

**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, Draft for Public Comment was released in September 2003. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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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.

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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.


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*Legislative Background

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 November 7, 2003 (68 FR 63098). 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); October 21, 1999 (64 FR 56792) and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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

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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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • 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.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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-methylnaphthalene'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.

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.

CONTENTS

DISCLAIMER	ii
UPDATE STATEMENT	iii
FOREWORD	v
QUICK REFERENCE FOR HEALTH CARE PROVIDERS.....	vii
CONTRIBUTORS	ix
PEER REVIEW	xi
CONTENTS.....	xiii
LIST OF FIGURES	xvii
LIST OF TABLES	xix
1. PUBLIC HEALTH STATEMENT.....	1
1.1 WHAT ARE NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE?	1
1.2 WHAT HAPPENS TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE WHEN THEY ENTER THE ENVIRONMENT?.....	2
1.3 HOW MIGHT I BE EXPOSED TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE?	4
1.4 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE ENTER AND LEAVE MY BODY?.....	5
1.5 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE AFFECT MY HEALTH?.....	6
1.6 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE AFFECT CHILDREN?	8
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE?	9
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE?	9
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	10
1.10 WHERE CAN I GET MORE INFORMATION?	11
2. RELEVANCE TO PUBLIC HEALTH	13
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE IN THE UNITED STATES.....	13
2.2 SUMMARY OF HEALTH EFFECTS	14
2.3 MINIMAL RISK LEVELS (MRLs)	21
3. HEALTH EFFECTS	27
3.1 INTRODUCTION	27
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	27
3.2.1 Inhalation Exposure	28
3.2.1.1 Death	28
3.2.1.2 Systemic Effects	29
3.2.1.3 Immunological and Lymphoreticular Effects	43

3.2.1.4	Neurological Effects	43
3.2.1.5	Reproductive Effects	44
3.2.1.6	Developmental Effects	44
3.2.1.7	Cancer	44
3.2.2	Oral Exposure.....	46
3.2.2.1	Death	46
3.2.2.2	Systemic Effects	47
3.2.2.3	Immunological and Lymphoreticular Effects.....	72
3.2.2.4	Neurological Effects	74
3.2.2.5	Reproductive Effects	75
3.2.2.6	Developmental Effects	76
3.2.2.7	Cancer.....	77
3.2.3	Dermal Exposure.....	78
3.2.3.1	Death	78
3.2.3.2	Systemic Effects	78
3.2.3.3	Immunological and Lymphoreticular Effects.....	84
3.2.3.4	Neurological Effects	85
3.2.3.5	Reproductive Effects	85
3.2.3.6	Developmental Effects	85
3.2.3.7	Cancer.....	85
3.3	GENOTOXICITY	85
3.4	TOXICOKINETICS	91
3.4.1	Absorption.....	93
3.4.1.1	Inhalation Exposure.....	93
3.4.1.2	Oral Exposure.....	93
3.4.1.3	Dermal Exposure.....	94
3.4.2	Distribution	95
3.4.2.1	Inhalation Exposure.....	95
3.4.2.2	Oral Exposure.....	96
3.4.2.3	Dermal Exposure.....	97
3.4.2.4	Other Routes of Exposure	97
3.4.3	Metabolism.....	98
3.4.4	Elimination and Excretion.....	105
3.4.4.1	Inhalation Exposure.....	105
3.4.4.2	Oral Exposure.....	105
3.4.4.3	Dermal Exposure.....	107
3.4.4.4	Other Routes of Exposure	107
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	108
3.5	MECHANISMS OF ACTION	112
3.5.1	Pharmacokinetic Mechanisms.....	112
3.5.2	Mechanisms of Toxicity.....	114
3.5.3	Animal-to-Human Extrapolations	123
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	124
3.7	CHILDREN'S SUSCEPTIBILITY	125
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	129
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene.....	130
3.8.2	Biomarkers Used to Characterize Effects Caused by Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene.....	132
3.9	INTERACTIONS WITH OTHER CHEMICALS	132
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	133

3.11	METHODS FOR REDUCING TOXIC EFFECTS.....	135
3.11.1	Reducing Peak Absorption Following Exposure	135
3.11.2	Reducing Body Burden.....	136
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	136
3.12	ADEQUACY OF THE DATABASE.....	137
3.12.1	Existing Information on Health Effects of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene	137
3.12.2	Identification of Data Needs	141
3.12.3	Ongoing Studies.....	156
4.	CHEMICAL AND PHYSICAL INFORMATION.....	159
4.1	CHEMICAL IDENTITY.....	159
4.2	PHYSICAL AND CHEMICAL PROPERTIES.....	159
5.	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL.....	163
5.1	PRODUCTION	163
5.2	IMPORT/EXPORT	166
5.3	USE.....	166
5.4	DISPOSAL.....	167
6.	POTENTIAL FOR HUMAN EXPOSURE	169
6.1	OVERVIEW	169
6.2	RELEASES TO THE ENVIRONMENT	173
6.2.1	Air	174
6.2.2	Water.....	177
6.2.3	Soil	178
6.3	ENVIRONMENTAL FATE.....	179
6.3.1	Transport and Partitioning.....	179
6.3.2	Transformation and Degradation	180
6.3.2.1	Air.....	180
6.3.2.2	Water	181
6.3.2.3	Sediment and Soil.....	182
6.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	183
6.4.1	Air	184
6.4.2	Water.....	186
6.4.3	Sediment and Soil	187
6.4.4	Other Environmental Media.....	188
6.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	190
6.6	EXPOSURES OF CHILDREN	193
6.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	195
6.8	ADEQUACY OF THE DATABASE.....	195
6.8.1	Identification of Data Needs	195
6.8.2	Ongoing Studies	199
7.	ANALYTICAL METHODS	203
7.1	BIOLOGICAL MATERIALS	203
7.2	ENVIRONMENTAL SAMPLES.....	204
7.3	ADEQUACY OF THE DATABASE.....	209
7.3.1	Identification of Data Needs	210
7.3.2	Ongoing Studies	211

8. REGULATIONS AND ADVISORIES	213
9. REFERENCES	219
10. GLOSSARY	285
APPENDICES	
A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS	A-1
B. USER'S GUIDE	B-1
C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS.....	C-1
D. INDEX	D-1

LIST OF FIGURES

3-1. Levels of Significant Exposure to Naphthalene (Nap) or Methylnaphthalene (1-Mn or 2-Mn)— Inhalation.....	37
3-2. Levels of Significant Exposure to Naphthalene (Nap) or Methylnaphthalene (1-Mn or 2-Mn)— Oral.....	61
3-3. Scheme for Naphthalene Metabolism and Formation of Multiple Reactive Metabolites, That May Be Involved in Naphthalene Toxicity	99
3-4. Metabolism of 2-Methylnaphthalene.....	103
3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	110
3-6. Existing Information on Health Effects of Naphthalene	138
3-7. Existing Information on Health Effects of 1-Methylnaphthalene.....	139
3-8. Existing Information on Health Effects of 2-Methylnaphthalene.....	140
6-1. Frequency of NPL Sites with Naphthalene Contamination.....	170
6-2. Frequency of NPL Sites with 1-Methylnaphthalene Contamination.....	171
6-3. Frequency of NPL Sites with 2-Methylnaphthalene Contamination.....	172

LIST OF TABLES

3-1. Levels of Significant Exposure to Naphthalene (Nap) or Methylnaphthalene (1-Mn or 2-Mn)— Inhalation.....	30
3-2. Levels of Significant Exposure to Naphthalene (Nap) or Methylnaphthalene (1-Mn or 2-Mn)— Oral.....	48
3-3. Levels of Significant Exposure to Naphthalene (Nap) or Methylnaphthalene (1-Mn or 2-Mn)— Dermal.....	79
3-4. Results of Genotoxicity Testing of Naphthalene or Metabolites.....	86
3-5. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene <i>In Vitro</i>	92
4-1. Chemical Identity of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene	160
4-2. Physical and Chemical Properties of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene	161
5-1. Facilities that Produce, Process, or Use Naphthalene.....	164
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Naphthalene	175
6-2. Ongoing Studies on the Potential for Human Exposure to Naphthalene.....	200
7-1. Analytical Methods for Determining Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene in Biological Samples	205
7-2. Analytical Methods for Determining Naphthalene in Environmental Samples	206
7-3. Analytical Methods for Determining 2-Methylnaphthalene in Environmental Samples	208
8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methyl- naphthalene	215

1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have been found in at least 654, 36, and 412, respectively, of the 1,662 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that the number of sites at which naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene, many factors will determine whether you will 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 any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

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

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

1. PUBLIC HEALTH STATEMENT

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 methyl-naphthalene. 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 methyl-naphthalene. 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

1. PUBLIC HEALTH STATEMENT

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.

1. PUBLIC HEALTH STATEMENT

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

1.3 HOW MIGHT I BE EXPOSED TO NAPHTHALENE, 1-METHYLNAPHTHALENE, 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.

1. PUBLIC HEALTH STATEMENT

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-methylnaphthalene, or 2-methylnaphthalene.

1.4 HOW CAN NAPHTHALENE, 1-METHYLNAPHTHALENE, AND 2-METHYLNAPHTHALENE 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, or 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, 1-methylnaphthalene, or 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.

1. PUBLIC HEALTH STATEMENT

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

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

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

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.

1. PUBLIC HEALTH STATEMENT

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. Under the EPA 1986 cancer guidelines, naphthalene was assigned to Group C – possible human carcinogen.

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.

1. PUBLIC HEALTH STATEMENT

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

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

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

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. PUBLIC HEALTH STATEMENT

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

If your doctor finds that you have been exposed to substantial amounts of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, ask whether your children might also have been 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-methylnaphthalene, 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-METHYLNAPHTHALENE?

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-methylnaphthalene, 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.

1. PUBLIC HEALTH STATEMENT

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

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

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically 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 over an 8-hour workday. NIOSH set a limit of 500 ppm for the level of naphthalene in workplace air expected to be immediately

1. PUBLIC HEALTH STATEMENT

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.

