). These results suggest that pregnant animals may be more susceptible to the potential neurotoxicity of naphthalene than non-pregnant animals. The minimal LOAEL of 50 mg/kg/day for transient signs of neurotoxicity and the LOAEL of 150 mg/kg/day for more persistent signs of neurologic impairment accompanied with depressed weight gain in pregnant rats exposed on gestation days 6–15 are the basis of the acute oral MRL (0.6 mg/kg/day) for naphthalene (see Section 2.3 and Appendix A).

There were no changes in the brain weights in mice exposed to naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the brain were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b). Transient clinical signs of neurotoxicity were observed in rats following daily gavage administration of 400 mg/kg, but not 200 mg/kg, doses (NTP 1980b). In mice, transient lethargy was observed following dose administration only between weeks 3 and 5 in the highest dose group, 200 mg/kg/day (NTP 1980a).

Absolute brain weight was significantly increased in male mice fed diets containing 71.6 or 140.2 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993), or 54.3 or 113.8 mg/kg/day 2-methylnaphthalene for 81 weeks (Murata et al. 1997). The increases in brain weights were not dose

related and there were no histopathological abnormalities of the brain. There were no differences in brain weights or histopathology in the female mice given comparable doses (Murata et al. 1993, 1997).

No studies were located that documented neurological effects in animals after oral exposure to 2-methylnaphthalene.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects for naphthalene exposure in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. The highest NOAEL values for neurological effects in the intermediate-duration 1-methylnaphthalene and 2-methylnaphthalene mouse studies are also recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located that documented reproductive effects in humans after oral exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

Oral exposures of pregnant rabbits to naphthalene at dosages up to 400 mg/kg/day (gestational days 6–18), using methylcellulose as the vehicle, resulted in no apparent adverse reproductive effects (PRI 1986). When administered in corn oil to pregnant mice, however, a dosage of 300 mg/kg/day (gestational days 7–14) resulted in a decrease in the number of live pups per litter (Plasterer et al. 1985). It is not clear whether the observed differences in response are attributable to species differences or a possible increase in the absorption of naphthalene when it is administered in corn oil compared with administration as a suspension in methyl cellulose.

Transient signs of neurotoxicity were present in female rats exposed to doses of 50, 150, or 450 mg/kg/day on gestational days 6–15 (NTP 1991a). Effects on maternal weight gain were noted in the mid- and high-dose groups but not in the lowest dose group. The mid-dose group had a 31% decrease in weight gain while the high-dose group had a 53% weight gain decrease.

No treatment-related effects were reported on testicular weights of mice administered naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the testes were noted in mice at doses of up to 200 mg/kg/day (NTP 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (NTP 1980b).

No gross or histopathological lesions of the testis, seminal vesicles, ovaries, uterus, or vagina were observed in mice exposed to 1-methylnaphthalene doses as high as 143.7 mg/kg/day (Murata et al. 1993) or 2-methylnaphthalene doses as high as 113.8 mg/kg/day (Murata et al. 1997).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

In humans, transplacental exposure of the fetus to naphthalene that had been ingested by the mother resulted in neonatal (and presumably fetal) hemolytic anemia (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). No estimates of dose or duration were available, although in one case, naphthalene consumption was described as being most pronounced during the last trimester (Zinkham and Childs 1958).

No studies were located that documented developmental effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

No congenital abnormalities were observed after oral administration of naphthalene at 300 mg/kg/day to pregnant mice on days 7–14 of gestation (Plasterer et al. 1985), or at doses up to 400 mg/kg/day to pregnant rabbits on days 6–18 of gestation (PRI 1986). Similarly, naphthalene was not teratogenic in rats at doses up to 450 mg/kg/day during gestation days 6–15 (NTP 1991a). However, there was a slight, but dose-related, increase in fused sternebrae in female pups of rabbits administered doses of 20–120 mg/kg/day on days 6 through 19 of gestation (NTP 1992b). These effects were seen in 2 of 21 litters at 80 mg/kg/day and 3 of 20 litters at 120 mg/kg/day. No other developmental effects were noted in this study.

No studies were located that evaluated developmental end points in animals after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located that documented carcinogenic effects in humans after oral exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

In a 2-year feeding study of rats receiving naphthalene at about 41 mg/kg/day, no tumors were reported (Schmahl 1955). Specific details pertaining to the tissues examined were not provided.

The chronic dietary studies with 1-methylnaphthalene or 2-methylnaphthalene provide limited evidence for the carcinogenicity of these chemicals. Long-term exposure (81 weeks) of mice to 71.6 or 140.2 mg/kg/day 1-methylnaphthalene in the diet was associated with statistically significant increases in bronchiolar/alveolar adenomas in males, but not in females (Murata et al. 1993). Incidences for mice with lung adenomas were 2/49, 13/50, and 12/50 for control through high-dose male mice, and 4/50, 2/50, and 4/49 for female mice. Combined incidence for mice with lung adenomas or adenocarcinomas were 2/49, 13/50, and 15/50 for male mice, and 5/50, 2/50, and 5/50 for female mice. In mice exposed to 2-methylnaphthalene in the diet for 81 weeks, incidences for mice with lung adenomas were 2/49, 9/49, and 5/49 in males groups that received 0, 54.3, or 113.8 mg/kg/day, and 4/50, 4/49, and 5/48 in female groups that received comparable doses (Murata et al. 1997). Only the incidence in the 54.3-mg/kg/day group was elevated to a statistically significant degree.

3.2.3 Dermal Exposure

3.2.3.1 Death

Two cases of hemolytic anemia were observed in infants exposed to naphthalene-treated diapers (Schafer 1951; Valaes et al. 1963). One case was fatal. Jaundice, methemoglobinemia, hemolysis, and cyanosis were noted. In the fatal case the symptoms persisted, even after the naphthalene-containing diapers were no longer used (Schafer 1951). The author suggested that use of baby oil on the infant's skin might have facilitated the naphthalene absorption.

No treatment-related deaths occurred within the 14-day observation period when naphthalene was applied at 2,500 mg/kg to the skin of male and female rats or when doses of up to 1,000 mg/kg/day were applied to the skin for 6 hours/day, 5 days/week for 13 weeks (Frantz et al. 1986; Gaines 1969). There were also

no deaths in New Zealand White rabbits after application of 2,000 mg/kg naphthalene to intact and abraded shaved areas of skin in an LD_{50} study (Papciak and Mallory 1990).

No studies were located that documented lethal effects in humans or animals after dermal exposure to 1-methylnaphthalene or 2-methylnaphthalene.

3.2.3.2 Systemic Effects

No studies were located that documented musculoskeletal effects in humans or animals after dermal exposure to naphthalene. The highest NOAEL and all LOAEL values for dermal exposure to naphthalene are recorded in Table 3-3. Data for systemic effects in humans or animals from dermal exposure to 1-methylnaphthalene or 2-methylnaphthlene are restricted to two studies that only examined the lung for lesions following repeated dermal exposure to methylnaphthalene, a mixture of 1-methylnaphthalene and 2-methylnaphthalene (Emi and Konishi 1985; Murata et al. 1992).

Respiratory Effects. No studies were located that documented respiratory effects in humans after dermal exposure to naphthalene.

No histological changes of the lungs were noted in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Pulmonary alveolar proteinosis was noted in nearly all female B6C3F1 mice given dermal doses of methylnaphthalene (a mixture of 1-methylnaphthalene and 2-methylnaphthalene) twice a week at a dose level of 119 mg/kg for 30 weeks (Murata et al. 1992) or 61 weeks (Emi and Konishi 1985). Endogenous lipid pneumonia was the term used to describe this lesion in the earlier study. With the longer-duration exposure to 119 mg/kg methylnaphthalene, an unspecified number of mice died early. Pulmonary alveolar proteinosis developed in 3/11 female mice treated twice weekly with dermal doses of 30 mg/kg for 61 weeks, compared with 0/4 controls (Emi and Konishi 1985).

Cardiovascular Effects. No studies were located that documented cardiovascular effects in humans after dermal exposure to naphthalene.

No differences in organ weight or histological changes of the heart were noted in rats dermally treated with 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Table 3-3 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit New Zealand White	once 24hr contact	Dermal		2000 mg/kg	(skin irritation, edema, fissuring)	Papciak and Mallory 1990
Rabbit	once	Dermal		125 mg/kg	(reversible erythema)	PRI 1985a
Immuno/ Lymphoret						
Gn Pig	3 wk 1x/wk		1000 mg/kg			PRI 1985c
INTERMEDIATE EXPOSURE						
Systemic						
Rat	90 d 5d/wk 6 hr/d	Resp	1000 mg/kg/day			Frantz et al. 1986
		Cardio	1000 mg/kg/day			
		Gastro	1000 mg/kg/day			
		Hemato	1000 mg/kg/day			
		Hepatic	1000 mg/kg/day			
		Renal	1000 mg/kg/day			
		Dermal	300 mg/kg/day	1000 mg/kg/day	(increased incidence of excoriated skin and papules)	
Mouse (B6C3F1)	30 wk 2x/wk	Resp		119 mg/kg	(100% incidence of mice with pulmonary alveolar proteinosis)	Murata et al. 1992 1-MN+2-MN

Table 3-3 Levels of Significant Exposure to Naphthalene Or Methylnaphthalene (1-Mn Or 2-Mn) - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious	Serious		
CHRONIC EXPOSURE							
Systemic							
Mouse (B6C3F1)	61 wk 2x/wk	Resp	30 mg/kg		119 mg/kg	(31/32 mice had pulmonary alveolar proteinosis; an unspecified number died)	Emi and Konishi 1985 1-MN+2-MN

Cardio = cardiovascular; d = day(s); Gastro = gastrointestinal; Gn Pig = Guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s). 1-Mn = 1-methylnaphthalene; 2-Mn = 2-methylnaphthalene.

Gastrointestinal Effects. No studies were located that documented gastrointestinal effects in humans after dermal exposure to naphthalene.

No histological changes of the esophagus, stomach, or intestines were noted in rats dermally treated with 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Hematological Effects. Hemolytic anemia was reported in infants dermally exposed to diapers or other clothing treated with naphthalene mothballs (Dawson et al. 1958; Schafer 1951; Valaes et al. 1963). Jaundice, fragmentation of erythrocytes, Heinz bodies, methemoglobinemia, and reticulocytosis were observed. Several of the infants had G6PD deficiencies. Individuals with this genetic disorder are particularly susceptible to hemolysis from chemical agents. The application of oil to the skin may have aided absorption of naphthalene, as shown by the increasing severity of symptoms (jaundice and cyanosis) even after the use of the naphthalene-containing diapers ceased (Schafer 1951).

There were no changes in hemoglobin, hematocrit, red blood cell count, leukocyte count, or platelet count at 4 and 13 weeks in rats treated with doses of up to 1,000 mg/kg/day applied to the skin (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Hepatic Effects. The liver was enlarged in two infants who experienced acute hemolysis after dermal exposure to naphthalene (Dawson et al. 1958; Schafer 1951). The relationship between liver enlargement and potential naphthalene-induced hemolysis is unknown.

There were no differences in liver weights or histological damage to the liver in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986). In addition, the levels of aspartate amino transferase, alanine amino transferase, urea nitrogen, and bilirubin were not elevated in the exposed rats as compared to the controls.

Renal Effects. No studies were located that documented renal effects in humans after dermal exposure to naphthalene.

There were no differences in kidney weights or histological damage to the liver in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986). In addition, the results of urinalysis conducted at 4 and 13 weeks on the treated rats were not different from the control results, indicating that there was no impairment of kidney function.

Dermal Effects. No studies were located that documented dermal effects in humans after dermal exposure to naphthalene.

A study in rabbits has shown that naphthalene is a mild dermal irritant, causing erythema and fissuring, when directly applied to the shaved, abraded, or nonabraded skin under a dressing; healing occurred within 6–7 days (Papciak and Mallory 1990; PRI 1985a). In rats that were dermally treated for 6 hours/day, 5 days/week, for 13 weeks with 1,000 mg/kg/day naphthalene, there was an increased incidence of excoriated skin lesions and papules (Frantz et al. 1986). However, similar lesions were seen in the controls and lower dose group animals. At the high dose, naphthalene appeared to exacerbate the severity of the lesions. Acute and chronic exposures of animal skin to naphthalene appear to cause dermal irritation.

Ocular Effects. Two case studies were reported in which humans experienced eye irritation and conjunctivitis as a result of naphthalene exposure (van der Hoeve 1906). In one case, a worker accidentally got naphthalene powder in his left eye. The exact amount was unknown, but was described by the worker as large. Despite immediate cleansing of the eye, the subject experienced conjunctivitis and pain shortly after exposure. Symptoms of irritation subsided, but then reappeared 6 weeks later. At that time, the subject noticed decreased vision in his left eye. When examined by a doctor, the eye had retinal lesions (one fresh and others seemingly older); the entire retina appeared clouded. The subject's vision in the left eye was poorer than in the right. Five years earlier, vision was the same in both eyes.

In the second case study, an adult male who worked in a storage area where naphthalene was used as a pesticide complained of ocular pain, conjunctivitis, and impaired vision (van der Hoeve 1906). Neither the duration nor the mode of exposure was described. The subject most likely was exposed to naphthalene vapors. When examined by a doctor, the subject was found to have retinal bleeding and the beginning of a cataract.

Dermal and ocular contact with naphthalene vapors accompanied by inhalation may have contributed to the development of multiple lens opacities in 8 of 21 workers involved with a dye manufacturing process that used naphthalene as a raw material (Ghetti and Mariani 1956). Workers, who were employed at the plant for up to 5 years, melted naphthalene in open vats, resulting in high atmospheric vapor concentrations.

Mild ocular irritation was observed in the nonrinsed eyes of rabbits after instillation of naphthalene at 0.1 mg/eye (Papciak and Mallory 1990; PRI 1985b). Observed effects were reversible within 7 days after exposure. When the eyes were rinsed with water immediately after exposure, there were no signs of irritation (Papciak and Mallory 1990). Oral administration of naphthalene in rats resulted in cataract formation beginning at the posterior outer cortex, suggesting that this region is the most sensitive part of the lens (Kojima 1992). The lenses of pigmented Brown-Norway rats had changes, such as water cleft formation, during the first week that 10 mg/kg/day naphthalene was orally administered every other day (Murano et al. 1993). These rats were more sensitive to cataract formation than albino Sprague-Dawley rats, presumably because they more effectively metabolized naphthalene to the toxic compound naphthoquinone (Murano et al. 1993).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located that documented immunological or lymphoreticular effects in humans after dermal exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. An enlarged spleen was noted in two human subjects dermally exposed to unspecified doses of naphthalene (Dawson et al. 1958; Schafer 1951). However, spleen enlargement is a result of hemolysis rather than a direct effect of naphthalene on the spleen.

In animals, dermal application of pure naphthalene (1,000 mg/kg) 1 time/week for 3 weeks did not result in delayed hypersensitivity reactions in guinea pigs (Papciak and Mallory 1990; PRI 1985c).

No studies were located that documented immunological or lymphoreticular effects in animals after dermal exposure to 1-methylnaphthalene or 2-methylnaphthalene.

A NOAEL for immunological/lymphoreticular effects following dermal exposure to naphthalene is recorded in Table 3-3.

No studies were located that documented the following health effects in humans or animals after dermal exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

No studies of genotoxic effects in humans exposed to naphthalene were located.

Table 3-4 summarizes results for naphthalene and its metabolites in bacterial mutation assays; *in vitro* eukaryotic gene mutation, cytogenetic, or DNA damage assays; and *in vivo* eukaryotic gene mutation, cytogenetic, or DNA damage assays.

Bacterial Gene Mutation Assays for Naphthalene. Naphthalene was not mutagenic in *Salmonella typhimurium* assays in the presence or absence of rat liver metabolic preparations (Bos et al. 1988; Connor et al. 1985; Florin et al. 1980; Gatehouse 1980; Godek et al. 1985; Kaden et al. 1979; McCann et al. 1975; Mortelmans et al. 1986; Nakamura et al. 1987; Narbonne et al. 1987; NTP 1992a; Sakai et al. 1985). The metabolites, 1-naphthol and 1,4-naphthoquine, were not mutagenic in several *S. typhimurium* strains in the presence or absence of metabolic activation (McCann et al. 1975; Narbonne et al. 1987; Sakai et al. 1985). Naphthalene was not mutagenic, with or without metabolic activation, in the Pol A- or Rec assays in several *Escherichia coli* strains (Mamber et al. 1983). Naphthalene did not damage DNA (as assayed by the induction of the SOS-repair system) in *E. coli* PQ37 (Mersch-Sundermann et al. 1993), in *E. coli* K12 (Mamber et al. 1984), or in *S. typhimurium* TA1535/p5K1002 (Nakamura et al. 1987).

1,2-Naphthoquinone induced reverse mutations in several *S. typhimurium* strains without a metabolic activation system (Flowers-Geary et al. 1996), and naphthalene, in the presence of rat liver metabolic activation, induced reverse mutations in the marine bacterium *Vibrio fischeri* (Arfsten et al. 1994).

In Vitro Eukaryotic Gene Mutation, Cytogenetic, or DNA Damage Assays for Naphthalene. *In vitro* eukaryotic gene mutation assays are restricted to a single report that naphthalene and 1,4-naphthoquinone (1,2-naphthoquinone was not tested) did not induce mutations at the hprt and tk loci in human

Table 3-4. Results of Genotoxicity Testing of Naphthalene or Metabolites[a]

Assay	Test system	Dose/ concentration	HID or LED	Result	Reference
Bacterial gene mutation assays					
Reverse mutation	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100	100 µg/plate ±S9 activation	100	Negative	McCann et al. 1975
	S. typhimurium TA1535, TA1537, TA98, TA100	0.3–100 µg/plate ±S9 activation	100	Negative	Mortelmans et al. 1986
	S. typhimurium TA1535, TA1537, TA98, TA100	0.3–100 µg/plate ±S9 activation	100	Negative	NTP 1992a
	S. typhimurium TA1537, TA1538	10–200 µg/plate ±S9 activation	100	Negative, toxic above 100 µg/plate	Gatehouse 1980
	S. typhimurium TA98, TA100	10–50 µg/plate ±S9 activation	50	Negative	Bos et al. 1988
	S. typhimurium TA1535, TA1537, TA98, TA100	0.03–30 µmol/plate ±S9 activation	3	Negative, toxic above 3 µmol/plate	Florin et al. 1980
	S. typhimurium TA1535, TA1537, TA98, TA100	250 µg/plate ±S9 activation	250	Negative	Sakai et al. 1995
	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	3–300 µg/plate ±S9 activation	300	Negative, toxic above 300 µg/plate	Godek 1985
	S. typhimurium TM677	1–2 mM ±S9 activation	2	Negative	Kaden et al. 1979
	S. typhimurium TA98, TA1535	5–1,000 µg/plate ±S9 activation	1,000	Negative	Narbonne et al. 1987
	S. typhimurium UTH8413, UTH8414, TA98, TA100	100–2,000 µg/plate ±S9 activation	2,000	Negative	Conner et al. 1985
	S. typhimurium TA1535, TA1537, TA98, TA100	1,000 µg/plate ±S9 activation	1,000	Negative (1-naphthol)	McCann et al. 1975
	S. typhimurium TA98, TA1535	5–1,000 µg/plate ±S9 activation	1,000	Negative (1-naphthol)	Narbonne et al. 1987
	S. typhimurium TA1535, TA1537, TA98, TA100	250 µg/plate ±S9 activation	250	Negative (1,4-naphthoquinone)	Sakai et al. 1995

Table 3-4. Results of Genotoxicity Testing of Naphthalene or Metabolites[a]

Assay	Test system	Dose/ concentration	HID or LED	Result	Reference
Bacterial gene mutation assays (continued)					
	S. typhimurium TA97a, TA98, TA100, TA104	0–100 nmol/plate ±S9 activation	17.5	Positive (1,2-naphthoquinone), 1.8- to 3.4-fold increase without S9; +S9 results similar to -S9 results	Flowers-Geary et al. 1996
SOS response	*S. typhimurium* TA1535/p5K1002 (uMuC-lacZ)	83 µg/mL ±S9 activation	83	Negative	Nakamura et al. 1987
	Escherichia coli K12 inductest (λ lysogen GY5027; uvrB-, envA-)	2,000 µg/plate ±S9 activation	2,000	Negative	Mamber et al. 1984
SOS chromotest	*E. coli* PQ37 (sfiA::lacZ fusion)	0.156–10.0 µg/assay ±S9 activation	10	Negative	Mersch-Sundermann et al. 1993
Pol A- or Rec assay	*E. coli* WP2/WP10 (uvrA-, recA-)	2,000 µg/mL ±S9 activation	2,000	Negative	Mamber et al. 1983
	E. coli WP2/WP67 (uvrA-, pol A-)	Dose not specified ±S9 activation	NS	Negative	Mamber et al. 1983
Pol A- or Rec assay	*E. coli* WP2/WP3478 (pol A-)	Dose not specified ±S9 activation	NS	Negative	Mamber et al. 1983
Mutatox (reversion to luminescence)	*Vibrio fischeri* M169	Up to 5,000 µg/tube ±S9 activation	0.203 0.625	Negative without S9 activation Positive with S9 activation	Arfsten et al. 1994
***In vitro* eukaryotic gene mutation, cytogenetic, or DNA damage assays**					
Mutation at hprt and tk loci	Human B-lymphoblastoid cell line MCL-5	40 µg/mL	40	Negative	Sasaki et al. 1997
	Human B-lymphoblastoid cell line MCL-5	40 µg/mL	40	Negative (1,4-naphthoquinone)	Sasaki et al. 1997
Chromosomal aberrations	Chinese hamster ovary cells	15–75 µg/mL ±S9 activation	30 75	Positive with S9 activation Negative without S9 activation	NTP 1992a
Chromosomal aberrations	Preimplantation whole mouse embryos	0.16 mM ±S9 activation	0.16	Positive, more pronounced with S9 activation	Gollahon et al. 1990 [abstract only]

Table 3-4. Results of Genotoxicity Testing of Naphthalene or Metabolites[a]

Assay	Test system	Dose/ concentration	HID or LED	Result	Reference
***In vitro* eukaryotic gene mutation, cytogenetic, or DNA damage assays (continued)**					
Sister chromatid exchange	Human mononuclear leukocytes	100 µM ± human liver microsomes	100	Negative	Tingle et al. 1993; Wilson et al. 1995
Sister chromatid exchange	Human mononuclear leukocytes	0–100 µM ± human liver microsomes	10	Positive (1,2- and 1,4-naphthoquinone) Negative (naphthalene 1,2-epoxide)	Wilson et al. 1996
Sister chromatid exchange	Chinese hamster ovary cells	9–90 µg/mL ±S9 activation	27	Positive with S9 in the second of two trials and without S9 in both trials	NTP 1992a
Alkaline elution (*in vitro*)	Rat hepatocytes	3 mM, 3-hour exposure	3 mM	Negative for increased incidence of DNA single-strand breaks	Sina et al. 1983
Unscheduled DNA synthesis (*in vitro*)	Rat primary hepatocytes	0.16–5,000 µg/mL	16	Negative, toxic above 16 µg/mL	Barfknecht et al. 1985
	Rat primary hepatocytes	0.5–1,000 nM/mL	1,000	Negative (1-naphthol, 2-naphthol)	Probst et al. 1981
Cell transformation	Fischer rat embryo cells (F1706P96)	0.1, 0.5 µg/mL	0.5	Negative	Freeman et al. 1973
	Syrian baby hamster kidney cells (BHK-21C13)	0.08–250 µg/mL +S9	250	Negative	Purchase et al. 1978
	Mouse (BALB/c) whole mammary gland cultures	0.001–1.0 µg/gland	0.1	Negative, cytotoxic above 0.1 µg/gland	Tonelli et al. 1979
	Mouse BALB/c 3T3 cell culture	15–150 µg/mL	150	Negative, toxic at highest dose	Rundell et al. 1983
	Human diploid fibroblasts (WI-38)	0.08–250 µg/mL +S9	250	Negative	Purchase et al. 1978
***In vivo* eukaryotic gene mutation, cytogenetic, or DNA damage assays**					
Somatic mutation, recombination	*Drosophila melanogaster*	1, 5, 10 mM (feeding larvae)	5	Positive, loss of heterozygosity of two recessive wing genes (about 2-fold increase in number of wing spots)	Delgado-Rodriguez et al. 1995
Micronuclei induction	Male ICR Swiss mice: bone marrow cells	50, 250, and 500 mg/kg gavage	500	Negative	Harper et al. 1984

Table 3-4. Results of Genotoxicity Testing of Naphthalene or Metabolites[a]

Assay	Test system	Dose/ concentration	HID or LED	Result	Reference
***In vivo* eukaryotic gene mutation, cytogenetic, or DNA damage assays (continued)**					
	Male and female CD-1 mice: bone marrow cells	250 mg/kg intraperitoneal	250	Negative	Sorg 1985
Micronuclei induction	Salamander larvae (*Pleurodeles waltl*): erythrocytes	0.125–0.5 ppm in the tank water	0.25	Positive at 0.5 ppm, weakly positive at 0.25 ppm	Djomo et al. 1995
Alkaline elution (*in vivo*)	DNA from hepatocytes of female rats given single oral doses	359 mg/kg oral	359	Negative for DNA single-strand breaks	Kitchin et al. 1992, 1994
Unscheduled DNA synthesis (*in vivo*)	Hepatocytes from rats given single oral doses	600, 1,000, and 1,600 mg/kg gavage	1,600	Negative	RTC 1999
DNA fragmentation	DNA fragmentation in liver or brain tissue from mice given single doses	0, 3, 32, and 158 mg/kg (0.01, 0.1, 0.5 of LD50=316 mg/kg)	32	Positive (1.0- to 1.5-fold and 1.8- to 2.2-fold increase in DNA fragmentation at 32 and 158 mg/kg, respectively)	Bagchi et al. 2002
DNA fragmentation	DNA fragmentation in liver or brain tissue from rats given daily doses for up to 120 days	0, and 110 mg/kg in corn oil	110	Positive (1.9- to 2.5-fold maximal increases in DNA fragmentation in brain and liver tissue)	Bagchi et al. 1998a
DNA fragmentation	DNA fragmentation in liver or brain tissue from p53-deficient and standard mice given single oral doses	0, 3, 32, and 158 mg/kg (0.01, 0.1, and 0.5 of LD50=316 mg/kg)	158 (std) 3 (-p53)	Positive (1.8- to 3.9-fold increases in DNA fragmentation in brain and liver tissue; p53-deficient (tumor suppressor gene) strain was more sensitive	Bagchi et al. 2000
Neoplastic transformation (*in vivo*)	F344 partially hepatectomized rats (sex not specified)	100 mg/kg gavage (in corn oil)	100	Negative for gamma-glutamyl transpeptidase foci	Tsuda et al. 1980

[a]Metabolites are noted in result column.

DNA=dioxyribonucleic acid; HID=highest ineffective dose for negative tests; LED=lowest effective dose for positive tests; NS=not specified; SOS=an emergency system to repair single strand DNA breaks

lymphoblastoid cells (Sasaki et al. 1997). However, naphthalene (in the presence of rat liver metabolic activation) induced chromosomal aberrations in Chinese hamster ovary cells (NTP 1992a) and preimplantation whole mouse embryos (Gollahon et al. 1990). Naphthalene also induced sister chromatid exchanges (in the presence or absence of rat liver metabolic activation) in Chinese hamster ovary cells (NTP 1992a), but did not do so in human mononuclear leukocytes in the presence or absence of human liver microsomes (Tingle et al. 1993; Wilson et al. 1995). In contrast, 1,2-naphthoquinone and 1,4-naphthoquinone (but not 1,2-naphthalene oxide), in the absence of metabolic activation, induced sister chromatid exchanges in human leukocytes at concentrations (10 and about 50 μM) that depleted cellular glutathione levels and induced about 35-45% cell death (Wilson et al. 1996). Naphthalene did not induce cell transformations in several mammalian cell types (see Table 3-4) or DNA single-strand breaks (Sina et al. 1983) or unscheduled DNA synthesis (Barfknecht et al. 1985; Probst et al. 1981) in rat hepatocytes.

In cell-free test systems (not included in Table 3-4), 1,2-naphthoquinone formed N7 adducts with deoxyguanosine (McCoull et al. 1999) and caused DNA strand scission in the presence of NADPH and copper via reactive oxygen species from a Cu(II)/Cu(I) oxidation/reduction cycle (Flowers et al. 1997).

In Vivo Eukaryotic Gene Mutation, Cytogenetic, or DNA Damage Assays for Naphthalene. Naphthalene was mutagenic in *Drosophila melanogaster* (Delgado-Rodriquez et al. 1995), but no *in vivo* mutagenicity tests of naphthalene or its metabolites are available in mammalian systems (Table 3-4). Naphthalene induced micronuclei in erythrocytes of salamander (*Pleurodeles waltl*) larvae exposed to concentrations of 0.5 mM, but did not induce micronuclei in bone marrow of mice given single oral doses (50, 250, or 500 mg/kg) or intraperitoneal doses (250 mg/kg) (Harper et al. 1984; Sorg 1985). Naphthalene did not cause increased single-stranded DNA breaks in hepatocytes of rats given single oral doses of 359 mg/kg (Kitchin et al. 1992, 1994), unscheduled DNA synthesis in hepatocytes from rats given single doses as high as 1,600 mg/kg (RTC 1999), or transformation foci (γ-glutamyl transpeptidase-positive) in livers of F344 partially hepatectomized rats given single 100 mg/kg doses, but did cause DNA fragmentation in brain and liver tissue from mice given single doses of 32 or 158 mg/kg (Bagchi et al. 2000, 2002) and rats exposed to 110 mg/kg/day for up to 120 days (Bagchi et al. 1998a). In the DNA fragmentation assays, the effect was accompanied by increased lipid peroxidation in the same tissues. It is unclear whether the apparent DNA damage in these assays was due to direct effects of naphthalene metabolites or reactive oxygen species or was secondary to cell death induced at an extranuclear site.

No studies were located that examined possible genotoxic effects of naphthalene or its metabolites in sensitive target tissues of naphthalene in rodents (lung and nasal epithelial tissue).

Genotoxicity Assays for 1-Methylnaphthalene and 2-Methylnaphthalene. No studies were located that documented genotoxic effects of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals by any route of exposure. Data are limited to one *in vitro* study where 1-methylnaphthalene and 2-methylnaphthalene failed to induce chromosomal aberrations or sister chromatid exchanges in human peripheral lymphocytes (Kulka et al. 1988). In an *in vitro* microbial assay employing *S. typhimurium*, mutagenic activity was not detected with either compound, with either the presence or absence of microsomal activation (Florin et al. 1980). These studies are presented in Table 3-5.

3.4 TOXICOKINETICS

Little information is available that documented the toxicokinetics of naphthalene in humans by any route of exposure. No information on the toxicokinetics of 1-methylnaphthalene or 2-methylnaphthalene in humans was located. The available animal data pertaining to naphthalene are described in the following sections. The relevance of this information to the toxicokinetics of naphthalene in exposed humans, however, is not known.

No toxicokinetic data on 1-methylnaphthalene-exposed animals were located. Animal data pertaining to 2-methylnaphthalene were limited.

3.4.1 Absorption

Based on the presence of adverse effects following exposure, humans and animals can absorb naphthalene by pulmonary, gastrointestinal, and cutaneous routes. However, the rate and extent of naphthalene absorption are unknown in many instances.

3.4.1.1 Inhalation Exposure

Clinical reports suggest that prolonged exposure to naphthalene vapors can cause adverse health effects in humans (Harden and Baetjer 1978; Linick 1983; Valaes et al. 1963). Unfortunately, the rate and extent of naphthalene absorption were not determined in these studies. Presumably naphthalene moves across the alveolar membrane by passive diffusion through the lipophilic matrix.

Table 3-5. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
1-Methylnaphthalene				
Prokaryotic organisms:				
Salmonella typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Florin et al. 1980
Mammalian cells:				
Human lymphocytes	Chromosomal aberration, sister chromatid exchange	–	–	Kulka et al. 1988
2-Methylnaphthalene				
Prokaryotic organisms:				
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Florin et al. 1980
Mammalian cells:				
Human lymphocytes	Chromosomal aberration, sister chromatid exchange	–	–	Kulka et al. 1988

– = negative result

No animal data that documented the absorption of naphthalene after inhalation were located. The only data observed in animal studies involved localized effects in the lungs and nasal passages. Thus, it is not possible to conclude that they were the consequence of absorbed naphthalene. However, absorption can be presumed to occur based on the human data.

No information has been located that documented the absorption of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals after inhalation exposure. Fogging studies in dogs suggest some absorption of these chemicals through the alveolar membrane.

3.4.1.2 Oral Exposure

Several case reports indicate that naphthalene ingested by humans can be absorbed in quantities sufficient to elicit toxicity (Bregman 1954; Chusid and Fried 1955; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Mackell et al. 1951; Ojwang et al. 1985; Santhanakrishnan et al. 1973; Shannon and Buchanan 1982; Zuelzer and Apt 1949). However, no studies have been located that report the rate or extent of absorption. Absorption of naphthalene presumably occurs by passive diffusion through the lipophilic matrix of the intestinal membrane.

In one patient who died as a result of naphthalene ingestion, 25 mothballs were found in the stomach 5 days after her death (Kurz 1987). A single naphthalene mothball reportedly weighs between 0.5 and 5 g depending on its size (Ambre et al. 1986; Siegel and Wason 1986). The gastric contents of a person who mistakenly ingested naphthalene flakes still smelled strongly of naphthalene at least 2 days following ingestion (Ojwang et al. 1985). These findings suggest that dissolved naphthalene is transported slowly into the intestines. Uptake from the intestines is governed by the partition coefficient between the materials in the intestinal lumen and the membrane lipids. Ingestion of mothballs or other forms of particulate naphthalene will lead to continued absorption over a period of several days as the solid dissolves. Unfortunately, none of the human data permit a quantitative evaluation of absorption coefficients or rates.

No information that documented the absorption of naphthalene after oral administration to animals has been located. The occurrence of systemic effects in dogs, mice, rats, and rabbits indicates that gastrointestinal absorption does occur.

No information was located that documented the absorption of 1-methylnaphthalene in humans or animals after oral administration. Systemic effects observed after the ingestion of 1-methylnaphthalene demonstrate that intestinal absorption does occur in rats.

No information has been located that documented absorption in humans after oral exposure to 2-methylnaphthalene. Small doses of 2-methylnaphthalene appear to be rapidly absorbed from the gastrointestinal tract in guinea pigs. At least 80% of a 10 mg/kg oral dose of 2-methylnaphthalene was absorbed within 24 hours based on recovery of the radiolabel in the urine (Teshima et al. 1983).

3.4.1.3 Dermal Exposure

Several cases of naphthalene toxicity in neonates have been reported in which the proposed route of exposure was dermal (Dawson et al. 1958; Schafer 1951). Each case involved the use of diapers which had been stored in contact with naphthalene (mothballs or naphthalene flakes). The authors proposed that the naphthalene was absorbed through the skin, causing hemolytic anemia. It was suggested that this absorption may have been enhanced by the presence of oils which had been applied to the babies' skin (Schafer 1951). Inhalation of vapors from the treated diapers probably contributed to the total exposure.

^{14}C-Naphthalene was rapidly absorbed when the neat material (43 µg) was applied for a 48-hour period under a sealed glass cap to shaved 13-cm^2 areas of rat skin. Half of the sample (3.3 µg/cm^3) was absorbed in 2.1 hours (Turkall et al. 1994). When the naphthalene was mixed with either a sandy soil or a clay soil prior to contact with the skin, the presence of the soil slowed the absorption (Turkall et al. 1994). The absorption half-time from the clay and sandy soil samples were 2.8 and 4.6 hours, respectively. The rate of absorption did not influence the total amount of naphthalene absorbed in 48 hours since the areas under the plasma concentration curve did not differ significantly with any of the three exposure scenarios (0.42–0.63%/mL hour). The authors proposed that naphthalene was absorbed more slowly from the sandy soil than the clay soil because the sandy soil had a higher organic carbon content (Turkall et al. 1994). The sandy soil contained 4.4% organic matter and the clay soil 1.6% organic matter.

No studies were located that examined the absorption of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals after dermal administration.

3.4.2 Distribution

There are limited data concerning the distribution of naphthalene in human tissues. Naphthalene was present in 40% of the adipose tissue samples that were analyzed as part of the National Human Adipose Tissue Survey (EPA 1986g). The maximum concentration observed was 63 ng/g. Naphthalene was also detected in human milk samples (concentration not reported) (Pellizzari et al. 1982). The sources of naphthalene in these milk and body fat samples are not known.

Information is available for the distribution of naphthalene in swine after oral exposure, the distribution of naphthalene in rats after dermal exposure, and the distribution of 2-methylnaphthalene in guinea pigs after oral exposure. No data were located for the inhalation exposure routes and no data were identified on the distribution of 1-methylnaphthalene by any route of exposure.

3.4.2.1 Inhalation Exposure

No studies were located that examined the distribution of naphthalene, 1-methylnaphthalene, or 2-methyl-naphthalene in humans or animals after inhalation exposure.

3.4.2.2 Oral Exposure

Naphthalene can cross the human placenta in concentrations high enough to cause red cell hemolysis and lead to anemia in newborn infants of mothers who consumed naphthalene during pregnancy (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958).