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 that result 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 toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

1. PUBLIC HEALTH STATEMENT

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological 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. 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 2002, environmental releases of naphthalene reported under the EPA Toxics Release Inventory (TRI) program were about 2.07 million pounds in air emissions, 0.03 million pounds in surface water discharges, 0.23 million pounds in underground injection discharges, and 0.37 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 $\mu\text{g}/\text{m}^3$, with a median naphthalene concentration of 0.94 $\mu\text{g}/\text{m}^3$ (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 $\mu\text{g}/\text{m}^3$ (0.00008–0.0009 ppm). In indoor air, emissions

2. RELEVANCE TO PUBLIC HEALTH

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 $2.2 \mu\text{g}/\text{m}^3$ (0.0004 ppm) and $1.0 \mu\text{g}/\text{m}^3$ (0.0002 ppm), respectively. A study of indoor and outdoor air in 24 low-income homes in North Carolina found naphthalene levels ranging from $0.33\text{--}9.7 \mu\text{g}/\text{m}^3$ and $0.57\text{--}1.82 \mu\text{g}/\text{m}^3$ respectively. Methyl naphthalenes have also been detected in ambient outdoor and indoor air. For example, average concentrations of 1-methyl naphthalene and 2-methyl naphthalene in ambient outdoor air samples were reported to be 0.51 and $0.065 \mu\text{g}/\text{m}^3$, respectively, whereas 2-methyl naphthalene in indoor air samples showed an average concentration of $1.5 \mu\text{g}/\text{m}^3$ (0.0003 ppm). Based on a median concentration of $0.95 \mu\text{g}/\text{m}^3$ (0.0002 ppm) naphthalene in urban and suburban air samples and an inhalation rate of $20 \text{ m}^3/\text{day}$, the average daily intake of naphthalene from ambient air is estimated at $19 \mu\text{g}/\text{day}$, or $0.3 \mu\text{g}/\text{kg}/\text{day}$ assuming 70-kg body weight.

Levels of naphthalene (and methyl naphthalenes), when detected in water, sediments, and soil tend to be low: usually $<10 \mu\text{g}/\text{L}$ in surface water or groundwater, $<500 \mu\text{g}/\text{kg}$ in sediments, and $0\text{--}3 \mu\text{g}/\text{kg}$ 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 $2.9 \text{ mg}/\text{kg}$ were reported for naphthalene and methyl naphthalene, 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

2. RELEVANCE TO PUBLIC HEALTH

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 (lethargy and prone position) and severe 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

2. RELEVANCE TO PUBLIC HEALTH

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 in the NTP studies 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

2. RELEVANCE TO PUBLIC HEALTH

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 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 in the respiratory tract of rodents 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-tetrahydronaphthalene (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 nonneoplastic 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

2. RELEVANCE TO PUBLIC HEALTH

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. To date, mechanistic understanding of species differences in naphthalene bioactivation in the respiratory tissues is too incomplete to definitively rule out the possible human relevance of naphthalene-induced nasal lesions in rodents (nonneoplastic lesions in rats and mice and neoplastic lesions in rats; see Section 3.5).

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-naphthoquinone; 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-naphthoquinone; 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;

2. RELEVANCE TO PUBLIC HEALTH

(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 *11th Report on Carcinogens* includes naphthalene in its list of chemicals *reasonably anticipated to be human carcinogen*.

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 (1998c) *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 1986e cancer guidelines, naphthalene was assigned to Group C—*possible human carcinogen*. Under the EPA 1996a 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-methyl-

2. RELEVANCE TO PUBLIC HEALTH

naphthalene 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

2. RELEVANCE TO PUBLIC HEALTH

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 *11th 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 concluded that the available data for 2-methylnaphthalene are *inadequate to assess human carcinogenic potential*, noting that there are no human data and the available evidence of 2-methylnaphthalene in animals is limited and insufficient to determine that 2-methylnaphthalene is carcinogenic to humans.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (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 1990), 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.

Inhalation MRLs

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

2. RELEVANCE TO PUBLIC HEALTH

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 (3×10^{-3} mg/m³).

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-methylnaphthalene.

Oral MRLs

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

2. RELEVANCE TO PUBLIC HEALTH

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 the transient nature of these observations 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 toxicity. At 150 and 450 mg/kg/day, clinical signs of toxicity were more persistent and were accompanied with severe 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 toxicity 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 clinical signs 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

2. RELEVANCE TO PUBLIC HEALTH

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.

2. RELEVANCE TO PUBLIC HEALTH

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 pulmonary alveolar proteinosis in female mice was used for the derivation of the MRL (see Appendix A), 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 0.04 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

2. RELEVANCE TO PUBLIC HEALTH

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 lower 95% confidence limit on a benchmark dose associated with 5% extra risk for pulmonary alveolar proteinosis in male mice (4 mg/kg/day) was selected as the point of departure for deriving the chronic-duration oral MRL for 2-methylnaphthalene (see Appendix A). A benchmark response of 5% extra risk was selected over a default value of 10% extra risk in order to provide protection for children who may develop pulmonary alveolar proteinosis. This selection is supported by reports that children with pulmonary alveolar proteinosis (albeit of unknown etiology) experience more severe symptoms of respiratory dysfunction than do adults (EPA 2003r; Mazzone et al. 2001). The point of departure was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive the chronic oral MRL of 0.04 mg/kg/day for 2-methylnaphthalene.

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

3. HEALTH EFFECTS

"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.

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.

3. HEALTH EFFECTS

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; Long et al. 2003; 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

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Systemic							
1	Rat (Sprague- Dawley)	4 h	Resp	100			West et al. 2001 NAP
2	Mouse B6C3F1	14 d 5 d/wk 6 hr/d	Hemato	30			NTP 1992a NAP

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form	
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)		
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 NAP
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 (Nap) Or Methylnaphthalene (1-Mn Or 2-Mn) - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)	
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) NAP
			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 (Nap) Or Methylnaphthalene (1-Mn Or 2-Mn) - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)	
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 NAP

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)	
8	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d	Cardio	30			NTP 1992a NAP
			Gastro	30			
			Hepatic	30			
			Renal	30			
			Dermal	30			
9	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d vapor	Neurological	60			NTP 2000 (Abdo et al. 2001) NAP

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)	
10	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d		30			NTP 1992a NAP
		Reproductive					
11	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d vapor		60			NTP 2000 (Abdo et al. 2001) NAP

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (ppm)	Less Serious (ppm)	Serious (ppm)	
12	Mouse B6C3F1	104 wk 5d/wk 6 hr/d		30			NTP 1992a NAP
		Cancer					
13	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) NAP
14	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d				30	(CEL: pulmonary alveolar adenomas in females) NTP 1992a NAP

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 (NAP) Or Methylnaphthalene (1-MN Or 2-MN)- Inhalation