The distribution of naphthalene and its metabolites in young pigs given a single dose of 0.123 mg/kg (4.8 Ci/kg) ^{14}C-labeled naphthalene was monitored at 24 and 72 hours (Eisele 1985). At 24 hours, the highest percentage of the label (3.48±2.16% dose/mg tissue) was in the adipose tissue. The kidneys had the next highest concentration of label (0.96% dose/mg tissue), followed by the liver (0.26±0.06% dose/mg tissue) and lungs (0.16% dose/mg tissue). The heart contained 0.09±0.04% dose/mg tissue and the spleen contained 0.07±0.01% dose/mg tissue. At 72 hours, the amount of label in the fat had fallen to 2.18±1.16% dose/mg tissue, that in the liver to 0.34±0.24% dose/mg tissue, and the kidneys and lungs contained the same concentration (0.26% dose/mg tissue).

Pigs were also given oral doses of 0.006 mg/kg/day (0.22 Ci/kg/day) ^{14}C-labeled naphthalene for 31 days (Eisele 1985). With repeated administration of the radiolabel, the tissue distribution differed considerably from that observed with a single dose of the compound. The highest concentration of label was in the lungs (0.15% dose/mg tissue), followed by the liver and heart (0.11% dose/mg tissue). There was very little label in the fat tissue (0.03% dose/mg tissue). The spleen had 0.09±0.05% dose/mg tissue and the kidney had 0.09% dose/mg tissue.

In one dairy cow, naphthalene distributed to milk with both single and repeated doses of ^{14}C-labeled naphthalene. The label was distributed between the milk and the milk fat (Eisele 1985). When the cow was given naphthalene for a 31-day period, the amount of label found in the milk remained relatively constant throughout the exposure period. The amount in the milk fat was lower for the first 7 days than it was for the remainder of the exposure.

The tissue distribution of 2-methylnaphthalene was measured in guinea pigs 3, 6, 24, and 48 hours after oral administration of tritium-labeled 2-methylnaphthalene (10 mg/kg; 59 µCi/kg) (Teshima et al. 1983). The highest concentration of label was present in the gallbladder with 20.17 µg at 3 hours and 15.72 µg at 6 hours. (All concentrations are expressed in µg equivalents of ^{3}H/g wet tissue.) At 24 hours, the value fell to 0.43 µg and at 48 hours, to 0.04 µg. The presence of label in the gallbladder presumably reflects the excretion of hepatic metabolites in the bile. The values for the kidney were 5.64 µg at 3 hours, 7.62 µg at 6 hours, 0.29 µg at 24 hours, and 0.09 µg at 48 hours.

Radiolabelled compound was detected in the liver immediately after exposure (Teshima et al. 1983). When converted to units of mass, hepatic concentrations were 1.71 µg at 3 hours and 2.66 µg at 6 hours, falling to 0.18 µg at 24 hours. Lung concentrations were similar to those for blood at all time points. The amount in blood at 3 hours was 0.75 µg and that for the lungs was 0.69 µg; at 6 hours, the blood had a concentration of 0.71 µg and the lung had 0.76 µg. The half-life of 2-methylnaphthalene in the blood was 10.4 hours. The decay of naphthalene in the other tissues examined was described as biphasic.

3.4.2.3 Dermal Exposure

No information was located that documented the distribution of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene in humans after dermal exposure.

In rats, radiolabel from naphthalene distributed to the ileum, duodenum, and kidney (0.01−0.02% of initial dose) when tissues were analyzed 48 hours after naphthalene contact with the skin (Turkall et al. 1994). The largest concentration was found at the site of application (0.56% of initial dose). A total of 20 tissues were evaluated; the percentage of label in all other tissues was minimal.

No information that documented the distribution of 1-methylnaphthalene or 2-methylnaphthalene in dermally exposed animals was located.

3.4.2.4 Other Routes of Exposure

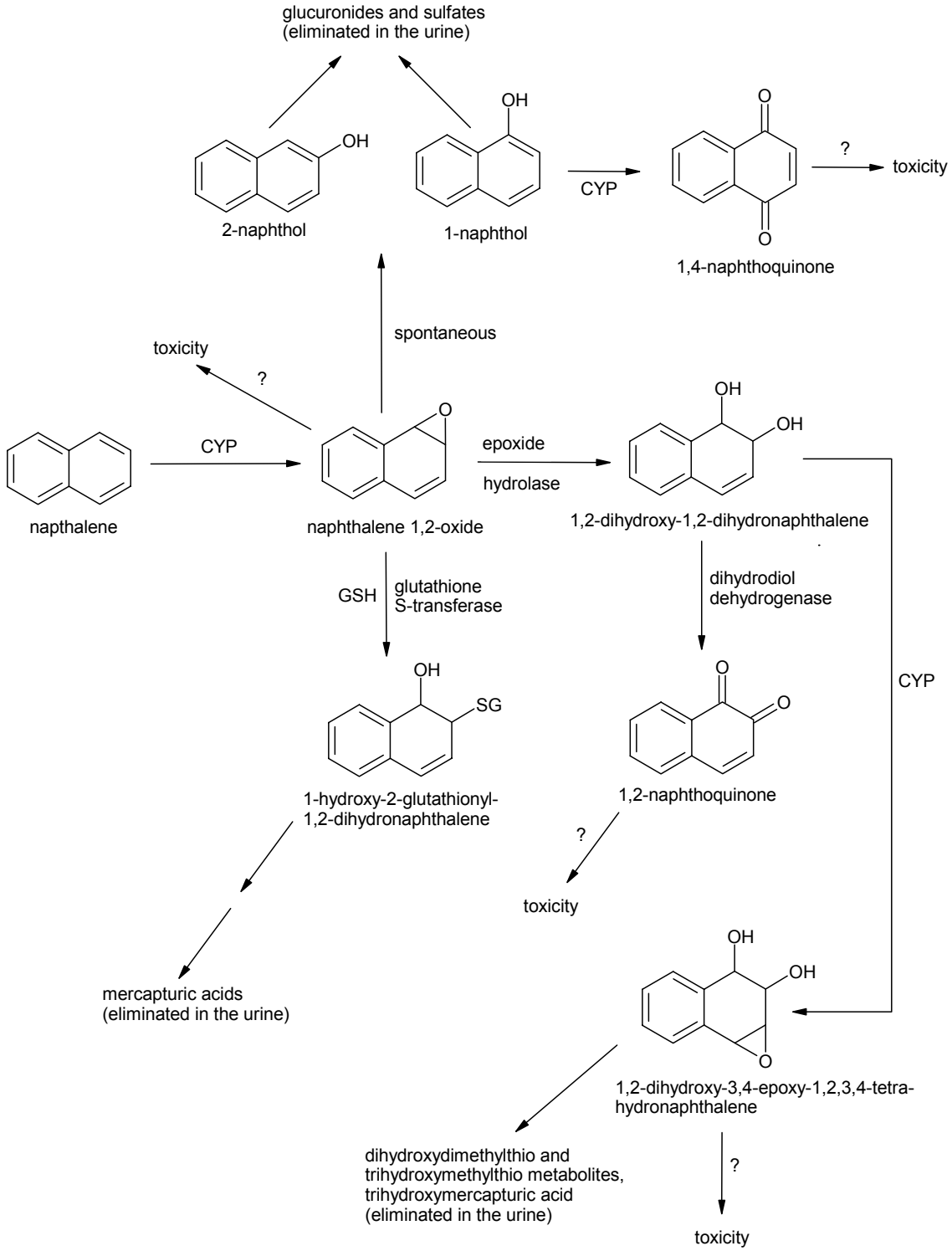
After intraperitoneal administration in mice, ^{14}C-labeled 2-methylnaphthalene distribution was measured in the fat, kidney, liver, and lung for 24 hours (Griffin et al. 1982). The amount of label in the fat peaked 3 hours after exposure and remained higher than the amount of label in other tissues at 8 hours. The liver, kidney, and lung followed the fat in order of decreasing concentration. The maximum concentration in the fat was 13 nmol equivalents/mg wet weight. The maximum value for the liver was 3.5 nmol equivalents/mg wet weight at 1 hour. Maximum values were about 1.75 nmol equivalents/mg wet weight for the kidneys at 2 hours and 0.8 nmol equivalents/mg wet weight for the lungs at 4 hours.

3.4.3 Metabolism

The metabolism of naphthalene in mammalian systems has been studied extensively and is depicted in Figure 3-3. The metabolic scheme in Figure 3-3 illustrates that there are multiple reactive metabolites formed from naphthalene: 1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene. This section presents an overview of the metabolic scheme and the evidence for the involvement of the 1,2-epoxide and the naphthoquinones in naphthalene toxicity. The fourth metabolite listed above is expected to be reactive, but its potential role in naphthalene toxicity has not been investigated. A recent review of the metabolism and bioactivation of naphthalene has been published by Buckpitt et al. (2002).

The first step in naphthalene metabolism is catalyzed by cytochrome P-450 (CYP) oxygenases and produces a reactive electrophilic arene epoxide intermediate, 1,2-naphthalene oxide. In mammalian systems, several CYP isozymes have been demonstrated to metabolize naphthalene, including 1A1, 1A2,

Figure 3-3. Scheme for Naphthalene Metabolism and Formation of Multiple Reactive Metabolites, Which May Be Involved in Naphthalene Toxicity*



CYP = cytochrome P450 enzyme(s); GSH = reduced glutathione; SG = glutathione

*Adapted from Buckpitt et al. (2002) and Waidyanatha et al. (2002)

1B1, 3A7, 3A5 (Juchau et al. 1998), 2E1 (Wilson et al. 1996), 2F2 (Buckpitt et al. 1995; Shultz et al. 1999), and 2B4 (Van Winkle et al. 1996). The epoxide can spontaneously rearrange to form naphthols (predominantly 1-naphthol) and subsequently conjugate with glucuronic acid or sulfate to form conjugates, which are excreted in urine.

Alternatively, the 1,2-epoxide can react with tissue macromolecules. This reaction is thought to be involved in several aspects of naphthalene toxicity, especially injury to Clara cells (ciliated cells in the epithelium of proximal and distal airways of the lung) from acute exposure to naphthalene (Buckpitt et al. 2002; Zheng et al. 1997). In pH 7.4 buffer, the epoxide has been shown to have a half-life of approximately 2–3 minutes, which is extended by the presence of albumins to about 11 minutes (Buckpitt et al. 2002; Kanekal et al. 1991). Mice are markedly more susceptible than rats to acute naphthalene-induced Clara cell injury (Buckpitt et al. 1992; West et al. 2001). The susceptibility difference apparently extends to chronic exposure scenarios. Mice exposed by inhalation to 10 or 30 ppm naphthalene for 2 years showed lung inflammation, but rats exposed to concentrations up to 60 ppm showed no lung inflammation (Abdo et al. 2001; NTP 1992a, 2000). The species difference in lung susceptibility has been correlated with higher rates of formation of a specific enantiomeric epoxide (1*R*,2*S*-naphthalene oxide) in lung microsomes and isolated dissected airways of mice compared with rats (Buckpitt et al. 1992, 1995). Rat, hamster, and monkey lung microsomes preferentially formed the 1*S*,2*R*-naphthalene oxide enantiomer and showed lower rates of formation of epoxides than mouse lung microsomes (Buckpitt et al. 1992). Microsomes from human lymphoblastoid cells expressing recombinant human CYP2F1 also showed preferential formation of the 1*S*,2*R*-naphthalene oxide enantiomer, providing some evidence that human transformation of naphthalene to reactive epoxides in lung tissue may be more like rats than mice (Lanza et al. 1999).

In contrast to the lung, species differences in susceptibility at another sensitive target of naphthalene, the olfactory and respiratory epithelia of the nose, do not correlate with differences in rates of transformation to 1,2-epoxide derivatives in extracts of olfactory tissue (Buckpitt et al. 1992; Plopper et al. 1992a). Metabolic rates (units of nmol naphthalene converted to epoxide derivatives/minute/mg protein) in olfactory tissue extracts showed the following order: mouse (87.1) > rat (43.5) > hamster (3.9). However, rats were more susceptible to naphthalene-induced cell injury than mice or hamsters. The lowest single intraperitoneal doses producing necrosis and exfoliation in olfactory epithelium were 200 mg/kg in rats and 400 mg/kg in mice and hamsters. These observations suggest that the reasons for species differences in susceptibility to naphthalene toxicity are complex and do not solely involve the formation of the 1,2-epoxide metabolites. Although CYP monooxygenases, which might be involved in naphthalene

metabolism and bioactivation, have been demonstrated to exist in nasal respiratory epithelial and olfactory epithelial tissue from rodents and humans (Thornton-Manning and Dahl 1997), studies designed to specifically characterize metabolism of naphthalene in nasal tissue are restricted to those by Buckpitt et al. (1992) and Plopper et al. (1992a).

In addition to being converted to the naphthols, the 1,2-epoxide can be conjugated with glutathione via glutathione-S-transferase catalysis. Figure 3-3 shows one such conjugate, 1-hydroxy-2-glutathionyl-1,2-dihydronaphthalene. The glutathionyl conjugates are converted in several steps to mercapturic acids, which are excreted in the urine. The conjugation of the epoxide is thought of as a detoxication mechanism, as evidenced by studies showing that glutathione depletion increased the degree of acute naphthalene-induced Clara cell injury in mice (Warren et al. 1982; West et al. 2000a). In addition, elevated activities of γ-glutamylcysteine synthetase, the enzyme catalyzing the rate limiting step in glutathione synthesis, were observed in dissected airways from mice that developed tolerance to acute naphthalene Clara cell cytotoxicity (West et al. 2000a).

The 1,2-epoxide can also be enzymatically hydrated by epoxide hydrolase to form 1,2-dihydroxy-1,2-dihydronaphthalene (Figure 3-3). This 1,2-dihydrodiol derivative was the major stable metabolite of naphthalene produced by human liver microsomes, whereas the major stable metabolite formed by mouse liver microsomes was 1-naphthol (Tingle et al. 1993). In the presence of an inhibitor of epoxide hydrolase (trichloropropene oxide), the major stable metabolite with human liver microsomes was 1-naphthol. How this species difference in liver metabolism may relate to the human relevance of toxicity of inhaled naphthalene in sensitive target tissues in the nose and lung of mice is unknown.

The 1,2-dihydrodiol can be catalytically transformed by dihydrodiol dehydrogenase to 1,2-naphtho-quinone (also known as naphthalene-1,2-dione). 1,2-Naphthoquinone is both reactive itself and capable of producing reactive oxygen species through redox cycling (Flowers et al. 1997) and has been shown to be mutagenic in several strains of *S. typhimurium* (Flowers-Geary et al. 1996). In isolated Clara cells incubated with 0.5 mM naphthalene, 1,2-naphthoquinone was the major naphthalene derivative covalently bound to proteins, although covalent binding with the 1,2-epoxide was also observed (Zheng et al. 1997). The formation of the other naphthoquinone, 1,4-naphthoquinone, from 1-naphthol, presumably via a CYP monooxygenase, has been proposed based on the finding that, following incubations of liver microsomes with 1-naphthol, ethylene diamine, a compound that reacts readily with 1,2-naphthoquinone, did not trap reactive metabolites (D'Arcy Doherty et al. 1984). Cysteinyl adducts of both 1,2-naphthoquinone and 1,4-naphthoquinone (and of 1,2-naphthalene oxide) with hemoglobin and albumin have been detected in

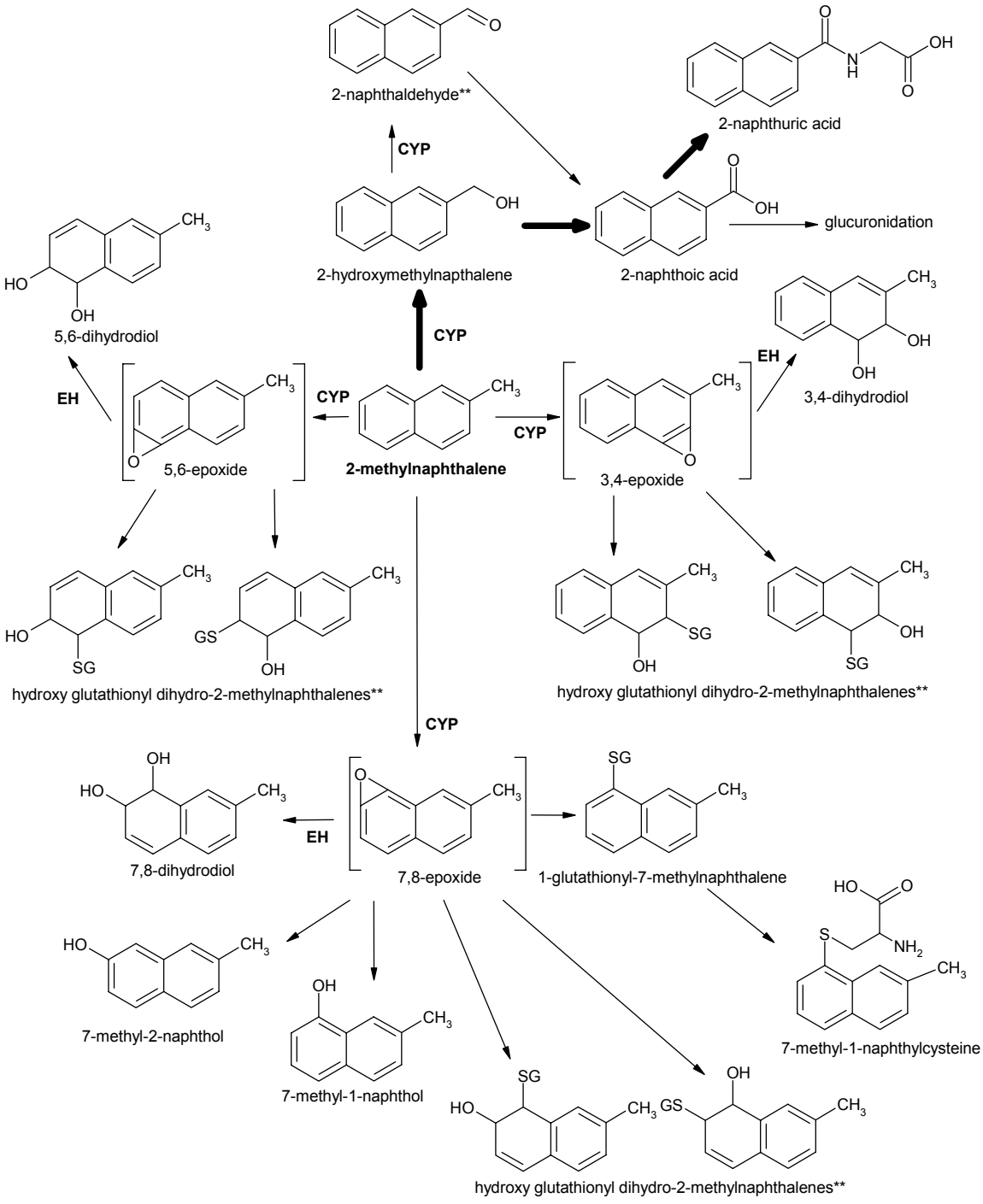
blood of rats given single oral doses of naphthalene ranging from 100 to 800 mg/kg (Troester et al. 2002; Waidyanatha et al. 2002). Levels of 1,2-naphthalene oxide adducts were greater than levels of 1,2-naphthoquinone adducts, which were greater than levels of 1,4-naphthoquinone adducts (Troester et al. 2002; Waidyanatha et al. 2002). In *in vitro* studies with whole human blood samples, 1,2- or 1,4-naphthoquinone induced increased frequencies of sister chromatid exchanges at concentrations ≥10 μM, whereas naphthalene 1,2-epoxide did not at concentrations up to 100 μM (Wilson et al. 1996). Similarly, incubation of human mononuclear leukocytes with 1,2-naphthoquinone or 1,4-naphthoquinone caused significant depletion of cellular glutathione levels and significant cytotoxicity at concentrations between 1 and 100 μM, whereas naphthalene 1,2-epoxide did not display these toxic actions in this concentration range (Wilson et al. 1996).

1,2-Naphthoquinone formed in lens tissue is thought to be involved in naphthalene-induced cataracts in rats and rabbits. The enzyme involved in the transformation of the 1,2-dihydrodiol to 1,2-naphthoquinone in lens tissue is thought to be aldose reductase (this enzyme is not specified in Figure 3-3). Support for this hypothesis includes findings that aldose reductase inhibitors prevent cataract formation in naphthalene-fed rats (Tao et al. 1991; Xu et al. 1992a), dihydrodiol dehydrogenase is apparently absent in rat lens (Greene et al. 2000), and aldose reductase appears to be the only enzyme in rat lens that can transform 1,2-dihydroxy-1,2-dihydronaphthalene to 1,2-naphthoquinone (Sugiyama et al. 1999).

Support for the *in vivo* formation of another potentially reactive metabolite, 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene, comes from the identification of several urinary metabolites, including a number of trihydroxytetrahydromethylthio derivatives (Horning et al. 1980) and a trihydroxytetrahydro-mercapturic acid (Pakenham et al. 2002). These urinary metabolites, however, are minor, and the importance of their common proposed precursor in naphthalene toxicity is unstudied to date. Figure 3-3 proposes an oxidative transformation of dihydrodiol derivative to the tetrahydrodiol epoxide derivative via CYP catalysis.

The methyl substituent of 1-methylnaphthalene and 2-methylnaphthalene presents the opportunity for side chain oxidation reactions in addition to the ring oxidation, which is the sole initial step in naphthalene metabolism. A proposed metabolic scheme for 2-methylnaphthalene in mammals is shown in Figure 3-4. CYP monooxygenases catalyze the first competing steps, which involve oxidation at the methyl group (the predominant path) or oxidation at several positions on the rings (Figure 3-4). No information was located that documented the metabolism of 1-methylnaphthalene. It may be similar to that for 2-methyl-naphthalene with oxidation of the side chain and the ring.

Figure 3-4. Metabolism of 2-Methylnaphthalene*



[ ] = putative metabolite; CYP = cytochrome P450 enzyme(s); EH = epoxide hydrolase; GS = glutathione

*Adapted from Buckpitt and Franklin (1989), Shultz et al. (2001), and Teshima et al. (1983)
**Metabolites identified *in vitro* only

Approximately 50-80% of 2-methylnaphthalene is oxidized at the 2-methyl group to produce 2-hydroxymethylnaphthalene (Breger et al. 1983; Teshima et al. 1983). 2-Hydroxymethylnaphthalene is further oxidized to 2-naphthoic acid (Grimes and Young 1956; Melancon et al. 1982; Teshima et al. 1983), either directly or through the intermediate, 2-naphthaldehyde (Figure 3-4). 2-Naphthaldehyde has been detected only following *in vitro* incubation of 2-methylnaphthalene with recombinant mouse CYP2F2 (Shultz et al. 2001). 2-Naphthoic acid may be conjugated with glycine or with glucuronic acid (Figure 3-4). The conjugation of 2-naphthoic acid with glycine forms 2-naphthuric acid, the most prevalent metabolite of 2-methylnaphthalene detected in urine of exposed animals (Grimes and Young 1956; Melancon et al. 1982; Teshima et al. 1983).

Approximately 15-20% of 2-methylnaphthalene undergoes ring epoxidation at the 7,8-, 3,4-, or 5,6-positions (Breger et al. 1983; Melancon et al. 1985). These reactions are catalyzed by CYP isozymes, including CYP1A and CYP1B. The epoxides themselves have not been isolated, but are proposed intermediates based on observed metabolites (Figure 3-4). These epoxides are thought either to be further oxidized by epoxide hydrolase to produce dihydrodiols (the 7,8-dihydrodiol, 3,4-dihydrodiol, or 5,6-dihydrodiol of 2-methylnaphthalene) or conjugated with glutathione (Griffin et al. 1982; Melancon et al. 1985). Glutathione conjugation can be catalyzed by glutathione S-transferase or can proceed spontaneously. The hydroxy glutathionyl dihydro-2-methylnaphthalenes (Figure 3-4) were detected after incubation of 2-methylnaphthalene with hepatic microsomes from Swiss-Webster mice or with isolated recombinant mouse CYP2F2 enzyme and glutathione S-transferase (Shultz et al. 2001). Figure 3-4 shows six hydroxy glutathionyl 2-methylnaphthalenes; two are formed for each of the epoxide intermediates (3,4-, 5,6-, and 7,8-epoxides), and each can exist in two enantiomeric forms not shown in Figure 3-4 (Shultz et al. 2001).

Figure 3-4 also shows three other minor metabolites formed via the 7,8-epoxide pathway. 1-Glutathionyl-7-methylnaphthalene was identified in the urine of guinea pigs and by *in vitro* experiments with guinea pig microsomes (Teshima et al. 1983). 7-Methyl-1-naphthol and 7-methyl-2-naphthol were identified in the urine of four species (rats, mice, guinea pigs, and rabbits) following oral exposure (Grimes and Young 1956).

In rats administered subcutaneous injections of 2-methylnaphthalene (0.3 mg/kg 2-methyl-[8-^{14}C]-naphthalene), 2-naphthoic acid, and naphthoic acid conjugates were identified in the urine (Melancon et al. 1982). The naphthoic acid and various conjugates of the acid were estimated to account for 36–43% of the radiolabel in collected urine. Most of this (30–35% of radiolabel in urine) was found as a glycine

conjugate. The urine contained 3−5% unreacted 2-methylnaphthalene; free dihydrodiols accounted for 6−8% of the label. Unidentified highly polar metabolites comprised another 36−45% of the excreted label. At least three diol derivatives of 2-methylnaphthalene were produced by hepatic microsomes from mice (Griffin et al. 1982) suggesting that the ring oxidation reactions of 2-methylnaphthalene are similar to those for naphthalene. Rat liver microsomes also produced 2-hydroxymethylnaphthalene and three diols from 2-methylnaphthalene (Breger et al. 1981, 1983; Melancon et al. 1985). The three diols were identified as 3,4-dihydrodiol, 5,6-dihydrodiol, and 7,8-dihydrodiol (Breger et al. 1983).

Metabolites isolated in the urine of guinea pigs after oral dosing with tritium labeled 2-methylnaphthalene (10 mg/kg) were 2-naphthoic acid and its glycine and glucuronic acid conjugates (Teshima et al. 1983). These metabolites accounted for 76% of the label in collected urine. Glucuronic acid and sulfate conjugates of 7-methyl-1-naphthol along with *S*-(7-methyl-1-naphthyl)cysteine accounted for 18% of the excreted label. No diol metabolites were identified.

Animal studies provide evidence that glutathione conjugation is an important detoxication pathway for 2-methylnaphthalene. Pretreatment of male C57BL/6J mice with 625 mg/kg of diethylmaleate (a depletor of glutathione) 1 hour prior to intraperitoneal administration of 400 mg/kg of 2-methylnaphthalene resulted in mortality in 4/5 mice, whereas treatment without glutathione depletion was not fatal (Griffin et al. 1982). No bronchiolar necrosis was observed in male ddY mice given single intraperitoneal injections of 200 mg/kg of 2-methylnaphthalene; but pretreatment with diethylmaleate (600 µL/kg) 1 hour prior to injections caused “extensive sloughing and exfoliation of bronchiolar epithelial cells” in all animals (5/5) (Honda et al. 1990). In contrast, pretreatment of male DBA/2J mice (5/group) with 625 mg/kg of diethylmaleate did not increase the severity of pulmonary necrosis induced by 400 mg/kg of 2-methyl-naphthalene (Griffin et al. 1983). The observed differences among mouse strains in response to depletion of glutathione remain unexplained. Other experiments (without pretreatment) observed decreased tissue or intracellular levels of glutathione in response to exposure to high acute doses of 2-methylnaphthalene, demonstrative of glutathione conjugation (Griffin et al. 1982, 1983; Honda et al. 1990). Similarly, depletion of glutathione (by 35% compared to controls) was detected in primary cultures of female Sprague-Dawley rat hepatocytes treated with 1,000 µM of 2-methylnaphthalene (Zhao and Ramos 1998).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Little information is available pertaining to the excretion of naphthalene in humans after inhalation exposure to naphthalene. Workers employed in the distillation of naphthalene oil and at a coke plant had peak levels of urinary 1-naphthol 1 hour after finishing a shift. Of three workers and a nonoccupationally exposed group, naphthalene oil distribution plant workers had the highest concentrations of urinary 1-naphthol, with a mean excretion rate of 0.57% mg/hour. Investigators calculated the half-life for the urinary excretion of 1-naphthol as approximately 4 hours (Bieniek 1994). This urinary metabolite may indicate both exposure to naphthalene and low concentrations of 1-naphthol during naphthalene oil distillation (Bieniek 1994). No studies were located that documented excretion in humans after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

No studies were located that documented excretion in animals after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

3.4.4.2 Oral Exposure

Little information is available pertaining to the excretion of orally ingested naphthalene by humans. The urine of one patient was tested for naphthalene and its derivatives. Naphthol was found at the time of hospital admission (4 days post-ingestion). Smaller quantities were present 1 day later, but naphthalene was not detected in later specimens (Zuelzer and Apt 1949). In another instance, the urine of an 18-month-old child was found to contain 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone (but no naphthalene) 9 days after exposure (Mackell et al. 1951). With the exception of the 1,4-naphthoquinone, these metabolites were still detectable on day 13, but not on day 17. These data indicate that urinary excretion of metabolites may be prolonged following exposure. It is important to note, however, that delayed dissolution and absorption from the gastrointestinal tract may also be a contributing factor. Unabsorbed naphthalene was visible in the fecal matter after ingestion of naphthalene flakes or mothballs in several individuals (Zuelzer and Apt 1949).

In nonhuman primate studies, Rhesus monkeys given naphthalene at oral doses up to 200 mg/kg did not excrete naphthalene as thioethers in urine or feces (Rozman et al. 1982). In a similar study, chimpanzees

orally administered naphthalene at 200 mg/kg did not excrete naphthalene as thioethers in urine (Summer et al. 1979). These data suggest that glutathione conjugation of naphthalene may not occur to any great extent in nonhuman primates. Data from two chimpanzees indicate that most of the naphthalene excreted in this species is excreted as glucuronic acid and sulfate conjugates (Summer et al. 1979).

In rats administered radiolabeled naphthalene, the amount of label recovered in 24 hours was 77–93% in urine and 6–7% in feces (Bakke et al. 1985). There was a dose-dependent increase in urinary thioether excretion following gavage doses of naphthalene at 30, 75, and 200 mg/kg within 24 hours (Summer et al. 1979). The levels of thioethers excreted accounted for approximately 39, 32, and 26% of the three dose levels tested.

No information was located that documented excretion in humans after oral exposure to 2-methyl-naphthalene. In guinea pigs, 80% of a 10 mg/kg tritium-labeled dose was excreted in the urine within 24 hours and about 10% was recovered in the feces (Teshima et al. 1983). Most of the excreted material (76%) was found as 2-naphthoic acid or its conjugates. About 18% of the recovered label was found as conjugates of 7-methyl-1-naphthol.

No studies were located that examined excretion in humans or animals after oral exposure to 1-methyl-naphthalene.

3.4.4.3 Dermal Exposure

No reports have been located which discuss the excretion of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene in humans following dermal exposure.

The dermal exposure of rats to ^{14}C-labeled naphthalene was evaluated over a 48-hour period (Turkall et al. 1994). Naphthalene (43 µg) samples were applied to shaved 13-cm^2 areas on the skin under a sealed plastic cap. Neat naphthalene or naphthalene adsorbed to the surface of sandy soil or clay soil was tested. In all three cases, excretion of the label was primarily through the urine (70–87%). With the pure naphthalene and naphthalene adsorbed to clay soil, the exhaled air accounted for 6–14% of the administered label. Exhaled air contained only 0.9% of the label in the sandy soil group. This finding was presumably related to the slower adsorption of naphthalene from the sandy soil and its more rapid metabolism to nonvolatile metabolites. Less than 0.02% of the label was exhaled as carbon dioxide in all groups. The feces contained 2–4% of the label.

The primary metabolites in the urine after dermal application of naphthalene were 2,7-dihydroxy-naphthalene, 1,2-dihydroxynaphthalene, and 1,2-naphthoquinone (Turkall et al. 1994). The ratio of these metabolites for pure naphthalene and naphthalene adsorbed to clay soil were roughly 3:2:1. For the sandy soil, the corresponding ratio was 3:2:1.5. Small amounts of 1-naphthol and 2-naphthol were also excreted. In all cases, the amount of urinary free naphthalene was less than 0.4% of the administered label.

No studies were located that documented excretion in animals after dermal exposure to 1-methyl-naphthalene or 2-methylnaphthalene.

3.4.4.4 Other Routes of Exposure

In mouse studies using the intraperitoneal or subcutaneous exposure routes, several naphthalene metabolites were excreted in the urine. After intraperitoneal administration of 100 mg/kg naphthalene, conjugates accounted for 80–95% of the urinary metabolites (Horning et al. 1980; Stillwell et al. 1982). Much of the conjugated material was present as thioethers (glutathione conjugates and their derivatives). The major oxidation products of naphthalene metabolism were 1-naphthol and trans-1,2-di-hydro-1,2-naphthalenediol.

Following subcutaneous administration of 0.3 mg/kg ^{14}C-labeled 2-methylnaphthalene, 55% was found in the urine of rats (Melancon et al. 1982). Naphthoic acid and its glycine conjugate were identified. Three other metabolites were tentatively identified as isomeric diols.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

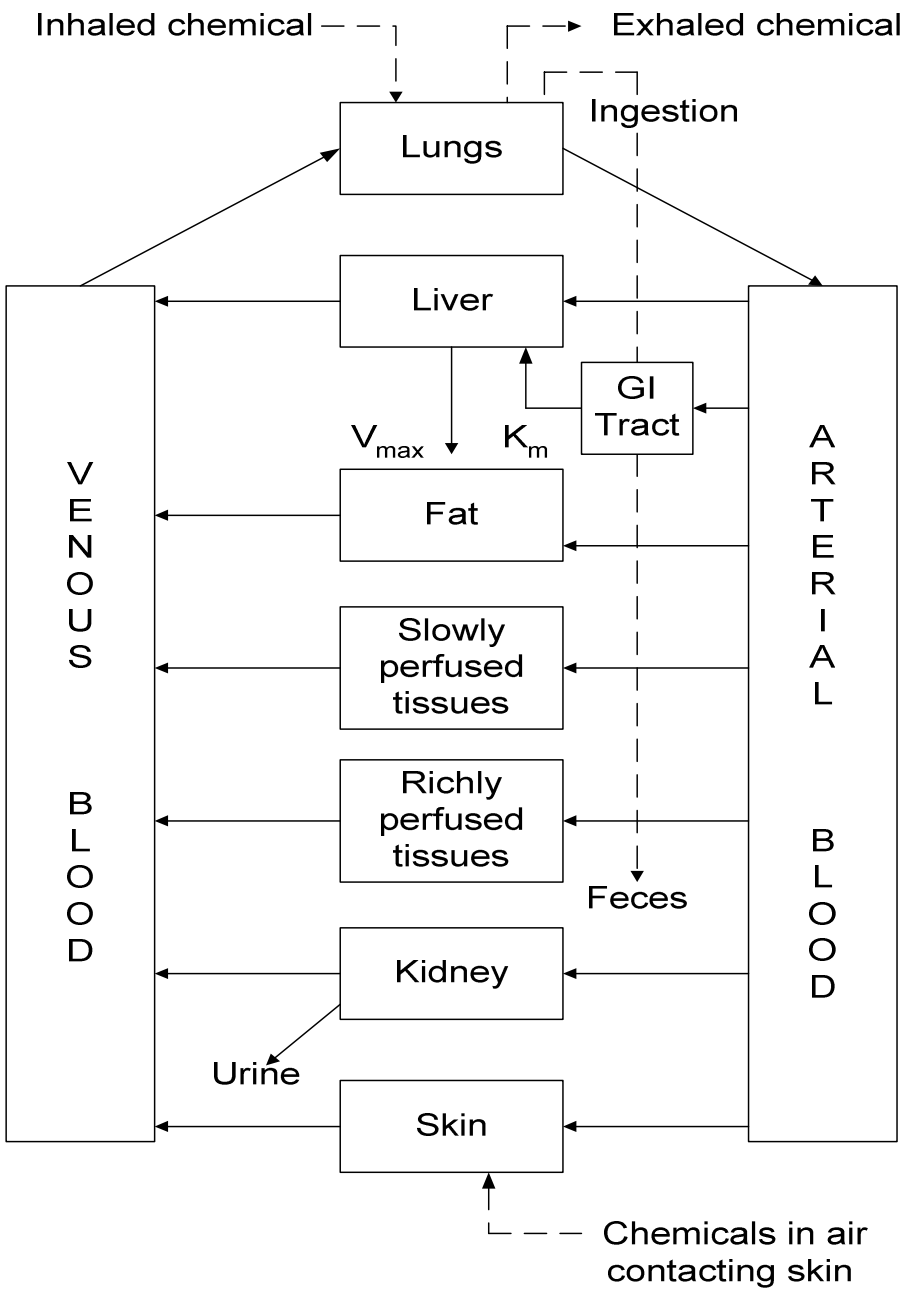
sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

This section will discuss the structure and application of the most recent PBPK models for naphthalene that were developed with *in vivo* data for the time-course of naphthalene in blood in rats and mice following inhalation exposure or intravenous administration (Willems et al. 2001). The inhalation data were used to select best-fitting models with the fewest assumptions possible and to optimize model parameters. The intravenous data were used to examine the validity of the final models. These models are refinements of earlier PBPK models for naphthalene in rats and mice, which were developed using parameters estimated from *in vitro* data (Ghanem and Shuler 2000; Quick and Shuler 1999; Sweeney et al. 1996). The most recent models have been used to attempt to explain why naphthalene-induced lung tumors in female B6C3F1 mice, but did not induce lung tumors in F344/N rats in chronic inhalation studies (Abdo et al. 2001; NTP 1992a, 2000). The use of these models to extrapolate dosimetry from rodents to humans is not possible until appropriate validated human physiologically based toxicokinetic (PBTK) models for naphthalene are developed.

The models do not include nasal compartments that metabolize naphthalene, because no data were available on nasal deposition and epithelial absorption of naphthalene (Willems et al. 2001). Without such data, reliable models for nasal deposition, tissue dosimetry, and nasal-tissue metabolism cannot be developed for naphthalene (models similar to those developed for other nasal toxicants such as acrylic acid [Frederick et al. 2001]). The existence of validated PBTK models with metabolizing nasal compartments would be useful to help to explain why male and female rats develop nasal tumors with chronic inhalation exposure to naphthalene, but mice do not, even though both species develop nonneoplastic lesions in the nasal tissues in which tumors developed in rats (Abdo et al. 2001; NTP 1992a, 2000). In addition, development of human models incorporating anatomical and physiological characteristics of nasal tissue will be useful to decrease uncertainty in extrapolating dose-response relationships for nasal effects in rodents to humans.

The final best-fitting models for rats and mice are comprised of two parts: (1) a diffusion-limited naphthalene submodel with compartments for arterial and venous blood, alveolar space, and tissue and capillary spaces for the lung, liver, kidney, fat, and other organs (with naphthalene metabolism occurring in the liver and lung by the same CYP isozyme with one set of Michaelis-Menten metabolic rate constants); and (2) a flow-limited 1,2- naphthalene oxide submodel describing metabolism and

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

distribution of naphthalene oxide in the same compartments as in the naphthalene submodel (but without tissue capillary spaces) (Willems et al. 2001). Physiological parameters in both submodels (e.g., cardiac output, ventilation rates, tissue volumes, tissue capillary volumes, tissue blood flows) were taken from the literature and scaled to body weights of rats in the NTP (2000) bioassay and reference values for mice. Partition coefficients between the various compartments were calculated from octanol-water partition coefficients. Metabolic rate constants (Vmax and Km) and permeability constants (blood:fat and blood:other tissues) for naphthalene were estimated by fitting the models to naphthalene blood time-course data from the inhalation studies. The naphthalene oxide submodel was essentially the same as that developed by Quick and Shuler (1999) with *in vitro* data, with the exception that it contained a subroutine for reduced glutathione synthesis involving γ-glutamylcysteine synthetase modeled with Michaelis-Menten rate constants and noncompetitive inhibition by reduced glutathione. The metabolic fate of naphthalene oxide in the lung and liver was restricted to dihydrodiol formation via epoxide hydrolase and conjugation to glutathione via glutathione-*S*-transferase. The model did not include spontaneous conversion of naphthalene oxide to 1-naphthol or metabolic transformations to the naphthoquinones. Because no *in vivo* data were available on naphthalene oxide distribution or metabolism, the model predictions for naphthalene oxide tissue dosimetry could not be verified.

Under exposure conditions used in the rat (0, 10, 30, or 60 ppm) and mouse (0, 10, or 30 ppm) NTP (1992a, 2000) chronic inhalation bioassays with naphthalene (6 hours/day), the models predicted that: (1) steady-state lung concentrations of the parent compound, naphthalene, were not very different in rats and mice at equivalent exposure concentrations; (2) cumulative daily naphthalene metabolism in the lung was greater in the mouse than in the rat (by about 1.5- to 2.5-fold) at equivalent exposure concentrations; (3) cumulative daily naphthalene metabolism in the lung (64.9 mg/kg) and estimated maximal lung concentrations of naphthalene oxide (about 12 nmol/mL) for 30-ppm female mice, some of which developed lung tumors, were greater than respective values of 45.9 mg/kg and about 8 nmol/mL in 60-ppm female rats, which did not develop lung tumors; and (4) cumulative daily naphthalene metabolism in the lung was only slightly greater in 30-ppm female mice (64.9 mg/kg) than in the 30-ppm male mice (60.7 mg/kg), which did show statistically significant increased incidence of lung tumors (comparisons of lung concentrations of naphthalene oxide in female and male mice were not reported).

The model simulations are consistent with the hypothesis that the difference in lung tumor response between mice and rats may be due to a combination of greater maximal levels of naphthalene oxide or other metabolites in the mouse lung and, perhaps, a greater susceptibility of the mouse lung to epoxide-induced carcinogenesis. Results with other chemicals, such as ethylene oxide, suggest that the mouse

lung may be more susceptible to epoxides than the rat lung (Willems et al. 2001). Differences in predicted cumulative lung metabolism of naphthalene in 30-ppm female mice and 30-ppm male mice were smaller than the difference noted between 30-ppm female mice and 60-ppm female rats; thus the model simulations do not explain the apparent gender difference in tumor response of the mouse lung. The formation of naphthoquinone metabolites was not included in the model. Thus, the model simulations do not provide a basis for identifying which metabolite is responsible for the nonneoplastic and neoplastic responses to naphthalene in the female mouse lung.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. No studies were located regarding the mechanisms by which naphthalene, 1-methyl-naphthalene, or 2-methylnaphthalene are absorbed from the guts, lungs, or skin. Although absorption of these compounds at these sites has been demonstrated, it is unknown if the transport is passive, active, or carried out by a facilitated diffusion mechanism. The relatively small molecular weights and lipophilicity of these compounds indicate that passive diffusion across cell membranes is a possible mechanistic path.

There is some evidence that different vehicles may influence the rate and extent of gastrointestinal or dermal absorption. Naphthalene adsorbed to organic-rich soils was absorbed across the skin more slowly than naphthalene from organic-poor soils (Turkall et al. 1994).

Distribution. As discussed in more detail in Section 3.4.2, there are limited data on the distribution of naphthalene and 2-methylnaphthalene in animals following oral or parenteral administration, but there are no data for these compounds following inhalation exposure or for 1-methylnaphthalene by any exposure route. The available data are inadequate to characterize the mechanisms by which 2-methylnaphthalene may be transported following oral exposure to the lung, the site of toxic action with acute or chronic exposure. No data are available on differences in deposition and absorption of inhaled naphthalene in nasal epithelial tissue, two of which (olfactory epithelium and respiratory epithelium) are key toxicity targets in rats and mice following chronic inhalation exposure to naphthalene.

Metabolism. As discussed in more detail in Section 3.4.3, results from *in vitro* and *in vivo* metabolic studies in mammalian systems indicate that naphthalene metabolism is complex, with multiple competing pathways leading to the formation of several reactive metabolites (e.g., 1,2-naphthalene oxide,

1,2-naphthoquinone, and 1,4-naphthoquinone) and an array of conjugated and nonconjugated metabolites that are excreted predominantly in the urine. Conjugation of the reactive metabolites is viewed as a detoxifying mechanism for the reactive metabolites. With oral exposure, the liver is expected to be the principal site of metabolism, but metabolism of naphthalene at other tissue sites, including the nasal olfactory epithelium, Clara cells in pulmonary epithelial tissue, and eye tissue, has been demonstrated. A first-pass metabolic effect due to liver metabolism is expected with oral exposure, but the degree to which a first-pass effect due to respiratory tissue metabolism occurs with inhalation exposure to naphthalene has not been studied quantitatively.

Section 3.4.3 also discusses in more detail the complexity of 2-methylnaphthalene metabolism, which, in contrast to naphthalene, involves several competing initial steps: oxidation of the methyl side group and oxidation at several positions on the rings. Oxidation of the methyl side group is the principal metabolic pathway, representing about 50–80% of administered doses in animal studies. An array of conjugated and nonconjugated metabolites that are principally excreted in the urine have been identified in animal studies. Although conjugation of metabolites (principally with glutathione) appears to be a detoxication mechanism with acute exposure in animal studies, the involvement of reactive metabolites in the development of pulmonary alveolar proteinosis from chronic exposure to 2-methylnaphthalene is uncertain (see Section 3.5.2). No studies were located on the metabolism of 1-methylnaphthalene in humans or animals, but it is expected to be similar to 2-methylnaphthalene metabolism based on its similar chemical, physical, and toxicological properties.

Excretion. As discussed in more detail in Section 3.4.4, results from animal studies involving oral or parenteral exposure indicate that naphthalene and 2-methylnaphthalene are principally excreted as metabolites in urine. Excretion in the feces represents a minor excretion pathway for these chemicals, and the possibility of excretion via exhalation of unmetabolized parent compounds has not been examined in available studies. Data for 1-methylnaphthalene were not located, but excretion is likely to be similar to 2-methylnaphthalene given the similarity in chemical and physical properties of these chemicals.

3.5.2 Mechanisms of Toxicity

Some information on the mechanism of toxicity is available for three of the health effects associated with naphthalene exposure: hemolysis, the development of lens opacities (cataracts), and nonneoplastic and neoplastic respiratory tract lesions. Mechanistic hypotheses for these naphthalene-induced effects are

discussed below, followed by a discussion of the limited mechanistic information on 1-methyl-naphthalene- and 2-methylnaphthalene-induced pulmonary alveolar proteinosis.

Naphthalene-induced Hemolysis. Humans experience red-cell hemolysis after naphthalene exposure by the inhalation, oral, and dermal routes. In general, animal species are less susceptible than humans. There are no reports of naphthalene-induced hemolysis in either rats or mice; however, hemolysis has been observed in dogs.

Chemically induced red blood cell hemolysis is caused by a breakdown of the system that protects the erythrocyte biomolecules from oxidation. In the erythrocyte, glutathione peroxidase rather than catalase is the major antioxidant enzyme. Glutathione peroxidase (Gpx) is a selenium containing metalloprotein that utilizes reduced glutathione as a cofactor. Oxidized glutathione is reduced by glutathione reductase, a nicotinamide adenine dinucleotide phosphate (NADPH)-requiring enzyme.

The primary source of erythrocyte NADPH is glucose-6-phosphate oxidation by the enzyme G6PD. Individuals who suffer from a genetic defect resulting in a modified enzyme structure (a recessive trait) have a reduced capacity to produce NADPH. Accordingly, they are more susceptible to red cell hemolysis than individuals without this defect (Gosselin et al. 1984). There is some evidence that heterozygotes may also have an increased susceptibility to red cell hemolysis (Dawson et al. 1958).

When the red blood cell is exposed to oxidizing agents, heme iron is oxidized to the ferric state, producing methemoglobin. This in turn leads to Heinz body formation. It is believed that free radical oxygen modifies membrane lipids leading to increased membrane fragility and lysis. Destruction of the red blood cells decreases erythrocyte counts and stimulates hematopoiesis (leading to increased numbers of reticulocytes). The oxygen carrying capacity of the blood is reduced. Cell lysis releases heme and protein into the blood. Heme breakdown produces bilirubin and biliverdin, causing jaundice. Both erythrocytes and heme breakdown products (urobilinogen) spill into the urine.

Several suggestions can be made regarding the impact of naphthalene on this sequence of events. Since naphthalene is conjugated with glutathione for excretion, it can reduce the supplies of glutathione available for glutathione peroxidase and increase the vulnerability of the cell to oxidation. It is also possible that a naphthalene metabolite may act as an inhibitor for either glutathione peroxidase or glutathione reductase. Glutathione reductase activity was reduced in children who experienced hemolysis following dermal exposure to naphthalene and in related family members (Dawson et al. 1958). Both

glutathione peroxidase and glutathione reductase activity were decreased in the lens of rats orally exposed to naphthalene (Rathbun et al. 1990; Tao et al. 1991).

Each of the hypotheses discussed above would serve to increase the sensitivity of any naphthalene-exposed subject to an external oxidizing agent. However, given the severity of the hemolysis that follows naphthalene exposure, it is probable that naphthalene or a naphthalene metabolite also acts as an oxidizing agent in the erythrocyte. Unfortunately, data could not be identified which would correlate the production of any particular metabolite with initiation of red cell peroxidation.

Naphthalene-induced Cataracts. Although there are reports that inhalation, oral, and dermal naphthalene exposure in humans can lead to lens opacities (Grant 1986), the case studies or industrial exposure reports that link naphthalene to cataracts in humans have not been verified by well-conducted epidemiological studies of individuals exposed to naphthalene vapors on a chronic basis. In addition, impurities present in the naphthalene may have contributed to the cataract development in all recorded human cases. Conversely, there are data from a number of well-conducted studies which demonstrate that naphthalene can induce cataracts in animals.

Much of the animal data regarding ocular effects suggest that the toxicity of naphthalene is mediated by the *in situ* formation of 1,2-naphthalenediol in the lens. It has been proposed that metabolism of naphthalene starts in the liver, yielding epoxide metabolites that are subsequently converted to stable hydroxy compounds that circulate to the lens (Van Heyningen and Pirie 1967). The 1,2-naphthalenediol metabolite is subsequently oxidized to 1,2-naphthaquinone and hydrogen peroxide. The quinone metabolite binds to constituents of the lens (protein, amino acids, and glutathione), disrupting its integrity and transparency (Rees and Pirie 1967; Uyama et al. 1955; Van Heyningen and Pirie 1967; Van Heyningen 1976, 1979; Wells et al. 1989).

Intraperitoneal administration of naphthalene (125−1,000 mg/kg), 1-naphthol (56−562 mg/kg), 1,2-naphthoquinone (5−250 mg/kg), and 1,4-naphthoquinone (5−250 mg/kg) caused a dose-related increase in cataracts in C57BL/6 mice, but administration of 2-naphthol (56−456 mg/kg) did not (Wells et al. 1989). The cataractogenic potency of the naphthoquinones was about 10 times that of naphthalene. The cataractogenic potency of 1-naphthol was intermediate to that of naphthalene and the naphthoquinones. The potency of naphthalene was increased by pretreatment with cytochrome P-450 inducers and a glutathione-depleting agent. It was inhibited by pretreatment with a cytochrome P-450 inhibitor. This suggests that the unconjugated oxidized naphthoquinone metabolites are a

necessary prerequisite for cataract formation. There are differences in species and strain susceptibility to cataract formation that theoretically relate to the animals' ability to form these metabolites. Naphthalene, 1-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone did not form cataracts in DBA/2 mice suggesting the difference between strains is not simply due to metabolite exposure (Wells et al. 1989).

Because hydrogen peroxide is also formed following the oxidation of 1,2-dihyroxynaphthalene, peroxides may play a role in naphthalene-induced ocular damage. Increased levels of ocular lipid peroxides were noted in rats given incremental doses of naphthalene which increased from 100 to 750 mg/kg/day during a 9 week period (Germansky and Jamall 1988). The antioxidants caffeic acid (527 mg/kg) and vitamin E (250 mg/kg), which have free radical protection properties, and the free radical spin trapping agent α-phenyl-N-t-butylnitrone (PBN) (518 mg/kg) diminished the incidence of cataracts in animals given 750 mg/kg naphthalene (Wells et al. 1989). There were no cataracts in the rats given only PBN.

Support for this mechanism of cataract formation was provided by a gavage study in which five rat strains (pigmented and albino) were given 500 mg/kg/day naphthalene for 3 days and 1,000 mg/kg/day for the remainder of the 28-day treatment period (Xu et al. 1992b). After 3 weeks, there was a decrease in reduced glutathione (GSH) in the lens, an increase in protein-glutathione mixed disulfides, and an increase in high molecular weight insoluble proteins (Xu et al. 1992a, 1992b). The only metabolite detected in the aqueous humor of the lens was 1,2-dihydro-1,2-naphthalenediol. The authors hypothesized that 1,2-dihydro-1,2-naphthalenediol was oxidized to 1,2-naphthalenediol and then to 1,2-naphthoquinone. The 1,2-naphthoquinone is believed to be responsible for the chemical changes in the eyes either through crosslinking reactions or by generating free radicals (Xu et al. 1992a). All of the rats developed cataracts.

The complete mechanism for this sequence of reactions is not clear. In *in vitro* studies of cataract formation, 1,2-dihydro-1,2,naphthalenediol was the only metabolite that resulted in cataracts that were morphologically the same as those generated *in vivo* (Xu et al. 1992a). Although 1,2-naphthalenediol and naphthoquinone also formed cataracts in lens culture studies, the opacities were located in the outer layer of the cortex rather than inside the lens. Also, the permeability of the cultured lens to the metabolites in the media may have contributed to the differences in lesion location.

When the aldose reductase inhibitor, AL01576, was given to rats along with the same naphthalene doses, no cataracts developed (Xu et al. 1992a, 1992b). Aldose reductase is an enzyme found in the lens, liver, and peripheral neurons that reduces aldehyde sugars such as glucose to their corresponding alcohols

(McGilvery 1983). It is believed to oxidize 1,2-naphthalenediol to 1,2-naphthoquinone; therefore, when this reaction is inhibited, the quinone hypothetically does not form and there is no eye damage (Xu et al. 1992a). Support for this hypothesis includes observations that aldose reductase inhibitors inhibit cataract formation in naphthalene-exposed rats (Tao et al. 1991; Xu et al. 1992a), dihydrodiol dehydrogenase is apparently absent in rat lens (Greene et al. 2000), and aldose reductase appears to be the only enzyme in rat lens that can transform 1,2-dihydroxy-1,2-dihydronaphthalene to 1,2-naphthoquinone (Sugiyama et al. 1999).

Naphthalene-induced Nonneoplastic and Neoplastic Respiratory Tract Lesions. The mechanisms by which naphthalene affects mouse lung epithelial tissue and mouse and rat nasal epithelial tissue are thought to involve metabolic intermediates that can react with tissue macromolecules: 1,2-naphthalene oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone (Buckpitt et al. 2002). The innate reactivity of 1,2-naphthalene oxide is demonstrated by a half-life of approximately 2–3 minutes in buffer at pH 7.4; the half-life is extended by the presence of albumins to about 11 minutes (Buckpitt et al. 2002; Kanekal et al. 1991). The reactivity of 1,2-naphthoquinone has been demonstrated by its ability to form N7-adducts with deoxyguanosine under acidic conditions (McCoull et al. 1999). A second mode by which 1,2-naphthoquinone may damage tissue macromolecules involves redox cycling of the ortho-quinone moiety and the subsequent generation of reactive oxygen species, which can lead to lipid peroxidation, consumption of reducing equivalents, oxidation of DNA, or DNA strand breaks (Bolton et al. 2000). 1,2-Naphthoquinone caused hydroxyl radical formation and DNA strand scission in buffered solutions in the presence of NADPH and $CuCl_2$ (Flowers et al. 1997), was directly mutagenic in *S. typhimurium* (Flowers-Geary et al. 1996), and directly induced sister chromatid exchanges in human mononuclear leukocytes (Wilson et al. 1996). The comparative importance of these reactive metabolic intermediates of naphthalene in producing nonneoplastic and neoplastic lesions in lung or nasal epithelial tissue is unknown, although the difference between mice and rats in susceptibility to naphthalene-induced lung damage has been associated with greater rates of naphthalene transformation to epoxides and the formation of a different enantiomeric form of 1,2-naphthalene oxide in mice compared with rats.

A fourth reactive metabolic intermediate, 1,2-dihyroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene, has been proposed based on molecular structure characterizations of some urinary metabolites (Horning et al. 1980; Pakenham et al. 2002), but these metabolites represent minor metabolic fates of naphthalene and the potential importance of their proposed precursor in naphthalene toxicity is unstudied to date.

Mice are markedly more susceptible than rats to acute naphthalene-induced Clara cell injury (Buckpitt et al. 1992; West et al. 2001), as well as to lung inflammation and tumor development from chronic inhalation exposure (Abdo et al. 2001; NTP 1992a, 2000). The species difference in lung susceptibility has been correlated with higher rates of formation of a specific enantiomeric epoxide (1*R*,2*S*-naphthalene oxide) in lung microsomes and isolated dissected airways of mice compared with rats (Buckpitt et al. 1992, 1995). Rat, hamster, and monkey lung microsomes preferentially formed the 1*S*,2*R*-naphthalene oxide enantiomer and showed lower rates of formation of epoxides than mouse lung microsomes (Buckpitt et al. 1992). Microsomes from human lymphoblastoid cells expressing recombinant human CYP2F1 also showed preferential formation of the 1*S*,2*R*-naphthalene oxide enantiomer, providing some evidence that human transformation of naphthalene to reactive epoxides in lung tissue may be more like rats than mice (Lanza et al. 1999).

Although these observations on epoxide formation suggest that naphthalene may be metabolized to epoxide intermediates at faster rates and with different stereoselectivity in the mouse lung than in the human lung, the toxicologic significance of this species difference is uncertain. The uncertainty arises due to the possibility (and potential toxicological importance) of species differences in several steps in downstream metabolism including glutathione conjugation of the epoxide, transformation to the dihydrodiol via epoxide hydrolase, and transformations to 1,2- or 1,4-naphthoquinone. For example, human liver microsomes have been reported to be more proficient at converting naphthalene to the dihydrodiol metabolite than rat and mouse liver microsomes (Kitteringham et al. 1996). These results suggest that epoxide hydrolase activities may be higher in humans than mice (although they do not necessarily reflect activities in the pertinent naphthalene target tissues) and that this may decrease the potential for epoxide-induced tissue damage in humans relative to mice (see Figure 3-3). However, this difference may cause relatively greater formation of 1,2-naphthoquinone (from the dihydrodiol via dihydrodiol dehydrogenase) in human tissue than in mouse tissue. While the toxicologic significance of such a difference is uncertain, it is possible that humans may be more susceptible than mice, due to the possible involvement of 1,2-naphthoquinone in naphthalene-induced lung injury as suggested by a report that 1,2-naphthoquinone was the predominant naphthalene metabolite covalently bound to proteins obtained from freshly isolated mouse Clara cells incubated for 1 hour with 0.5 mM naphthalene (Zheng et al. 1997). To date, mechanistic understanding of species differences in naphthalene bioactivation in the lung is too incomplete to definitively identify which naphthalene metabolite is responsible for the development of nonneoplastic or neoplastic lung lesions, or to rule out the possible human relevance of naphthalene-induced lung lesions in mice.

Species differences in susceptibility to naphthalene-induced nonneoplastic and neoplastic lesions in the olfactory and respiratory epithelia of the nose have not been correlated with differences in rates of transformation to 1,2-epoxide derivatives in extracts of olfactory tissue (Buckpitt et al. 1992; Plopper et al. 1992a). Rates of epoxide formation showed the order, mouse > rat > hamster, but rats were the most susceptible to acute nasal injury from naphthalene, showing olfactory epithelial necrosis and exfoliation following single intraperitoneal doses as low as 200 mg/kg naphthalene, compared with 400 mg/kg in mice and hamsters (Plopper et al. 1992a). These observations suggest that the reasons for species differences in susceptibility to naphthalene nasal toxicity are complex and do not solely involve differences in the formation of the 1,2-epoxide metabolic intermediates.

Involvement of the naphthoquinone metabolites is possible, but studies comparing species in their ability to form or accumulate reacted derivatives of naphthoquinones (or 1,2-naphthalene oxide) in nasal tissues (i.e., protein adducts) are not available. In blood of rats following gavage administration of single oral doses of naphthalene (100-800 mg/kg), levels of hemoglobin and albumin adducts with 1,2-naphthalene oxide were greater than levels of adducts of 1,2- and 1,4-naphthoquinone (Troester et al. 2002; Waidyanatha et al. 2002). These findings suggest that levels of the epoxide in the rats' blood were greater than levels of the naphthoquinones, but do not provide information on the relative amounts of these reactive metabolites in the target tissue, the nose.

Current information is inadequate to identify which metabolite(s) are responsible for nonneoplastic or neoplastic nasal lesions that develop in rodents following chronic inhalation exposure, or to explain why nasal tumors develop in rats but not in mice.

Evidence to support a nongenotoxic mode of action in naphthalene carcinogenicity involving sustained cell proliferation following repeated naphthalene-induced tissue damage includes the negative results in the genotoxicity database (see Section 3.3) suggesting that naphthalene and its metabolites (with the likely exception of 1,2-naphthoquinone) are not mutagens, and the findings that naphthalene-induced tumors in mice and rats occur in the same general tissues as those displaying nonneoplastic lesions. Evidence to support a genotoxic mode of action includes the consistently positive results for genotoxic action by 1,2-naphthoquinone and the limited and scattered positive results for genotoxic action by naphthalene in the presence of metabolic activation. Current evidence is not adequate to rule out the possibility of naphthalene genotoxic action or to determine pertinent threshold levels for genotoxic action, due to the absence of studies examining genotoxic end points in naphthalene target tissues, the nose and lung.

1-Methylnaphthalene or 2-Methylnaphthalene-induced Pulmonary Alveolar Proteinosis. Exposure of mice to 1-methylnaphthalene or 2-methylnaphthalene in the diet for 81 weeks induced increased incidences of pulmonary alveolar proteinosis (Murata et al. 1993, 1997). The absence of nonneoplastic lesions in other lung regions or in other tissues indicates that the alveolar region of the lung is a critical and specific toxicity target of chronic oral exposure to 1-methylnaphthalene or 2-methylnaphthalene. Increased incidences of pulmonary alveolar proteinosis have also been observed in mice exposed to dermal doses of methylnaphthalene (a 2:1 mixture of 2-methylnaphthalene and 1-methylnaphthalene) applied twice weekly for 20-61 weeks (Emi and Konishi 1985; Murata et al. 1992).

There is evidence to suggest that type II pneumocytes are specific cellular targets of the methyl-naphthalenes. Light microscopic examination of lung tissue from mice that were repeatedly exposed to dermal doses of methylnaphthalene (119 mg/kg methylnaphthalene twice a week for 30 weeks) showed hyperplasia and hypertrophy of type II pneumocytes in alveolar regions with proteinosis (Murata et al. 1992). Electron microscopic examination showed that alveolar spaces were filled with numerous myelinoid structures resembling lamellar bodies of type II pneumocytes (Murata et al. 1992). Associated with this extracellular material were mononucleated giant cells (called balloon cells) containing numerous myelinoid structures, lipid droplets, and electron dense ascicular crystals. Murata et al. (1992) hypothesized that, in response to 1-methylnaphthalene or 2-methylnaphthalene, type II pneumocytes produce increased amounts of lamellar bodies due to hyperplasia and hypertrophy, and eventually transform into balloon cells. The rupture of balloon cells is hypothesized to lead to the accumulation of the myelinoid structures in the alveolar lumen. No in-depth ultrastructural studies of the pathogenesis of pulmonary alveolar proteinosis from chronic exposure to 2-methylnaphthalene or 1-methylnaphthalene alone were available. However, the lesions detected by light microscopy following chronic oral exposure to 2-methylnaphthalene or 1-methylnaphthalene alone were very similar to the lesions detected following chronic dermal exposure to the mixture; these similarities suggest that the mechanistic hypotheses prompted by observations for the mixture are relevant to the individual methylnaphthalenes.

The mechanism of targeting type II pneumocytes is consistent with what is generally known regarding the etiology of pulmonary alveolar proteinosis in humans. The disease in humans, characterized by the accumulation of surfactant material in the alveolar lumen, has been hypothesized to be caused by either excessive secretion of surfactant by type II pneumocytes, or disruption of surfactant clearance by macrophages (Lee et al. 1997; Mazzone et al. 2001; Wang et al. 1997). The condition in humans has been associated with pulmonary dysfunction, characterized by decreased functional lung volume, reduced

diffusing capacity, and symptoms such as dyspnea and cough. Pulmonary alveolar proteinosis has not been associated with airflow obstruction (Lee et al. 1997; Mazzone et al. 2001; Wang et al. 1997).

The development of pulmonary alveolar proteinosis in mice appears to require prolonged oral exposure to 2-methylnaphthalene (or 1-methylnaphthalene). Exposure to a dietary concentration of 0.075% 2-methylnaphthalene for 81 weeks induced increased incidences of the lesion, but 13-week exposure to concentrations as high as 1.33% 2-methylnaphthalene did not (Murata et al. 1997). No further studies of the temporal development of methylnaphthalene-induced pulmonary alveolar proteinosis are available.

It is unknown whether the parent compounds or metabolites are responsible for the development of methylnaphthalene-induced pulmonary alveolar proteinosis. Type II pneumocytes are enriched in CYP monooxygenases (Castranova et al. 1988), which are involved in metabolizing 2-methylnaphthalene, and it is possible that metabolites may play a role in the pathogenesis of pulmonary alveolar proteinosis. Studies designed to test this hypothesis, however, have not been conducted.

In contrast to chronic oral exposure, which targets alveolar type II pneumocytes, acute intraperitoneal injection of 2-methylnaphthalene into mice targets bronchiolar Clara cells, inducing Clara cell abnormalities, focal or complete sloughing of Clara cells, or complete sloughing of the entire bronchiolar lining (Buckpitt et al. 1986; Griffin et al. 1981, 1982, 1983; Honda et al. 1990; Rasmussen et al. 1986). Mechanistic studies have not provided clear evidence that metabolites are involved in this response to acute exposure to 2-methylnaphthalene. For example, pretreatment of male C57BL/6J mice with phenobarbital (an inducer of CYP2B; 75 mg/kg, 4 days prior) or 3-methylcholanthrene (an inducer of CYP1A; 80 mg/kg, 2 days prior) prior to injection with 400 mg/kg 2-methylnaphthalene reduced the severity of bronchiolar necrosis in all mice compared to those injected without pretreatment (Griffin et al. 1982). However, CYP inhibitors, such as piperonyl butoxide (a mixed monoxygenase inhibitor; 1,000 mg/kg, 30 minutes prior) and SKF 525-A (an inhibitor of CYP1B; 25 mg/kg, 30 minutes prior), had no effect on the severity of the lung lesions. The mechanism of acute Clara cell toxicity of 2-methylnaphthalene may be similar to that of naphthalene, which involves CYP-mediated metabolism via ring epoxidation to reactive species such as the 1,2-naphthalene oxide and 1,2-naphthoquinone (Cho et al. 1995; Greene et al. 2000; Lakritz et al. 1996; Van Winkle et al. 1999). The observation that 2-methylnaphthalene is less acutely toxic than naphthalene (Buckpitt and Franklin 1989; Cho et al. 1995) supports this hypothesis, since only a small fraction of 2-methylnaphthalene (15-20%) undergoes metabolic ring epoxidation (Breger et al. 1983; Melancon et al. 1985). Information on the mechanism of the acute response of Clara cells is not expected to be directly related to the pathogenesis of pulmonary alveolar

proteinosis from chronic oral or dermal exposure to 2-methylnaphthalene, because in mice chronically exposed to 2-methylnaphthalene or 1-methylnaphthalene for 81 weeks, no evidence for exposure-related bronchiolar Clara cell lesions was found (Murata et al. 1993, 1997). This finding may be related to observations suggesting that Clara cells can develop resistance to naphthalene acute toxicity (Lakritz et al. 1996). However, the possible development of Clara cell resistance to the acute toxicity of 2-methylnaphthalene has not been studied.

There are limited data to suggest that rats may be less sensitive than mice to the lung damage caused by acute exposure to 2-methylnaphthalene. Wistar rats given intraperitoneal doses of 142 mg/kg 2-methylnaphthalene did not develop lung lesions (Dinsdale and Verschoyle 1987). In contrast, bronchiolar necrosis was induced in Swiss-Webster mice injected with the same dose (Rasmussen et al. 1986) and in C57BL/6J and DBA/2J mice injected with 100 mg/kg 2-methylnaphthalene (Griffin et al. 1981, 1982, 1983). No data are available for interspecies comparisons of the chronic toxicity of 1-methynaphthalene or 2-methylnaphthalene.

3.5.3 Animal-to-Human Extrapolations

Naphthalene-induced lesions in nasal epithelia of mice and rats appear to be the critical nonneoplastic effect (i.e., the effect occurring at the lowest exposure level) associated with inhalation exposure to naphthalene. As discussed in Section 3.5.2, studies with microsomes from human and animal cells indicate that there are species differences in specific steps of naphthalene metabolism (Buckpitt et al. 1992; Kitteringham et al. 1996; Lanza et al. 1999), but mechanistic understanding of these differences is too incomplete to effectively argue that they rule out the possible human relevance of naphthalene-induced lung lesions in mice or nasal lesions in rats or mice. Rodents and humans also display distinct differences in nasal anatomy and respiratory physiology that may cause different deposited doses, and subsequently different responses, in human nasal tissue relative to rats or mice. However, the anatomical and physiological differences alone are insufficient to rule out the possible human relevance of naphthalene-induced nasal lesions in rats or mice. For example, rat and human hybrid computational fluid dynamics and PBPK models, developed for acrylic acid, another rodent nasal toxicant, predicted that tissue concentrations of acrylic acid in human and rat nasal tissues would be similar when exposure conditions were the same (Frederick et al. 2001). Current PBPK models for naphthalene do not include nasal compartments that metabolize naphthalene, because no data were available on nasal deposition and epithelial absorption of naphthalene (Willems et al. 2001). In the absence of this type of data or a pertinent validated human PBPK model, it is reasonable to assume that naphthalene-induced

nonneoplastic and neoplastic lesions observed in nasal tissues of rats and mice are relevant to humans. Development of rat, mouse, and human hybrid computational fluid dynamics and PBPK models that include metabolizing nasal compartments and the application of the models to extrapolating rat or mouse nasal doses to humans will likely decrease uncertainty in extrapolating naphthalene health hazards from rodents to humans.

In animals orally exposed to naphthalene, the critical effects appear to be decreased weight gain and clinical signs of neurological impairment in pregnant rats with acute exposure and decreased body weight in rats with intermediate-duration exposure. Mechanisms associated with these effects are unstudied. Reliable data to preclude the relevance of these effects to humans were not located.

Pulmonary alveolar proteinosis induced in mice following chronic oral exposure to 1-methylnaphthalene or 2-methylnaphthalene is assumed to be relevant to humans, in the absence of data to indicate otherwise. Pulmonary alveolar proteinosis is a condition that has been described in humans, although reports noting associations with human exposure to 1-methylnaphthalene or 2-methylnaphthalene were not located.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]…". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of

natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding the possible effect of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene on the neuroendocrine axis in humans or animals or in *in vitro* systems.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates

because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxication. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Newborns and infants are thought to be more susceptible to adverse health effects from naphthalene (e.g., hemolytic anemia from acute exposure) because hepatic enzyme systems involved in conjugation and excretion of naphthalene metabolites are not well developed shortly after birth (EPA 1987a). No studies were located, however, that specifically examined the influence of age on naphthalene toxicokinetic capabilities in humans.

Although the occurrence of hemolytic anemia in neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958), oral-exposure developmental toxicity studies in animals do not

provide evidence that naphthalene was fetotoxic or impaired fetal development, even at maternally toxic dose levels as high as 450 mg/kg/day (NTP 1991a; Plasterer et al. 1985; PRI 1986).

Naphthalene has been detected in human milk samples (concentration not reported) (Pellizzari et al. 1982), but no studies were located that have specifically examined the rate or extent of naphthalene distribution to breast milk in exposed humans or animals.

Children with genetically determined glucose-6-phosphate dehydrogenase (G6PD) deficiency are expected to be especially susceptible to the hemolytic action of naphthalene (Owa 1989; Owa et al. 1993; Santucci and Shah 2000; Valaes et al. 1963). In support of this hypothesis, in 21 cases of hemolytic anemia in Greek infants exposed to naphthalene, 10 of the children had a genetically determined deficiency in G6PD (Valaes et al. 1963). In a 10-year chart review of 24 African-American children hospitalized with acute hemolytic anemia, 14 were noted to have been exposed to naphthalene-containing moth repellants (Santucci and Shah 2000). Deficiency in G6PD makes red blood cells more susceptible to oxidative damage from a wide range of causes including naphthalene exposure. Relatively high rates of genetically determined G6PD deficiency have been reported in males of certain subpopulations of Asian, Arabic, Caucasian, African, and African-American ancestry (EPA 1987a).

The limited mobility of infants when they are wearing naphthalene-treated clothing or when they are near other naphthalene-treated articles (e.g., blankets treated with naphthalene-containing moth repellants) may maximize exposure due to the development of a microenvironment with a high level of naphthalene vapor in the space around the infant. The tendency for infants and small children to place small objects, such as mothballs, in their mouths also increases their risk.

An association between elevated maternal exposure to naphthalene and increased maternal cord-blood levels of one of four T cell types, IL-4, has recently been reported (Lehmann et al. 2002). The study looked for possible associations between maternal indoor exposure to 28 volatile organic chemicals (including naphthalene) and putative immune status at birth assessed by cord-blood levels of cytokine-producing T cells [interleukin-4 (IL-4), interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α)]. Levels of 28 volatile organic chemicals in air samples, collected during a 4-week postnatal period in bedrooms of 85 newborn children, were measured as surrogate indices of maternal indoor exposure. A logistic regression analysis found an elevated odds ratio (OR=2.9; 95% CI 1.0-8.2) for elevated naphthalene air concentrations (>75^{th} percentile) and elevated percentage of IL-4-producing T cells in cord blood. The analysis adjusted for possible confounding factors of family allergic (i.e.,

atopic) history and maternal smoking during pregnancy. Several other statistically significant associations were found for changes in levels of different types of T cells and air levels of other chemicals, including methylcyclopentane, trichloroethylene, and tetrachloroethylene. The significance of the observed variations in cord blood T cell levels to the immune status of the newborn children is unknown. The findings from this study are inadequate to determine if maternal exposure to naphthalene may influence the immune status of newborn children.