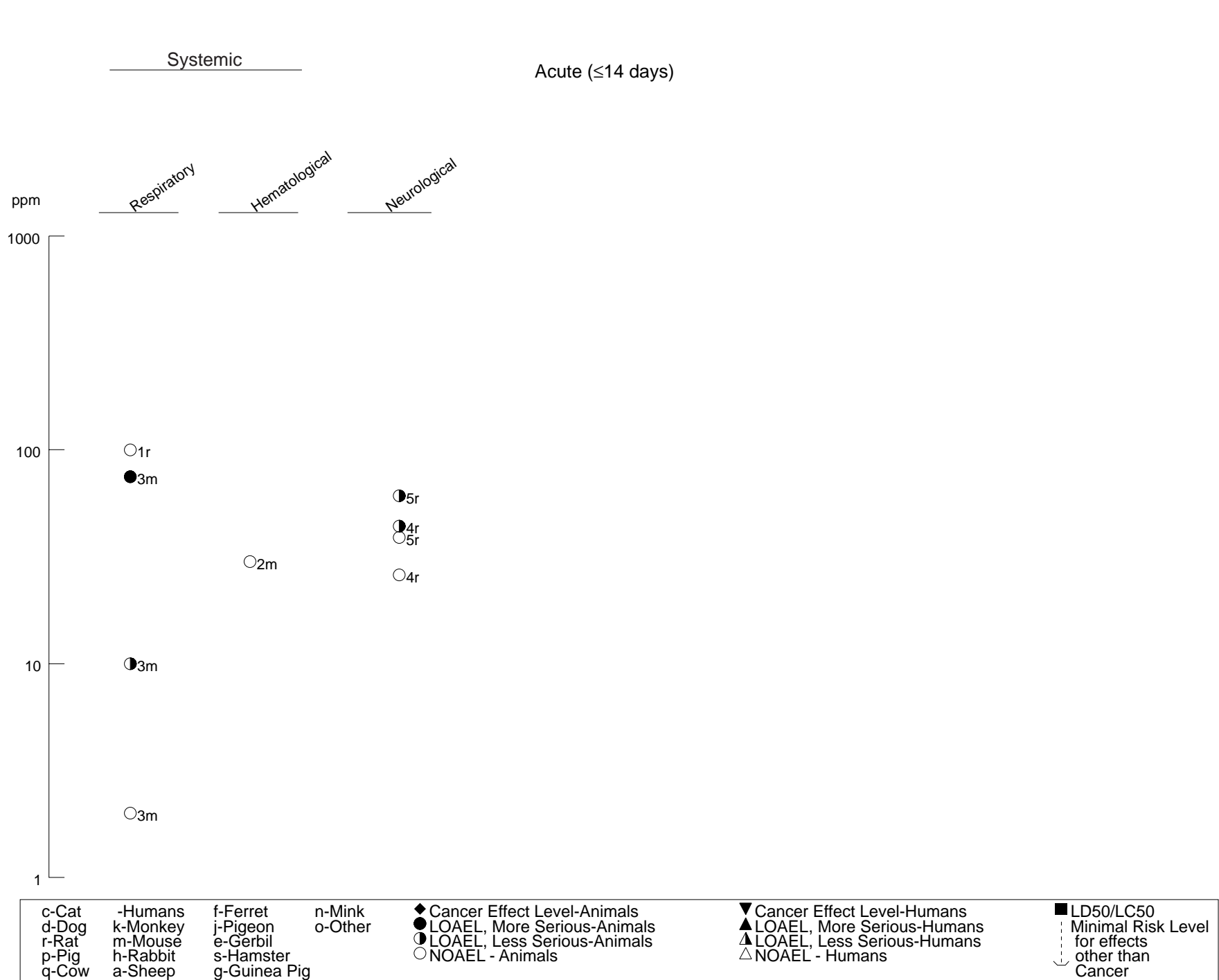
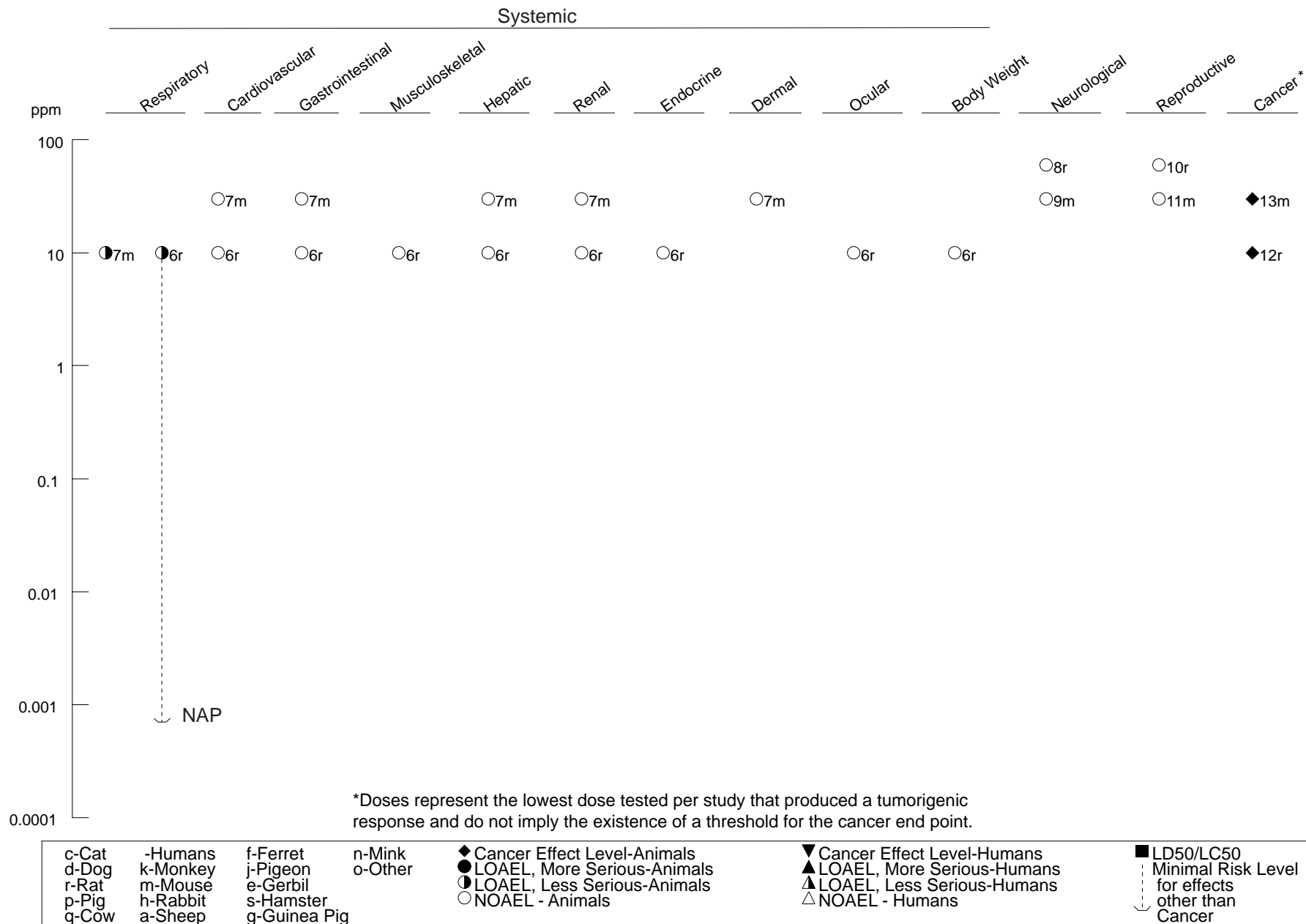


Figure 3-1. Levels of Significant Exposure to Naphthalene (NAP) Or Methylnaphthalene (1-MN Or 2-MN) - Inhalation (Continued)
Chronic (≥365 days)



3. HEALTH EFFECTS

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 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 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.

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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/m³ 1-methylnaphthalene (44 or 70 ppm), or 352 or 525 mg/m³ 2-methylnaphthalene (61 or 90 ppm), but not after exposure to 152 mg/m³ (26 ppm) 1-methylnaphthalene or 229 mg/m³ (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.

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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 LD₅₀ values in male and female mice were 533 and 710 mg/kg, respectively (Shopp et al. 1984). An LD₅₀ 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 LD₅₀ 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

3. HEALTH EFFECTS

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 doses 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

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

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat Sherman	once (GO)				2200 (LD50 - male) 2400 (LD50 - female)	Gaines 1969 NAP
2	Rat Sprague-Dawley	once (GO)				2600 LD50	Papciak and Mallory 1990 NAP
3	Mouse CD-1	8 d 1x/d (GO)				300 (5/33 died)	Plasterer et al. 1985 NAP
4	Mouse CD-1	once (GO)				710 (LD50) 533 (LD50)	Shopp et al. 1984 NAP
5	Mouse CD-1	14 d 1x/d (GO)				267 (10/96 male, 3/60 female)	Shopp et al. 1984 NAP
Systemic							
6	Human	once	Gastro		109 (adbominal pain)		Gidron and Leurer 1956 NAP
			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 NAP

NAPHTHALENE, 1 METHYLNAPHTHALENE, AND 2 METHYLNAPHTHALENE
 3. HEALTH EFFECTS

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

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg)	Serious (mg/kg)	
8	Rat Sprague-Dawley	once (GO)	Resp	1000	lung lesions		Papciak and Mallory 1990 NAP
9	Rat Sprague-Dawley	once (GO)	Gastro	1000	stomach lesions		Papciak and Mallory 1990 NAP
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 NAP
			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 NAP
			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 NAP

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

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
13	Rabbit NS	5 d (F)	Hepatic	2000			Srivastava and Nath 1969 NAP
			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 NAP
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 NAP
Neurological							
16	Rat Sprague-Dawley	9d Gd 6-15 (GO)			^b 50	(transient clinical signs of toxicity in dams; at higher exposure levels, signs were more persistent and accompanied by decreases in body weight gain)	NTP 1991a NAP
17	Mouse CD-1	14 d (GO)		267			Shopp et al. 1984 NAP
Reproductive							
18	Rat Sprague-Dawley	9 d Gd 6-19 (GO)		450			NTP 1991a NAP

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

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
19	Mouse CD-1	8d Gd 7-14 (GO)				300 (>10% maternal mortality)	Plasterer et al. 1985 NAP
20	Rabbit New Zealand white	14 d Gd 6-19 (GO)		120			NTP 1992b NAP
Developmental							
21	Rat Sprague-Dawley	9 d Gd 6-15 (GO)				150 (decreased maternal weight gain >20%; no fetotoxic or teratogenic effects at 150 or 450 mg/kg/day)	NTP 1991a NAP
				50			
22	Mouse CD-1	8d Gd 7-14 (GO)				300	Plasterer et al. 1985 NAP
23	Rabbit New Zealand white	14 d Gd 6-19 (GO)				120	NTP 1992b NAP
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 NAP

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Systemic							
25	Rat blue spruce	9 wk 3.5d/wk (GO)	Resp	169			Germansky and Jamall 1988 NAP
			Hepatic		169	(elevated lipid peroxides)	
			Bd Wt			169	(20% decreased body weight gain)
26	Rat Brown-Norway	4 wk 3.5d/wk (GO)	Ocular			500	(lens opacity) Kojima 1992 NAP
27	Rat Sprague-Dawley Brown-Norway	6 wk	Ocular			500	(cataract formation) Murano et al. 1993 NAP

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

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
28	Rat Fischer 344	13 wk 5x/wk (GO)	Resp	400			NTP 1980b NAP	
			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 NAP	
30	Rat Brown-Norway	102 d NS (GO)	Ocular			700 (lens opacity)	Tao et al. 1991 NAP	
31	Rat 5 strains	4-6 wk (GO)	Ocular			1000 (lens opacity)	Xu et al. 1992b NAP	

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
32	Rat Wistar	18 d 1x/d (G)	Hepatic	200	1000	(elevated lipid peroxides)	Yamauchi et al. 1986 NAP
			Ocular		1000	(cataracts)	
33	Mouse B6C3F1	13 wk 5x/wk 1x/d (GO)	Resp	200			NTP 1980a NAP
			Cardio	200			
			Gastro	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Ocular	200			
			Bd Wt	200			

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

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
34	Mouse CD-1	90 d 7d/wk 1x/d (GO)	Resp	133			Shopp et al. 1984 NAP	
			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 NAP
36	Rabbit Chinchilla Bastard New Zealand white	12 wk 2d/wk 1x/d (GO)	Ocular			1000	(cataracts)	Rossa and Pau 1988 NAP
37	Rabbit NS	4 wk 1x/d (GO)	Ocular		1000		(increased ascorbic acid in lens)	van Heyningen 1970 NAP

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

(continued)

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

NAPHTHALENE, 1 METHYLNAPHTHALENE, AND 2 METHYLNAPHTHALENE
 3. HEALTH EFFECTS

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

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
45	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)		200			NTP 1980a NAP
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 (nap) Or Methylnaphthalene (1-mn Or 2-mn) - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
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		143.7			Murata et al. 1993 1-MN
		(F)					
49	Mouse (B6C3F1)	81 wk (F)		113.8			Murata et al. 1997 2-MN

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
50	Mouse B6C3F1	81 wk 1x/d		143.7			Murata et al. 1993 1-MN
		(F)					
51	Mouse (B6C3F1)	81 wk (F)		113.8			Murata et al. 1997 2-MN
Reproductive							
52	Mouse B6C3F1	81 wk 1x/d		143.7 F			Murata et al. 1993 1-MN
		(F)					
53	Mouse (B6C3F1)	81 wk (F)		113.8			Murata et al. 1997 2-MN

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

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer								
54	Mouse B6C3F1	81 wk 1x/d				71.6	(CEL: increased incidence of lung adenomas in males only)	Murata et al. 1993 1-MN
		(F)						
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 toxicity 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 0.04 mg/kg/day for 2-MN; based on a BMDL (LED05) of 4 mg/kg/day which was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; BMDL (LED05) = lower 95% confidence limit on a dose associated with 5% extra risk; 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 (NAP) or Methylnaphthalene (1-MN or 2-MN) - Oral
Acute (≤ 14 days)

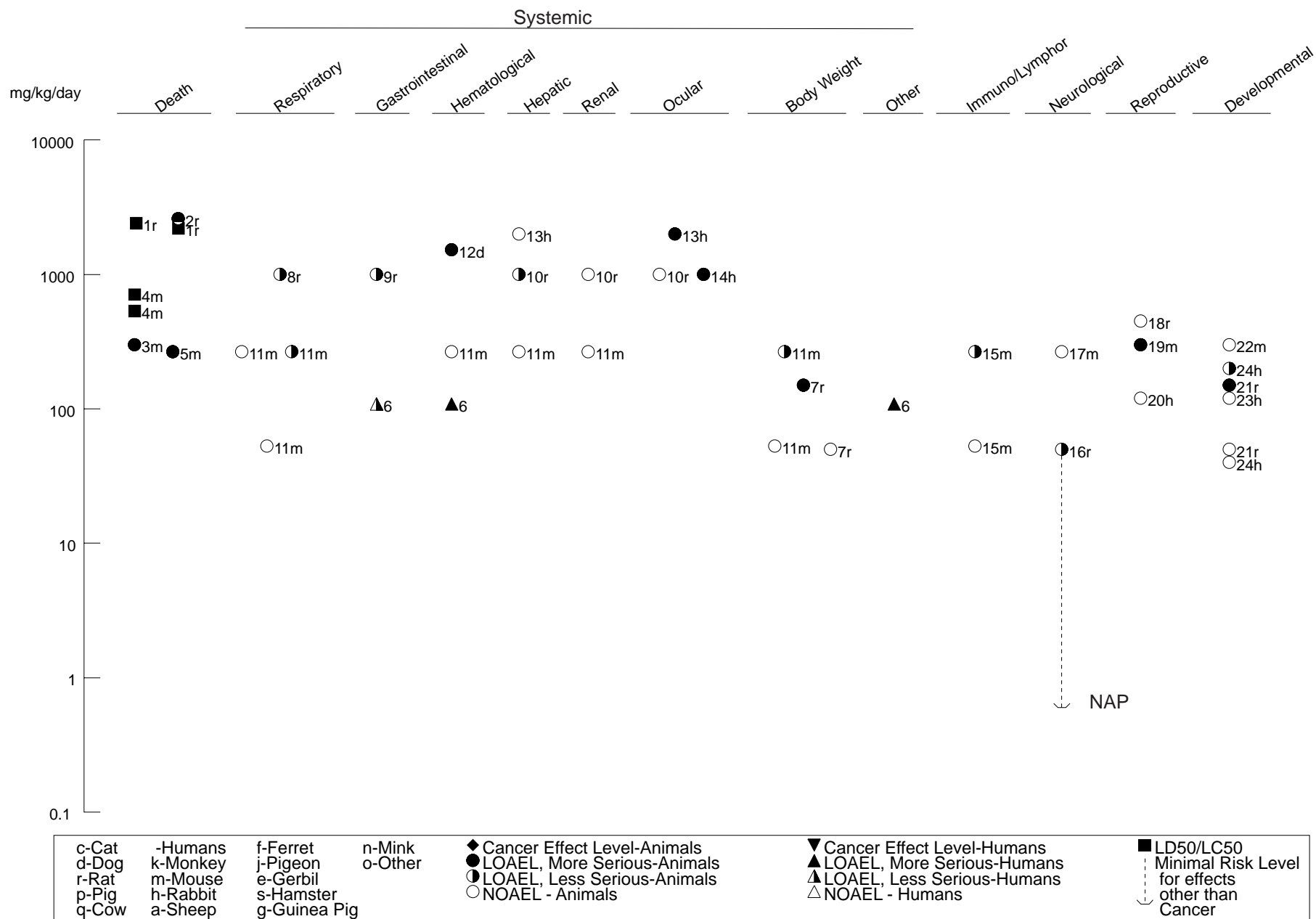
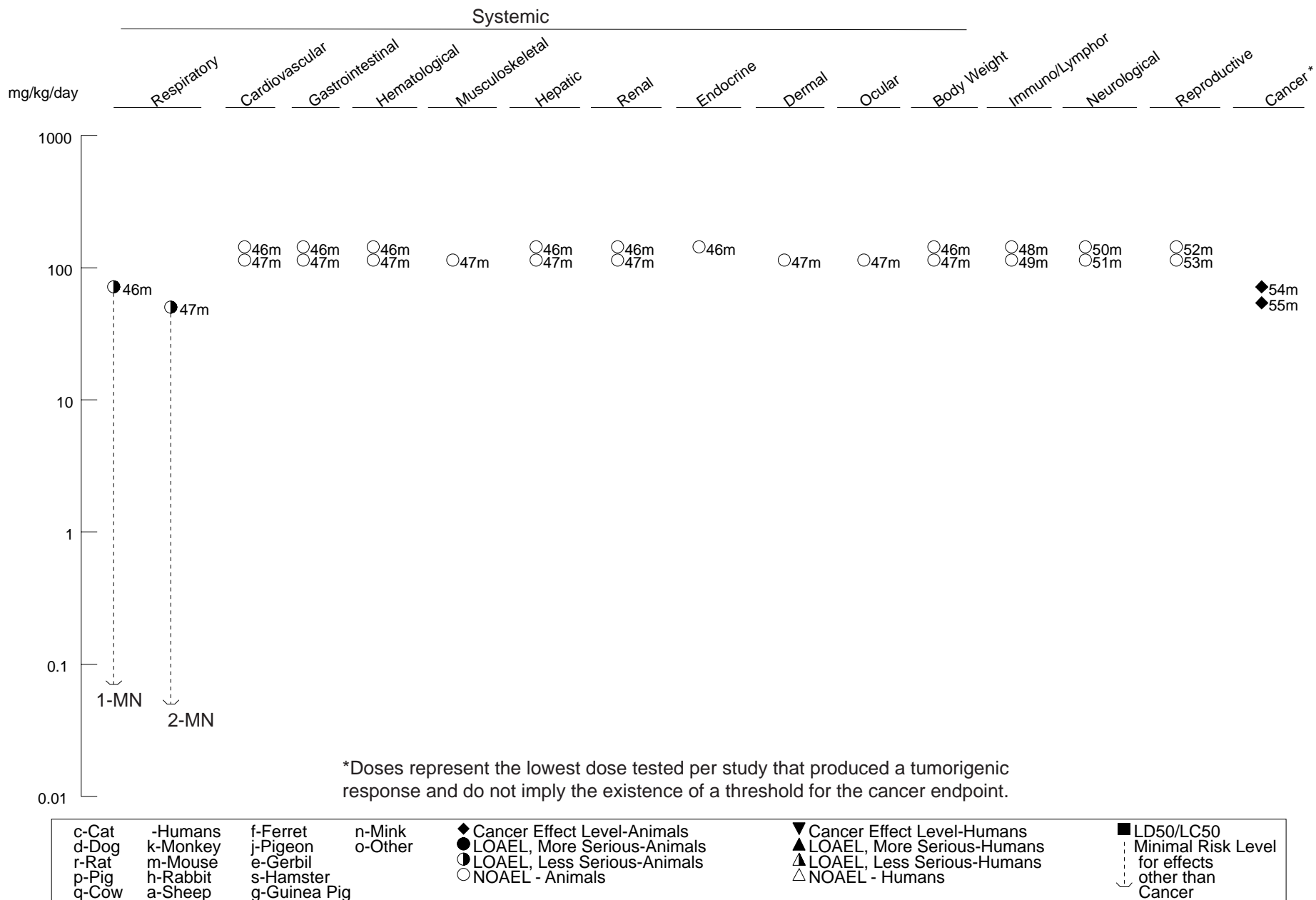


Figure 3-2. Levels of Significant Exposure to Naphthalene (NAP) or Methylnaphthalene (1-MN or 2-MN) - Oral (Continued)

Chronic (≥365 days)



3. HEALTH EFFECTS

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 LD₅₀ 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.

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 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

3. HEALTH EFFECTS

(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 for 2-methylnaphthalene.

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 LD₅₀ 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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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-methylnaphthalene 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).

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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 clinical signs of toxicity (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 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 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

3. HEALTH EFFECTS

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).

3. HEALTH EFFECTS

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-methylnaphthalene studies for immunological/lymphoreticular effects are also recorded in Table 3-2 and plotted in Figure 3-2.

3. HEALTH EFFECTS

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 toxicity 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. Clinical signs of toxicity 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). It is not known if the observed clinical signs were due to treatment-related effects on the nervous system or were the indirect consequence of severe systemic toxicity, as indicated by the dramatic decreases in body weight gain. Comparable 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 effects of naphthalene than non-pregnant animals. The minimal LOAEL of 50 mg/kg/day for transient clinical signs of toxicity and the LOAEL of 150 mg/kg/day for more persistent signs of toxicity accompanied with depressed weight gain in pregnant rats exposed on gestation days 6–15 are the basis of the acute oral MRL for naphthalene (see Section 2.3 and Appendix A).

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

in the absorption of naphthalene when it is administered in corn oil compared with administration as a suspension in methyl cellulose.

Transient signs of toxicity 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

3. HEALTH EFFECTS

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 6–19 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. HEALTH EFFECTS

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 LD₅₀ 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-methylnaphthalene 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).

Table 3-3 Levels of Significant Exposure to Naphthalene (Nap) 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 NAP
Rabbit	once	Dermal		125 mg/kg	(reversible erythema)	PRI 1985a NAP
Immuno/ Lymphoret						
Gn Pig	3 wk 1x/wk		1000 mg/kg			PRI 1985c NAP

Table 3-3 Levels of Significant Exposure to Naphthalene (Nap) 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	
INTERMEDIATE EXPOSURE						
Systemic						
Rat	90 d 5d/wk 6 hr/d	Resp	1000 mg/kg/day			Frantz et al. 1986 NAP
		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 (Nap) 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.