Studies that have examined age-related effects of toxicokinetic variables specifically related to naphthalene are restricted to a study with results indicating that neonatal mice may be more susceptible than adult mice to lung injury from single intraperitoneal doses of 25, 50, or 100 mg/kg naphthalene (Fanucchi et al. 1997). Epithelial damage in terminal bronchioles (principally in the Clara cells) was observed in 7-day-old mice exposed to 25 mg/kg, but was absent in adult mice at the same dose level. In adult mice exposed to 50 mg/kg, injury was only mild and variable (from mouse to mouse) and only became consistent with exposure to 100 mg/kg. Epithelial damage in 14-day-old mice was less severe than the damage in 7-day-old mice. Activities of CYP-mediated naphthalene metabolism in bronchiolar tissues were 2.5 times lower in neonatal mice than in adult mice, suggesting that the difference in susceptibility is not explained by differences in ability to form reactive metabolites alone (e.g., 1,2-naphthalene oxide). Differences between neonates and adults in the balance between formation of reactive naphthalene metabolites and downstream transformations could potentially explain the difference in susceptibility to naphthalene toxicity, but the possibilities for specific, age-related differences in downstream enzyme activities for naphthalene (e.g., epoxide hydrolase, dihydrodiol dehydrogenase) have not been studied to date. Alternatively, toxicodynamic differences may exist between neonatal and adult mice (e.g., different target macromolecules). Based on findings that *in utero* exposure to other chemicals, which are bioactivated by CYP, caused Clara cell tumors in adult offspring, Fanucchi et al. (1997) postulated that naphthalene exposure during the neonatal period, when increased susceptibility to naphthalene-induced cytotoxicity occurs, may lead to loss of regulatory mechanisms resulting in Clara cell proliferation and tumor formation in adult animals, but direct evidence for naphthalene in support of this hypothesis is not available (e.g., demonstration that *in utero* or neonatal naphthalene exposure will cause increased incidence of lung tumors in adult mice).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible".

Additional information concerning biomarkers for effects on the immune, renal, and hepatic systems can be found in the CDC/ATSDR Subcommittee Report on Biological Indicators of Organ Damage (CDC/ATSDR 1990), and on the neurological system in the Office of Technology Assessment Report on Identifying and Controlling Poisons of the Nervous System (OTA 1990). Additional details concerning the health effects caused by naphthalene can be found in Section 3.2.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

In cases where humans have swallowed one or more mothballs, it is possible to identify the undissolved naphthalene in the stomach or duodenum by radioluminescence (Woolf et al. 1993). Thus, radiography of the abdominal area is of value in determining if exposure has occurred, especially in children who are often unreliable sources of exposure information. Of the 2,400 cases on naphthalene ingestion reported to 72 Poison Control Centers in the United States, 2,100 involve children less than 6 years old. Radioluminescence has the advantage of differentiating naphthalene-containing solids in the gastrointestinal tract from paradichlorobenzene or other materials used in moth repellants and deodorizers.

Methods are available for the determination of naphthalene in human adipose tissue (EPA 1986g; Liao et al. 1988). In the National Human Adipose Tissue Survey, 40% of the subjects surveyed had measurable levels of naphthalene with concentrations of up to 63 ng/g. Naphthalene and its metabolites can be detected in human and animal urine (Horning et al. 1980; Mackell et al. 1951; Stillwell et al. 1982). Investigators have reported strong correlations between 1-naphthol concentrations in the urine of exposed workers and naphthalene concentrations in the breathing zone air (Bieniek 1994). Peak naphthalene concentrations in the urine occurred immediately after the end of the exposure period and declined thereafter. In some instances, 1-naphthol concentrations had returned to baseline 8 hours later. Few current data are available relating naphthalene levels in adipose tissue or urine with the human exposure concentrations.

In swine, a good correlation existed between 1-naphthol levels in hydrolyzed urine samples collected in the first and second 24 hours after dosing with as little as 7 µg/kg/day naphthalene (Keimig and Morgan 1986). Thus, 1-naphthol may be an appropriate biomarker for monitoring naphthalene exposures in the

occupational setting. Some caution must be exercised in using 1-naphthol as a biomarker of naphthalene exposure in the general population since this metabolite is also excreted after exposure to the common insecticide, carbaryl (Benson and Dorough 1984).

Early work to develop biomarkers of exposure, such as naphthalene mercapturic acid derivatives in urine (Marco et al. 1993) and naphthalene hemoglobin adducts in blood (Cho et al. 1994b), has been extended to develop techniques to measure cysteinyl adducts formed from reactions of hemoglobin and albumin with reactive metabolites of naphthalene (Troester et al. 2002; Waidyanatha et al. 2002). One of the reasons for developing these techniques is that it is difficult to measure reactive metabolites of naphthalene *in vivo*. Using these techniques, hemoglobin and albumin adducts of 1,2-naphthalene oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone were shown to increase with increasing dose in F344 rats given single oral doses of 0, 100, 200, 400, or 800 mg/kg naphthalene (Waidyanatha et al. 2002). The stabilities of the adducts were measured in rats following exposure to naphthalene (Troester et al. 2002). Some were found to be stable and others unstable, although they all were more stable than the reactive metabolites themselves. As such, the adducts are expected to be useful in estimating internal doses of these metabolites.

An analytical method is available to determine levels of 2-methylnaphthalene and its derivatives in rat urine (Melancon et al. 1982). This method would probably also be useful in measuring 2-methyl-naphthalene levels in human urine. Because of the lack of information for 1-methylnaphthalene, it is not possible to identify a biomarker of exposure for this substance.

3.8.2 Biomarkers Used to Characterize Effects Caused by Naphthalene, 1-Methyl-naphthalene, and 2-Methylnaphthalene

Hemolytic anemia has been frequently reported to be a consequence of exposure to naphthalene. However, this effect can also occur without exposure to naphthalene, and may not be useful as a specific biomarker of effect.

Clara cell damage may be identified by the presence of naphthalene/protein adducts in lung lavage fluids (Cho et al. 1994a). Additional research is needed to improve the specificity of this technique as a biomarker of effect.

Because of the lack of information for 1-methylnaphthalene or 2-methylnaphthalene, it is not possible to identify a biomarker of effects for these chemicals.

3.9 INTERACTIONS WITH OTHER CHEMICALS

When either naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene was applied dermally in combination with benzo[a]pyrene (BaP), there was an inhibitory effect on the induction of skin tumors in female mice (Schmeltz et al. 1978). These investigators also reported that a mixture containing naphthalene (0.02%), 2-methylnaphthalene (0.02%) and 10 other methylated and ethylated naphthalenes (each at 0.02%) also appeared to inhibit the development of BaP-induced skin tumors. The authors suggested that it is likely that certain naphthalenes compete with BaP for the same enzyme sites, resulting in alteration of the BaP metabolic pathway and decreased production of the active BaP metabolite. This hypothesis is consistent with the observation that benzo(a)pyrene hydroxylase is inhibited by naphthalene (Shopp et al. 1984). Dermal application of the naphthalene mixture did not induce tumors in the absence of BaP. The results of these studies were not analyzed statistically.

Several studies have been conducted to assess factors that influence the toxicity of naphthalene. For the most part, these studies have evaluated the effects of mixed function oxidase activity (MFO) and alterations in glutathione levels on pulmonary and ocular toxicities. The effects of cyclooxygenase activity, antioxidants, and epoxide hydrolase inhibitors on the cataractogenic effect of naphthalene have also been evaluated. The administration of MFO inhibitors (SKF-525A, metyrapone) and antioxidants (caffeic acid and vitamin E) decreased ocular toxicity in mice (Wells et al. 1989). Use of ALO1576, an inhibitor of the enzyme aldose reductase, prevented cataract formation in both *in vivo* and *in vitro* studies (Xu et al. 1992a, 1992b). On the other hand, naphthalene-induced cataracts were enhanced by pretreatment with a MFO inducer (phenobarbital) and a glutathione depletor (diethyl maleate) (Wells et al. 1989). Pulmonary damage was decreased by prior treatment with a MFO inhibitor (piperonyl butoxide), but enhanced by prior treatment with a glutathione depletor (diethyl maleate) (Warren et al. 1982). For the most part, these studies support the role for mixed function oxidase activity and glutathione conjugation in naphthalene-induced pulmonary and ocular lesions.

Mixed function oxidase inducers also affect the metabolism of 2-methylnaphthalene. Inducers that influence cytochrome P-450 increase the oxidation of the side chain and the concentration of one dihydrodiol. Induction of cytochrome P-450 increased the production of two other dihydrodiols

(Melancon et al. 1985). The production of naphthoic acid in preference to the diols may explain why acute exposure to 2-methylnaphthalene is less toxic to Clara cells than acute exposure to naphthalene.

In general, interactions with environmental contaminants, such as polycyclic aromatic hydrocarbons, should be expected at hazardous waste sites. Most hazardous waste sites (with the notable exception of certain pharmaceutical sites) would not be expected to contain substantial volumes of certain types of contaminants, such as antioxidants or cytochrome P-450 inhibitors.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene than will most persons exposed to the same level of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxication or excretion of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene, or compromised function of organs affected by naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. Populations who are at greater risk due to their unusually high exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are discussed in Section 6.7, Populations With Potentially High Exposures.

The hemolytic response to naphthalene is enhanced by the presence of inherited erythrocyte G6PD deficiency. Although any human may experience acute hemolysis if exposed to a sufficiently high dose of naphthalene, this enzyme deficiency may cause some persons to be unusually sensitive. The incidence of the deficiency among Caucasians of European origin is relatively low, while there is a higher incidence among certain groups of Asians and Middle Eastern populations. A study of hemolytic anemia in African-American children with G6PD deficiency by Shannon and Buchanan (1982) suggests that this is a population that may be susceptible to the hemolytic effects of naphthalene exposure. It was also reported that 16% of African-American males are G6PD-deficient (Calabrese 1986). According to Shannon and Buchanan (1982), a syndrome of acute severe hemolysis following exposure to oxidative stress is associated with the Mediterranean variant of the deficiency, whereas the hemolytic anemia seen in African-Americans is generally mild.

Results from a recent study indicate that female mice are more susceptible than male mice to lung injury from acute parenteral exposure to naphthalene (Van Winkle et al. 2002). Male and female Swiss-Webster

mice were given intraperitoneal injections of 0 or 200 mg/kg naphthalene in corn oil, and lungs were removed at 1, 2, 3, 6, and 24 hours after treatment. Acute lung injury was determined by (1) high-resolution microscopic assessment of differential permeability to fluorescent nuclear dyes in cells along the long axis of conducting airway trees of microdissected right middle lung lobes and (2) high-resolution histopathology of sections of Karnovsky-fixed left lung lobes. Clara cell injury occurred in the terminal bronchioles of both male and female mice. Clara cell injury in terminal bronchioles, however, occurred earlier, affected cells farther up the airway tree, and showed a different temporal pattern of changes in female mice compared with male mice. Twenty-four hours after injection, Clara cell injury in the lobar bronchus of female mice was evidenced by numerous vacuolated cells, whereas normal bronchiolar epithelium containing Clara and ciliated cells was found in vehicle-control males and females, as well as in exposed male mice. Assessment of *in vitro* naphthalene metabolism in microdissected regions of airways from male and female mice by high performance liquid chromatography (HPLC) analysis indicated that the rate of formation of a dihydrodiol metabolite (1,2-dihydroxy-1,2-dihydronaphthalene) was greater in female tissue than in male tissue. This metabolic difference may be related to the apparent gender difference in susceptibility to acute lung injury from naphthalene. It is unknown whether or not the gender difference in susceptibility to acute lung injury is relevant to nasal or lung lesions formed with chronic-duration exposure to naphthalene.

There are no data that indicate whether there are populations that are unusually susceptible to the toxic effects of 1-methylnaphthalene or 2-methylnaphthalene.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene:

Kurz JM. 1987. Naphthalene poisoning: Critical care nursing techniques. Dimens Crit Care Nurs 6:264-270.

Melzer-Lange M, Walsh-Kelly C. 1989. Naphthalene-induced hemolysis in a black female toddler deficient in glucose-6-phosphate dehydrogenase. Pediatr Emerg Care 5:24-26.

Siegel E, Wason S. 1986. Mothball toxicity. Pediatr Clin North Am 33:369-374.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. Second edition. Beltsville, MD: Bradford Communications Corporation.

3.11.1 Reducing Peak Absorption Following Exposure

If inhalation of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene has occurred, movement to fresh air is recommended. In cases where a small amount (e.g., one mothball, 0.5–3.6 g) of naphthalene has been ingested, measures are implemented to empty the stomach contents. Syrup of Ipecac, which may be used for this purpose, is administered after ingestion to induce vomiting and is most effective if initiated within a 2-hour period after exposure (Siegel and Wason 1986). If large quantities of naphthalene have been ingested, syrup-of-ipecac-induced vomiting is usually followed by gastric aspiration using a large gauge lavaculator (to remove mothballs) (Kurz 1987). This will only be of value if the naphthalene particles are small enough to be aspirated. Measures are usually taken to protect the respiratory tract from aspiration of gastric contents. Activated charcoal can be given to bind dissolved naphthalene in the gastrointestinal tract. Further treatment with a cathartic (e.g., magnesium sulfate) to speed fecal excretion is recommended (Melzer-Lange and Walsh-Kelly 1989). Milk or fatty meals ingested within 2–3 hours after exposure may increase absorption (Siegel and Wason 1986).

In order to reduce absorption of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene through the skin, areas of skin that have come in contact with the compound should be washed with soap and water. Application of oil based lotions should be avoided. If these compounds are splashed into the eyes, irrigation with large amounts of water for 15–30 minutes may be useful to wash away unabsorbed material (Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Some evidence exists that naphthalene metabolites may be retained in the body in adipose tissue (EPA 1986g). Naphthalene was identified in 40% of the samples evaluated for the Human Adipose Tissue Survey (EPA 1986g). Naphthalene metabolites were detected in urine up to 13 days following exposure (Mackell et al. 1951).

The most frequently documented acute toxic effect of naphthalene in humans is red cell hemolysis. In cases of clinically significant hemolysis, accelerated urinary excretion of naphthol metabolites is recommended to protect the kidney from products of hemolysis (EPA 1989d). In cases of renal failure, hemodialysis may be effective in controlling extracellular fluid (plasma) composition (EPA 1989d). It should be noted that this method is not very effective in removing lipophilic compounds from blood. Ocular effects have also been reported in humans; however, there are no specific treatments for reducing the toxic effects on the eyes. Respiratory effects have been observed in animals but these effects have not been reported in humans. Due to lack of data, it is difficult to speculate regarding the benefits of treatments that enhance elimination of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene and their metabolites as a basis for reducing toxic effects.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Existing data indicate that lung, nose, and eye toxicity may be mediated by reactive metabolites for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, although the evidence for the involvement of reactive metabolites is greater than the evidence for methylnaphthalenes. More information is needed on the bioactivation of naphthalene and transport mechanisms before methods for blocking those mechanisms can be developed.

Many of the symptoms of acute naphthalene poisoning in humans are a direct consequence of red blood cell hemolysis. Blood transfusions, packed red blood cell transfusions, and exchange transfusions (particularly in infants) can be used to replenish the concentration of red blood cells and diminish the risks of cellular anoxia (Bregman 1954; Chusid and Fried 1955; MacGregor 1954; Mackell et al. 1951). Bicarbonate is also administered to hemolysis patients to increase the alkalinity of the urine and thereby minimize deposition of hemoglobin in the kidney tubules (Chusid and Fried 1955; Gidron and Leurer 1956).

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of naphthalene, 1-methylnaphthalene, and 2-methyl-

naphthalene are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

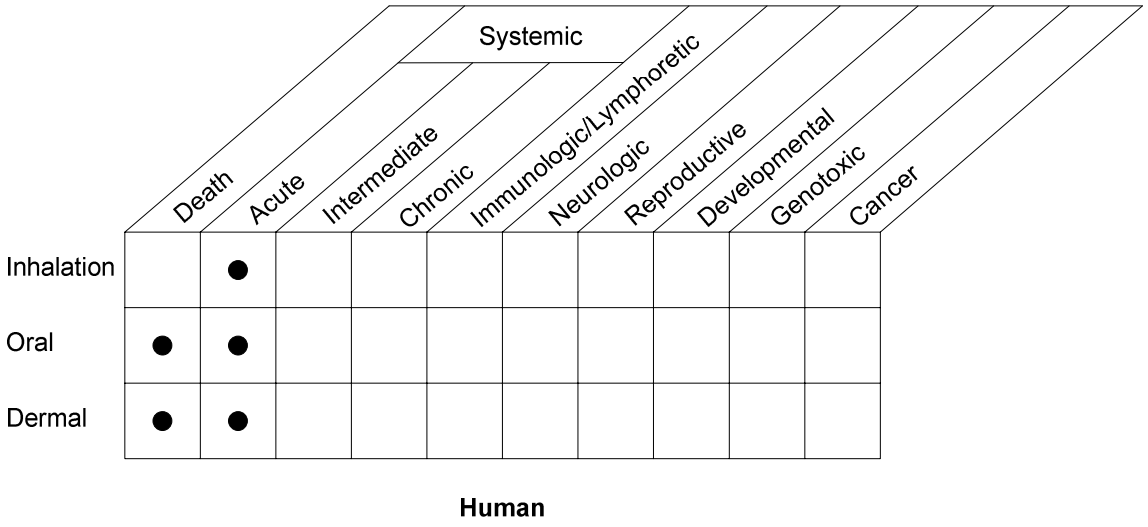
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

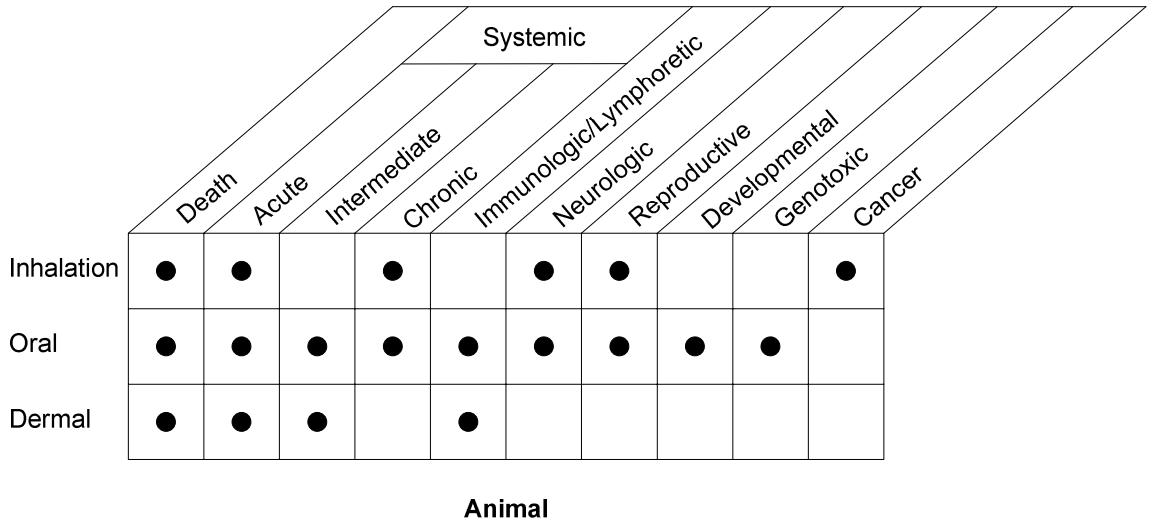
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are summarized in Figures 3-6, 3-7, and 3-8, respectively. The purpose of this figure is to illustrate the existing information concerning the health effects of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-6 shows that the database on naphthalene toxicity in humans is not extensive. There are case reports and case series of deaths, acute hemolytic anemia, and ocular effects in humans, but these reports lack quantitative information on exposure levels. Epidemiologic studies designed to examine possible associations between intermediate- or chronic-duration human exposure to naphthalene by any route of exposure and neoplastic or nonneoplastic health effects are not available. Animal data on naphthalene exist in several areas. Oral toxicity data are adequate for deriving acute- and intermediate-duration oral MRLs, but adequate chronic-duration oral toxicity studies in animals are not available. Available toxicology and carcinogenesis studies of chronic inhalation exposure to naphthalene in rats and mice are

Figure 3-6. Existing Information on Health Effects of Naphthalene



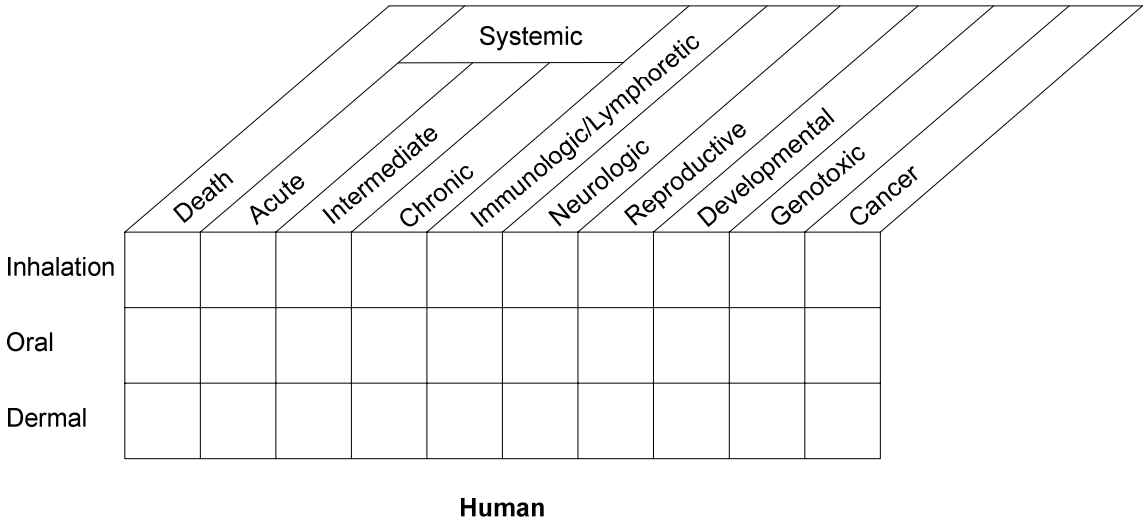
Human



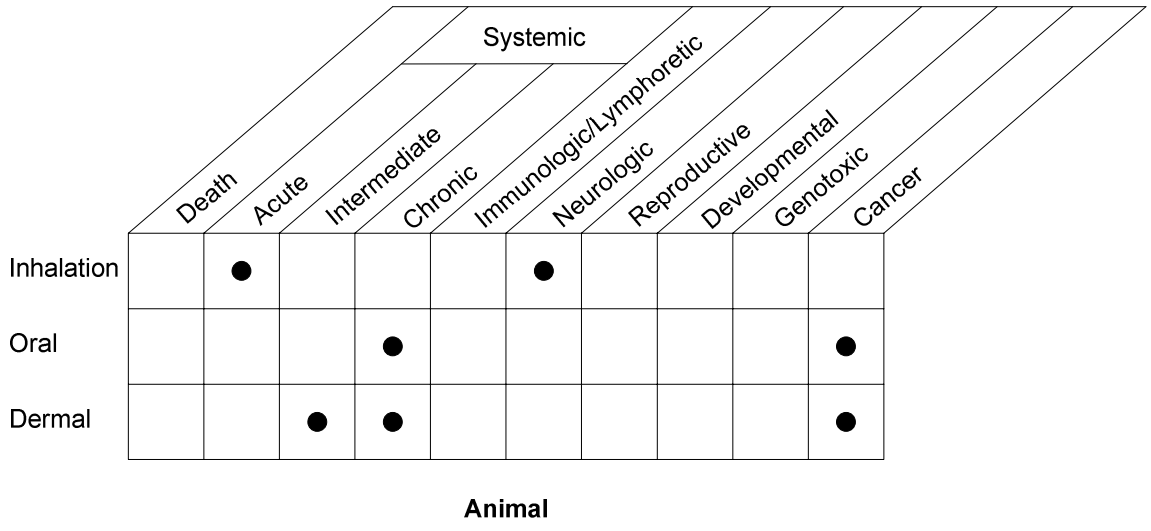
Animal

● Existing Studies

Figure 3-7. Existing Information on Health Effects of 1-Methylnaphthalene



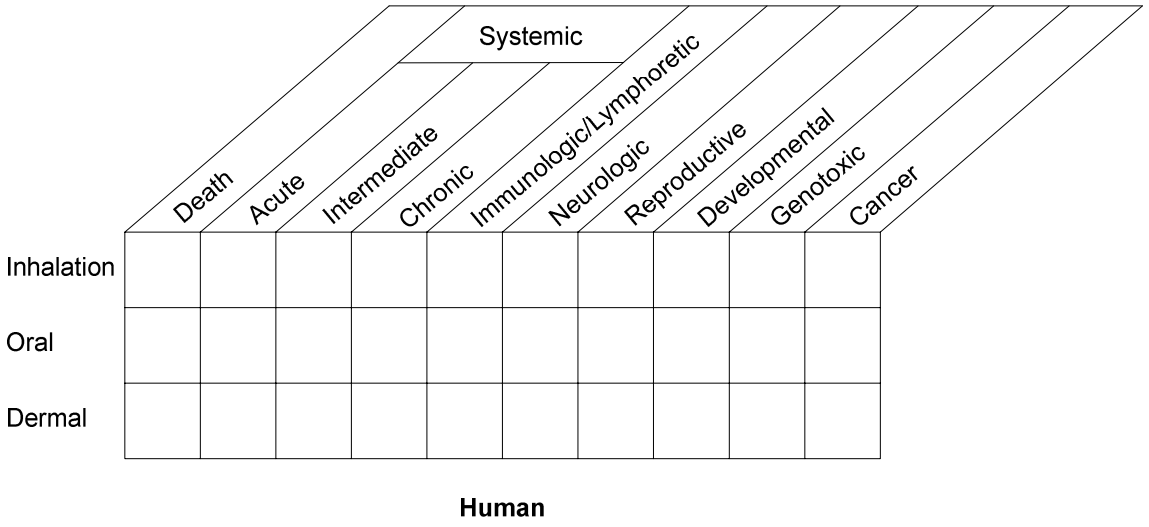
Human



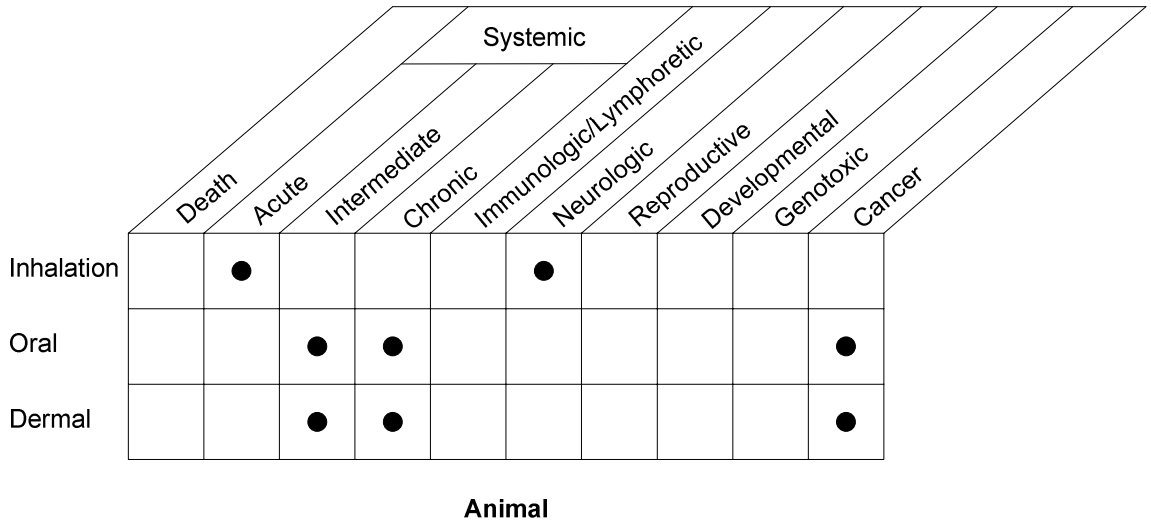
Animal

● Existing Studies

Figure 3-8. Existing Information on Health Effects of 2-Methylnaphthalene



Human



Animal

● Existing Studies

adequate for deriving a chronic-duration inhalation MRL for naphthalene and assessing the potential carcinogenicity of naphthalene, but available acute- and intermediate-duration inhalation toxicity studies are not adequate for deriving MRLs.

Figures 3-7 and 3-8 show that no information was located on the health effects of 1-methylnaphthalene or 2-methylnaphthalene in humans via inhalation, oral, or dermal exposure. These figures also reflect that data in animals are limited to cancer and toxicity studies of intermediate- and chronic-duration oral exposure of mice to 1-methylnaphthalene or 2-methylnaphthalene, a single poorly reported acute inhalation exposure study of hematologic end points in dogs exposed by inhalation to 1-methyl-naphthalene or 2-methylnaphthalene, a study that reported decreased pain sensitivity, but no effects on the ability to balance on a rotating rod, in rats exposed for 4 hours by inhalation to 1-methylnaphthalene or 2-methylnaphthalene, and cancer and toxicity studies of intermediate- and chronic-duration dermal exposure of mice to a mixture of 1-methylnaphthalene and 2-methylnaphthalene.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. A number of reports of human exposure to acute inhalation, oral, or dermal doses of naphthalene have established the erythrocyte as a toxicity target (Dawson et al. 1958; Haggerty 1956; Kurz 1987; Linick 1983; MacGregor 1954; Mackell et al. 1951; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Schafer 1951; Shannon and Buchanan 1982; Valaes et al. 1963). However, the data from these reports were not useful in predicting toxic or lethal dose levels by any of these routes because the exposure levels were not defined.

The acute oral toxicity of naphthalene has been studied in animals but there are limited data for acute inhalation and dermal exposures.

The most frequently reported adverse effects associated with acute oral exposure are ocular lesions (primarily cataracts). These have been observed in rabbits (Srivastava and Nath 1969; Van Heyningen and Pirie 1967) and rats (Kojima 1992; Murano et al. 1993; Rathburn et al. 1990; Tao et al. 1991; Yamauchi et al. 1986) and occur following exposure to high (>500 mg/kg) doses. Acute oral exposure of pregnant rats to naphthalene doses of 150 or 450 mg/kg/day (but not 50 mg/kg/day) during gestation produced maternal toxicity including clinical signs of neurological impairment (lethargy and prone position) and marked decreases in body weight gain (NTP 1991a), but clear effects on the developing fetus have not been found at maternal oral doses as high as 450 mg/kg/day in rats (NTP 1991a),

300 mg/kg/day in mice (Plasterer et al. 1985), or 120 (NTP 1992b) or 400 mg/kg/day (PRI 1985i,1986) in rabbits. Slightly reduced numbers of mouse pups per litter were observed when naphthalene in corn oil was orally administered to pregnant mice (Plasterer et al. 1985); however, no effects were seen when pregnant rabbits were orally administered naphthalene at even higher doses but delivered in methylcellulose rather than in an oil vehicle (PRI 1986). It is unclear if these differences are due to species differences in sensitivity or to possible differences in the effects of the two vehicles on naphthalene absorption. Effects on liver (Rao and Pandya 1981) and lung (Shopp et al. 1984) weights have been reported, but no treatment-related histopathological lesions were observed in these acute oral exposure studies. Lethal doses have been identified in mice (Plasterer et al. 1985; Shopp et al. 1984) and rats (Gaines 1969).

The finding of transient clinical signs of neurotoxicity in orally exposed pregnant rats (NTP 1991a) serves as the basis of the acute-duration oral MRL for naphthalene of 0.6 mg/kg/day. The MRL was calculated from a minimal LOAEL of 50 mg/kg/day using an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability). An uncertainty factor of 3 was used for human variability because the critical effect is based on effects in a sensitive animal subpopulation. Dermal or inhalation developmental toxicity studies in animals are not available. Pregnant rats appear to be more sensitive for the effects observed (clinical signs of neurotoxicity in response to gavage exposure and decreased body weight gain) than nonpregnant rats. In 13-week gavage studies with nonpregnant rats (NTP 1980b), similar persistent neurologic symptoms were not observed following administration of doses as high as 200 mg/kg/day, but were observed at 400 mg/kg/day. In nonpregnant rats exposed for 13 weeks, significant body weight decreases occurred at 200 mg/kg/day throughout exposure, but not at 100 mg/kg/day (NTP 1980b) or in nonpregnant mice exposed for 13 weeks to 133 mg/kg/day (Shopp et al. 1984) or 200 mg/kg/day (NTP 1980a). Mice in the NTP (1980a) study showed transient signs of toxicity (lethargy, rough hair coats, and decreased food consumption), but these only occurred between weeks 3 and 5 in the 200-mg/kg/day group.

Data are inadequate for deriving an acute-duration inhalation MRL for naphthalene. Data are restricted to a 14-day (6 hours/day, 5 days/week) range-finding study in B6C3F1 mice (NTP 1992a), which only examined hematologic end points and did not histologically examine expected critical toxicity targets (lung and nasal cavity epithelial tissue) (NTP 1992a), and a study (West et al. 2001) with Swiss Webster mice and Sprague-Dawley rats, which involved single 4-hour exposure periods. The more recent study, however, only histologically examined the lung and did not examine nasal tissue. A comprehensive inhalation study involving an acute repeated exposure scenario and examining the other critical target (the

nose, based on the findings from chronic mouse and rat bioassays) is not currently available. Results from such a study may be useful for deriving an acute-duration inhalation MRL for naphthalene.

Hemolysis is the best documented effect of acute naphthalene exposures in humans, but it has not been observed in studied strains of rats (F344) or mice (CD-1, B6C3F1). Dose-response data for hemolysis from a susceptible animal species (such as dogs or the Jackson Laboratory hemolytic anemia mouse) may be useful to obtain data that could be used for considering changes to the acute-duration oral MRL. Data from both inhalation and oral exposure protocols would be useful.

No acute-duration studies are available on 1-methylnaphthalene or 2-methylnaphthalene exposure in humans using the inhalation, oral, or dermal routes. Two acute inhalation studies in animals were identified. The first study reported that 1-methylnaphthalene (pure) administered in a kerosene aerosol was associated with increased reticulocyte and lymphocyte counts in splenectomized dogs and practical grade 1-methylnaphthalene was associated with increased leucocyte and neutrophil counts (Lorber 1972). Neither grade of 1-methylnaphthalene had any effect on hematocrit values. None of these parameters were affected when 2-methylnaphthalene aerosols were used. The physiological significance of these findings is not apparent and the exposure levels in the study were not clearly specified. As such, the data are not suitable for use in deriving of an MRL for 1-methylnaphthalene or 2-methylnaphthalene. The second study measured decreased sensitivity to pain in rats exposed by inhalation for 4 hours to 1-methylnaphthalene (44 ppm) or 2-methylnaphthalene (61 ppm), but found no effects on the ability to balance on a rotating rod at exposure levels as high as 70 ppm 1-methylnaphthalene or 90 ppm 2-methylnaphthalene (Korsak et al. 1998). The biological significance of these findings is uncertain, and, in the absence of corroborative evidence of acute neurotoxicity, the findings are not suitable for deriving acute inhalation MRLs for 1-methylnaphthalene or 2-methylnaphthalene.

Parenteral studies in animals revealed that a single intraperitoneal injection of 2-methylnaphthalene (1,000 mg/kg) was lethal in mice (Griffin et al. 1981). When a glutathione-depleting agent (diethyl maleate) was administered prior to administration of 2-methylnaphthalene, a lower dose of 2-methylnaphthalene (400 mg/kg) was also lethal. A single intraperitoneal injection of 1-methylnaphthalene (426 mg/kg) was not lethal in mice (Griffin et al. 1982). Systemic effects have been reported and were limited to effects on the respiratory system (Rasmussen et al. 1986). Exfoliation of the bronchiolar epithelium in mice was reported following a single intraperitoneal injection of 2-methylnaphthalene (Buckpitt et al. 1986; Griffin et al. 1981, 1983). A single intraperitoneal injection of 2-methylnaphthalene (1,000 mg/kg) did not cause liver or kidney lesions (Griffin et al. 1981, 1983).

Because populations living near hazardous waste sites might be exposed to 1-methylnaphthalene or 2-methylnaphthalene for short periods, comprehensive toxicity studies of acute exposure in animals by the inhalation and oral routes to determine potential target tissues and dose-related effects would be useful in assessing possible health hazards to humans. The studies would be most useful if they included a battery of neurological end points and comprehensive histological examination of nasal and lung tissue.

Intermediate-Duration Exposure. Quantitative data were not provided in any intermediate-duration inhalation case studies of human naphthalene exposure and, in one case, there was simultaneous exposure to paradichlorobenzene (Harden and Baetjer 1978; Linick 1983).

The results from three intermediate-duration oral toxicity studies in animals (two in mice and one in rats) identified body weight changes as the most sensitive biologically significant effect on which to base the intermediate-duration oral MRL for naphthalene. Comprehensive intermediate-duration oral toxicity studies found no evidence for naphthalene-induced lesions in any tissue or organs in male or female Fischer 344 rats exposed to doses up to 400 mg/kg/day (NTP 1980b) or in male or female B6C3F1 mice exposed to doses up to 200 mg/kg/day (NTP 1980a). The only biologically significant effect found in these studies was decreased body weight (>10% decreased compared with control values) in rats at doses of 200 and 400 mg/kg/day. The other intermediate-duration oral study (with CD-1 mice) focused on a battery of immunologic tests, but did not include comprehensive histopathologic examination of tissues (Shopp et al. 1984). No biologically significant effects were found except for decreases in weights of several organs (brain, liver, and spleen) in mice exposed to 133 mg/kg/day, but not to 53 or 5.3 mg/kg/day. The lack of naphthalene-induced lesions in these organs in the NTP (1980a, 1980b) studies suggests that the brain, liver, and spleen are not sensitive targets of naphthalene following intermediate-duration oral exposure. Statistically significant changes were reported in several hematological parameters, hepatic enzyme activities, and serum chemical parameters (Shopp et al. 1984), but these changes are not considered to be biologically significant or adverse. The acute-duration oral MRL of 0.6 mg/kg/day was adopted as the intermediate-duration oral MRL for naphthalene, because a potential intermediate-duration oral MRL (0.7 mg/kg/day; see Section 2.3 and Appendix A) based on the NOAEL for decreased body weight changes in rats exposed by gavage 5 days/week for 13 weeks (NTP 1980b) was slightly larger than the acute MRL value.

No data were suitable for the development on an intermediate-duration inhalation MRL for naphthalene.

Intermediate-duration dermal toxicity data are restricted to an report that dermal exposure of male and female Sprague-Dawley rats (occluded exposure 6 hours/day, 5 days/week) to technical-grade naphthalene at doses up to 1,000 mg/kg/day for 13 weeks did not affect comprehensive ophthalmologic, hematologic, serum chemistry, or urinalysis parameters (Frantz et al. 1986). In addition, exposure did not produce increased incidences of histological lesions in 34 tissues that were examined (however, the nasal cavity was not included). The only exposure-related effect found was an increased incidence of excoriated skin and papules at the site of exposure at the highest dose level (1,000 mg/kg/day).

Intermediate-duration studies on 1-methylnaphthalene or 2-methylnaphthalene exposure in humans or animals using the inhalation, oral, or dermal routes are restricted to a study that found no pulmonary alveolar proteinosis in male or female mice exposed to diets containing up to 1.33% 2-methylnaphthalene for 13 weeks (Murata et al. 1997). The reporting of the experimental protocol and results from this study, however, is too limited to reliably use the results as a basis for an intermediate-duration oral MRL for 2-methylnaphthalene. New intermediate-duration toxicity studies using the inhalation route of exposure may be the most useful to better assess the health hazard of intermediate-duration exposure to naphthalene, based on the findings that the alveolar region of the lung is the most sensitive tissue in mice chronically exposed to 1-methylnaphthalene or 2-methylnaphthalene in the diet (Murata et al. 1993, 1997).

Chronic-Duration Exposure and Cancer. There is one report of cataracts occurring in humans following chronic-duration inhalation exposure to naphthalene (Ghetti and Mariani 1956) but no information on effects from exposures by the oral or dermal routes. The only studies of cancer in humans exposed to naphthalene are two case series reports of cancer; one report of four laryngeal cancer cases (all of whom were smokers) among workers in a naphthalene purification plant in East Germany (Wolf 1976, 1978), and another report of 23 cases of colorectal carcinoma admitted to a hospital in Nigeria (Ajao et al. 1988). NTP (2002b), EPA (2002b), and IARC (2002) concurred that these studies provide inadequate evidence of naphthalene carcinogenicity in humans. No cohort mortality or morbidity studies or case-control studies examining possible associations between naphthalene exposure and increased risk of cancer (or other health effects) are available.

There are two comprehensive chronic-duration inhalation toxicology and carcinogenicity studies of naphthalene in animals, one in rats (Abdo et al. 2001; NTP 2000) and one in mice (NTP 1992a). These studies identify respiratory tissues as the most sensitive toxicity targets of chronic-duration exposure to inhaled naphthalene in animals: nonneoplastic and neoplastic lesions in the nose of rats, nonneoplastic

lesions in the nose of mice, and nonneoplastic and neoplastic lesions in the lungs of mice. Exposure-related lesions in other tissues were not found in these studies. NTP (2002b) and IARC (2002) concurred that these studies provide sufficient evidence of naphthalene carcinogenicity in animals. The chronic-duration inhalation MRL for naphthalene is based on the LOAEL of 10 ppm for nonneoplastic lesions in the olfactory epithelium and respiratory epithelium of the nose of rats.

No appropriate studies were located for deriving an MRL for chronic-duration oral exposure to naphthalene. One chronic study was located that examined the toxicity of naphthalene in rats (Schmahl 1955). No treatment-related effects were reported at a dose level of 41 mg/kg/day for 700 days. The study was not suitable as the basis for deriving a chronic MRL or for assessing carcinogenicity because only one dose level was evaluated (apparently below the maximum tolerated dose), histopathological examination was limited, and dosing was not precisely controlled.

New chronic oral or dermal toxicity studies would be useful to better determine the possible carcinogenicity and noncancer toxicity of naphthalene via these routes of exposure.

Epidemiology studies, case reports, or controlled-exposure studies examining the potential health effects of human chronic exposure to 1-methylnaphthalene or 2-methylnaphthalene by any route of exposure are not available.

No chronic-duration studies are available on 1-methylnaphthalene or 2-methylnaphthalene exposure in animals using the inhalation routes.

A chronic-duration study of 1-methylnaphthalene in the diet that identified a LOAEL of 71.6 mg/kg/day for the occurrence of pulmonary alveolar proteinosis in mice (Murata et al. 1993) was used as the basis of the oral MRL of 0.07 mg/kg/day for 1-methylnaphthalene. A chronic-duration oral study of 2-methyl-naphthalene in the diet (Murata et al. 1997) that identified a LOAEL of 50.3 mg/kg/day for pulmonary alveolar proteinosis in mice was the basis of the chronic oral MRL of 0.05 mg/kg/day for 2-methyl-naphthalene. Support for pulmonary alveolar proteinosis as the critical effect for the chronic oral MRLs for 1-methylnaphthalene and 2-methylnaphthalene comes from dermal chronic-duration studies with methylnaphthalene (a mixture of 1- and 2-methylnaphthalene), which reported increased incidences of this lesion in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (Emi and Konishi 1985; Murata et al. 1992). Increased incidences of lung adenomas were found in several exposed groups in the oral chronic-duration studies, but the evidence for carcinogenicity is considered to be

limited. The tumorigenic response was predominantly benign and was only consistently seen in male mice exposed to 1-methylnaphthalene. The available data on the methylnaphthalenes appear inadequate to determine the potential carcinogenicity in humans.

A new chronic-duration oral study in rats or another animal species may help to better assess the potential carcinogenicity and noncancer toxicity of the methylnaphthalenes. Because the lung is the most sensitive toxicity target of the methylnaphthalenes in mice exposed orally or dermally, it is plausible that chronic inhalation exposure may also target the lung. The availability of repeated-exposure inhalation carcinogenicity and toxicity studies would help to better determine this possibility.

Genotoxicity. As discussed in Section 3.3, results in bacterial mutation assays were predominantly negative (see Table 3-4 for citations) with the exceptions that the metabolite, 1,2-naphthoquinone, was mutagenic in *S. typhimurium* without metabolic activation (Flowers-Geary 1996), and naphthalene was mutagenic in *V. fischeri* with metabolic activation (Arfsten et al. 1994).

Results from a limited number of *in vitro* eukaryotic genotoxicity assays are mixed. Negative results were obtained for mutations and sister chromatid exchanges in cultured human cells exposed to naphthalene, for DNA single strand breaks and unscheduled DNA synthesis in rat hepatocytes, and for cell transformation in several types of mammalian cells (see Table 3-3 for citations). Positive results included increased chromosomal aberrations in Chinese hamster ovary cells and preimplantation whole mouse embryos exposed to naphthalene, and increased sister chromatid exchanges in human mononuclear leukocytes exposed to 1,2- or 1,4-naphthoquinone and in Chinese hamster ovary cells exposed to naphthalene (see Table 3-3 for citations). Other studies in cell-free systems reported that 1,2-naphthoquinone formed N7 adducts with deoxyguanosine (McCoull et al. 1999) and caused DNA strand scission in the presence of NADPH and copper via reactive oxygen species from an oxidation/reduction cycle (Flowers et al. 1997).

In vivo genotoxicity assays with naphthalene are also limited and do not provide consistently negative or positive results for naphthalene genotoxicity. Positive results were obtained for somatic mutations in *D. melanogaster*, micronuclei in salamander larvae erythrocytes, and DNA fragmentation in liver and brain tissue from mice and rats orally exposed to naphthalene (see Table 3-3 for citations). Negative results were obtained for micronuclei formation in bone marrow of mice given oral or intraperitoneal injections of naphthalene, DNA single strand breaks and unscheduled DNA synthesis in hepatocytes of

rats given oral doses of naphthalene, and neoplastic transformations in liver cells of partially hepatectomized rats given oral doses of naphthalene (see Table 3-3 for citations).

The available data suggest that genotoxic action by the naphthalene metabolite, 1,2-naphthoquinone, is plausible and that the mutagenic/genotoxic potential of naphthalene and its metabolites may be weak. Assays of possible genotoxic action in sensitive target tissues of naphthalene in rodents (lung and nasal epithelial tissue), however, are not available. New studies examining genotoxic end points in lung and nasal epithelial tissue following inhalation exposure to naphthalene would help to better determine the potential genotoxicity of naphthalene and it metabolites.

For the methylnaphthalenes, data in humans are limited to one study that reported no effects on human chromosomes in tests evaluating the effects of 1-methylnaphthalene or 2-methylnaphthalene on human peripheral lymphocytes *in vitro* (Kulka et al. 1988). 1-Methylnaphthalene and 2-methylnaphthalene were also determined to be nonmutagenic in four strains of *S. typhimiurim* (Florin et al. 1980). Additional mutagenicity studies using an *in vivo* approach would be useful to better assess the genotoxicity potentials of 1-methylnaphthalene and 2-methylnaphthalene.

Reproductive Toxicity. No information is available on the reproductive effects of naphthalene in humans, although the occurrence of hemolytic anemia in the neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). Animal studies involving naphthalene exposure during gestation reported no reproductive effects in rabbits administered doses of up to 120 mg/kg/day by gavage or in rats given doses of up to 450 mg/kg/day, although doses of 150 mg/kg/day and greater were maternally toxic to rats. There was a decrease in the number of live mouse pups per litter with a dose of 300 mg/kg/day given during gestation (Plasterer et al. 1985) and *in vitro* studies of naphthalene embryotoxicity in the presence of liver microsomes support the concept that naphthalene metabolites may be harmful to the developing embryo (Iyer et al. 1991). No exposure-related lesions in reproductive tissues were found in intermediate-duration oral exposure studies in rats (NTP 1980b) and mice (NTP 1980a) or in chronic inhalation studies in rats (Abdo et al. 2001; NTP 2000) or mice (NTP 1992a). One- or two-generation reproductive toxicity studies evaluating reproductive performance variables in male and female animals exposed to naphthalene are not available. Results from such studies may help to better determine the potential reproductive toxicity of naphthalene.

No studies are available on the reproductive toxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure, with the exceptions of the reports that 81-week oral exposure to 1-methylnaphthalene or 2-methylnaphthalene did not induce lesions in reproductive tissues of male or female mice (Murata et al. 1993; 1997). One- or two-generation reproductive toxicity studies evaluating reproductive performance variables in male and female animals exposed to 1-methylnaphthalene or 2-methylnaphthalene are not available. Results from such studies may help to better determine the potential reproductive toxicity of the methylnaphthalenes.

Developmental Toxicity. There is no information on the potential developmental effects of naphthalene in humans, although, as mentioned previously, naphthalene and/or its metabolites can cross the placental barrier and cause hemolytic anemia in newborns (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). Studies of the developmental effects of orally administered naphthalene in rats (NTP 1991a), mice (Plasterer et al. 1985), and rabbits (NTP 1992b; PRI 1985i, 1986) have been negative, except for a slight nonsignificant increase in fused sternebrae in female rabbit pups from a small number of litters at doses of 80 and 120 mg/kg/day (NTP 1992b). No developmental toxicity studies involving inhalation or dermal exposure to naphthalene are available. The availability of such studies would help to better determine the developmental toxicity potential of naphthalene.

No studies are available on the developmental toxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure.

Immunotoxicity. There have been no comprehensive studies of the immunotoxicity of naphthalene in humans exposed by the inhalation, oral, or dermal routes. The animal oral exposure data indicate that naphthalene did not affect humoral or cell-mediated immunity in mice (Shopp et al. 1984). Minor effects on the thymus and spleen were noted in mice and rats (NTP 1980b; Shopp et al. 1984), but in no case were animals of both sexes affected. Because there are few data pertaining to the immunotoxicity of naphthalene, a battery of *in vitro*/*in vivo* screening assays of immune function may be useful to determine whether more detailed and longer-term studies are needed.

No studies are available on the immunotoxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure. However, the reported increase in the level of monocytes in mice following long-term oral exposure to 1-methylnaphthalene (Murata et al. 1993) may deserve additional study. As with naphthalene, a battery of *in vitro*/*in vivo* screening assays of immune function may be useful to determine whether more detailed and longer-term studies are needed.

Neurotoxicity. The direct effects of naphthalene on the central nervous system have not been investigated in either humans or animals. Neurotoxic effects seen in humans exposed to naphthalene via inhalation or oral exposure may be a consequence of the diminished oxygen-carrying capacity of the blood which results from red cell hemolysis (Bregman 1954; Gupta et al. 1979; Kurz 1987; Linick 1983; MacGregor 1954; Ojwang et al. 1985; Zuelzer and Apt 1949). Persistent gross clinical signs of neurotoxicity (lethargy and prone position) were seen in pregnant rats following gavage administration of naphthalene at dose levels of 150 or 450 mg/kg/day; at 50 mg/kg/day, the signs were only observed during the first 2 days of dose administration (NTP 1991a). Comparable neurological effects were not observed in F344/N rats exposed to doses of up to 400 mg/kg/day for 13 weeks or in B6C3F1 mice at doses of up to 200 mg/kg/day (NTP 1980a, 1980b). With inhalation exposure, no treatment-related gross or histopathological lesions of the brain were observed in mice (NTP 1992a) or rats (Abdo et al. 2001; NTP 2000) exposed for 2 years to naphthalene concentrations as high as 30 or 60 ppm, respectively. Clinical observations revealed no gross behavioral changes indicative of neurological impairment. Additional studies involving batteries of neurological end points following oral and/or inhalation exposure may help to better determine the potential neurotoxicity of naphthalene and explain why pregnant rats appear to be more susceptible to acute-duration neurological impairment from naphthalene.

No studies on the neurotoxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans following inhalation, oral, or dermal exposure were located with the exception of a single study that found decreased sensitivity to pain in rats exposed by inhalation for 4 hours to 1-methylnaphthalene (44 ppm) or 2-methylnaphthalene (61 ppm), but no effects on rotarod performance at exposure levels as high as 70 ppm 1-methylnaphthalene or 90 ppm 2-methylnaphthalene (Korsak et al. 1998). The biological significance of these findings is uncertain. Additional studies involving batteries of neurological endpoints may help to better determine the potential neurotoxicity of the methylnaphthalenes.

Epidemiological and Human Dosimetry Studies. A small number of reports have equivocally suggested that workers exposed to naphthalene for long periods of time may have an elevated risk of cataract development (Ghetti and Mariani 1956; Lezenius 1902). This information, coupled with the cataractogenic effects of naphthalene in orally exposed rats (Kojima 1992; Xu et al. 1992b; Yamauchi et al. 1986) and rabbits (Rossa and Pau 1988; Srivastava and Nath 1969; Van Heyningen and Pirie 1967) in acute- and intermediate-duration studies, suggests that studies of occupationally-exposed workers would help to determine its potential to produce ocular toxicity in humans. The incidence of tumors, anemia, and reproductive problems in this population could be determined at the same time. Available

case reports of cancer in naphthalene-exposed humans provide inadequate evidence of naphthalene carcinogenicity. Currently, no cohort mortality or morbidity studies or case-control studies examining possible associations between naphthalene exposure and increased risk of cancer (or other health effects) are available. If human populations that are specifically and repeatedly exposed to naphthalene can be identified, epidemiological studies of these populations may help to better assess the potential chronic-duration toxicity and carcinogenicity of naphthalene.

No epidemiological or human dosimetry studies on the effects of 1-methylnaphthalene or 2-methyl-naphthalene were located. Exposure to these compounds, particularly through dermal contact or inhalation, can occur in workplaces where the compounds are produced or used. Populations living near hazardous waste sites can potentially be exposed by the oral, inhalation, and dermal routes. If an appropriate population can be identified, it may be helpful to conduct epidemiological studies to determine if there are toxic effects (particularly on the lungs) resulting from exposure to these substances.

Biomarkers of Exposure and Effect.

Exposure. There are methods to determine the presence of naphthalene in adipose tissue and these methods have been used in a national monitoring program for the analysis of naphthalene in the adipose tissue of the general population (EPA 1986g). Metabolites of naphthalene, such as naphthols and naphthoquinones, have been detected in the urine of a patient 4 days after ingestion of naphthalene (Zuelzer and Apt 1949), but not in another patient at 17 days after ingestion (Mackell et al. 1951). 1-Naphthol is present in the urine of workers occupationally exposed to naphthalene. Maximum 1-naphthol levels occurred immediately after the end of the work period and in some cases had returned to baseline levels 8 hours later (Bieniek 1994). New techniques have been developed to measure cysteinyl adducts formed from reactions of hemoglobin and albumin with reactive metabolites of naphthalene (Troester et al. 2002; Waidyanatha et al. 2002). The adducts are expected to be useful in estimating internal doses of these metabolites, and with further development, they may become useful biomarkers of exposure.

Effect. There are no known specific biomarkers of effects for naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. Hemolytic anemia has been frequently associated with human exposure to naphthalene, but may also be the result of exposure to other chemicals. Pulmonary alveolar proteinosis in mice has been associated with chronic oral exposure to 1-methylnaphthalene and 2-methylnaphthalene. The condition has been described in humans, but has not been associated with human exposure to

1-methylnaphthalene or 2-methylnaphthalene. Currently, these effects (hemolytic anemia or pulmonary alveolar proteinosis) do not hold promise as specific biomarkers of effect for naphthalene or methylnaphthalenes. Identification of specific biomarkers of effect such as particular protein adducts in naphthalene-affected target tissues in animals (e.g., nasal epithelium tissue) may be useful to test whether similar biomarkers of effect may exist in naphthalene-exposed human populations.

Absorption, Distribution, Metabolism, and Excretion. Although human absorption of naphthalene has not been quantitatively characterized, case reports indicate that humans can absorb toxicologically significant amounts of this compound by the oral, inhalation, or dermal routes (Bregman 1954; Chusid and Fried 1955; Dawson et al. 1958; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; Linick 1983; MacGregor 1954; Mackell et al. 1951; Ojwang et al. 1985; Santhanakrishnan et al. 1973; Schafer 1951; Shannon and Buchanan 1982; Valaes et al. 1963; Zuelzer and Apt 1949). Laboratory animals such as rats, mice, and rabbits also absorb the chemical via their skin and gastrointestinal and respiratory tracts (NTP 1992a; Rao and Pandya 1981; Shopp et al. 1984; Srivastava and Nath 1969; Turkall et al. 1994; van Heyningen and Pirie 1967). Naphthalene adsorbed to organic-rich soils is absorbed across the skin more slowly than naphthalene from organic-poor soils (Turkall et al. 1994). The compound apparently partitions between the soil organic carbon and the hydrophobic components of the epidermis and dermis. More information concerning the mechanism of absorption (facilitated versus passive transport) across nasal and pulmonary epithelial membranes, the gastrointestinal tract, and the skin may be helpful in estimating the effect of dose on absorption coefficients and in better determining the effect of the medium of exposure (water, oil, food, etc.) on oral or dermal absorption. Empirical measurements of permeability coefficients for naphthalene in blood or air with various tissues from various species may be useful to further develop PBPK models for naphthalene.

As discussed in Sections 3.4.3 and 3.5.2, extensive research on the bioactivation and metabolic transformations of naphthalene in mammalian systems has identified several reactive metabolites that are potentially responsible for the nasal, pulmonary, and ocular toxicity of naphthalene (1,2-naphthalene oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone), but the relative importance of these metabolites in affecting these toxicity targets remains uncertain. Because nasal respiratory and olfactory epithelia are the most sensitive targets in rodents following acute or chronic inhalation exposure, better understanding of the deposition, absorption, and metabolism of inhaled naphthalene in different regions of nasal epithelia, and the degree to which species (particularly rodents and primates) differ in these processes, may be useful for decreasing uncertainty in extrapolating human health hazards from data for rodents

exposed to naphthalene. *In vivo*, *in vitro*, and modeling research approaches are likely to create better understanding of these processes, which may also provide explanations for observed species differences in response to naphthalene. For example, both rats and mice developed nonneoplastic nasal lesions following chronic inhalation exposure to naphthalene concentrations as low as 10 ppm, but only rats developed nasal tumors (Abdo et al. 2001; NTP 1992a, 2000). Other examples are the findings that *in vitro* rates of epoxide formation from naphthalene in extracts of nasal olfactory tissue showed the order, mouse>rat>hamster, but rats were more susceptible to acute nasal injury from naphthalene than mice or hamsters (Buckpitt et al. 1992; Plopper et al. 1992a). Mechanistic explanations for these differences are not currently available.

The most recently developed PBPK models for naphthalene in mice and rats (Willems et al. 2001) do not include nasal compartments that metabolize naphthalene and do not include the spontaneous conversion of 1,2-naphthalene oxide to 1-naphthol or metabolic transformations to the naphthoquinones. Additional toxicokinetic data are needed to further refine these models to include these potentially important processes. Application of such further refined models, and the development of comparable models for humans, may be useful to decrease uncertainty in extrapolating dose-response relationships for nasal effect in rodents to humans.

No studies were located on the absorption, metabolism, and excretion of 1-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure. There was one study of 2-methylnaphthalene in guinea pigs (Teshima et al. 1983). Parenteral studies in animals show that 2-methylnaphthalene is converted to both monohydrated compounds and dihydrodiols (Breger et al. 1981, 1983; Melancon et al. 1982). In addition, 2-naphthoic acid and the glycine or the cysteine conjugates were identified in rats (Melancon et al. 1982) and guinea pigs (Teshima et al. 1983). Studies by relevant exposure routes would further characterize the toxicokinetics of these compounds and may enhance the understanding of the potential risk associated with exposure to these compounds.

Comparative Toxicokinetics. Data suggest that there are strain- and species-specific effects associated with naphthalene toxicity. Laboratory animals, such as rats and mice, do not exhibit red cell hemolysis after exposure to naphthalene, while humans and dogs do (NTP 1980a, 1980b, 1992a; Shopp et al. 1984; Zuelzer and Apt 1949). Mice and rats both develop nonneoplastic nasal lesions after chronic inhalation exposure to naphthalene, but only rats develop nasal tumors, and only mice develop nonneoplastic lung lesions or lung tumors (Abdo et al. 2001; NTP 1992a; 2000). There are differences in susceptibility to the acute pulmonary toxicity of naphthalene among mice, rats, hamsters, and guinea pigs

(Buckpitt et al. 2002; Plopper et al. 1992a, 1992b). Differences in the susceptibility of rats and mice, and of different mouse strains, to the cataractogenic properties of naphthalene have also been reported (Wells et al. 1989). These differences may relate to differences in tissue distribution of specific CYP isoenzymes, rates of formation of reactive metabolites, rates of transformation of reactive metabolites to nonreactive metabolites, or partitioning of the parent compound or metabolites within and between tissues. For example, the difference in susceptibility to the acute pulmonary toxicity of naphthalene between mice and rats has been correlated with higher rates of metabolic formation and different stereoselectivity of epoxide metabolites in mice compared with rats (Buckpitt et al. 1992; 1995; 2002). In contrast, differences among rat, mice and hamsters in susceptibility to naphthalene-induced nasal lesions were not correlated with species differences in rates of epoxide formation from naphthalene in extracts of olfactory epithelial tissue (Plopper et al. 1992; see Section 3.5.2). Further evaluation of these differences and comparative studies of distribution and metabolic patterns among species may help to decrease uncertainty in extrapolating estimates of human health hazards from data for animals exposed to naphthalene.

There are no data available concerning the toxicokinetics of 1-methylnaphthalene or 2-methylnaphthalene in humans following inhalation, oral, or dermal exposure. There are no data from studies of 1-methyl-naphthalene in animals, but there are limited data for 2-methylnaphthalene (Breger et al. 1983; Griffin et al. 1982; Melancon et al. 1982, 1985; Teshima et al. 1983). New studies that evaluate toxicokinetic parameters in several animal species may be useful to decrease uncertainty in the chronic oral MRLs for 1-methylnaphthalene and 2-methylnaphthalene, which are based on the occurrence of pulmonary alveolar proteinosis in mice.

Methods for Reducing Toxic Effects. Available methods are sufficient for reducing peak absorption of naphthalene following ingestion (Melzer-Lange and Walsh-Kelly 1989; Siegel and Wason 1986; Stutz and Janusz 1988). No antidotal methods are available that would be useful for treatment of naphthalene exposure based on any proposed hypothesis pertaining to the mechanism of action. Additional studies to characterize the metabolic activation of naphthalene and the role of circulating reactive metabolites from nontarget tissues may be useful in developing methods for interfering with the mechanism of action. Further studies to identify ways to reduce or prevent accumulation of toxic metabolites in target tissues may be warranted when mechanisms of naphthalene toxic action are better understood.

There are no compound-specific methods for reducing the toxic effects of 1-methylnaphthalene and 2-methylnaphthalene. Additional information on the toxicokinetics and mechanism of action for these compounds may be beneficial in identifying possible approaches for reducing compound toxicity.

Children's Susceptibility. Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

As discussed in Section 3.7, cases of naphthalene-induced hemolytic anemia in children have been frequently reported (Owa 1989; Owa et al. 1993; Santucci and Shah 2000; Valaes et al. 1963). Newborns and infants are thought to be more susceptible than older people because hepatic enzymes involved in conjugation and excretion of naphthalene metabolites are not well developed after birth, and children with genetically determined G6PD deficiency are thought to be especially susceptible to chemically-induced hemolytic anemia (EPA 1987a). There are no studies that have specifically examined the influence of age on naphthalene toxicokinetic capabilities in humans. Although the availability of such studies may increase the understanding of the specific physiological basis for the apparent susceptibility of newborns, they are unlikely to be conducted. Experiments examining the most sensitive targets in animals (see below) are likely surrogates.

Although naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958), oral-exposure developmental toxicity studies in animals do not provide evidence that naphthalene was fetotoxic or impaired fetal development, even at maternally toxic dose levels as high as 450 mg/kg/day (NTP 1991a; Plasterer et al. 1985; PRI 1986). Additional developmental toxicity studies in animals with inhalation or dermal exposure would determine if naphthalene exposure by these routes represents a greater developmental hazard than oral exposure.

Neonatal mice (7 days old) appear to be more susceptible than adult mice to lung injury induced by acute intraperitoneal injection of naphthalene (Fanucchi et al. 1997). The mechanistic basis of this difference is currently unknown, but does not appear to be explained by differences in CYP catalytic capabilities to produce epoxide metabolites, since CYP activities were 2.5 time lower in neonates than in adults. Downstream metabolic capabilities, however, were not examined in this study. Comparison of neonatal and adult tissues in these metabolic steps may help to explain this apparent susceptibility of neonatal mice. Based on findings that *in utero* exposure to other CYP-bioactivated chemicals caused Clara cell tumors in adult offspring, Fanucchi et al. (1997) postulated that naphthalene exposure during the neonatal period may lead to loss of regulatory mechanisms resulting in Clara cell proliferation and tumor

formation in adult animals. Direct evidence for naphthalene in support of this hypothesis, however, is not available. Additional research may help to determine whether or not *in utero* or neonatal naphthalene exposure will cause increased incidence of lung tumors in adult mice.

3.12.3 Ongoing Studies

Dr. Alan Buckpitt and colleagues at the University of California, Davis have been conducting studies in several areas related to naphthalene toxicology including (1) identifying specific naphthalene-protein adducts in lungs of mice, rats, and Rhesus macaques and characterizing the time course of their generation and disappearance; (2) identifying cellular and molecular events involved in the development of naphthalene-induced acute lung injury by comparing lung tissue from rodents, Rhesus macaques, and humans; and (3) comparing the cellular distribution and catalytic activities of CYP monooxygenases in lung tissues from various species.

Dr. Charles Plopper and colleagues at the University of California, Davis have been conducting studies comparing acute naphthalene-induced lung injury in neonatal mice and adult mice and the biochemical effects of *in utero* or neonatal exposure to lung toxicants on the development of bronchiolar repair capabilities. This work is part of an effort to increase understanding of molecular mechanisms involved in lung diseases that may originate in childhood exposures.

Dr. Leena Nylander French and colleagues at the University of North Carolina, Chapel Hill have been conducting studies to test the hypothesis that low levels of exposure to benzene or naphthalene can be detected using samples of keratinized epidermis removed by tape stripping.

Dr. Y. Awasthi and colleagues at the University of Texas, Galveston are studying the roles of glutathione S-transferases in protecting against ocular cytotoxicity and apoptosis caused by several oxidants, including naphthalene. Studies include the use of genetically altered knock-out mice strains, which are deficient in specific types of glutathione-*S*-transferases.

Dr. Barry Stripp and colleagues at the University of Pittsburgh are studying the role of proliferative cells originating from the neuroepithelial body in repair of airway epithelial cell damage in mice exposed to ozone or naphthalene.

Dr. John Markley and colleagues at the University of Wisconsin, Madison are studying the 1-, 2-, and 3-dimensional molecular structures of toluene 4-monooxygenase, an enzyme that catalyzes NADH- and O_2-dependent conversion of toluene to p-cresol, as well as the oxidation of numerous hydrocarbons, including naphthalene.

4. CHEMICAL AND PHYSICAL INFORMATION

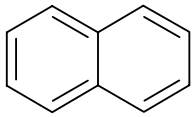
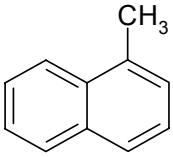
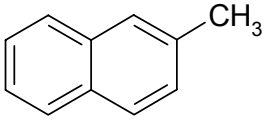
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is located in Table 4-2.

Table 4-1. Chemical Identity of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Characteristic	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Reference
Synonyms	Tar camphor; albocarbon; naphthene; mothballs; mothflakes; white tar; and others	Alpha-methyl-naphthalene; naphthalene, 1-methyl; naphthalene, alpha-methyl	Beta-methyl-naphthalene; naphthalene, 2-methyl; naphthalene, beta-methyl	HSDB 2003
Trade name	Caswell No. 5877®	No data	No data	HSDB 2003
Chemical formula	$C_{10}H_8$	$C_{11}H_{10}$	$C_{11}H_{10}$	HSDB 2003
Chemical structure				HSDB 2003
Identification numbers:				
CAS registry	91-20-3	90-12-0	91-57-6	HSDB 2003
NIOSH RTECS	QJ0525000	QJ9630000	QJ9635000	NIOSH 1987
EPA hazardous waste	U165	No data	No data	HSDB 2003
OHM/TADS	7216808	No data	No data	Agency for Toxic Substances and Disease Registry 1995
DOT/UN/NA/IMCO shipping	UN1334, UN2304, IMCO 4.1	No data	No data	HSDB 2003
HSDB	184	5268	5274	HSDB 2003
NCI	C52904	No data	No data	HSDB 2003

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Property	Naphthalene	1-Methyl-naphthalene	2-Methyl-naphthalene	Reference
Molecular weight	128.19	142.20	142.20	Weast et al. 1985
Color	White	Colorless	No data	Verschueren 1983
Physical state	Solid	Liquid	Solid	Verschueren 1983
Melting point	80.5 °C	-22 °C	34.6 °C	Weast et al. 1985
Boiling point	218 °C	244.6 °C	241 °C	Sax and Lewis 1989; Weast et al. 1985
Density at 20 °C	1.145 g/mL	1.0202 g/mL	1.0058 g/mL	Weast et al. 1985
Odor	Strong (tar or mothballs)	No data	No data	HSDB 2003
Odor threshold:				
Water	0.021 mg/L	0.0075 mg/L	0.01 mg/L	Amoore and Hautala 1983; HSDB 2003; Verschueren 1983
Air	0.44 mg/m^3	No data	0.0581–0.2905 mg/m^3	Amoore and Hautala 1983; Ruth 1986
Solubility:				
Water at 25 °C	31.7 mg/L	25.8 mg/L	24.6 mg/L	EPA 1982e; HSDB 2003
Organic solvents	Soluble in benzene, alcohol, ether, acetone	Soluble in alcohol, ether, benzene	Soluble in alcohol, ether, benzene	Sax and Lewis 1989; Weast et al. 1985
Partition coefficients:				
Log K_{ow}	3.29	3.87	3.86	EPA 1982e; HSDB 1995
Log K_{oc}	2.97	No data	3.39	EPA 1982e; GDCH 1992; Kenaga 1980
Vapor pressure	0.087 mmHg	0.054 mmHg	0.068 mmHg	EPA 1982e; HSDB 1995
Henry's law constant	4.6x10^{-4} atm-m^3/mol	3.6x10^{-4} atm-m^3/mol	4.99x10^{-4} atm-m^3/mol	EPA 1982e; Yaws et al. 1991
Autoignition temperature	567 °C	529 °C	No data	Sax and Lewis 1989
Flashpoint	79 °C (open cup)	No data	No data	Sax and Lewis 1989
Flammability limits	0.9–5.9%	No data	No data	HSDB 2003
Conversion factors	1 ppm=5.24 mg/m^3 1 mg/m^3=0.191 ppm	1 ppm=5.91 mg/m^3 1 mg/m^3=0.17 ppm	1 ppm=5.91 mg/m^3 1 mg/m^3=0.17 ppm	Verschueren 1983
Explosive limits	No data	No data	No data	

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Naphthalene may be produced from either coal tar or petroleum. Distillation and fractionation of coal tar is the most common production process. The middle fraction (containing most of the naphthalene) is cooled, crystallizing the naphthalene. The crude naphthalene may be refined by distillation, washing, and sublimation (EPA 1982d; Hughes et al. 1985). 1-Methylnaphthalene and 2-methylnaphthalene are also produced from coal tar by first extracting the heteroaromatics and phenols, then filtering off the crystallized 2-methylnaphthalene and redistilling the filtrate to yield 1-methylnaphthalene (GDCH 1992; Sax and Lewis 1987).

Since 1960, recovery of naphthalene from petroleum by dealkylation of methyl naphthalenes in the presence of hydrogen at high temperature and pressure has become a commercial production process. The naphthalene is then recovered by fractionation, decolorized, and purified by crystallization. Naphthalene produced from petroleum is about 99% pure. In the United States, most naphthalene is produced from petroleum (EPA 1982d; Hughes et al. 1985).

The production volume of naphthalene in the United States decreased significantly from a peak of 900 million pounds (409,000 metric tons) in 1968 to 222 million pounds (101,000 metric tons) in 1994. Production capacity has remained relatively stable in recent years, with estimated capacity for 2002 at 215 million pounds (97,700 metric tons) (Hughes et al. 1985; Mason 1995; SRI 2002).

There are currently three companies in the United States producing naphthalene: Advanced Aromatics, L.P., Baytown, Texas; Koch Industries, Inc., Corpus Christi, Texas; and Koppers Industries, Inc., Follansbee, West Virginia. Koppers Industries, Inc. produces 1-methylnaphthalene; Flint Hills Resources L.P., Corpus Christi, Texas, produces 2-methylnaphthalene; and Crowley Chemical Company, Inc., Kent, Ohio and Oklahoma City, Oklahoma, produces 1-methylnaphthalene/2-methylnaphthalene (mixed isomers) (SRI 2002). No data on production volume of 1-methylnaphthalene or 2-methylnaphthalene were located.

Table 5-1 lists information on United States companies that reported the manufacture and use of naphthalene in 2001 (TRI01 2003). The Toxics Release Inventory (TRI) data should be used with caution

Table 5-1. Facilities that Produce, Process, or Use Naphthalene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	1,000	999,999	1, 4, 5, 7
AL	17	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
AR	10	1,000	999,999	1, 2, 3, 6, 7, 9, 11, 12, 14
CA	34	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
CO	1	1,000	9,999	1, 10, 13
CT	4	10,000	49,999,999	6, 7, 9, 12
DE	1	100,000	999,999	1, 2, 3, 5, 6, 7, 12
FL	11	0	999,999	1, 4, 5, 7, 9, 11, 12
GA	10	100	999,999	2, 3, 6, 7, 10, 11, 12
GU	1	0	99	9
HI	2	100,000	9,999,999	1, 3, 4, 5, 6, 7, 10, 13, 14
IA	8	100	9,999,999	1, 4, 5, 7, 9, 10, 14
IL	38	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	24	1,000	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
KS	9	100	99,999	1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 13, 14
KY	11	100	9,999,999	1, 3, 4, 5, 7, 8, 10, 11, 12, 13
LA	40	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	6	1,000	49,999,999	6, 7, 9, 11, 12
MD	1	1,000	9,999	10
ME	3	10,000	49,999,999	2, 3, 8, 9, 11
MI	22	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	3	1,000	9,999,999	1, 2, 3, 4, 6, 9, 10, 11, 12, 14
MO	11	1,000	9,999,999	7, 9, 10, 12
MS	8	100	9,999,999	1, 2, 5, 7, 9, 10, 11, 12, 13, 14
MT	3	100,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
NC	6	100	999,999	7, 11, 12
ND	2	10,000	9,999,999	1, 3, 4, 6, 7, 9, 10, 11
NE	2	1,000	9,999	11, 12
NJ	19	100	49,999,999	1, 2, 3, 4, 6, 7, 9, 10, 11, 12
NM	4	10,000	9,999,999	7, 8, 12
NY	10	10,000	9,999,999	1, 5, 7, 9, 11, 12, 13
OH	37	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	10	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13
OR	1	100,000	999,999	7, 9

Table 5-1. Facilities that Produce, Process, or Use Naphthalene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PA	47	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	6	10,000	99,999,999	2, 4, 9, 12, 13, 14
SC	5	100	99,999	6, 11, 12
SD	1	100,000	999,999	12
TN	7	100	9,999,999	1, 2, 3, 5, 7, 8, 9, 10, 12
TX	115	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	10	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
VA	7	1,000	9,999,999	1, 2, 3, 4, 6, 7, 9, 12, 13
VI	1	10,000,000	49,999,999	1, 2, 3, 4, 6
WA	14	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	5	100	99,999	7, 10, 11
WV	12	100	49,999,999	1, 4, 6, 7, 8, 10, 11, 12, 13, 14
WY	5	0	9,999,999	1, 2, 3, 4, 5, 9, 10, 12, 13, 14

Source: TRI01 2003

aPost office state abbreviations used
bAmounts on site reported by facilities in each state
cActivities/Uses:

1. Produce
2. Import
3. Onsite Use/Processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

since only certain types of facilities are required to report. TRI is not an exhaustive list. 1-Methylnaphthalene and 2-methylnaphthalene are not included in the list of chemicals for which reporting is required for the TRI.