3. HEALTH EFFECTS

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).

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).

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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;

3. HEALTH EFFECTS

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-naphthoquinone, were not mutagenic in several *S. typhimurium*

3. HEALTH EFFECTS

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	<i>Salmonella typhimurium</i> TA1535, TA1537, TA98, TA100	100 µg/plate ±S9 activation	100	Negative	McCann et al. 1975
	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	0.3–100 µg/plate ±S9 activation	100	Negative	Mortelmans et al. 1986
	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	0.3–100 µg/plate ±S9 activation	100	Negative	NTP 1992a
	<i>S. typhimurium</i> TA1537, TA1538	10–200 µg/plate ±S9 activation	100	Negative, toxic above 100 µg/plate	Gatehouse 1980
	<i>S. typhimurium</i> TA98, TA100	10–50 µg/plate ±S9 activation	50	Negative	Bos et al. 1988
	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	0.03–30 µmol/plate ±S9 activation	3	Negative, toxic above 3 µmol/plate	Florin et al. 1980
	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	250 µg/plate ±S9 activation	250	Negative	Sakai et al. 1995
	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA98, TA100	3–300 µg/plate ±S9 activation	300	Negative, toxic above 300 µg/plate	Godek 1985
	<i>S. typhimurium</i> TM677	1–2 mM ±S9 activation	2	Negative	Kaden et al. 1979
	<i>S. typhimurium</i> TA98, TA1535	5–1,000 µg/plate ±S9 activation	1,000	Negative	Narbonne et al. 1987
	<i>S. typhimurium</i> UTH8413, UTH8414, TA98, TA100	100–2,000 µg/plate ±S9 activation	2,000	Negative	Conner et al. 1985
	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	1,000 µg/plate ±S9 activation	1,000	Negative (1-naphthol)	McCann et al. 1975
	<i>S. typhimurium</i> TA98, TA1535	5–1,000 µg/plate ±S9 activation	1,000	Negative (1-naphthol)	Narbonne et al. 1987
	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	250 µg/plate ±S9 activation	250	Negative (1,4-naphthoquinone)	Sakai et al. 1995

3. HEALTH EFFECTS

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)					
	<i>S. typhimurium</i> TA97a, TA98, TA100, TA104	0–100 nmol/plate ±S9 activation	17.5	Positive (1,2-naphtho- quinone), 1.8- to 3.4-fold increase without S9; +S9 results similar to -S9 results	Flowers-Geary et al. 1996
SOS response	<i>S. typhimurium</i> TA1535/p5K1002 (uMuC-lacZ)	83 µg/mL ±S9 activation	83	Negative	Nakamura et al. 1987
	<i>Escherichia coli</i> K12 inductest (λ lysogen GY5027; uvrB-, envA-)	2,000 µg/plate ±S9 activation	2,000	Negative	Mamber et al. 1984
SOS chromotest	<i>E. coli</i> PQ37 (sfiA::lacZ fusion)	0.156– 10.0 µg/assay ±S9 activation	10	Negative	Mersch- Sundermann et al. 1993
Pol A- or Rec assay	<i>E. coli</i> WP2/WP10 (uvrA-, recA-)	2,000 µg/mL ±S9 activation	2,000	Negative	Mamber et al. 1983
	<i>E. coli</i> WP2/WP67 (uvrA-, pol A-)	Dose not specified ±S9 activation	NS	Negative	Mamber et al. 1983
Pol A- or Rec assay	<i>E. coli</i> WP2/WP3478 (pol A-)	Dose not specified ±S9 activation	NS	Negative	Mamber et al. 1983
Mutatox (reversion to luminescence)	<i>Vibrio fischeri</i> 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]

3. HEALTH EFFECTS

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

Assay	Test system	Dose/ concentration	HID or LED	Result	Reference
<i>In vitro</i> 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 (<i>in vitro</i>)	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 (<i>in vitro</i>)	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
<i>In vivo</i> eukaryotic gene mutation, cytogenetic, or DNA damage assays					
Somatic mutation, recombination	<i>Drosophila melanogaster</i>	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

3. HEALTH EFFECTS

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

Assay	Test system	Dose/ concentration	HID or LED	Result	Reference
<i>In vivo</i> 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 (<i>Pleurodeles waltl</i>): 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 (<i>in vivo</i>)	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 (<i>in vivo</i>)	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 LD ₅₀ =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 LD ₅₀ =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 (<i>in vivo</i>)	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

^aMetabolites are noted in result column.

DNA = deoxyribonucleic 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; std = standard deviation

3. HEALTH EFFECTS

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 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 μ M) 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-Rodriguez 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

3. HEALTH EFFECTS

(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. HEALTH EFFECTS

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:				
<i>Salmonella typhimurium</i> (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:				
<i>S. typhimurium</i> (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

3. HEALTH EFFECTS

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.

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.

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

3. HEALTH EFFECTS

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 ocular effects in rats and rabbits indicates that gastrointestinal absorption does occur (Kojima 1992; Murano et al. 1993; Srivastava and Nath 1969).

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 (Murano et al. 1993).

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.

¹⁴C-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-cm² areas of rat skin. Half of the sample (3.3 µg/cm³) was absorbed

3. HEALTH EFFECTS

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-methylnaphthalene in humans or animals after inhalation exposure.

3. HEALTH EFFECTS

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) ¹⁴C-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) ¹⁴C-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 ¹⁴C-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 ³H/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

3. HEALTH EFFECTS

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, ¹⁴C-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. HEALTH EFFECTS

3.4.3 Metabolism

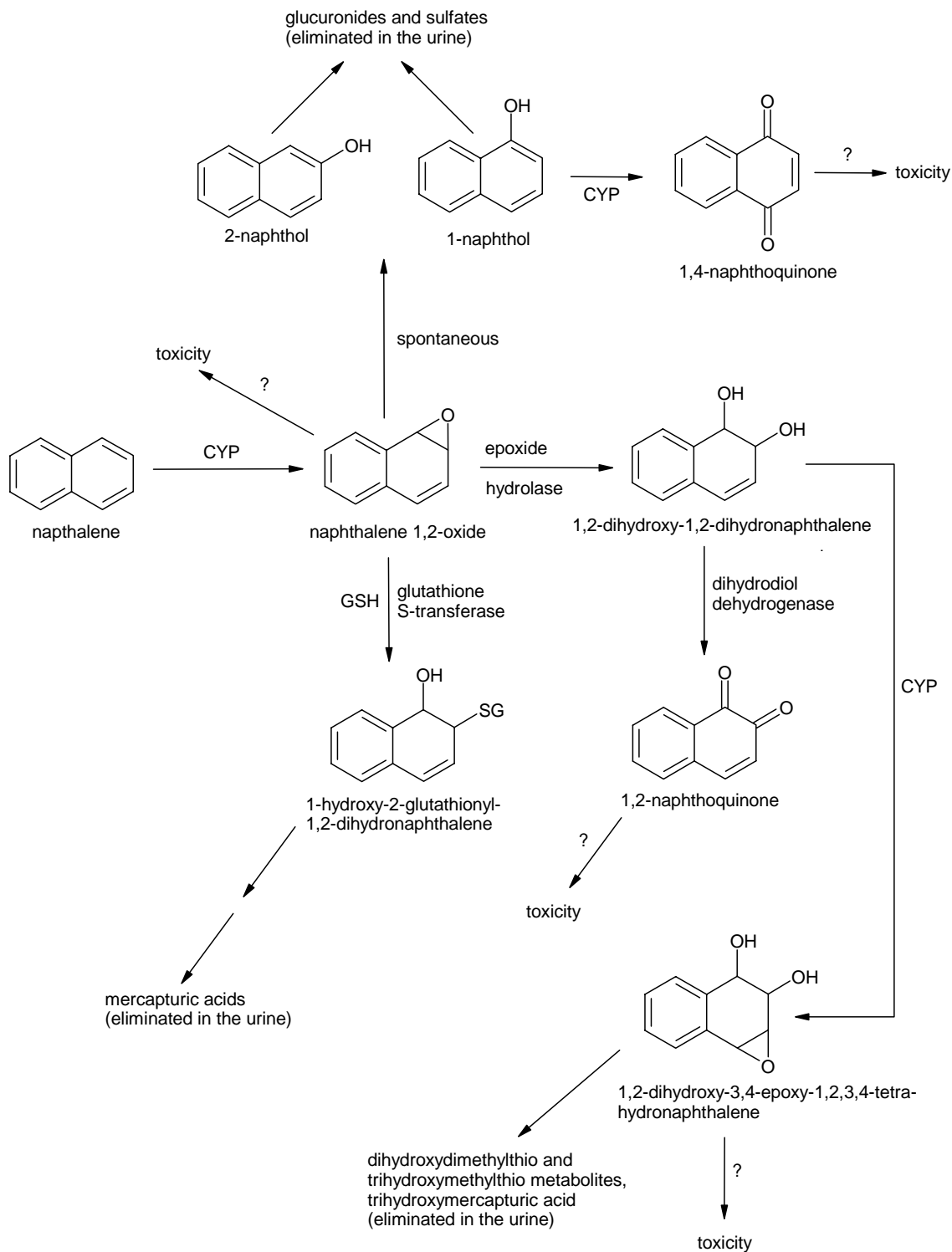
The metabolism of naphthalene in mammalian systems has been studied extensively and is depicted in Figure 3-3. The metabolic scheme in Figure 3-3 illustrates that there are multiple reactive metabolites formed from naphthalene: 1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene. 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, 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

3. HEALTH EFFECTS

Figure 3-3. Scheme for Naphthalene Metabolism and Formation of Multiple Reactive Metabolites, That 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)

3. HEALTH EFFECTS

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-gluthionyl-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

3. HEALTH EFFECTS

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-naphthoquinone (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 $\geq 10 \mu\text{M}$, whereas naphthalene 1,2-epoxide did not at concentrations up to $100 \mu\text{M}$ (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 $100 \mu\text{M}$, 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).