5.2 IMPORT/EXPORT

In 1978, about 7 million pounds (3,260 metric tons) of naphthalene were imported to the United States and 9 million pounds (3,960 metric tons) were exported from the United States (EPA 1982d). More recently, imports increased to about 8 million pounds (3,600 metric tons), while exports increased to 38 million pounds (17,000 metric tons) in 2002 (USITC 2003). In 1986, 24,400 pounds of 1-methylnaphthalene were imported in the United States (HSDB 1995). No recent information was located for 1-methylnaphthalene. No information was located on import or export quantities of 2-methylnaphthalene.

5.3 USE

The U.S. consumption of naphthalene was 238 million pounds (108,000 metric tons) in 1996 (Lacson et al. 2000; EPA 2002b). The principal end use for naphthalene is as an intermediate in the production of phthalic anhydride (more than 60% of consumption), which is used as an intermediate in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellents, and other materials. It is also used in the production of the insecticide carbaryl, synthetic leather-tanning agents and surface active agents (naphthalene sulfonates and derivatives, which are used as dispersants or wetting agents in paint, dye, and paper-coating formulations), and miscellaneous organic chemicals, including dyes and resins. Crystalline naphthalene is also used as a moth repellent. In 1989, about 12 million pounds (5,500 metric tons) of naphthalene were used for this purpose (CEH 1993; HSDB 1995). Crystalline naphthalene has also been used as a solid block deodorizer for diaper pails and toilets (Haggerty 1956). Also, in the early 1900s naphthalene was used in medicine as an antiseptic, expectorant, and anthelmintic (Grant 1986; Lezenius 1902). It was commonly administered for diseases of the gastrointestinal tract and applied externally for treatment of skin disorders (Lezenius 1902).

It is anticipated that consumption of naphthalene for phthalic anhydride and production of naphthalene sulfonates will increase due to increased demand for these products. About 15–16 million pounds (6,800–7,300 metric tons) of naphthalene were expected to be used for moth repellents by 1994 (CEH 1993).

1-Methylnaphthalene is used in the synthesis of 1-methylnaphthoic acid and, to a lesser degree, as a dyeing agent and as a test substance for determining the ignition capability of diesel fuels. 2-Methylnaphthalene is used in vitamin K production by oxidation to 2-methyl-1,4-naphthoquinone, which can then be reacted to yield phytomenadione (vitamin K). It can also be chlorinated and oxidized to form dyes and small amounts in sulfonated form are used as textile aids, wetting agents, and emulators (GDCH 1992).

5.4 DISPOSAL

Naphthalene and waste containing naphthalene are classified as hazardous wastes by EPA. Generators of waste containing this contaminant must conform to EPA regulations for treatment, storage, and disposal (see Chapter 8). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for these wastes (EPA 1988a, 1989e).

According to the TRI, about 353,136 pounds of naphthalene were transferred off-site, including to publicly owned treatment works (POTW) in 2001 (TRI01 2003). Although data on quantities of naphthalene disposed of by various disposal methods in the past were not located, it was estimated that about 524,000 pounds (238 metric tons) of naphthalene were disposed of on land and 504,000 pounds (229 metric tons) were discharged to POTWs from production and inadvertent sources in 1978 (EPA 1982d).

No information was located on disposal methods or quantities of wastes containing 1-methylnaphthalene or 2-methylnaphthalene. However, these chemicals have been detected at hazardous waste sites (see Section 6.1).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have been identified in at least 647, 37, and 410, respectively, of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are not known. The frequency of these sites can be seen in Figures 6-1, 6-2, and 6-3, respectively. Of these sites 647, 37, and 409, respectively, are located within the United States and 0, 0, and 1, respectively, are located in the Virgin Islands (not shown).

Most of the naphthalene entering the environment is discharged to the air. The largest releases result from the combustion of wood and fossil fuels and the off-gassing of naphthalene-containing moth repellents. Smaller amounts of naphthalene are introduced to water as the result of discharges from coal-tar production and distillation processes. The coal-tar industry is also a major source of the small amounts of naphthalene that are directly discharged to land.

Naphthalene in the atmosphere is subject to a number of degradation processes, including reaction with photochemically produced hydroxyl radicals. Naphthalene has a short half-life in most natural waters and soils because of its tendency to volatilize and biodegrade. As a consequence of these processes, there is little tendency for naphthalene to build up in the environment over time.

The concentration of naphthalene in air tends to be low in rural areas, but is elevated in urban areas. The highest atmospheric concentrations have been found in the immediate vicinity of specific industrial sources and hazardous waste sites. Naphthalene is also a common indoor contaminant in households using naphthalene-containing moth repellents or where tobacco is smoked. Sidestream smoke from one cigarette contained 46, 30, and 32 μg of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively. Levels in water, sediments, and soil tend to be low, except in the immediate vicinity of point sources of release, such as chemical waste sites.

The most likely pathway by which the general public is exposed to naphthalene is by inhalation due to the release of this substance from combustion fuels, moth repellents, and cigarette smoke. The estimated average per capita daily intake from ambient air is 19 μg. Exposure by other routes is not likely.

Figure 6-1. Frequency of NPL Sites with Naphthalene Contamination

Figure 6-2. Frequency of NPL Sites with 1-Methylnaphthalene Contamination

Figure 6-3. Frequency of NPL Sites with 2-Methylnaphthalene Contamination

High naphthalene exposure levels could occur near industrial sources or chemical waste sites, but the extent of such exposure to individuals can only be evaluated on a site-by-site basis. High naphthalene exposure levels could also occur in certain work environments in industries that produce and use naphthalene such as wood preserving, tanning, coal distillation, and ink and dye production.

Based on limited data, potential human exposure to 1-methylnaphthalene or 2-methylnaphthalene is expected to be mainly by inhalation from ambient air. Exposure to these chemicals from tobacco smoke is likely.

1-Methylnaphthalene and 2-methylnaphthalene have also been detected in the environment, particularly in air. These are released from many of the same natural and industrial sources as naphthalene (combustion of wood and fossil fuels, tobacco smoke, coal distillation), but in smaller quantities.

Naphthalene has been identified in at least 647 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). 1-Methylnaphthalene has been identified in at least 37 of these sites, and 2-methylnaphthalene has been identified in at least 410 of these sites. However, the number of sites evaluated for these chemicals is not known. The frequency of the sites at which naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have been identified within the United States can be seen in Figures 6-1 through 6-3.

6.2 RELEASES TO THE ENVIRONMENT

Most of the naphthalene entering environmental media is from combustion, mainly residential wood heating, or from the use of naphthalene in moth repellents. About 10% of environmental releases are attributable to coal production and distillation, while naphthalene production losses contribute <1% of environmental releases (EPA 1982d). Methylnaphthalenes are released from similar sources, including fuel combustion and industrial discharges (GDCH 1992). Smoking tobacco also releases small amounts of naphthalene and methylnaphthalenes into the environment.

6.2.1 Air

Nearly all naphthalene entering the environment is released directly to the air (92.2%). The largest source of emission (more than 50%) is through inadvertent releases due to residential combustion of wood and

fossil fuels (EPA 1982d). Naphthalene emissions from unvented kerosene space heaters have been reported (Traynor et al. 1990).

The second greatest contribution comes from the use of naphthalene as a moth repellent (EPA 1982d). Because it volatilizes appreciably at room temperature, virtually all of the naphthalene contained in moth repellent is emitted to the atmosphere. Thus, in 1989, about 12 million pounds of naphthalene were released to air from moth repellent use (see Section 5.3).

Naphthalene may also enter the atmosphere during coal-tar production and distillation processes, through volatilization processes (aeration) in publicly owned treatment works (POTWs), from the use of naphthalene in the manufacture of phthalic anhydride, during the production of naphthalene, and from tobacco smoke. Methylnaphthalenes may be released to air in stack emissions and from fuel combustion, forest fires, and tobacco smoke (GDCH 1992; HSDB 2003; IARC 1993). 1-Methylnaphthalene and 2-methylnaphthalene were reported in jet exhaust at average concentrations of 421 and 430 μg/m^3, respectively, and in the gas phase of diesel motor exhaust at 1.57 μg/m^3 each (GDCH 1992). The smoke of an American unfiltered cigarette contains 2.8 μg of naphthalene, 1.2 μg of 1-methylnaphthalene, and 1.0 μg of 2-methylnaphthalene. Smoke from an equivalently filtered "little cigar" contains 1.2 μg of naphthalene, 0.9 μg of 1-methylnaphthalene, and 0.7 μg of 2-methylnaphthalene (Schmeltz et al. 1976).

As shown in Table 6-1, an estimated total of 2.0 million pounds of naphthalene, amounting to about 77% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 2001 (TRI01 2003). The TRI data should be used with caution since only certain types of facilities are required to report. TRI is not an exhaustive list.

6.2.2 Water

About 5% of all naphthalene entering the environment is released to water (EPA 1982d). Most of that amount is attributable to coal-tar production and distillation processes. Some naphthalene (about 60%) from these sources is discharged directly to surface waters; the remainder is distributed to POTWs. The effluent and oil-spills from the wood-preserving industry is the only other source of consequence that releases naphthalene into the nation's waterways,

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Naphthalene[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AK	2	571	5	0	255	831	0	831
AL	19	112,982	30	0	0	113,012	44,483	157,495
AR	10	11,904	25	0	0	11,929	535	12,464
CA	40	16,537	107	0	14	16,658	14,627	31,285
CO	5	22	0	0	0	22	0	22
CT	4	15,655	0	0	0	15,655	1	15,656
DE	3	620	0	0	0	620	0	620
FL	12	433,302	0	0	0	433,302	0	433,302
GA	13	61,116	0	0	0	61,116	0	61,116
GU	1	148	No data	0	5	153	0	153
HI	2	451	18	0	0	469	42	511
IA	9	2,558	0	0	0	2,558	40	2,598
IL	48	178,082	92	0	0	178,174	24,126	202,300
IN	27	113,194	519	14,000	5	127,718	22,970	150,688
KS	10	8,511	15	0	0	8,526	36,732	45,258
KY	16	17,496	954	0	5	18,455	4,504	22,959
LA	54	103,467	3,629	0	2,191	109,287	2,317	111,604
MA	7	25,714	43	0	0	25,757	8,106	33,863
MD	5	500	No data	0	0	500	0	500
ME	3	8,655	No data	0	0	8,655	0	8,655
MI	29	87,445	0	0	18,651	106,096	4,560	110,656
MN	3	3,350	0	0	0	3,350	42	3,392
MO	16	8,171	6	0	5	8,182	0	8,182
MS	10	49,743	81	0	0	49,824	181	50,005
MT	3	1,640	8	0	16	1,664	0	1,664
NC	11	7,305	No data	0	0	7,305	2	7,307
ND	4	2,035	2	0	0	2,037	26	2,063
NE	2	1,673	No data	0	0	1,673	11,906	13,579
NJ	20	35,041	879	0	0	35,920	4,659	40,579
NM	6	9,137	5	250	0	9,392	0	9,392
NY	20	9,814	750	0	0	10,564	500	11,064
OH	48	49,547	40	0	18	49,605	86,968	136,573
OK	13	82,542	300	0	19,455	102,297	3,571	105,868
OR	1	490	0	0	0	490	2	492
PA	55	82,432	389	0	0	82,821	17,563	100,384
PR	8	1,960	0	0	0	1,960	0	1,960

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Naphthalene[a]

		Reported amounts released in pounds per year[b]						
State[c]	Number of facilities	Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
SC	9	56,980	34,000	0	0	90,980	35	91,015
SD	1	32	No data	0	0	32	0	32
TN	10	6,450	0	0	0	6,450	421	6,871
TX	141	293,071	954	146,960	1,986	442,971	54,196	497,167
UT	10	3,616	10	0	0	3,626	1,837	5,463
VA	8	1,012	5	0	0	1,017	475	1,492
VI	2	1,686	0	0	0	1,686	90	1,776
WA	14	5,239	0	0	159	5,398	1,250	6,648
WI	8	3,703	No data	0	0	3,703	1,787	5,490
WV	12	86,134	496	0	3	86,633	4,332	90,965
WY	7	1,163	No data	0	0	1,163	250	1,413
Total	761	2,002,896	43,362	161,210	42,768	2,250,236	353,136	2,603,372

Source: TRI01 2003

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Naphthalene was detected in 1.6% of effluent samples reported on the STORET database from 1980 to 1982 (Staples et al. 1985). Analysis of STORET data for 1978–1981 indicated that the range of detectable naphthalene concentrations in effluents was <1–36,000 µg/L (EPA 1982d).

The detection of naphthalene and methylnaphthalenes in groundwater in the vicinity of industrial facilities and landfills (see Section 6.4.2) (Brown and Donnelly 1988; Rosenfeld and Plumb 1991) indicates that these chemicals are released to water from these sources. Methylnaphthalenes have been detected in effluents from industrial sources (GDCH 1992; HSDB 2003). 1-Methylnaphthalene and 2-methyl-naphthalene were reported in process sewage and production water samples from coal gasification plants at concentrations ranging from 78 to 278 µg/L and from 66 to 960 µg/L, respectively (GDCH 1992).

As shown in Table 6-1, an estimated total of 43,362 pounds of naphthalene, amounting to about 1.7% of the total environmental release, was discharged to surface water from manufacturing and processing facilities in the United States in 2001 (TRI01 2003). An additional 161,210 pounds (6.2% of the total) was discharged by underground injection. The TRI data should be used with caution since only certain types of facilities are required to report.

6.2.3 Soil

It is estimated that only about 2.7% of the environmental releases of naphthalene are discharged to land (EPA 1982d). Sources include coal-tar production and minor contributions from naphthalene production, POTW sludge disposal, and the use of organic chemicals that include naphthalene.

As shown in Table 6-1, an estimated 42,768 pounds of naphthalene, amounting to about 1.6% of the total environmental release, was discharged to land from manufacturing and processing facilities producing and using naphthalene in the United States in 2001 (TRI01 2003). The TRI data should be used with caution since only certain types of facilities are required to report.

No information was located on releases of 1-methylnaphthalene or 2-methylnaphthalene to soil.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Naphthalene released to the atmosphere may be transported to surface water and/or soil by wet or dry deposition. Since most airborne naphthalene is in the vapor phase, deposition is expected to be very slow (about 0.04–0.06 cm/sec). It has been estimated that about 2–3% of naphthalene emitted to air is transported to other environmental media, mostly by dry deposition (EPA 1982d).

Naphthalene in surface water may volatilize to the atmosphere. With a vapor pressure of 0.087 mm Hg at 25 °C, solubility in water of 31.7 mg/L at 20 °C, and a Henry's law constant of $4.6x10^{-4}$ (EPA 1982e), it is likely that volatilization will be an important route of naphthalene loss from water. The rate of volatilization also depends upon several environmental conditions, including temperature, wind velocity, and mixing rates of the air and water columns (EPA 1982d). The half-life of naphthalene in the Rhine River was 2.3 days, based on monitoring data (Zoeteman et al. 1980). In an experiment using a mesocosm, that simulated Narragansett Bay, the half-life in water was 12 days during winter, with loss primarily due to volatilization (Wakeham et al. 1983).

Log octanol/water partition coefficients (K_{ow}) for naphthalene range from 3.29 to 3.37 and log organic carbon coefficients (K_{oc}) range from 2.97 to 3.27 (Bahnick and Doucette 1988; EPA 1982e; Howard 1989; Klecka et al. 1990; Thomann and Mueller 1987). These values include both experimentally determined and calculated values. The reported experimentally determined log K_{oc} is 3.11 (Bahnick and Doucette 1988). Based on the magnitude of these values, it is expected that only a small fraction (<10%) of naphthalene in typical surface water would be associated with particulate matter (Thomann and Mueller 1987). Thus, naphthalene discharged to surface waters would remain largely in solution, with smaller quantities being associated with suspended solids and benthic sediments.

Naphthalene is easily volatilized from aerated soils (Park et al. 1990) and is adsorbed to a moderate extent (10%) (Karickhoff 1981; Schwarzenbach and Westall 1981). The extent of sorption depends on the organic carbon content of the soil, with rapid movement expected through sandy soils (Howard 1989). The estimated soil adsorption coefficient for naphthalene in a soil with <0.6% organic carbon is 1.8 (Klecka et al. 1990). Because it adsorbs to aquifer material (Ehrlich et al. 1982), naphthalene's passage through groundwater will be somewhat retarded. Nevertheless, naphthalene frequently appears in effluent drainage from disposal sites (Rittman et al. 1980; Roberts et al. 1980; Schwarzenbach et al.

1983). However, sorption of naphthalene to aquifer materials with low organic carbon content (<0.03%) may be enhanced by the presence of nonionic low-polarity organics, such as tetrachloroethene, commonly found at hazardous waste sites (Brusseau 1991a).

Bioconcentration factors (BCFs) for naphthalene have been measured and calculated from the K_{ow}, K_{oc}, or water solubility. The values reported for log BCF range from 1.6 to 3 (Banerjee and Baughman 1991; Bysshe 1982; Geyer et al. 1982; Kenaga 1980; Southworth et al. 1978; Veith et al. 1979), indicating moderate bioconcentration in aquatic organisms. Naphthalene is reported to be rapidly eliminated from invertebrates when the organisms are placed in pollutant-free water (Eastmond et al. 1984; Tarshis 1981), and naphthalene is readily metabolized in fish (Howard 1989). Based on the magnitude of the K_{ow}, bioaccumulation in the food chain is not expected to occur (Thomann 1989). However, naphthalene exposure of cows and chickens could lead to the presence of naphthalene in milk and eggs (Eisele 1985).

Limited data were located on transport and partitioning of methylnaphthalenes in the environment. The respective vapor pressures (0.054 and 0.068 mmHg), water solubilities (25.8 and 24.6 mg/L), and Henry's law constants ($3.60x10^{-4}$ and $4.99x10^{-4}$ atm-m^3/mol) for 1-methylnaphthalene and 2-methylnaphthalene are of similar magnitude to these properties for naphthalene (HSDB 2003; Yaws et al. 1991). Thus, it is likely that loss of methylnaphthalenes from ambient water occurs by volatilization. In a mesocosm experiment, that simulated Narragansett Bay, the half-life of 2-methylnaphthalene in water was 13 days in winter, with loss primarily due to volatilization (Wakeham et al. 1983). Based on the magnitude of log K_{ow} for 1-methylnaphthalene and 2-methylnaphthalene (3.87 and 3.86, respectively) (HSDB 2003) and the experimental log K_{oc} for 2-methylnaphthalene (3.93) (Bahnick and Doucette 1988), these chemicals may partition similarly to naphthalene in environmental media and are expected to be slightly mobile to immobile in soils (HSDB 2003). Log BCFs calculated for 2-methylnaphthalene range from 2 to 2.8 (Kenaga 1980) and measured log BCFs for 1-methylnaphthalene and 2-methylnaphthalene in oysters ranged from 2.7 to 4.1 (GDCH 1992). Methylnaphthalenes are also metabolized and excreted rapidly by fish and shellfish when they are removed from polluted waters (Breger et al. 1981; GDCH 1992).

6.3.2 Transformation and Degradation

6.3.2.1 Air

The most important atmospheric removal process for naphthalene is reaction with photochemically produced hydroxyl radicals (Howard 1989). The rate for this reaction is 2.17×10^{-11} cm^3/molecule-sec (Atkinson et al. 1987) and the atmospheric half-life for naphthalene based on this reaction is <1 day. The major products of this reaction are 1- and 2-naphthol and 1- and 2-nitronaphthalene (Atkinson et al. 1987). Naphthalene also reacts with N_2O_5, nitrate radicals, and ozone in the atmosphere (Atkinson et al. 1984, 1987) and photolysis is expected to occur, although no experimental data were located (Howard 1989).

Methylnaphthalenes also react with hydroxyl radicals. The reported rate constants are 5.30×10^{-11} and 5.23×10^{-11} cm^3/molecule-sec for 1-methylnaphthalene and 2-methylnaphthalene, respectively. Based on an atmospheric hydroxyl radical concentration of $1 \times 10^6/cm^3$, the corresponding atmospheric half-lives are 3.6 and 3.7 hours (GDCH 1992). Reactions of 1-methylnaphthalene and 2-methylnaphthalene with N_2O_5 radicals have half-lives of 24 and 19 days, respectively (GDCH 1992). These chemicals also react with atmospheric ozone.

6.3.2.2 Water

Naphthalene and methylnaphthalenes are degraded in water by photolysis and biological processes. The half-life for photolysis of naphthalene in surface water is estimated to be about 71 hours, but the half-life in deeper water (5 m) is estimated at 550 days (Zepp and Schlotzhauer 1979). The half-lives for photolysis of 1-methylnaphthalene and 2-methylnaphthalene were estimated at 22 and 54 hours, respectively (GDCH 1992).

Biodegradation of naphthalene is sufficiently rapid for it to be a dominant fate process in aquatic systems (Tabak et al. 1981). Data on biodegradation of naphthalene in biodegradability tests and natural systems suggest that biodegradation occurs after a relatively short period of acclimation (rapidly, half-life about 7 days] in oil-polluted water) and the biodegradation rate increases with the naphthalene concentration. The biodegradation occurs slowly (half-lives up to 1,700 days) in unpolluted water (Herbes 1981; Herbes and Schwall 1978; Herbes et al. 1980; Howard 1989; Kappeler and Wuhrmann 1978). Reported

biodegradation half-lives range from 3 to 1,700 days in various water systems (Howard 1989). In a static-flask-screening test, naphthalene showed rapid acclimation and 100% loss from the test medium in 7 days (Tabak et al. 1981). In an experiment with Narragansett Bay seawater, the half-life of naphthalene in late summer was reported at 0.8 days, mainly due to biodegradation (Wakeham et al. 1983). The half-life of 2-methylnaphthalene was 0.7 days in the same experiment.

Methylnaphthalenes are biodegraded under aerobic conditions after adaptation. The highest degradation rates were reported in water constantly polluted with petroleum (GDCH 1992).

6.3.2.3 Sediment and Soil

Naphthalene biodegradation rates are about 8–20 times higher in sediment than in the water column above the sediment (Herbes and Schwall 1978). Half-lives reported in sediment include 4.9 hours and >88 days in oil-contaminated and uncontaminated sediment, respectively (Herbes and Schwall 1978), 9 days in sediment near a coal-coking discharge (Herbes 1981), 3, 5, and >2,000 hours in sediments with high, medium, and low PAH levels, respectively (Herbes et al. 1980), and ranging from 2.4 weeks in sediments exposed to petroleum hydrocarbons to 4.4 weeks in sediments from a pristine environment (Howard 1989). Methylnaphthalenes biodegrade more slowly. Reported half-lives in sediments were 46 weeks for 1-methylnaphthalene and ranged from 14 to 50 weeks for 2-methylnaphthalene (GDCH 1992).

In soils, biodegradation potential is important to biological remediation of soil. Studies on biodegradation of PAHs suggest that adsorption to the organic matter significantly reduces the bioavailability for microorganisms, and thus the biodegradability, of PAHs, including naphthalene (Heitzer et al. 1992; Weissenfels et al. 1992). There is considerable variability in reported naphthalene soil half-lives. The estimated half-life of naphthalene reported for a solid waste site was 3.6 months (Howard 1989). In less contaminated soils, more rapid biodegradation is expected to occur (Howard 1989). In soils with 0.2–0.6% organic carbon and 92–94% sand, the half-lives were 11–18 days (Klecka et al. 1990). In another study, sandy loams with 0.5–1% organic carbon had naphthalene half-lives of 2–3 days (Park et al. 1990). Biodegradation is accomplished through the action of aerobic microorganisms and declines precipitously when soil conditions become anaerobic (Klecka et al. 1990). Studies indicate that naphthalene biodegrades to carbon dioxide in aerobic soils, with salicylate as an intermediate product (Heitzer et al. 1992).

Abiotic degradation of naphthalene seldom occurs in soils. In one study only about 10% of the naphthalene added to two soil samples treated with mercuric chloride to kill microorganisms was degraded over a 105- or 196-day period (Park et al. 1990).

The behavior of 1-methylnaphthalene in sandy loam was very similar to that of naphthalene. 1-Methylnaphthalene was easily volatilized from aerated soil, and the biodegradation half-life averaged between 1.7 and 2.2 days (Park et al. 1990). No data were identified on the biodegradation of 2-methylnaphthalene in soil.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Naphthalene has been reported in ambient air at several locations in the United States. The average reported concentration for 67 samples was 5.19 μg/m^3, with most (60) of the samples and the highest concentrations at source-dominated locations (EPA 1988g). A median naphthalene level in urban air in 11 U.S. cities of 0.94 μg/m^3 has been reported (Howard 1989). An average naphthalene concentration of 170 μg/m^3 in outdoor air was reported in a residential area of Columbus, Ohio (Chuang et al. 1991), and naphthalene was measured in ambient air in Torrance, California at a concentration of 3.3 μg/m^3 (Propper 1988). Average naphthalene concentrations ranging from 10 to 888 ng/m^3 were measured in several sites in Phoenix and Tucson, Arizona from 1994 to 1996 (Zielinska et al. 1998). A mean naphthalene concentration of 0.129 ng/m^3 was detected in ambient air at the Mississippi Sandhill Crane National Wildlife Refuge, Jackson County from May to September 1991 (White and Hardy 1994).

Average naphthalene concentrations detected in ambient air at five hazardous waste sites and one landfill in New Jersey ranged from 0.42 to 4.6 μg/m^3 (LaRegina et al. 1986).

Naphthalene concentrations in indoor air may be higher than outdoors, with reported average indoor concentrations in various areas of homes ranging from 0.860 to 1,600 μg/m^3 (Chuang et al. 1991; Hung et al. 1992; Wilson et al. 1989). However, based on a careful analysis of Chuang et al. (1991), the reported upper range value may be in error. A more representative upper limit concentration for indoor air may be 32 μg/m^3, recorded in buildings in heavily trafficked urban areas of Taiwan (Hung et al. 1992). Concentrations of naphthalene detected in indoor and outdoor air measured in 24 low-income homes in

North Carolina ranged from 0.33 to 9.7 and from 0.57 to1.82 μg/m^3 respectively (Chuang et al. 1999). In homes with smokers, indoor and outdoor air concentrations were measured to be 2.2 and 0.3 μg/m^3, respectively. Comparable values in homes without smokers were 1.0 and 0.1 μg/m^3, respectively (EPA 1991e; IARC 1993). The average reported concentration of naphthalene inside automobiles in commuter traffic is about 4.5 μg/m^3 (Lofgren et al. 1991).

Naphthalene has also been detected in air in industrial facilities. Reported naphthalene vapor levels ranged from 11 to 1,100 μg/m^3 in a coke plant and from 0.72 to 310 μg/m^3 in an aluminum reduction plant (Bjorseth et al. 1978a, 1978b). Reported particulate levels for the same facilities ranged from nondetected to 4.4 μg/m^3, and 0.9 to 4 μg/m^3, respectively.

Naphthalene has been detected in the emissions from motor vehicles. Mean concentrations of 104.3, 31.9, and 54.1 μg/m^3 of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively, were measured in the air samples collected from the Caldecott Tunnel located in San Francisco (Zielinska and Fung 1994). Mean concentrations of 1,709, 131, and 162.5 mg/m^3 of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively, were measured in the air samples collected from the Van Nuys Tunnel in Los Angeles (Fraser et al. 1998a). Mean concentration ranges of 0–589.2, 0–188.6, and 0–333.3 μg/m^3 of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively, were measured in the air samples collected from the Fort McHenry Tunnel in Baltimore. Mean concentration ranges of 16.2–68.9, 9.4–20.0, and 21.9–35.7 μg/m^3 of naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene, respectively, were measured in the air samples collected from the Tuscarora Tunnel on the Pennsylvania Turnpike (Zielinska et al. 1996). Average concentrations of 137–1714, 92–1,458, and 154–2,129 ng/m^3 of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, respectively, were detected during various flight related and ground-support activities of C-130H aircraft at an Air National Guard base (Childers et al. 2000).

1-Methylnaphthalene and 2-methylnaphthalene have been reported in ambient air at average concentrations of 0.51 and 0.065 μg/m^3, respectively (EPA 1988g). Most of the data reported are from source-dominated areas, where the highest concentrations were detected. Methylnaphthalene (isomer not specified) was detected (concentration not reported) in ambient air at a hazardous waste site in New Jersey (LaRegina et al. 1986). 2-Methylnaphthalene was also reported in indoor air at an average concentration of 1.5 μg/m^3 (EPA 1988g).

6.4.2 Water

Naphthalene has been detected in surface water and groundwater in the United States. An analysis of 1980–1982 data from the STORET database indicates that naphthalene was detectable in 7% of 630 ambient water samples (Staples et al. 1985). The median concentration for all samples was <10 µg/L. Analysis of earlier (1978–1980) STORET data for naphthalene showed concentrations in positive samples ranging from 0.005 to 17 µg/L (EPA 1982d). Naphthalene was also detected in 11% of 86 urban runoff samples at concentrations ranging from 0.8 to 2.3 µg/L (Cole et al. 1984). In a study of contaminants of an urban watershed of Chesapeake Bay, naphthalene was detected in the northeast and northwest branches of Anacostia River (an urban watershed of Chesapeake Bay) at a concentration range of 0.18–21.6 ng/L. 2-Methylnaphthalene was also detected at a concentration of 0.57–62.7 ng/L (Foster et al. 2000). The mean concentration of naphthalene found in the water samples taken from 31 freshwater and estuarine sites adjacent to, nearby, or downstream from potential pollutant sources in Florida was 33 mg/L (Miles and Delfino 1999).

Naphthalene was detected in fewer than 5% of the 208 wells sampled from a variety of urban setting across the United States (Koplin et al. 1997). Naphthalene was detected in 3% of the samples taken from urban and rural wells from 1985 to 1995 (Squillace et al. 1999).

Naphthalene is rarely detected in drinking water. Naphthalene was reported in drinking water supplies in one area in the United States at levels up to 1.4 µg/L (EPA 1982d). Low levels of naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene were detected in drinking water samples taken from a chlorine dioxide disinfection pilot plant in Evansville, Indiana. These compounds were identified as organic disinfection byproducts produced by chlorine dioxide treatment (Richardson et al. 1994).

Naphthalene and 2-methylnaphthalene were detected in groundwater at five wood treatment facilities (Rosenfeld and Plumb 1991). Naphthalene was reported in 35% of samples at all five sites at an average concentration of 3,312 µg/L. 2-Methylnaphthalene was reported in 27% of samples at four sites at an average concentration of 563 µg/L. Naphthalene was reported in leachate or groundwater plume from industrial and municipal landfills at concentrations ranging from <10 to 18.69 mg/L and from 0.11 to 19 mg/L, respectively. The methylnaphthalene (isomer not specified) concentration reported at a municipal landfill was 0.033 mg/L (Brown and Donnelly 1988). Naphthalene was detected in the groundwater in 12.7% of the 479 U.S. waste disposal sites (Barbee 1994). Naphthalene was also reported

in the leachate of a household hazardous waste disposal in sanitary landfill. The 4-year mean concentrations of naphthalene ranged from 128.9 to 496.6 µg/L (Kinman et al. 1995).

1-Methylnaphthalene and 2-methylnaphthalene were reported in an urban snow-pack in Michigan at concentrations ranging from <0.05 to 0.177 µg/L and from <0.05 to 0.251 µg/L, respectively (Boom and Marsalek 1988).

Naphthalene has been reported at a mean concentration of 6.3 ng/L in seawater in the south Atlantic Ocean (Cripps 1992).

6.4.3 Sediment and Soil

Naphthalene and methylnaphthalenes have been reported at low concentrations in uncontaminated soils and sediments and at higher concentrations near or within sources of contamination. Naphthalene has been reported in untreated agricultural soils at levels ranging from 0 to 3 µg/kg (Wild et al. 1990). Naphthalene was detected in urban soil samples taken from Boston, Massachusetts, Providence, Rhode Island, and Springfield, Massachusetts at a mean concentration of 0.125 mg/kg (Bradley et al. 1994). Reported naphthalene concentrations in contaminated soils included 6.1 µg/g in coal-tar contaminated soil (Yu et al. 1990), 16.7 mg/kg in soil from a former tar-oil refinery (Weissenfels et al. 1992) and up to 66 µg/kg in sludge-treated soils (Wild et al. 1990). Methylnaphthalenes (isomer not specified) were reported at a concentration of 2.9 µg/g in coal-tar contaminated soil (Yu et al. 1990).

Naphthalene was reported as detectable in 7% of 267 sediment samples entered into the STORET database (1980–1982), with the median concentration for all samples of <500 µg/kg (Staples et al. 1985). Another analysis of STORET data indicated that concentrations in positive sediment samples ranged from 0.02 to 496 µg/kg (EPA 1982d). Naphthalene and methylnaphthalenes (isomers not specified) were detected in contaminated and noncontaminated estuarine sediments (Brooks et al. 1990). Average concentrations of naphthalene detected in samples taken at 10 and 25 miles from an offshore coastal multiwell drilling platform were 54.7 and 61.9 µg/kg, respectively while concentrations of methyl-naphthalenes were 50.4 and 55.3 µg/kg, respectively. Naphthalene and methylnaphthalenes concentrations in nearby noncontaminated estuarine sediments were 2.1 and 1.9 µg/kg, respectively. Naphthalene was detected in 7% of 496 streambed sediment sites across the United States tested for the presence of semivolatile organic compounds. The maximum concentration of naphthalene measured was

4,900 µg/kg dry weight (Lopes and Furlong 2001). Concentration of naphthalene detected decreased from 33 to 2.1 ng/g dry weight with increasing depth (0–148 cm) in the sediment core in Richardson Bay and from 18–4.1 ng/g dry weight with increasing depth (0–239 cm) in the sediment core in San Pablo Bay (Pereira et al. 1999). These bays are located in the San Francisco Bay which is the larges urbanized estuary on the west coast of the United States.

6.4.4 Other Environmental Media

Naphthalene is not generally reported in fish, but has been detected in shellfish in the United States. Naphthalene was not detected in 83 biota samples (median detection limit 2.5 mg/kg) reported from 1980–1982 in the STORET database (Staples et al. 1985). Reported naphthalene concentrations ranged from 5 to 176 ng/g in oysters, from 4 to 10 ng/g in mussels, and from <1 to 10 ng/g in clams from U.S. 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 constituted 75–80% of total polyaromatic hydrocarbons (PAHs) found in the muscle, liver, and gonads of American plaice and yellow tail flounder caught off the coast of Newfoundland (Hellou and Warren 1996). Naphthalene and methylnaphthalene (isomer not specified) were detected in the muscle (1.5–3.1 ng/g wet weight), kidney (1.4–4.3 ng/g wet weight), liver (1.4–4.7 ng/g wet weight), and blubber (8.3–23.5 ng/g wet weight) of harp seals caught in southern Labrador on the eastern coast of Canada (Zitko et al. 1998). Naphthalene and methylnaphthalenes (isomer not specified) were detected at concentrations of 7.15 and 65.11 µg/kg of salmon tissue, respectively, and at 12.9 and 17.3 µg/kg of mussels, respectively. Both the salmon and mussels were caught in Exxon Valdez spill affected Snug Harbor in the Prince William Sound (Neff and Burns 1996). Methylnaphthalenes have occasionally been detected in fish from polluted waters. 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 also detected in oysters in Australia at <0.3–2 µg/g.

Naphthalene was detected in 2 of 13,980 samples of foods analyzed in six states (Minyard and Roberts 1991). In a Lower Rio Grande Valley environmental study, naphthalene (median concentration, 2.159 µg/kg body weight) was detected in five of the nine duplicate-diet samples (Berry et al. 1997). Naphthalene (1–7 µg/kg) was also detected in fresh tree-ripened apricots, plums, and their interspecific hybrids (Gomez et al. 1993). Naphthalene concentrations from vegetables grown in an industrial area of Thessaloniki, Greece were measured to be 0.37–15 µg/kg dry weight in cabbage; 8.9–30 µg/kg dry weight

in carrots; 6.3–35 µg/kg dry weight in leeks; 4.9–53 µg/kg dry weight in lettuce; and 27–63 µg/kg dry weight in endive (Kipopoulou et al. 1999). Naphthalene was among the volatile organic compounds identified in whole and ground sorghum (Seitz et al. 1999).

Naphthalene levels in sterilized milk drinks contained in low-density polyethylene (LDPE) bottles were shown to be low (0.02 µg/mL) at the time of purchase, increasing to 0.1 µg/mL 30 days later, and averaging 0.25 µg/mL at the expiration date of the milk (Lau et al. 1994). Residual naphthalene present in the LDPE packaging was hypothesized to be the source of naphthalene contamination. A later study by the same authors observed that the level of naphthalene in LDPE milk bottle material had been reduced to 0.1–0.4 µg/g due to the use of new packaging material (Lau et al. 1995).

No information was located that documented methylnaphthalenes in food products.

Naphthalene was detected in the gas phase (5,860 µg/kg of meat cooked) as well as the particle phase (1,440–1,690 µg/kg of cooked meat) in the emissions from the process of charbroiling hamburger meat over a natural gas grill (Schauer et al. 1999a). Naphthalene was detected at a concentration of 227 mg/kg of wood burned from the fireplace combustion of pine wood. 1-Methylnaphthalene was detected at concentrations of 10.6, 6.39, and 4.31 mg/kg of wood burned from the combustion of pine, oak, and eucalyptus wood respectively. 2-Methylnaphthalene was detected at concentrations of 15.0, 9.31, and 5.69 mg/kg of wood burned from combustion of pine, oak, and eucalyptus wood, respectively. Naphthalene was not measured from the oak and eucalyptus fires (Schauer et al. 2001). In another study, the respective median concentrations of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were determined to be 22.57, 4.14, and 4.76 mg/kg of burned soft wood in the fireplace; 60.86, 12.71, and 15.55 mg/kg for hardwood in the fireplace; and 34.96, 5.23 and 6.32 mg/kg for hardwood burned in a woodstove (McDonald et al. 2000).

Reported levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in measured in the smoke from U.S. commercial unfiltered cigarettes were 3, 1, and 1 µg, respectively (Schmeltz et al. 1978). Levels in sidestream smoke were found to be higher; 46, 30, and 32 µg/cigarette, respectively (Schmeltz et al. 1976).

Naphthalene has been detected in ash from municipal refuse and hazardous waste incinerators (EPA 1989g; Shane et al. 1990). Naphthalene was detected in 7 of 8 municipal refuse ash samples at 6–28,000 µg/kg (Shane et al. 1990) and in 5 of 18 hazardous waste incinerator ash samples at 0.17–

41 mg/kg (EPA 1989g). Higher concentrations were detected in bottom ash than in fly ash (Shane et al. 1990).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to naphthalene mainly by inhalation of ambient and indoor air. The use of naphthalene-containing moth repellents and smoke from cigarettes are the main sources of naphthalene in indoor air. Other sources include kerosene heaters. Based on an urban/suburban average air concentration of 0.95 μg/m^3 and an inhalation rate of 20 m^3/day, it has been estimated that the average daily intake from ambient air is 19 μg (Howard 1989). Intake from indoor air may be higher, depending on the presence of indoor sources.

The estimated average daily intake from ambient air may be about 10 μg for 1-methylnaphthalene and 1 μg for 2-methylnaphthalene. These estimates are based on ambient air samples taken from 64 (1-methylnaphthalene) and 17 (2-methylnaphthalene) locations (EPA 1988g) and an assumed human daily intake of 20 m^3. Naphthalene was one of the PAHs detected in an 8-home pilot study that was conducted in Columbus, Ohio to measure the PAH concentration profiles in house-dust. The average concentration of naphthalene was found to be dependant upon the method of extraction (2.8 mg/m^3 by soxhlet extraction and 1.8 mg/m^3 by sonication extraction) (Chuang et al. 1995). Concentrations of naphthalene detected in the indoor and outdoor air measured in 24 low-income homes in North Carolina ranged from 0.33 to 9.7 and from 0.57 to1.82 μg/m^3, respectively (Chuang et al. 1999). In a study reporting the concentrations of volatile organic compounds (VOCs) in a wide range of environments (viz homes, offices, restaurants, pubs, department stores, train and bus stations, heavily trafficked roadside locations, buses, trains and automobiles) in Birmingham, United Kingdom, naphthalene concentrations were found to range from 0.1 μg/m^3 (labs) to 12.1 μg/m^3 (heavily trafficked roadside) (Kim et al. 2001). A mean concentration of naphthalene was found to be 2.3 μg/m^3 in a German environmental survey that monitored 113 adults aged 25–69 years, selected at random, for personal exposure to VOCs including naphthalene (Hoffman et al. 2000). Low levels of naphthalene (average concentration, 0.44 μg/m^3) and 1-methylnaphthalene (average concentration 0.08 μg/m^3) were found in the indoor air of 92 and 81% of single family homes and apartments monitored, respectively (Kostianen 1995). Naphthalene has been detected in the smoke from charbroiling meat (Schauer et al. 1999a) and from the smoke from domestic fireplaces and wood burning stoves (McDonald et al. 2000; Schauer et al. 2001).

Exposure to naphthalene may occur from ingestion of drinking water and/or food, but these exposures are expected to be much less than inhalation exposures for the general population. Estimated exposure from drinking water, assuming a water concentration range of 0.001–2 μg/L, is 0.002–4 μg/day (Howard 1989). Estimates for food were not calculated. In a Lower Rio Grande Valley environmental study, naphthalene (median concentration, 2.159 μg/kg body weight) was detected in five of the nine duplicate-diet samples (Berry et al. 1997). Naphthalene was also detected in fresh tree-ripened apricots, plums, and their interspecific hybrids (Gomez et al. 1993), in vegetables such as cabbage, carrots, leeks, lettuce, and endive (Kipopoulou et al. 1999), and in whole and ground sorghum (Seitz et al. 1999). It has also been found in fish such as American plaice, yellow tail flounder (Hellou and Warren 1996), and salmon (Neff and Burns 1996).

Accidental ingestion of household products containing naphthalene such as mothballs or deodorant blocks frequently occurs in children. In 1990, 2,400 cases of accidental naphthalene ingestion were reported to 72 Poison Control Centers in the United States (Woolf et al. 1993). Nearly 90% of these cases occurred in children under 6 years of age.

Dermal exposure to naphthalene may occur from handling or wearing clothing stored in naphthalene-containing moth repellents. However, no data were located concerning the level of human exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene via this exposure route. Experimental studies have shown that naphthalene can be dermally absorbed and systemically metabolized in rats (Turkall et al. 1994).

Naphthalene was detected in 40% of human adipose tissue samples at concentrations ranging from <9 to 63 μg/kg in a National Human Adipose Tissue Survey (NHATS) (EPA 1986g). Naphthalene was also detected (concentrations not reported) in six of eight selected breast milk samples from women in four U.S. cities (Pellizzari et al. 1982).

Naphthalene exposure may also occur in the workplace. Bjorseth et al. (1978a, 1978b) have reported vapor levels of 11–1,100 μg/m^3 and from 0 (nondetected) to 44 μg/m^3 for naphthalene-containing particulate in a coke plant. Similar measurements in an aluminum reduction plant yielded somewhat lower levels of 0.72–310 μg/m^3 for vapor and 0.08–4 μg/m^3 for particulates. Higher levels would be anticipated in naphthalene-producing industries and naphthalene-using industries such as wood preserving, tanning, and ink and dye production. A NIOSH (1980) survey of worker exposures to polyaromatic hydrocarbons at a petroleum refinery in Tulsa, Oklahoma reported air concentrations of

naphthalene as high as 10.2 μg/m^3 in an area sample and 19.3 μg/m^3 for a personal sample. For 2-methyl-naphthalene, 17.6 μg/m^3 was the maximum area concentration reported and 31.9 μg/m^3 was the highest value for a personal sample. A National Occupational Exposure Survey (NOES) conducted by NIOSH estimated that 112,702 and 4,358 workers are potentially exposed to naphthalene and 2-methyl-naphthalene, respectively (NIOSH 1991). The workers at greatest risk of exposure included mining machine operators, aircraft engine mechanics, and miscellaneous machine operators.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are likely to be exposed to naphthalene via the same routes that affect adults, such as inhalation of contaminated air, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils or products treated with the compound. The EPA (1996c) calculated an estimated intake range of 0.0002–0.043 mg/kg/day of naphthalene for a 10-kg child, assuming an ingestion of 100 mg of soil per day. Assuming food ingestion of approximately 0.5–2.3 kg/day for children, an estimated daily intake of 204–940 ng/kg-day was calculated for a 10-kg child. An estimated average daily dose of 1,127 ng/kg-day was calculated, assuming an inhalation rate of 8.7 m^3/day for a 10-kg child.

Small children are more likely than adults to come into intimate contact with yard dirt, lawns, and dust from carpets. Dislodgeable pesticide residues in carpets or on uncovered floors may present a relatively important exposure route for infants and toddlers through dermal contact and oral ingestion. The tendency of young children to ingest soil, either intentionally through pica or unintentionally through

hand-to-mouth activity, is well documented. These behavioral traits can result in ingestion of naphthalene present in soil and dust. Naphthalene has been detected in the house-dust in an 8-home pilot study (Chuang et al. 1995).

Dermal exposure to naphthalene may occur from handling or wearing clothing stored in naphthalene-containing moth repellents. No studies are available that describe the dermal absorption of naphthalene in children. Experimental studies have shown that naphthalene can be dermally absorbed and systemically metabolized in rats (Turkall et al. 1994).

Inhalation exposure is a major source of exposure in both adults and children. Naphthalene has been detected in the indoor air of homes (Chuang et al. 1995, 1999; Kostianen 1995). Naphthalene has been detected in the smoke from charbroiling meat (Schauer et al. 1999a) and from the smoke from domestic fireplaces and wood burning stoves (McDonald et al. 2000; Schauer et al. 2001).

Naphthalene (mothballs) is commonly used as a moth repellant in clothes during storage and as a deodorizer in diaper pails. Acute hemolysis was reported in 21 children following a period of inhalation exposure of naphthalene. The source of naphthalene was woolen clothes and blankets that had been stored with mothballs over the summer (Valaes et al. 1963).

A potential source of exposure in infants is from the presence of naphthalene in breast milk or formula. Naphthalene was detected (concentrations not reported) in six of eight breast milk samples from women in four U.S. cities (Pellizzari et al. 1982).

Children may also be exposed to naphthalene from milk drinks that have been stored in LDPE bottles. Naphthalene concentrations of 0.02 µg/mL were found in milk drinks stored in LDPE bottles at the time of purchase, but increased to 0.1 µg/mL 30 days later and averaged 0.25 µg/mL at the expiration date of the milk drink (Lau et al. 1994). Residual naphthalene present in the LDPE packaging was hypothesized to be the source of naphthalene contamination. A later study by the same authors observed that the level of naphthalene in LDPE milk bottle material had been reduced to 0.1–0.4 µg/g due to new packaging material (Lau et al. 1995).

Accidental ingestion of household products containing naphthalene, such as mothballs or deodorant blocks, can occur in children. In 1990, 2,400 cases of accidental naphthalene ingestion were reported to

72 Poison Control Centers in the United States (Woolf et al. 1993). Nearly 90% of these cases occurred in children under 6 years of age.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population most likely to have high levels of exposure to naphthalene are users of naphthalene-containing moth repellents (including infants exposed to blankets or clothing stored in naphthalene-containing mothballs), smokers, and those in proximity to smokers. Workers in naphthalene-producing or naphthalene-using industries could be subject to heightened exposure, and individuals living or working near hazardous waste sites at which naphthalene has been detected could also be exposed to higher naphthalene concentrations if they came into contact with contaminated media.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of naphthalene that are required to evaluate its behavior in the environment have been determined (EPA 1982e; HSDB 2003). Information that documented the physical and chemical properties of 1-methylnaphthalene and 2-methyl-

naphthalene are also available (HSDB 2003). However, measured Henry's law constants and log K_{oc} values for methylnaphthalenes would allow more accurate prediction of environmental fate processes.

Production, Import/Export, Use, Release, and Disposal. Naphthalene producers, production locations and volumes, uses, releases, and disposal practices are well documented (Lacson et al. 2000; SRI 2003; TRI01 2003). Disposal of naphthalene-containing wastes are regulated by EPA, and major spills or accidental releases must be reported to EPA. No data were located on production volume, releases, and disposal practices for 1-methylnaphthalene or 2-methylnaphthalene. This information would be helpful to predict the potential for human exposure to these chemicals.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2001, became available in July of 2003. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Existing information indicates that most naphthalene is released to the atmosphere and undergoes rapid reaction with hydroxyl radicals (Atkinson et al. 1987; EPA 1982d; Howard 1989). Available data indicate that volatilization and biodegradation are important removal processes from water and soil (EPA 1982d; Howard 1989; Tabak et al. 1981; Wakeham et al. 1983). Additional studies on the rates of volatilization, degradation, and transport in groundwater would be helpful in assessing potential human exposure in the vicinity of industrial sources and chemical waste sites. Data describing the volatilization, biodegradation, and transport of 1-methylnaphthalene and 2-methylnaphthalene would be useful in predicting the potential for human exposure.

Bioavailability from Environmental Media. No studies were located on the bioavailability of naphthalene in various environmental media. Available toxicity data indicate that naphthalene present in contaminated air and ingested in drinking water or soil is probably absorbed. Confirmatory, quantitative data would be useful. Data on infants indicate that toxicologically significant amounts of naphthalene may be absorbed dermally from residues left on stored clothing, especially under circumstances where baby oil was used on the infants' skin (Schafer 1951). Quantitative studies of the dermal absorption of naphthalene from water and soil would be useful in determining potential exposure for populations living near hazardous waste sites.

No data have been located pertaining to the bioavailability of 1-methylnaphthalene or 2-methylnaphthalene in environmental media. Studies in laboratory animals to assess the absorption of this compound via the oral, inhalation, and dermal routes would be useful before bioavailability from each medium can be reasonably estimated.

Food Chain Bioaccumulation. Naphthalene is often readily degraded in the environment and is easily metabolized by a wide variety of organisms. Studies indicate that although naphthalene may bioconcentrate to a moderate degree for brief periods, it will not significantly bioaccumulate in organisms due to metabolism, and thus, is unlikely to biomagnify through the food chain (Howard 1989; Thomann 1989). Naphthalene has been found to be present in fish and shellfish (Bender and Huggett 1989; Hellou and Warren 1996; Miles and Roster 1999; Minyard and Roberts 199l; Neff and Burns 1996; Zitko et al. 1998). It has also been located in the flesh of fresh fruits and vegetables (Gomez et al. 1993; Kipopoulou et al. 1999; Seitz et al. 1999). Data were not located on 1-methylnaphthalene and 2-methylnaphthalene levels in foods. Additional data on naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene concentrations in foods and processed foods would be useful to assess the extent of human exposure via the food chain.

Exposure Levels in Environmental Media. The concentrations of naphthalene in the air, water, and soil have been documented (Bradley et al. 1994; Chuang et al. 1999; EPA 1988g; Howard 1989; Miles and Delfino 1999; Richardson et al. 1994; Squillace et al. 1999; Wild et al. 1990; Yu et al. 1990; Zielinska et al 1998). In addition, indoor air levels have been measured (Chuang et al. 1991; Hung et al. 1992; Wilson et al. 1989). Additional information regarding exposure levels of 1-methylnaphthalene and 2-methylnaphthalene in environmental media would be useful for deriving exposure estimates for the general population.

Reliable monitoring data for the levels of naphthalene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of naphthalene in the environment can be used in combination with the known body burden of naphthalene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. A national survey of adipose tissue samples indicates that about 40% of the study subjects had measurable levels of naphthalene (EPA 1986g). Naphthalene was also detected in six of eight samples of human milk (Pellizzari et al. 1982). Data on the effect of cigarette filters on

naphthalene uptake by the adipose tissues would be useful. Naphthalene has been detected in house dust (Chuang et al. 1995).

No data on exposure levels in humans were located for 1-methylnaphthalene or 2-methylnaphthalene. This information would be useful to determine whether any significant exposure to these chemicals occurs.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No monitoring studies have been performed to investigate the exposure to, and the body burden of, naphthalene in children. No studies are available on the dermal absorption of naphthalene in infants and toddlers due to activities such as crawling, which will result in contact with the floor (carpet) and soil or from exposure to clothes stored with mothballs. Since naphthalene is likely to be adsorbed to these materials, more information would allow the estimation of a child's exposure to naphthalene to be more rigorously determined. Naphthalene has been detected in house dust (Chuang et al. 1995). The EPA has calculated estimated amounts of naphthalene inhaled and naphthalene ingested via the intake of food and soil for a 10-kg child (EPA 2002b). No studies on amounts of naphthalene present in foods eaten by children are available. Such studies may help to identify childhood-specific means of decreasing exposure to naphthalene.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for naphthalene, 1-methylnaphthalene, or 2-methyl-naphthalene were located. These substances are not currently listed as compounds for which a subregistry has been established in the National Exposure Registry. These substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2003) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-2.

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Naphthalene[a]

Investigator	Affiliation	Research Description	Sponsor
Nylander French LA	University of North Carolina, Chapel Hill, North Carolina	Dermal exposure to benzene and naphthalene	National Institutes of Environmental Health Science
Aitken MD	University of North Carolina, Chapel Hill, North Carolina	Bacterial chemotaxis to naphthalene desorbing from non-aqueous phase liquid	National Science Foundation, Environmental Remediation Program
Atkinson R; Winer AM	University of California, Riverside, California	Photochemical and thermal reactions of combustion related particulate organic matter: A combined chemical and microbiological approach	ER-74 Office of Scientific and Technical Information
Boyd SA	Michigan State University, East Lansing, Michigan	Physicochemical and microbiological factors influencing the bioavailability of organic contaminants in subsoils	U.S. Department of Energy, Energy Research
Bryers JD	University of Connecticut Health Center, Farmington, Connecticut	Substrata surface chemistry, conformation of contaminant upon absorption, and availability for biodegradation	National Science Foundation, Environmental Remediation Program
Gabr MA	West Virginia University, Morgantown, West Virginia	Site remediation technologies: Drain-enhanced soil flushing for organic contaminants removal	U.S. Department of Energy, Fossil Energy
Kilduff JE	Rensselaer Polytechnic Institute, Troy, New York	Collaborative research: Sorption reversibility of hydrophobic compounds in geosorbents investigated with model sorbents	National Science Foundation, Environmental Remediation Program
Luthey R	Carnegie-Mellon University, Pittsburgh, Pennsylvania	Transport and degradation of synthetic fuel products/by-products in soils	U.S. Department of Energy
Palumbo AV; Lee SY; Herbes SE; Toran LE	Oak Ridge National Laboratory, Oak Ridge, Tennessee	Mixed-waste biodegradation	U.S. Department of Energy, Energy Research
Thompson AF	Connecticut Agricultural Experimental Station, New Haven, Connecticut	Collaborative research: Sorption reversibility of hydrophobic compounds in geosorbents investigated with model sorbents	National Science Foundation, Environmental Remediation Program

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Naphthalene[a]

Investigator	Affiliation	Research Description	Sponsor
Pulliam Holoman TR	University of Maryland, College Park, Maryland	Anaerobic degradation of polycyclic aromatic hydrocarbons in marine harbor sediments	National Science Foundation, Environmental Remediation Program
Sayler GS	University of Tennessee, Knoxville, Tennessee	On-line monitoring of aerobic bioremediation with bioluminescent reporter microbes	U.S. Department of Energy, Energy Research
Zylstra GJ	Rutgers University, New Brunswick, New Jersey	Molecular analysis of polycyclic aromatic hydrocarbon degradation by mycobacteria	National Science Foundation, Biomolecular Processes Cluster
Pignatello JJ	Connecticut Agricultural Experimental Station, New Haven, Connecticut	Chain-transfer complexation of aromatic compounds with soil organic matter	U.S. Department of Agriculture
Inskeep WP	Montana State University, Bozeman, Montana	Fate and transport of chemicals in soils: linking chemical transformations	U.S. Department of Agriculture
Madsen EL	Cornell University, Ithaca, New York	Methods for determining biochemical indicators of microbial metabolism of pollutants in soil	U.S. Department of Agriculture
Haggblom MM	Rutgers University, New Brunswick, New Jersey	Microbial degradation of PAHs in the rhizosphere of salt-marsh plants	U.S. Department of Agriculture
Pignatello JJ	Connecticut Agricultural Experimental Station, New Haven, Connecticut	Nonideal (specific) sorption of organic chemicals in soil organic matter	U.S. Department of Agriculture
Ogram AV; Hornsby AC	University of Florida, Gainesville, Florida	Pesticides and other toxic organics in soil and their potential for ground and surface water contamination	U.S. Department of Agriculture

[a]FEDRIP 2003

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, its metabolites, and other biomarkers of exposure and effect to naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Naphthalene is moderately volatile with a boiling point of 218 °C and low water solubility of 31.7 mg/L (20 °C). Its log octanol/water partition coefficient is 3.29, implying a moderate affinity for lipid tissues. It undergoes short-term bioaccumulation in tissues, but biochemical processes lead to its biodegradation and eventual elimination. Methylnaphthalenes have similar properties (see Table 4-2). All of these properties have implications for determination of naphthalene and methylnaphthalenes in biological materials.

Historically, diethyl ether has been a widely used solvent for the extraction of lipophilic organic analytes such as naphthalene from biological fluids (Zlatkis and Kim 1976). Homogenization of tissue with the extractant and lysing of cells improves extraction efficiency. When, as is often the case, multiple analytes are determined using solvent extraction, selective extraction and loss of compounds that have a low boiling point can cause errors. The commercial availability of highly purified solvents has largely eliminated problems with solvent impurities, although high costs, solvent toxicities, and restrictions on spent solvent disposal must be considered. Extraction is the first step in the overall cleanup process that places the analyte in a form and matrix suitable for introduction into the instrument used to quantitate it. Cleanup of biological samples may often be complex and involve a number of steps (Walters 1986). Directly coupled supercritical fluid extraction (SFE)-gas chromatography has been used for the

determination of polychlorinated biphenyls (Hawthorne 1988) and might also be applicable to determination of naphthalene and methylnaphthalenes in biological samples.

Naphthalene metabolites are less lipophilic than naphthalene itself. Metabolites are isolated from body fluids and tissue homogenates by extraction and separated by thin layer chromatography (TLC) and HPLC (Horning et al. 1980; Melancon et al. 1982; Stillwell et al. 1982). Final identification of metabolites, which include numerous oxygenated and sulfur-containing species, is accomplished by gas chromatography (GC) and mass spectrometry (MS).

New immunological methods are being developed for detecting selected naphthalene metabolites in urine or naphthalene protein adducts in the blood of lung lavage specimens (Cho et al. 1994b; Marco et al. 1993). Additional work in perfecting these techniques is necessary before they will be useful in research and clinical practice.

Analytical methods for the determination of naphthalene and for 1-methylnaphthalene and 2-methylnaphthalene in biological samples are given in Table 7-1. A method for the determination of radiolabelled 2-methylnaphthalene in rat urine has been described by Melancon et al. (1982). TLC and HPLC were used to characterize 2-methylnaphthalene and its metabolites, including 2-naphthoylglycine, 2-naphthoic acid, and others.

7.2 ENVIRONMENTAL SAMPLES

Gas chromatography and HPLC are the analytical methods most commonly used for detection of naphthalene and methylnaphthalenes in environmental samples. Several variations of these methods using different collection, extraction, and/or cleanup procedures and different detection methods have been approved by EPA and NIOSH for analysis of naphthalene in ambient water, drinking water, waste water, soil, and air (EPA 1982a, 1982b, 1986a, 1986b, 1986c, 1986d, 1990a, 1990b, 1990c, 1990d, 1990e; NIOSH 1984a, 1984b). The American Public Health Association (APHA) has recommended standard methods for analysis of naphthalene in water and waste water, each of which has been accepted by EPA as equivalent to one of the EPA-approved methods (APHA 1992a, 1992b, 1992c, 1992d, 1992e, 1992f). Analytical methods for naphthalene and 2-methylnaphthalene are presented in Tables 7-2 and 7-3, respectively. Although no standard methods were located that provided information on detection limits or accuracy for 1-methylnaphthalene, this compound may be analyzed in environmental media by GC and HPLC methods (HSDB 1995).

Table 7-1. Analytical Methods for Determining Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene in Biological Samples[a]

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Extract; bulk lipid removal; Florisil® fractionation	HRGC/MS	9 ng/g	No data	Stanley 1986
Adipose tissue (human and bovine)	Extract with hexane; Florisil® cleanup	Capillary column GC/MS	10 ng/g	90 (human) 63 (bovine)	Liao et al. 1988
Human milk	Purge with helium; desorb thermally	Capillary column GC/MS	No data	No data	Pellizzari et al. 1982
Human urine (1-naphthol analysis	No data	TLC or GS/ unspecified spectroscopy	No data	No data	Bieniek 1994
Fish tissue	Purge and trap to carbon adsorption tube; extract with carbon disulfide	HRGC/FID	<10 µg/L	43–51	Murray and Lockhart 1988
Fish tissue	Saponification with potassium hydroxide; extraction with cyclopentane-dichloromethane; adsorption enrichment with potassium silicate/silica gel; gel permeation chromatography enrichment	Capilliary column GC/PID	20 ng/g	76–202 (naphthalene) 77–82 (1-methyl-naphthalene) 75–131 (2-methyl-naphthalene)	Lebo et al. 1991
Rat urine	Extract with ammonium carbonate/ethyl acetate; evaporate under nitrogen stream; dissolve in pyridine	GC/MS	No data	No data	Horning et al. 1980
Mouse urine	Extract with ethyl acetate; evaporate under nitrogen stream; dissolve in pyridine	GC/MS	No data	No data	Stillwell et al. 1982
Burned tobacco	Extract with methanol/water and cyclohexane; enrich in dimethyl sulfoxide; fractional distillation and evaporation under dry nitrogen	GLC/MS	No data	85–95	Schmeltz et al. 1976

[a]Data are for naphthalene only unless otherwise specified.

FID = flame ionization detector; GC = gas chromatography; GLC = gas-liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; PID = photoionization detector; TLC = thin layer chromatography

Table 7-2. Analytical Methods for Determining Naphthalene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect in charcoal tube; elute with carbon disulfide	GC/FID	15 mg/m^3	No data	NIOSH 1977
Air	Collect in charcoal tube; elute with carbon disulfide	GC/FID	10 µg/sample	No data	NIOSH 1984a
Air	Collect in charcoal tube; elute with organic solvent	GC/FID	0.5 µg/sample	No data	NIOSH 1984b
Air	Collection filter or tube; extract with acetonitrile	HPLC/FD	0.080 µg/filter or 0.070 µg/tube	No data	Hansen et al. 1991
Indoor air	Medium flow rate samples; extract with methylene chloride; exchange to cyclohexane; clean up; exchange to acetonitrile	HPLC/UV	250 pg/µL	No data	EPA 1990a
Indoor air	Medium flow rate samples; extract with methylene chloride	GC/MS	No data	No data	EPA 1990a
Water	Purge and trap	HRGC/PID	0.06 µg/L	102±6.3	Ho 1989
Water	Extract with methylene chloride; exchange to cyclohexane; clean up; exchange to acetonitrile	HPLC/UV	1.8 µg/L	78±8.3	EPA 1982a
Water	Extract with methylene chloride at pH 11 and 2; concentrate	GC/MS	1.6 µg/L	75±35	EPA 1982b
Water	Adsorb on small bed volume Tenax® cartridges; thermally desorb	GC/MS	No data	No data	Pankow et al. 1988
Drinking water	Liquid-liquid extraction with methylene chloride; exchange to acetonitrile	HPLC/UV	3.3 µg/L	76–96	EPA 1990d
Drinking water	Liquid-solid extraction with methylene chloride; exchange to acetonitrile	HPLC/UV	2.2 µg/L	49.6–75.2	EPA 1990e
Drinking water	Purge and trap	Packed column GC/PID	0.01–0.05 µg/L	92	APHA1992e

Table 7-2. Analytical Methods for Determining Naphthalene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	Purge and trap	Capillary column GC/MS	0.02–0.2 µg/L	98–104	APHA 1992d
Drinking water	Purge and trap	Capillary column GC/PID	No data	102	APHA 1992f
Wastewater	Extract with methylene chloride	Isotope dilution, capillary column GC/MS	10 µg/L	75–149	EPA 1990c
Wastewater	Extract with methylene chloride; exchange to cyclohexane; clean up; exchange to acetonitrile	HPLC/UV	1.8 µg/L	21.5–100	APHA 1992b
Water	Extract with methylene chloride	Capillary column GC/MS	10 µg/L[a]	No data	EPA 1986c
Wastes, non-water miscible	Extract with methylene chloride	Packed column GC/MS	160 mg/kg	No data	EPA 1986b
Soil	Extract with methylene chloride	Packed column GC/MS	1 mg/kg	No data	EPA 1986b
Soil, sediment	Extract with methylene chloride	Capillary column GC/MS	660 µg/kg	No data	EPA 1986c
Wastes, soil	Extract with methylene chloride	GC/FTIR	20 µg/L[a, b]	No data	EPA 1986d

[a]Identification limit in water. Detection limits for actual samples are several orders of magnitude higher, depending upon the sample matrix and extraction procedure employed.
[b]Based on a 2 µL injection of a 1 L sample that was extracted and concentrated to a volume of 1 mL.

FD = fluorescence detection; FID = flame ionization detector; FTIR = Fourier transform infrared spectrometry; GC = gas chromatography; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectroscopy; PID = photoionization detection; UV = ultraviolet spectrometry

Table 7-3. Analytical Methods for Determining 2-Methylnaphthalene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery
Soil, sediment	Extract with methylene chloride	Capillary column GC/MS	660 µg/kg	No data
Water	Extract with methylene chloride	Capillary column GC/MS	10 µg/kg	No data

GC = gas chromatography; MS = mass spectroscopy

SOURCE = EPA 1986c

Air samples for analysis may be collected on filters or charcoal tubes. Since naphthalene may exist in both the vapor phase and the particle phase in air (Harkov 1986), collection on a charcoal tube is the preferred method for sampling naphthalene from air for analysis (NIOSH 1977, 1984a, 1984b).

Naphthalene is usually extracted from the matrix with organic solvents (liquid-liquid or liquid-solid extraction) or by purge and trap with an inert gas. SFE techniques for extraction of organic compounds from environmental matrices are currently being studied by EPA. A protocol for SFE with carbon dioxide for many organic compounds, including naphthalene, from soils and sediments has been developed (EPA 1991f).

A technique for the detection of naphthalene in PAH-contaminated media has been developed (Heitzer et al. 1994). The technique measures bioluminescence in the genetically engineered microorganism *Pseudomonas fluorescens* HK44, which carries a transcriptional gene for naphthalene and salicylate metabolism. After the addition of the bacteria to sterile water, naphthalene was detected down to 1.55 µg/L, the lowest concentration studied. In an experiment using JP-4 jet fuel, naphthalene was detected down to 0.55 µg/L in the effluent of the biosensor (Heitzer et al. 1994).

Detectors used for identification and quantification of naphthalene and methylnaphthalenes include the flame ionization detector (FID), photoionization detector (PID), ultraviolet detection (UV), Fourier transform infrared detection (FTIR), and fluorescence detection (FD). Mass spectrometry is used for confirmation.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of naphthalene, 1-methylnaphthalene, and 2-methyl-naphthalene are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Sensitive and selective methods are available for the qualitative and/or quantitative measurement of naphthalene and many of its metabolites present in biological materials such as adipose tissue and urine (EPA 1986g; Horning et al. 1980; Liao et al. 1988). In contrast to the relative ease of measuring naphthalene once it has been isolated from its sample matrix, the development of improved techniques for sample preparation would be beneficial.

Metabolites of naphthalene in biological materials are not readily determined in routine practice because of the lack of standard methods for their quantification. Furthermore, there is a need for modern validated standard methods for analysis of naphthalene itself in biological materials. It would also be helpful to have a method that can be used to associate levels of naphthalene or its metabolites in biological media with levels of naphthalene exposure in the environment.

A method for the determination of 2-methylnaphthalene and its degradation products in rat urine has been reported (Melancon et al. 1982). It would be useful to determine if this method could also be applied to human urine and other biological samples.

Effect. There are currently no methods that can be used to correlate levels of naphthalene, 2-methyl-naphthalene, or their metabolites in biological tissues or fluid with the probable onset of adverse health effects. The development of such methods would be useful insofar as they estimate the doses required to produce cataracts and hemolytic effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining naphthalene in water, air, and waste samples with excellent selectivity and sensitivity have been developed and are undergoing constant improvement (EPA 1982a, 1982b, 1986a, 1986b, 1986c, 1986d, 1990a, 1990b, 1990c, 1990d, 1990e; NIOSH 1984a, 1984b). For each medium, the existing methods are adequate to measure background levels in the environment and levels at

which health effects occur. Standard methods for 1-methylnaphthalene and 2-methylnaphthalene would be helpful in assessing data comparability.

It would be useful to have the means to rapidly and directly measure organic compounds such as naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in water and other environmental media without the necessity for tedious sample processing. The recently developed bioluminescent probe for naphthalene (Heitzer et al. 1994) may help satisfy this data need.

Degradation products of naphthalene in environmental media are difficult to determine. This difficulty is not so much an analytical problem as it is a problem of knowing the fundamental environmental chemistry of these compounds in water, soil, air, and biological systems.

There are some difficulties associated with sampling naphthalene from the atmosphere, where it is partially associated with particulate matter. High-volume sampling with glass fiber filters provides conditions conducive to artifact formation (Harkov 1986), thus introducing errors into the analysis of atmospheric naphthalene. This is an area in which further improvements would be useful.

7.3.2 Ongoing Studies

No ongoing studies involving analytical techniques of naphthalene, 1-methylnaphthalene, or 2-methyl-naphthalene were found in a search of the Federal Research in Progress database (FEDRIP 2003).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding naphthalene, 1-methyl-naphthalene, and 2-methynaphthalene in air, water, and other media are summarized in Table 8-1.

The EPA has calculated an oral exposure RfD of $2x10^{-2}$ mg/kg/day for naphthalene based on a NOAEL of 100 mg/kg/day for the absence of decreased mean terminal body weight in male rats exposed by gavage for 13 weeks (IRIS 2003; NTP 1980b). An inhalation RfC of $3x10^{-3}$ mg/m^3 for naphthalene was derived based on a LOAEL of 10 ppm ($LOAEL_{[human\ equivalent\ concentration]}$=9.3 mg/m^3) for nasal lesions in mice exposed by inhalation for 2 years (IRIS 2003; NTP 1992a).

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2002a
WHO	Drinking water guideline	No data	
NATIONAL			
Regulations and Guidelines:			
a. Air:			
ACGIH	TLV (8-hour TWA)		ACGIH 2003
	Naphthalene[b]	10 ppm	
	STEL	15 ppm	
EPA	Hazardous air pollutant	Naphthalene	EPA 2003g 40 CFR 63, Subpart CC, Appendix, Table 1
	National emission standards for hazardous air pollutants	No (zero) emissions are allowed	EPA 2003h 40 CFR 61.134
	Naphthalene processing, final coolers, and final-cooler cooling towers at coke by-product recovery plants		
NIOSH	REL (10-hour TWA)		NIOSH 2003
	Naphthalene	10 ppm	
	STEL	15 ppm	
	IDLH	250 ppm	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2003a 29 CFR 1910.1000, Table Z-1
	Naphthalene	10 ppm	
	PEL (8-hour TWA) for construction industry		OSHA 2003c 29 CFR 1926.55, Appendix A
	Naphthalene	10 ppm	
	PEL (8-hour TWA) for shipyard industry		OSHA 2003b 29 CFR 1915.1000
	Naphthalene	10 ppm	
USC	Hazardous air pollutant	Naphthalene	USC 2003

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Drinking water health advisories		EPA 2002
	1-day (10-kg child)	0.5 mg/L	
	10-day (10-kg child)	0.5 mg/L	
	DWEL[f]	0.7 mg/L	
	Life-time[g]	0.1 mg/L	
	Effluent guidelines and standards; toxic pollutants pursuant to Section 307(a)(1) of the Clean Water Act	Naphthalene	EPA 2003c 40 CFR 401.15
EPA	Hazardous substance designated in accordance with Section 311 (b)(2)(A) of the Clean Water Act	Naphthalene	EPA 2003p 40 CFR 116.4
	Pollutants of initial focus in the Great Lakes Water Quality Initiative	Naphthalene	EPA 2003q 40 CFR 132, Table 6
	Reportable quantities of hazardous substances (naphthalene) designated pursuant to Section 311 of the Clean Water Act	100 pounds	EPA 2003j 40 CFR 117.3
c. Food	No data		
d. Other			
ACGIH	Carcinogenicity classification	A4[h]	
EPA	Carcinogenicity classification	Group C[i]	IRIS 2003
	RfD (oral)	2.0×10^{-2} mg/kg/day	IRIS 2003
	RfC (inhalation)	3.0×10^{-3} mg/m^3	IRIS 2003
	Community right-to-know; release reporting; effective date of reporting	01/01/87	EPA 2003m 40 CFR 372.65
	Criteria for municipal solid waste landfills; hazardous constituent	Naphthalene 2-Methylnaphthalene	EPA 2003a 40 CFR 258, Appendix II
	Identification and listing of hazardous waste; hazardous waste number		EPA 2003d 40 CFR 261, Appendix VIII
	Naphthalene	U165	
	Land disposal restrictions; universal treatment standards for naphthalene		EPA 2003e 40 CFR 268.48
	Waste water standard	0.059 mg/L	
	Non-waste water standard	5.6 mg/L TCLP	

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
	Landfills point source effluent limitations attainable by the application of the best practicable control technology currently available			EPA 2003f 40 CFR 445.11
	Maximum daily	0.059 mg/L		
	Maximum monthly average	0.022 mg/L		
EPA	Reportable quantity of hazardous substance in accordance with Section 311 (b)(2) and 307(a) of the Clean Water Act, Section 112 of RCRA, and Section 112 of the Clean Air Act for naphthalene	100 pounds		EPA 2003b 40 CFR 302.4
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring	Suggested Method	PQL	EPA 2003k 40 CFR 264, Appendix IX
	Naphthalene	8100	200 µg/L	
		8270	10 µg/L	
	2-Methylnaphthalene	8270	10 µg/L	
	Standards for owners and operators of hazardous waste TSD facilities; health-based limits for exclusion of waste-derived residues; residue concentration limit	10 mg/kg		EPA 2003l 40 CFR 266, Appendix VII
	TSCA chemical information rules; health and safety data reporting for naphthalene			EPA 2003n 40 CFR 712.30
	Effective date	08/04/95		
	Reporting date[j]	10/03/95		
	TSCA health and safety data reporting for naphthalene[k]			EPA 2003o 40 CFR 716.120
	Effective date	08/04/95		
	Sunset date	10/03/95		
STATE				
a. Air	No data			
b. Water				
Maine	Drinking water guideline	25 µg/L		HSDB 2003
Minnesota	Drinking water guideline	300 µg/L		HSDB 2003
New Jersey	Drinking water standard	300 µg/L		HSDB 2003
Washington	Drinking water guideline	14 µg/L		HSDB 2003
Wisconsin	Drinking water guideline	40 µg/L		HSDB 2003
Florida	Drinking water guideline	6.8 µg/L		HSDB 2003

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information	Reference
STATE *(cont.)*			
c. Food	No data		
d. Other	No data		

[a]Group 2B: possibly carcinogenic to humans
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.
[c]Class D: refers to the retention (clearance half-times of <10 days) for all compounds except those given for W.
[d]The ALIs and DACs for inhalation are given for an aerosol with an activity median aerodynamic diameter (AMAD) of 1 μm and for class D and W of radioactive material, which refers to their retention (clearance half-times of <10 days and 10–100 days, respectively) in the pulmonary region of the lung.
[e]Class W: refers to the retention (clearance half-times of 10–100 days) for oxides, hydroxides, and carbides.
[f]DWEL: a lifetime exposure concentration protection of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from drinking water.
[g]Life-time: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for a lifetime of exposure. The Lifetime HA is based on exposure of a 70-kg adult consuming 2 L water/day.
[h]A4: not classifiable as a human carcinogen
[i]Group C: a possible human carcinogen
[j]Reporting date: manufacturers and importers of naphthalene must submit a Preliminary Assessment Information Manufacturer's Report for each site at which they manufacture or import naphthalene by the reporting date.
[k]TSCATS health and safety data reporting: naphthalene is subject to all provisions of part 716. Manufacturers, importers, and processors of naphthalene are subject to the reporting requirements of subpart A.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; LLI = lower large intestine; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation level; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TCLP = toxicity characteristic leachate procedure; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is

undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: September 5, 2003
Profile Status: Draft 3, pre-public
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 6
Species: Mouse

Minimal Risk Level: 0.0007 [ ] mg/kg/day [x] ppm

Reference(s): Abdo KM, Grumbein S, Chou BJ, et al. 2001. Toxicity and carcinogenicity study in F344 rats following 2 years of whole-body exposure to naphthalene vapors. Inhal Toxicol 13:931-950.