3. HEALTH EFFECTS

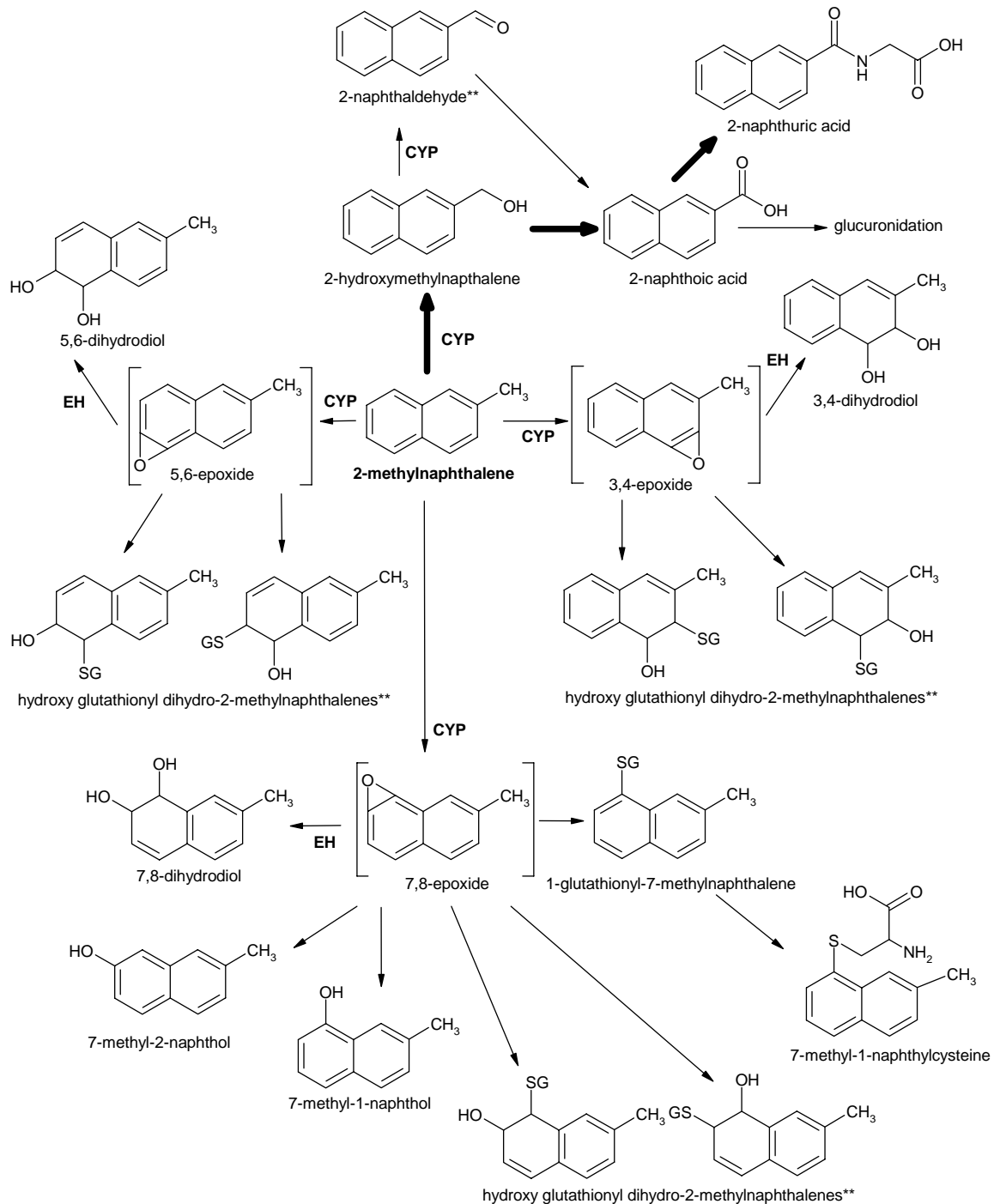
Support for the *in vivo* formation of another potentially reactive metabolite, 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene, comes from the identification of several urinary metabolites, including a number of trihydroxytetrahydromethylthio derivatives (Horning et al. 1980) and a trihydroxytetrahydro-mercapturic 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 is shown in Figure 3-4. Oxidation at the methyl group (the predominant path), or at several competitive positions on the rings, is catalyzed by CYP monooxygenases (Figure 3-4). No information was located that documented the metabolism of 1-methylnaphthalene. It may be similar to that for 2-methylnaphthalene with oxidation of the side chain and the ring.

In rats and mice, about 50–80% of 2-methylnaphthalene is oxidized at the 2-methyl group to produce 2-hydroxymethylnaphthalene (Breger et al. 1983; Teshima et al. 1983). This 2-hydroxymethylnaphthalene metabolite is further oxidized to 2-naphthoic acid (Grimes and Young 1956; Melancon et al. 1982; Teshima et al. 1983), and this step proceeds either directly or through the intermediate, 2-naphthaldehyde (Figure 3-4). Detection of 2-naphthaldehyde has only been reported following *in vitro* incubation of 2-methylnaphthalene with recombinant mouse CYP2F2 (Shultz et al. 2001). 2-Naphthoic acid may be conjugated with either glycine or glucuronic acid (Figure 3-4). The glycine conjugate of 2-naphthoic acid forms 2-naphthuric acid, which is the most prevalent urinary metabolite of 2-methylnaphthalene detected in exposed animals (Grimes and Young 1956; Melancon et al. 1982; Teshima et al. 1983).

Ring epoxidation at the 7,8-, 3,4-, or 5,6- positions occurs in approximately 15–20% of 2-methylnaphthalene (Breger et al. 1983; Melancon et al. 1985). These epoxidation reactions are catalyzed by CYP isozymes that include CYP1A and CYP1B. These epoxides are proposed intermediates based on experimentally-observed metabolites, but have not been individually isolated (Figure 3-4). These epoxides may be further oxidized by epoxide hydrolase to produce dihydrodiols (the 7,8-dihydrodiol, 3,4-dihydrodiol, or 5,6-dihydrodiol of 2-methylnaphthalene) or may be conjugated with glutathione (Griffin et al. 1982; Melancon et al. 1985) by glutathione S-transferase catalysis or can proceed

3. HEALTH EFFECTS

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), EPA (2003r); Shultz et al. (2001), and Teshima et al. (1983)

**Metabolites identified *in vitro* only

3. HEALTH EFFECTS

spontaneously. The hydroxy glutathionyl dihydro-2-methylnaphthalenes (Figure 3-4) have been 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 indicates 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).

Three other minor metabolites formed via the 7,8-epoxide pathway are shown in Figure 3-4. Urinary 1-glutathionyl-7-methylnaphthalene was identified in 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 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-[8-¹⁴C]-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.

Glutathione conjugation appears to be 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). Bronchiolar

3. HEALTH EFFECTS

necrosis was not observed in male ddY mice given single intraperitoneal injections of 200 mg/kg of 2-methylnaphthalene; pretreatment with the glutathione depletor diethylmaleate (600 μ L/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-methylnaphthalene (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 μ M 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

3. HEALTH EFFECTS

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 radiolabelled 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-methylnaphthalene. 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-methylnaphthalene.

3. HEALTH EFFECTS

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 ¹⁴C-labeled naphthalene was evaluated over a 48-hour period (Turkall et al. 1994). Naphthalene (43 µg) samples were applied to shaved 13-cm² 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-dihydroxynaphthalene, 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-methylnaphthalene 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-dihydro-1,2-naphthalenediol.

3. HEALTH EFFECTS

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 and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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

3. HEALTH EFFECTS

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) are 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.

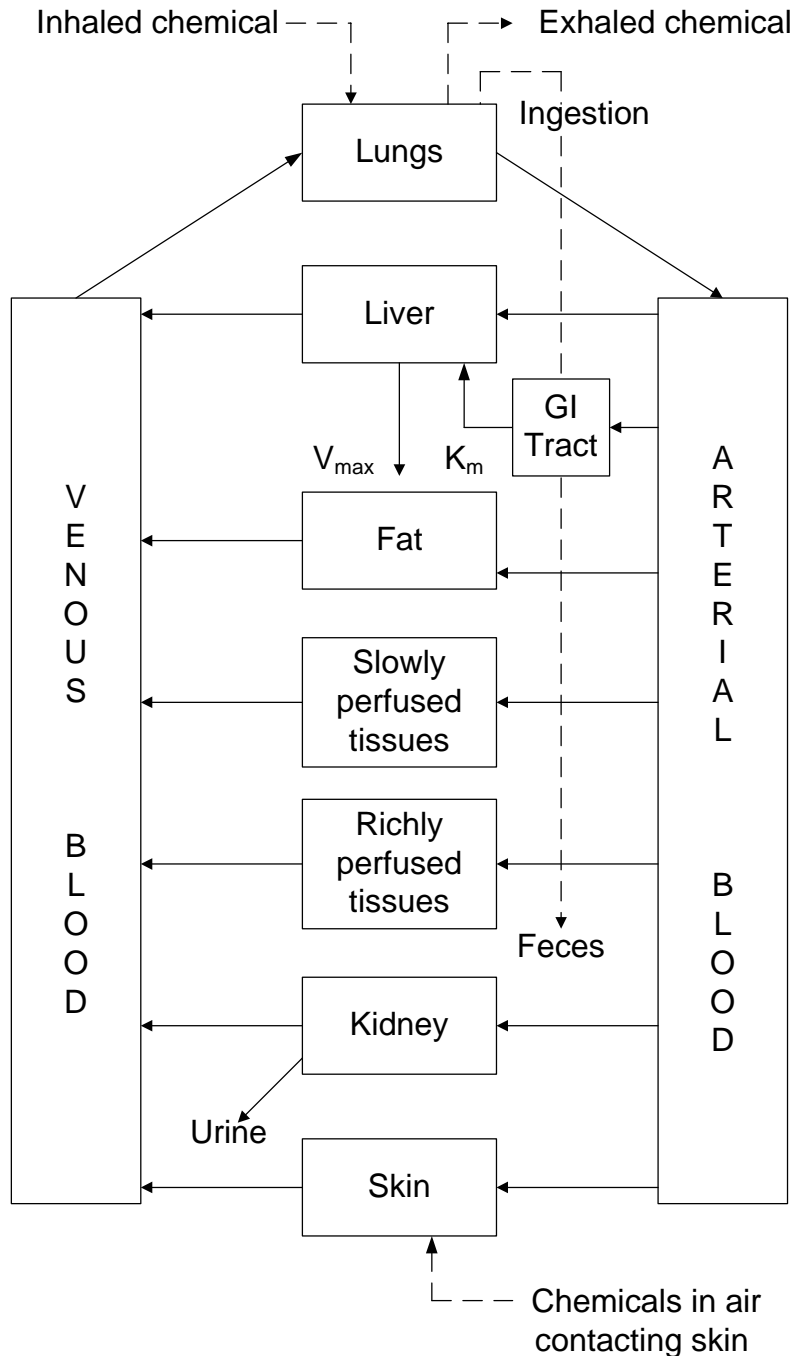
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in 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.

If PBPK models for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

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.

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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 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 (V_{max} and K_m) 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.

3. HEALTH EFFECTS

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-methylnaphthalene, 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.

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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-methylnaphthalene- 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

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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-dihydroxynaphthalene, 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-butyl nitron (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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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-dihydroxy-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,

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

Current information is inadequate to (1) identify which metabolite(s) are responsible for nonneoplastic or neoplastic nasal lesions that develop in rodents following chronic inhalation exposure, (2) explain why nasal tumors develop in rats but not in mice, or (3) rule out the possible human relevance of naphthalene-induced nasal lesions in rats or 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. As suggested by Moore and Harrington-Brock (2000), answering critical questions in human cancer risk assessment involves an understanding of the mode(s) of action of tumor induction in the target tissue(s) at environmentally-relevant concentrations. Such understanding can come from experiments examining genotoxic endpoints in target tissues. These data are not available for naphthalene.

In summary, the available evidence regarding the mechanism(s) by which naphthalene produces neoplastic and nonneoplastic lesions in the respiratory tract of rodents suggests the involvement of reactive metabolites. The identity of this metabolite(s), and evidence of its presence in known target tissues, remains unknown. The finding that mice are more susceptible than rats to naphthalene-induced lung toxicity may correlate with the *in vivo* generation of this reactive intermediate in target tissues. Whether the mechanism by which naphthalene produces neoplastic and nonneoplastic changes in the respiratory tract of rodents involves genotoxicity remains unknown.

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.

3. HEALTH EFFECTS

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 methylnaphthalenes. Pulmonary hyperplasia and hypertrophy of type II pneumocytes in alveolar regions with proteinosis was observed by light microscopy in mice that were repeatedly exposed to dermal doses of methylnaphthalene (119 mg/kg methylnaphthalene twice a week for 30 weeks [Murata et al. 1992]). In this same study, electron microscopic examination showed that alveolar spaces were filled with numerous myelinoid structures that resembled lamellar bodies of type II pneumocytes. This extracellular material was associated with mononucleated giant cells (called balloon cells) containing numerous myelinoid structures, lipid droplets, and electron dense ascicular crystals. The authors 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. Balloon cell rupture has been hypothesized to lead to the accumulation of the myelinoid structures in the alveolar lumen. Ultrastructural studies of the pathogenesis of pulmonary alveolar proteinosis from chronic exposure to 2-methylnaphthalene or 1-methylnaphthalene alone were not 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 (EPA 2003; 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-methyl-

3. HEALTH EFFECTS

naphthalene 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 monooxygenase 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). This hypothesis is supported by the finding that 2-methylnaphthalene is less acutely toxic than naphthalene (Buckpitt and Franklin 1989; Cho et al. 1995) and that 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 is not surprising, as Clara cells have been shown to develop resistance to the acute toxicity of naphthalene (Lakritz et al.

3. HEALTH EFFECTS

1996). The possible development of Clara cell resistance to the acute toxicity of 2-methylnaphthalene, however, has not been studied.

Data are limited to support the hypothesis that rats are 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). However, 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-methylnaphthalene 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

3. HEALTH EFFECTS

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 toxicity 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 ENDOCRINE 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 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), and in 1998, the EDSTAC 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 isoflavonoid 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

3. HEALTH EFFECTS

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 endocrine disruption in human or animals after exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

No *in vitro* studies were located regarding endocrine disruption of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

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

3. HEALTH EFFECTS

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 detoxification. 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.

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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 (>75th 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. HEALTH EFFECTS

No direct information was located on the relative susceptibility of children or young animals to 1-methylnaphthalene or 2-methylnaphthalene toxicity, compared with adults. However, clinical experience with humans displaying pulmonary alveolar proteinosis of unknown etiology has indicated that children with this condition experience more severe symptoms and a poor prognosis for survival than do adults (EPA 2003r; Mazzone et al. 2001).

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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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-methylnaphthalene 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. HEALTH EFFECTS

3.8.2 Biomarkers Used to Characterize Effects Caused by Naphthalene, 1-Methylnaphthalene, 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

3. HEALTH EFFECTS

(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-methylnaphthalene, 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 detoxification 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

3. HEALTH EFFECTS

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. HEALTH EFFECTS

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).

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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-methylnaphthalene is 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

3. HEALTH EFFECTS

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

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●								
Oral	●	●								
Dermal	●	●								

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●		●		●	●			●
Oral	●	●	●	●	●	●	●	●	●	
Dermal	●	●	●		●					

Animal

● Existing Studies

3. HEALTH EFFECTS

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

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										
Oral										
Dermal										

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●				●					
Oral			●							●
Dermal		●	●							●

Animal

● Existing Studies

3. HEALTH EFFECTS

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

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										
Oral										
Dermal										

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●				●				
Oral			●	●						●
Dermal			●	●						●

Animal

● Existing Studies

3. HEALTH EFFECTS

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 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-methylnaphthalene 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

3. HEALTH EFFECTS

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 (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 toxicity in orally-exposed pregnant rats (NTP 1991a) serves as the basis of the acute-duration oral MRL for naphthalene. 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 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 clinical signs were not observed following administration of doses as high as

3. HEALTH EFFECTS

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 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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

(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 was adopted as the intermediate-duration oral MRL for naphthalene, because a potential intermediate-duration oral MRL (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 a 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).

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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 for 1-methylnaphthalene. A chronic-duration oral study of 2-methylnaphthalene 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 for 2-methylnaphthalene. 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

3. HEALTH EFFECTS

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 its 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. typhimurium* (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

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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 clinical signs of toxicity (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 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 the behavioral effects of acute-duration exposures to 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

3. HEALTH EFFECTS

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 end points 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-methylnaphthalene 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).

3. HEALTH EFFECTS

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 methyl-naphthalenes. 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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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-methylnaphthalene 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

3. HEALTH EFFECTS

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. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

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

3. HEALTH EFFECTS

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.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

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

3. HEALTH EFFECTS

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 O₂-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

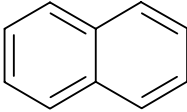
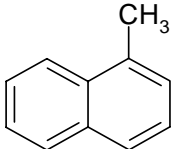
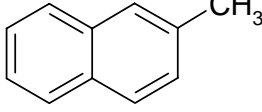
Information regarding the chemical identity of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is located in Table 4-1.

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.

4. CHEMICAL AND PHYSICAL INFORMATION

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

Characteristic	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Reference
Synonyms	Tar camphor; albicarbon; naphthene; mothballs; moth- flakes; white tar; and others	Alpha-methyl- naphthalene; naphthalene, 1-methyl; naphthalene, alpha- methyl	Beta-methyl- naphthalene; naphthalene, 2-methyl; naphthalene, beta- methyl	HSDB 2004
Trade name	Caswell No. 5877®	No data	No data	HSDB 2004
Chemical formula	C ₁₀ H ₈	C ₁₁ H ₁₀	C ₁₁ H ₁₀	HSDB 2004
Chemical structure				HSDB 2004
Identification numbers:				
CAS registry	91-20-3	90-12-0	91-57-6	HSDB 2004
NIOSH RTECS	QJ0525000	QJ9630000	QJ9635000	NIOSH 1987
EPA hazardous waste	U165	No data	No data	HSDB 2004
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 2004
HSDB	184	5268	5274	HSDB 2004
NCI	C52904	No data	No data	HSDB 2004

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

4. CHEMICAL AND PHYSICAL INFORMATION

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	Verschuieren 1983
Physical state	Solid	Liquid	Solid	Verschuieren 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 2004
Odor threshold:				
Water	0.021 mg/L	0.0075 mg/L	0.01 mg/L	Amoore and Hautala 1983; HSDB 2004; Verschuieren 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 2004
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 2004
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	Verschuieren 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 2004 at 215 million pounds (97,700 metric tons) (Hughes et al. 1985; Mason 1995; SRI 2002).

There are currently two companies in the United States producing naphthalene: Advanced Aromatics, L.P., Baytown, 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 2004). 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 2002 (TRI02 2004). The Toxics Release Inventory (TRI) data should be used with caution since only certain types of facilities are required to report. TRI is not an exhaustive list. 1-Methyl

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

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	9	1,000	9,999,999	1, 3, 4, 5, 7, 8, 9, 12
AL	79	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	36	0	49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	12	100	999,999	3, 6, 7, 8, 9, 10, 11, 12
CA	141	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	21	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13
CT	16	100	49,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12, 13
DE	12	10,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
FL	28	0	9,999,999	1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	36	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
GU	4	0	9,999,999	9, 12
HI	16	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
IA	32	100	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
ID	2	10,000	999,999	1, 5, 12
IL	96	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	76	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	40	100	499,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	53	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	117	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	15	1,000	49,999,999	2, 3, 6, 7, 9, 10, 11, 12
MD	20	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14
ME	7	1,000	49,999,999	2, 3, 8, 9, 11, 12
MI	70	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	25	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
MO	35	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MS	44	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	20	10,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
NC	34	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	8	100	9,999,999	1, 2, 3, 4, 6, 7, 9, 10, 11, 12
NE	9	0	99,999	2, 7, 10, 11, 12
NJ	65	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	12	1,000	9,999,999	1, 3, 4, 7, 8, 9, 12, 13
NV	3	1,000	999,999	2, 3, 4, 9, 12
NY	31	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
OH	97	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	46	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OR	21	100	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14
PA	87	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

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

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
PR	24	100	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
RI	4	1,000	9,999,999	1, 5, 9, 10, 12
SC	30	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
SD	7	100	999,999	7, 8, 12
TN	48	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	247	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	46	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
VA	35	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
VI	5	1,000	49,999,999	1, 2, 3, 4, 6, 7, 9, 12
VT	1	100,000	999,999	12
WA	50	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	30	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	43	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	33	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Source: TRI02 2004 (Data are from 2002)

^aPost office state abbreviations used

^bAmounts on site reported by facilities in each state

^cActivities/Uses:

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

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

naphthalene 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 2004). 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 2004). 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).