NTP. 1992a. Toxicology and carcinogenesis studies of naphthalene (CAS No. 91-20-3) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. National Toxicology Program. NIH Publication No. 92-3141. Technical report series no. 410.

NTP. 2000. Toxicology and carcinogenesis studies of naphthalene (CAS No. 91-20-3) in F344/N rats (inhalation studies). National Toxicology Program. NTP TR 500, NIH Publ. No. 01-4434.

Experimental design: NTP 1992a: Groups of 75 B6C3F1mice of each sex were exposed by inhalation at concentrations of 0, 10, or 30 ppm. Exposure occurred 5 times/week, 6 hours/day for 104 weeks.

Abdo et al. 2001; NTP 2000: Groups of 49 male and 49 female F344/N rats were exposed to naphthalene at concentrations of 0, 10, 30, or 60 ppm for 6 hours/day, 5 days/week for 105 weeks.

Effects noted in study and corresponding doses: In mice, exposure to 10 or 30 ppm of naphthalene resulted in inflammation of the nose (males: 0/70, 67/69, 133/135; females: 1/69, 65/65, 135/135) and lungs (males: 0/70, 21/69, 56/135; females: 3/69, 13/65, 52/135), metaplasia of the olfactory epithelium (males: 0/70, 66/69, 134/135; females: 0/69, 65/65, 135/135), and hyperplasia of the nasal respiratory epithelium (males: 0/70, 66/69, 134/135; females: 0/69, 65/65/ 135/135). Increased incidences of neoplastic lesions were restricted to the lung in females: alveolar/bronchiolar adenomas (5/69, 2/65, 28/135) and alveolar/bronchiolar carcinomas (0/69, 0/65, 1/135).

In rats, increased incidences of nonneoplastic and neoplastic lesions were restricted to the nose as shown in Table A-1.

Dose and end point used for MRL derivation: The lowest exposure level in both studies, 10 ppm, was a LOAEL in both sexes of both species for nonneoplastic lesions in nasal olfactory epithelium and respiratory epithelium. Applying EPA inhalation dosimetry (see below), a human equivalent LOAEL of 0.2 ppm, based on the rat LOAEL, was selected as the point of departure for the chronic inhalation MRL.

[ ] NOAEL [x] LOAEL

Modifying Factors used in MRL derivation: N/A

Table A-1. Nonneoplastic and Neoplastic Lesions of the Nose in Male and Female F344/N Rats Exposed to Naphthalene 6 Hours/Day, 5 Days/Week for 105 Weeks

	Concentration (ppm)							
	0		10		30		60	
Lesion	M	F	M	F	M	F	M	F
Nonneoplastic lesions								
Olfactory epithelium								
Hyperplasia	0/49	0/49	48/49	48/49	45/48	48/49	46/48	43/49
Atrophy	3/49	0/49	49/49	49/49	48/48	49/49	47/48	47/49
Chronic inflammation	0/49	0/49	49/49	47/49	48/48	47/49	48/48	45/49
Hyaline degeneration	3/49	13/49	46/49	46/49	40/48	49/49	38/48	45/49
Respiratory epithelium								
Hyperplasia	3/49	0/49	21/49	18/49	29/48	22/49	29/48	23/49
Squamous metaplasia	0/49	0/49	15/49	21/49	23/48	17/49	18/48)	15/49
Hyaline degeneration	0/49	8/49	20/49	33/49	19/48	34/49	19/48	28/49
Goblet cell hyperplasia	0/49	0/49	25/49	16/49	29/48	29/49	26/48	20/49
Gland hyperplasia	1/49	0/49	49/49	48/49	48/48	48/49	48/48	42/49
Gland squamous metaplasia	0/49	0/49	3/49	2/49	14/48	20/49	26/48	20/49
Neoplastic lesions								
Respiratory epithelial adenoma	0/49	0/49	6/49	0/49	8/48	4/49	15/48	2/49
Olfactory epithelial neuroblastoma	0/49	0/49	0/49	2/49	4/48	3/49	3/48	12/49

F = female; M = male

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor = 10x3x10=300

[x] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
10 ppm x 6 hours/24 hours x 5 days/7 days=1.8 ppm (duration-adjusted LOAEL for nasal effects in rats or mice)
1.8 ppm x 128.18/24.45=9.4 mg/m^3

Following EPA (1994d) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry,* equations for a category 1 gas producing nasal effects were used to derive human equivalent concentrations: HEC=Animal Concentration x $RGDR_{ET}$;

$RGDR_{ET}$= regional gas dose ratio in the extrathoracic (ET) region
= $(Dose_{ET})A/(Dose_{ET})H$= [minute volume/ETsurface area]$_A$÷[minute volume/ETsurface area]$_H$;

Reference minute volumes (L/min): 13.8 human, 0.137 rat, 0.0368 mouse;
Reference ET surface area (cm^2): 200 human, 15 rat, 3 mouse;

$RGDR_{ET}$(Rat to Human)=[0.137/15]÷[13.8/200]=0.132;
$LOAEL_{HEC}$=duration-adjusted LOAEL x 0.132=1.8 ppm x 0.132=0.2 ppm
$RGDR_{ET}$(Mouse to Human)=[0.0368/3]÷[13.8/200]=0.178;
$LOAEL_{HEC}$=duration-adjusted LOAEL x 0.132=1.8 ppm x 0.178=0.3 ppm

Using public health protection reasoning, the $LOAEL_{HEC}$ based on the rat data was selected as the point of departure for the chronic inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: Uncertainty in the MRL would likely be decreased with the development and application of hybrid computational fluid dynamics and physiologically based pharmacokinetic models that would estimate regional tissue doses of naphthalene metabolites in rats and humans. The models can incorporate species-specific information on nasal geometry, breathing patterns, and metabolism, as well as chemical-specific information on reactivity, partition coefficients, and diffusivity of the vapor in air and tissue. Such models have been developed for other gases that induce nasal lesions (see Frederick et al. 2001), but have not yet been developed for naphthalene.

Reactive naphthalene metabolites (1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene) have been proposed to be involved in naphthalene's toxic modes of action (Buckpitt et al. 2002). CYP isozymes, which might be involved in naphthalene metabolism and bioactivation, have been demonstrated to exist in nasal respiratory epithelial and olfactory epithelial tissue from rodents and humans (Thornton-Manning and Dahl 1997). Studies designed to specifically characterize metabolism of naphthalene in nasal tissue, however, have not been conducted (e.g., which CYP isozymes catalyze naphthalene transformations in nasal tissue?, are there species differences in nasal tissue efficiencies and capabilities for metabolism and/or bioactivation of naphthalene?), with the exception of a single study that examined *in vitro* rates of metabolism of naphthalene to naphthalene oxides in postmitochondrial supernatants from mouse, rat, and hamster olfactory tissue (Buckpitt et al. 1992). In this study, metabolic rates (units of nmol/min/mg protein)

showed the following order: mouse (87.1) > rat (43.5) > hamster (3.9). This order did not correspond with species differences in susceptibility to single intraperitoneal injections of naphthalene in a companion study (Plopper et al. 1992a). Rat nasal epithelial tissue (olfactory and respiratory epithelium) was more sensitive than tissue from mice and hamsters, which showed equivalent sensitivities.

Agency Contact (Chemical Manager): Moiz Mumtaz

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: September 5, 2003
Profile Status: Draft 3, pre-public
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.6 [x] mg/kg/day [ ] ppm

Reference: NTP. 1991a. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Research Triangle Park, NC: National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. TER91006.

Experimental design: Groups of 25–26 pregnant female Sprague-Dawley rats received doses of 0, 50, 150, and 450 mg/kg/day by gavage on gestation days 6–15. There were two replicate groups of 12–13 animals.

Effects noted in study and corresponding doses: Rat dams in exposed groups showed one or more of several clinical signs of toxicity (slow respiration, lethargy, or prone body posture) on the first day of dosing (81, 96, and 96% of rats in the 50-, 150-, and 450-mg/kg/day groups). By the third day of dosing, these signs did not occur in any of the 50-mg/kg/day rats. A similar trend was noted in the 150-mg/kg/day group, but apparent tolerance did not develop until the sixth day of dosing. In the 450-mg/kg/day group, the incidence of rats exhibiting these signs of toxicity also declined during the exposure period, but did not fall below 15%. With the development of "tolerance", the slow respiration, lethargy, and prone body posture were replaced with rooting behavior, a common behavior of rodents following gavage administration of chemicals with strong odors or irritant properties. At the end of the exposure period (gestation day 15), incidence of rats showing rooting behavior was 0% for the control and 50-mg/kg/day groups, compared with 24 and 92% of dams in the 150- and 450-mg/kg/day groups, respectively. Weight gain during exposure (gestation days 6–15) was similar between the control and 50-mg/kg/day group, but was decreased by 31 and 53% in the 150- and 450-mg/kg/day groups, compared with controls. From these results, 50 mg/kg/day was judged to be a minimal less serious LOAEL for transient clinical signs of maternal toxicity in pregnant rat dams. At higher doses (150 and 450 mg/kg/day), these effects were more persistent and were accompanied by decreased weight gain.

No statistically significant exposure-related effects were observed on the average number of corpora lutea per dam, implantation sites per litter, live fetuses per litter, or average fetal body weight. The percent of fetuses malformed per litter (4, 4, 7, and 10% for control through 450 mg/kg/day) and the percent of litters with malformed fetuses (23, 27, 33, and 50%) both showed a statistically significant trend test, but pairwise comparisons between individual exposure groups and the control were not statistically significant. The investigators concluded that naphthalene was not fetotoxic or teratogenic in this assay.

Dose and end point used for MRL derivation: A minimal LOAEL of 50 mg/kg/day for transient clinical signs of neurotoxicity in pregnant rat dams.

[x] NOAEL [ ] LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor= 3x10x3=90

[x] 3 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 3 for human variability

An uncertainty factor of 3 was selected for the use of a minimal LOAEL of 50 mg/kg/day. At this dose level, the only adverse effects observed in the pregnant rat dams were signs of neurotoxicity, which were only observed on the first 2 days of exposure.

An uncertainty factor of 10 was used for extrapolating from animals to humans.

An uncertainty factor of 3 was used for human variability because the critical effect is based on effects in a sensitive animal subpopulation. Pregnant rats appear to be more sensitive for the effects observed (clinical signs of neurotoxicity and decreased body weight gain) than nonpregnant rats. In 13-week gavage studies with nonpregnant rats (NTP 1980b), similar persistent neurologic symptoms were not observed following administration of doses as high as 200 mg/kg/day, but were observed at 400 mg/kg/day. In nonpregnant rats exposed for 13 weeks, significant body weight decreases occurred at 200 mg/kg/day throughout exposure, but not at 100 mg/kg/day (NTP 1980b) or in nonpregnant mice exposed for 13 weeks to 133 mg/kg/day (Shopp et al. 1984) or 200 mg/kg/day (NTP 1980a). Mice in the NTP (1980a) study showed transient signs of toxicity (lethargy, rough hair coats, and decreased food consumption), but these only occurred between weeks 3 and 5 in the 200-mg/kg/day group.

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: Neurologic symptoms similar to those observed in pregnant rats have been observed in humans following ingestion of naphthalene (at unknown, but presumably high dose levels). These include confusion (Ojwang et al. 1985) and listlessness and lethargy (Bregman 1954; Chusid and Fried 1955; Kurz 1987; Macgregor 1954; Zuelzer and Apt 1949), as well as decreased responses to painful stimuli and coma prior to death (Gupta et al. 1979; Kurz 1987). Persistent neurologic symptoms were not recorded in 13-week studies with rats or mice exposed to doses as high as 200 mg/kg/day (NTP 1980a, 1980b), but the highest exposure level tested in these studies, 400 mg/kg/day, produced lethargy in exposed rats (only rats were exposed to 400 mg/kg/day).

Hemolytic anemia has been identified in many human cases of acute accidental or intentional ingestion of naphthalene (e.g., Gidron and Leurer 1956; MacGregor 1954). Estimations of dose levels involved in these cases, however, are limited to a report (Gidron and Leurer 1956) of hemolytic anemia in a 16-year-old girl who swallowed 6 g of naphthalene (estimated dose=109 mg/kg, assuming body weight of 55 kg). Laboratory animals do not appear to be susceptible to the hemolytic activity of naphthalene. No pronounced changes in red-cell-related hematologic parameters were observed following 13-week oral exposures to doses up to 200 mg/kg/day in mice (NTP 1980a) and 400 mg/kg/day in rats (NTP 1980b), or in mice exposed by inhalation for 14 days to air concentrations as high as 30 ppm (NTP 1992a). Naphthalene-induced hemolytic anemia has been observed in dogs exposed to a single dose of 1,525 mg/kg or 263 mg/kg/day for 7 days (Zuelzer and Apt 1949), but more information on the dose-

response relationship for hemolytic anemia in humans or animals acutely exposed to naphthalene is not available.

Another effect associated with acute or repeated oral exposure to naphthalene in animals is cataracts (Kojima 1992; Murano et al. 1993; Van Heyningen and Pirie 1976; Xu et al. 1992b). These effects, however, appear to occur at dose levels (in the range of 500–1,000 mg/kg/day) much higher than the lowest dose level (150 mg/kg/day) producing body weight gain decreases and signs of neurotoxicity in pregnant rats.

Agency Contact (Chemical Manager): Moiz Mumtaz

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: September 5 2003
Profile Status: Draft 3, pre-public
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.6 [x] mg/kg/day [ ] ppm

Reference: NTP. 1991a. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Research Triangle Park, NC: National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. TER91006.

Experimental design: See the worksheet for the acute-duration oral MRL.

Effects noted in study and corresponding doses: See the worksheet for the acute-duration oral MRL.

Dose and end point used for MRL derivation: A minimal LOAEL of 50 mg/kg/day for transient clinical signs of neurotoxicity in pregnant rat dams.

[] NOAEL [x] minimal LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor =3x10x3=90

[x] 3 for use of a minimal LOAEL
[x] 10 for extrapolation from animals to humans
[x] 3 for human variability

See the worksheet for the acute-duration oral MRL for explanations of the uncertainty factors.

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL:

There are three intermediate-duration oral toxicity studies in laboratory animals that were considered for deriving the intermediate oral MRL for naphthalene. A 13-week comprehensive oral toxicity study in Fischer 344 rats found no adverse exposure related effects other than decreased body weight (NTP 1980b). This study identified 100 mg/kg/day as a NOAEL and 200 mg/kg/day as a LOAEL for decreased body weight in male and female rats. Another 13-week comprehensive oral toxicity study in B6C3F1 mice found no adverse effects in mice exposed to doses as high as 200 mg/kg/day (NTP 1980a). Another 90-day gavage study in mice focused on immune system variables and other toxicity variables (e.g., body

weight, organ weight, haematological parameters) and identified 133 mg/kg/day as a LOAEL and 53 mg/kg/day as a NOAEL for weight decreases in several organs (brain, liver, and spleen), but found no biologically significant exposure-related changes in other end points evaluated (Shopp et al. 1984). This study, however, did not include histopathological examination of tissues.

More detailed descriptions of the intermediate-duration oral toxicity studies follow. After the description of the studies, an analysis of their usefulness for MRL derivation is presented.

NTP. 1980b. Subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.

Naphthalene (>99% pure) in corn oil was administered by gavage to groups of 10 male and 10 female Fischer 344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg/day, 5 days/week for 13 weeks (NTP 1980b). End points included weekly measurement of food consumption and body weight, twice daily observation for clinical signs of toxicity, measurement of hematological parameters for blood collected at termination (hemoglobin, hematocrit, total and differential white blood cell count, red blood cell count, mean cell volume, mean cell hemoglobin concentration), necropsy of all rats in the study, and complete histopathological examination of 27 organs and tissues (including the eyes, lungs, stomach, liver, reproductive organs, thymus, and kidneys) from all control and 400-mg/kg rats. Male kidneys and female thymuses from the 200-mg/kg group were also examined histopathologically (according to the histopathology tables; however, the report text states that the 100 mg/kg group was examined). Organ weight data were not reported.

At the highest dose level, two male rats died during the last week of treatment, and rats of both sexes displayed diarrhea, lethargy, hunched posture, and rough coats at intermittent intervals throughout the study. Food consumption was not affected by exposure. Mean terminal body weights were decreased by more than 10% relative to the controls in several groups (28 and 12% decrease in the 400- and 200-mg/kg males, respectively and 23% decrease in 400-mg/kg females). The terminal body weights at 13 weeks' exposure were 250.6, 306.7, 333.4, 351.2, 353.4, and 348.9 g for males and 156.7, 190.5, 197.2, 203.5, 197.8, and 203.4 g for females for the 400, 200, 100, 50, 25, and 0 dose groups, respectively. Differences between mean values of hematological parameters in exposed groups and those in control groups were <10% of control values, except for a 94% increase in numbers of mature neutrophils and a 25.1% decrease in numbers of lymphocytes in male 400 mg/kg rats and a 37.2% increase in mature neutrophils in 400 mg/kg females. Due to a lack of a consistent pattern of change in the hematologic parameters, the observed changes are not considered adverse. Histological examinations revealed low incidences of lesions in exposed male kidneys and exposed female thymuses; no lesions were observed in respective control kidneys or thymuses. Focal cortical lymphocytic infiltration or focal tubular regeneration were observed in kidneys in 2/10 male rats exposed to 200 mg/kg naphthalene, and diffuse renal tubular degeneration occurred in 1/10 male rats exposed to 400 mg/kg naphthalene. Lymphoid depletion of the thymus occurred in 2/10 females exposed to 400 mg/kg naphthalene, but not in any other females or in males. No other tissue lesions were detected. In this study, 100 mg/kg/day was a NOAEL, 200 mg/kg/day was a LOAEL, and 400 mg/kg/day was a serious LOAEL for decreased body weight in rats orally exposed to naphthalene for 13 weeks.

NTP. 1980a. Subchronic toxicity study: Naphthalene (C52904), B6C3F1 mice. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.

Ten male and 10 female B6C3F1 mice were administered gavage doses of naphthalene in corn oil at levels of 0, 12.5, 25, 50, 100, or 200 mg/kg, 5 days/week for 13 weeks (NTP 1980a). Seven mice (three males and two females of the 200 mg/kg group, one female of the 25 mg/kg group, and one control male) died during the second, third, and fourth weeks from gavage trauma or accident. Transient signs of

toxicity (lethargy, rough hair coats, and decreased food consumption) occurred between weeks 3 and 5 in the 200-mg/kg groups. Due to their transient nature, these effects are not considered to be adverse. All exposed male mice gained more weight during the study than did control males (weight gains expressed as a percentage of control weight gain were 154.3, 116.0, 125.9, 122.2, and 107.4 for the 12.5–200 mg/kg groups, respectively). In contrast, exposed female mice displayed decreased weight gain compared with controls (weight gains expressed as a percentage of control weight gain were 97.5, 81.5, 81.5, 77.8, and 76.5% for the 12.5–200 mg/kg groups, respectively). The average change in body weight between day 0 and the 13th week was 6.2 g/mouse for the 200-mg/kg female mice compared with 8.1 g/mouse for the control females. The investigators believed that a difference in weight gain of 1.9 g over a 13-week period "was not large enough to conclusively indicate a toxic effect." Respective mean terminal body weights (g) for control through the 200-mg/kg group were: 33.2, 37.7, 34.7, 34.7, 36.0, and 34.7 for males, and 26.7, 26.8, 25.4, 26.0, 26.1, and 25.6 for females. Mean terminal body weight values in exposed females were ≥95% of control values.

All mice were necropsied, and 27 organs (including the eyes, thymus, reproductive organs, and lungs) from the mice in the control and high-dose groups were examined histologically. No exposure-related lesions were observed in any organs. The highest incidence of lesions observed was for minimal to mild, focal or multifocal, subacute pneumonia in both controls (4/10 males and 2/10 females) and high-dose mice (4/10 males and 5/10 females). Organ weight data were not reported. Hematological analyses were performed on all groups. Exposed groups displayed mean values that were within 10% of the control means for the following parameters: hemoglobin, hematocrit, total white blood cells, and total red blood cells. An increase in lymphocytes (18% increase) and a decrease in segmented neutrophils (38.8% decrease) in high-dose males were not considered biologically significant by the authors. The highest dose in this study, 200 mg/kg/day, is judged to be a NOAEL for nonneoplastic lesions, hematologic changes, and adverse neurologic symptoms.

Shopp GM, White KL JR, Holsapple MP, et al. 1984. Naphthalene toxicity in CD-1 mice: General toxicology and immunotoxicology. Fundam Appl Toxicol 4:406-419.

Groups of male and female albino CD-1 mice (approximately 6 weeks old at the start) were administered gavage doses of 0, 5.3, 53, or 133 mg/kg naphthalene (99.3% pure) in corn oil for 90 consecutive days (Shopp et al. 1984). A naive control group and the 5.3 and 53 mg/kg dose groups each contained 76 male mice and 40 female mice. The vehicle control group contained 112 male mice and 76 female mice. The high-dose group contained 96 male mice and 60 female mice. Statistical analysis consisted of a one-way analysis of variance of means and Dunnett's t-test to compare control and treatment means using a significance level of $p<0.05$. Statistically significant chemical-related decreases in terminal body weights or survival were not observed in either sex. Respective mean terminal body weight values were (naïve, vehicle, 5.3, 53, and 133 mg/kg/day groups): 39.3, 37.3, 37.2, 36.2, and 36.8 g for male mice and 29.2, 29.0, 27.9, 27.0, and 27.1 g for female mice. No significant alterations in absolute or relative organ weights occurred in exposed male mice. Significant decreases in absolute weights of brain (9%), liver (18%), and spleen (28%) and relative weight of spleen (24%) occurred in high-dose females compared with controls. Histopathological examination of organs was not conducted, but the authors noted that cataracts were not formed in exposed mice (methods used to assess the presence of cataracts were not specified).

Examination of hematological parameters (including numbers of leucocytes, erythrocytes, and platelets and determination of hematocrit and hemoglobin) at termination revealed only slight, but statistically significant, increases in hemoglobin in high-dose females only; however, the hematological data were not shown in the available report. Chemical analysis of serum showed statistically significant decreased blood urea nitrogen in all exposed female groups. Compared with vehicle controls, the percent decreases in BUN were 16, 20, and 34% for the 5.3, 53, and 133 mg/kg/day groups, respectively. Increased serum

globulin (about 55%) and protein (about 40%) occurred in the two highest female dose groups compared with vehicle control values. Hepatic microsomal activities of aniline hydroxylase and aminopyrine N-demethylases were not statistically significantly changed in exposed versus control mice, but benzo[a]pyrene hydroxylase activities were statistically significantly decreased in exposed groups compared with control values (0.8, 0.62*, 0.55* and 0.41* nmol/min/mg protein for males in the control through high-dose group, and 1.40, 1.24, 1.13*, and 0.89* nmol/min/mg protein for females; statistically significant differences from control noted with *). The toxicological significance of the statistically significant changes in hematological parameters, hepatic enzyme activities, and serum chemical parameters is not clear, and these changes are not considered to be adverse.

No exposure-related responses were found in a battery of immunological assays (humoral immune response, lymphocyte responsiveness, delayed-type hypersensitivity response, popliteal lymph node response, and bone marrow function); immunotoxic responses were observed in positive controls given intraperitoneal injections of 50 mg/kg cyclophosphamide on days 87, 88, 89, and 90. The study identified a LOAEL of 133 mg/kg/day and a NOAEL of 53 mg/kg/day for statistically significant decreases in absolute weight of brain, liver, and spleen and relative weight of spleen in female mice, but not male mice. The biological significance of these changes, however, is uncertain because the effects were only observed in female mice, and histological changes in these organs were not observed in Fischer 344 rats (NTP 1980b) or B6C3F1 mice (NTP 1980a) exposed to naphthalene for 13 weeks.

Intermediate-Duration Oral MRL Derivation Considerations

The findings from the three intermediate-duration oral toxicity studies (one in rats and two in mice) do not collectively identify a clear, biologically significant, toxicity target other than body weight changes in rats. Consideration was given to basing the MRL on the NOAEL of 53 mg/kg/day and LOAEL of 133 mg/kg/day for decreases in absolute weight of brain, liver, and spleen, and in relative weight of spleen, in female mice (Shopp et al. 1984). However, the biological significance of these effects is uncertain because (1) small changes in organ weights are difficult to consistently measure in mice; (2) the effects were only observed in females; and (3) histological effects in the affected organs were not observed in the other 13-week oral studies with rats and mice. The biological significance of these effects in female, but not male, mice was less clearly biologically significant than the naphthalene-induced body weight changes observed in male and female rats.

In deriving a potential intermediate-duration MRL, the NOAEL of 100 mg/kg/day for decreased body weight in male and female rats should be adjusted to a continuous duration dose (100x5 days/7 days=71 mg/kg/day). The use of this adjusted dose and a total uncertainty factor of 100 (10 for extrapolating from rats to humans and 10 for human variability) arrives at a potential intermediate-duration oral MRL of 0.7 mg/kg/day, which is slightly larger than the acute-duration oral MRL for naphthalene, 0.6 mg/kg/day. Thus, the acute-duration oral MRL of 0.6 mg/kg/day is expected to be protective for intermediate-duration exposure scenarios and was adopted as the intermediate-duration oral MRL.

Agency Contact (Chemical Manager): Moiz Mumtaz

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Methylnaphthalene
CAS Number: 91-20-3
Date: September 5, 2003
Profile Status: Draft 3, pre-public
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 0.07 [x] mg/kg/day [ ] ppm

Reference: Murata Y, Denda A, Maruyama H, et al. 1993. Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol 21:44-51.

Experimental design: Groups of 50 B6C3F1 mice ingested the following doses (in mg/kg/day) over an 81-week period: 0 (M/F), 71.6 (M), 75.1 (F), 140.2 (M), and 143.7 (F). Tissues were examined histologically: brain, salivary glands, heart, thymus, lung, liver, pancreas, spleen, kidneys, testis, adrenals, trachea, stomach, small intestine, seminal vesicle, ovary, uterus, vagina, mammary gland, skeletal muscle, eye, Harderian glands, spinal cord, bone, and skin.

Effects noted in study and corresponding doses: Exposure-related lesions were restricted to the lung. Incidences for pulmonary alveolar proteinosis were (control through high-dose groups): 5/50, 23/50, and 17/49 for females and 4/49, 23/50, and 19/50 for males.

The only other exposure-related lesions found were lung tumors. Incidences for mice with adenomas were 4/50, 2/50, and 4/49 in females, and 2/49, 13/50, and 12/50 for males. Combined incidences for mice with lung adenomas or adenocarcinomas were: 5/50, 2/50, and 5/50 for females, and 2/49, 13/50, and 15/50 for males.

Dose and end point used for MRL derivation: A LOAEL of 71.6 mg/kg/day for an increased incidence in alveolar proteinosis in males.

[ ] NOAEL [x] LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor=10x10x10=1,000

[x] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? If so, explain: Groups of 50 male and 50 female B6C3F1 mice were fed 0, 0.075, or 0.15% 1-methylnaphthalene (1-MN) in their diet for 81 weeks (567 days). Cumulative dose equivalents were provided by the investigators included: males: 0.075%=40,600 mg 1-MN/kg/body weight/567 days=71.6 mg/kg/day; 0.15%=79,500 mg 1-MN/kg/body weight/567 days=140.2 mg/kg/day; females: 0.075%=42,600 mg 1-MN/kg body weight/567 days=75.1 mg/kg/day; 0.15%=81,500 mg 1-MN/kg body weight/567 days=143.7 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: Increased incidence of pulmonary alveolar proteinosis has also been reported in B6C3F1 mice exposed to 2-methylnaphthalene in the diet for 81 weeks at dose levels of 50–54 and 108–114 mg/kg/day (Murata et al. 1997), and in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (a mixture of 1- and 2-methylnaphthalene) (Emi and Konishi 1985; Murata et al. 1992).

Agency Contact (Chemical Manager): Moiz Mumtaz

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2-Methylnaphthalene
CAS Number: 91-20-3
Date: September 5, 2003
Profile Status: Draft 3, pre-public
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 47
Species: Mouse

Minimal Risk Level: 0.05 [x] mg/kg/day [ ] ppm

Reference: Murata Y, Denda A, Maruyama H, et al. 1997. Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol 36(1):90-93.

Experimental design: Groups of 50 male and 50 female B6C3F1 mice were exposed to dietary levels of 0, 0.075, or 0.15% 2-MN for 81 weeks. Average intakes were reported as 0, 54.3, or 113.8 mg/kg/day for males and 0, 50.3, or 107.6 mg/kg/day for females.

Effects noted in study and corresponding doses: Survival and food consumption were not affected by exposure. Mean final body weights were decreased by 7.5 and 4.5% in high-dose males and females, respectively; these changes are not considered to be biologically significant. Histopathology only found exposure-related changes in the lung. Tissues examined were brain, heart, kidney, liver, lung, pancreas, salivary glands, spleen, testis, adrenals, bone, eye, Harderian glands, mammary gland, ovary, seminal vesicle, skeletal muscle, skin, small and large intestine, spinal cord, stomach, trachea, uterus, and vagina. No evidence of bronchiolar Clara cell necrosis or sloughing was found. Females showed statistically significantly decreased differential counts of stab and segmented form neutrophils and increased lymphocytes compared to controls, but biological significance of these changes is not clear due to a lack of reporting of the data (i.e., the report did not specify the response magnitudes or the dose levels at which they occurred).

Incidences for mice with pulmonary alveolar proteinosis were (control through high-dose groups): 5/50, 27/49, and 22/49 for females, and 4/49, 21/49, and 23/49 for males.

Incidences for mice with lung adenomas were: 4/50, 4/49, and 5/48 in females, and 2/49, 9/49, and 5/49 in males. Only the incidence in the male 54.3-mg/kg/day groups was significantly different from the control incidence. Combined incidences for lung adenomas or adenocarcinomas were: 5/50, 4/49, and 6/48 for females, and 2/49, 10/49, and 6/49 for males.

Dose and end point used for MRL derivation: LOAEL of 50.3 mg/kg/day for pulmonary alveolar proteinosis in female mice.

[ ] NOAEL [x] LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor=10x10x10=1,000

[x] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: Increased incidence of pulmonary alveolar proteinosis has also been reported in B6C3F1 mice exposed to 1-methylnaphthalene in the diet for 81 weeks at dose levels as low as 71.6 mg/kg/day (Murata et al. 1993), and in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (a mixture of 1- and 2-methylnaphthalene) (Emi and Konishi 1985; Murata et al. 1992).

In a range-finding study, groups of B6C3F1 mice (10/sex/group) were fed diets containing 2-methylnaphthalene for 13 weeks delivering approximate average daily doses of 0, 31, 92, 276, 827, or 2,500 mg/kg/day (Murata et al. 1997). No histopathologic lesions were found in tissues and organs of male or female mice exposed to 827 or 2,500 mg/kg-day; tissues from mice in lower dose groups were not examined histologically. Decreased body weights, compared with control values, were seen at the three highest dose levels in both males and females, and were attributed to food refusal (Murata et al. 1997). The absence of pulmonary alveolar proteinosis in the prechronically exposed mice, which were exposed to much higher doses than those experienced by mice with this lesion in the chronic study, suggests that the development of pulmonary alveolar proteinosis from oral exposure to 2-methylnaphthalene requires chronic-duration exposure. The limited reporting of experimental details and results from this intermediate-duration study, however, precludes its use as the basis of an intermediate oral MRL for 2-methylnaphthalene.

Agency Contact (Chemical Manager): Moiz Mumtaz

APPENDIX A

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

TABLE 3-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

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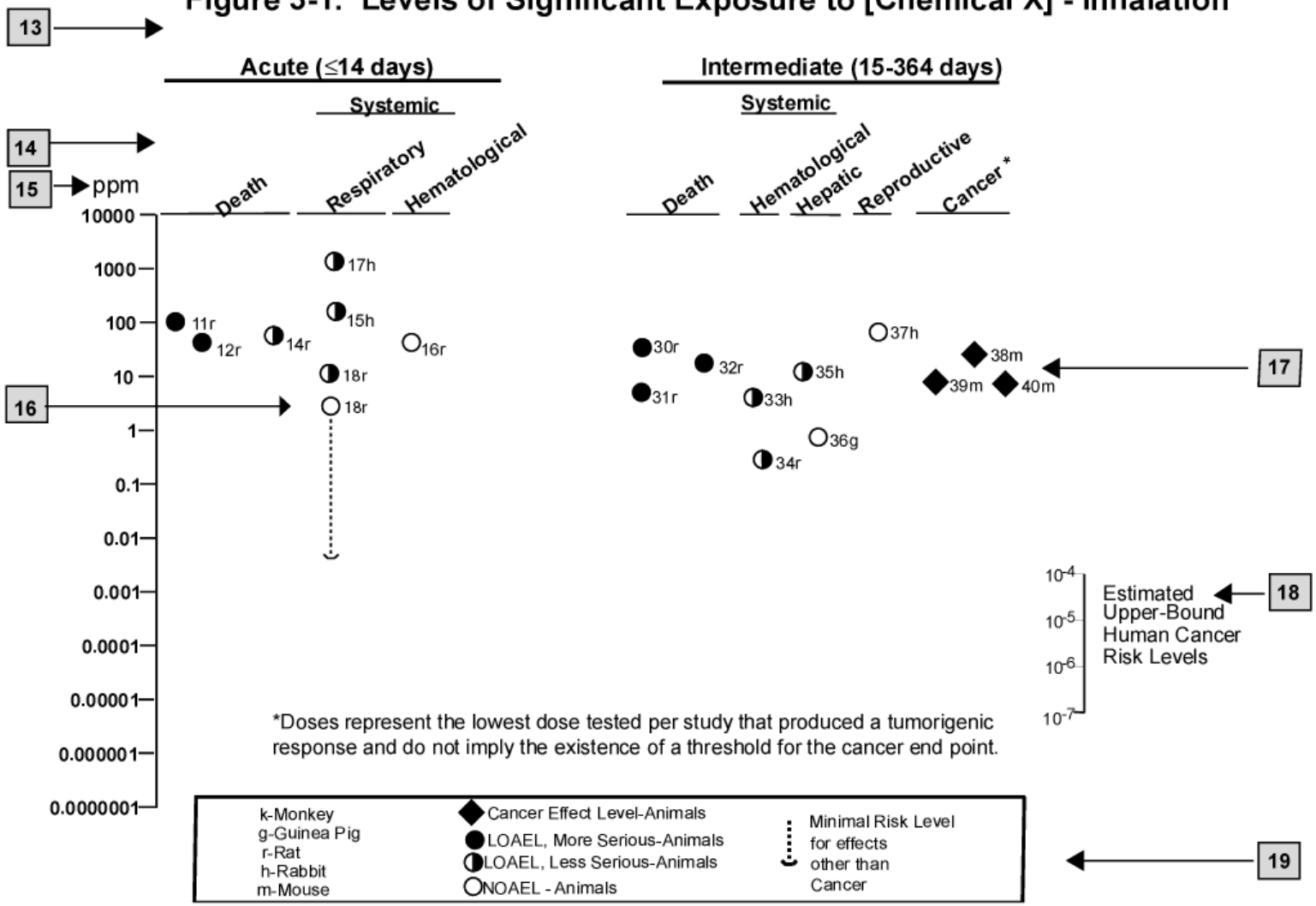
[a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection

ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury

mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector

pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result