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

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 phytymenadione (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 306,345 pounds of naphthalene were transferred off-site, including to publicly owned treatment works (POTW) in 2002 (TRI02 2004). 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 654, 36, and 412, respectively, of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). However, the number of sites evaluated for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene is not known. The frequency of these sites can be seen in Figures 6-1, 6-2, and 6-3, respectively. Of these sites, 654, 36, and 410, respectively, are located within the United States and 0, 0, and 2, respectively, are located in the Virgin Islands (not shown).

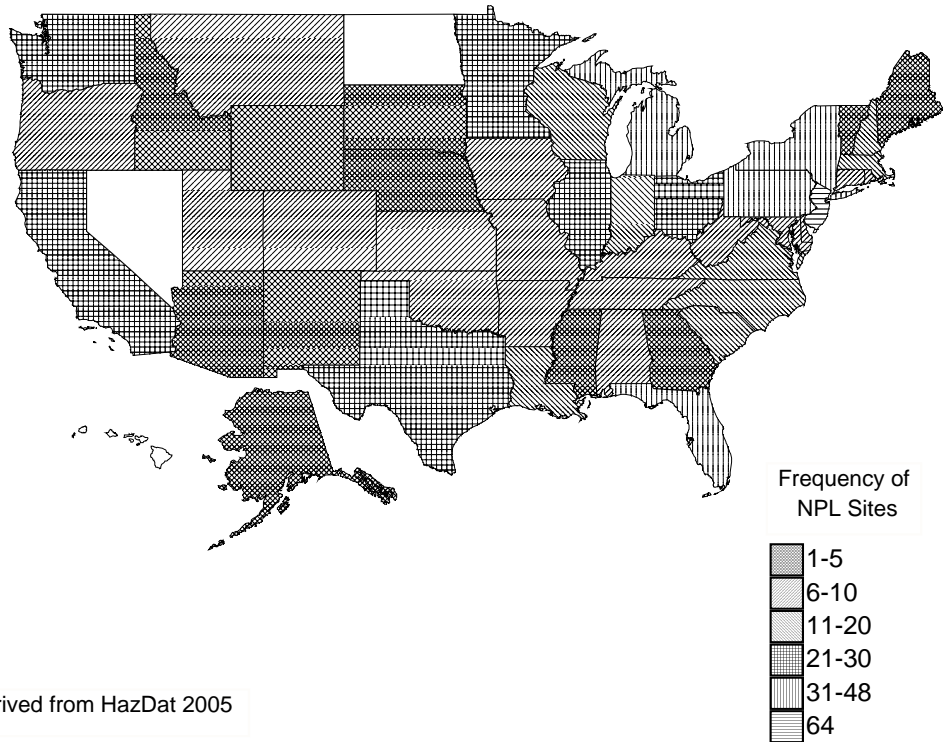
Most of the naphthalene entering the environment is discharged to the air. The largest releases result from the combustion of wood and fossil fuels and the off-gassing of naphthalene-containing moth repellents. Smaller amounts of naphthalene are introduced to water as the result of discharges from coal-tar 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. A large amount of naphthalene (often considerably more than 1,000 mg/kg) is present in soils contaminated with wastes from manufactured-gas plants.

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.

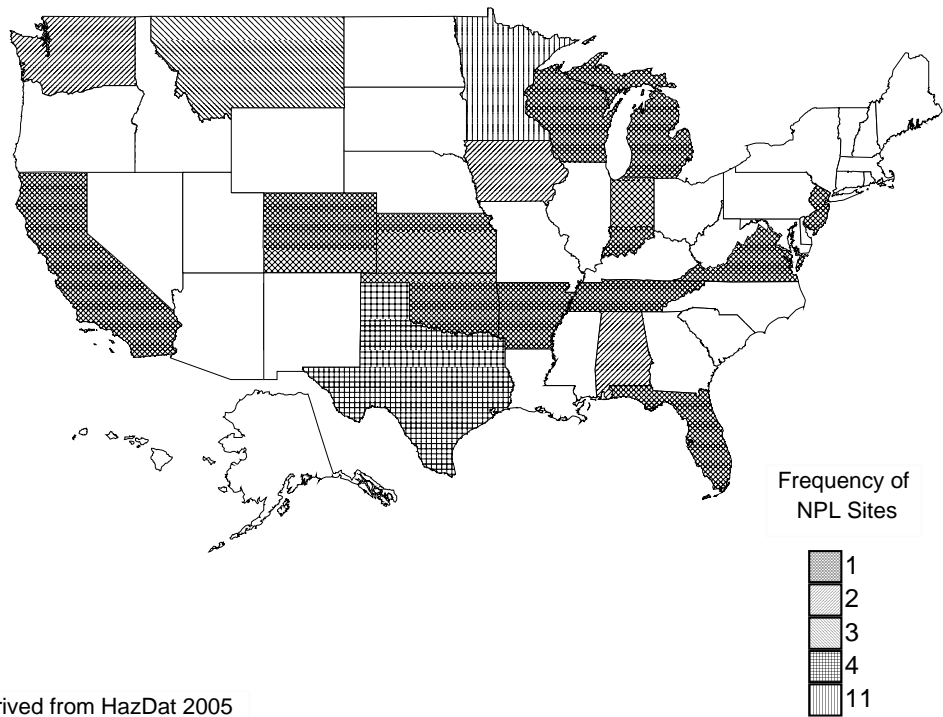
6. POTENTIAL FOR HUMAN EXPOSURE

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



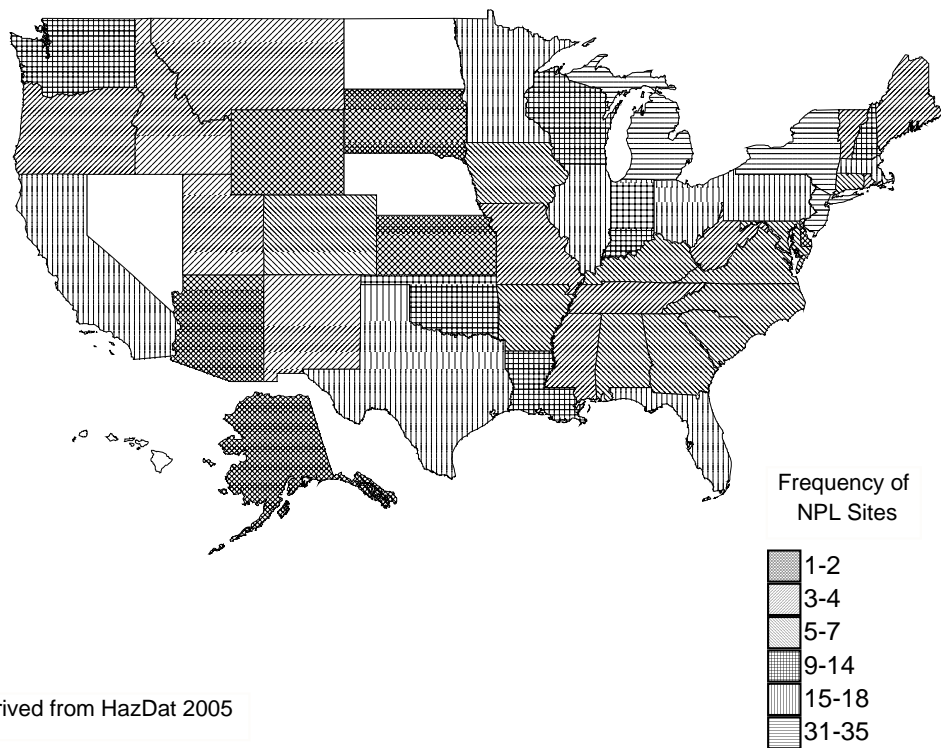
6. POTENTIAL FOR HUMAN EXPOSURE

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



6. POTENTIAL FOR HUMAN EXPOSURE

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



Derived from HazDat 2005

6. POTENTIAL FOR HUMAN EXPOSURE

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.

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 654 of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). 1-Methylnaphthalene has been identified in at least 36 of these sites, and 2-methylnaphthalene has been identified in at least 412 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

The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20–39; and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 1997).

6. POTENTIAL FOR HUMAN EXPOSURE

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). Methyl naphthalenes are released from similar sources, including fuel combustion and industrial discharges (GDCH 1992). Smoking tobacco also releases small amounts of naphthalene and methyl naphthalenes into the environment.

6.2.1 Air

Estimated releases of 2.07 million pounds (940.2 metric tons) of naphthalene to the atmosphere from 781 domestic manufacturing and processing facilities in 2002, accounted for about 72% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2004). These releases are summarized in Table 6-1.

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. Methyl naphthalenes may be released to air in stack emissions and from fuel combustion, forest fires, and tobacco smoke (GDCH 1992; HSDB 2004; IARC 1993). 1-Methyl naphthalene and 2-methyl naphthalene were reported in jet exhaust at average concentrations of 421 and 430 $\mu\text{g}/\text{m}^3$, respectively, and in the gas phase of diesel motor exhaust at 1.57 $\mu\text{g}/\text{m}^3$ each (GDCH 1992). The smoke of an American unfiltered cigarette contains 2.8 μg of naphthalene, 1.2 μg of 1-methyl naphthalene, and

6. POTENTIAL FOR HUMAN EXPOSURE

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

State ^c	RF ^d	Air ^e	Reported amounts released in pounds per year ^b							
			Water ^f	UI ^g	Land ^h	Other ⁱ	Total release			
							On-site ^j	Off-site ^k	On- and off-site	
AK	1	52	0		0	12	0	52	12	64
AL	22	108,624	58		0	221,582	5	295,685	34,585	330,270
AR	8	6,113	7		0	42	250	6,120	292	6,412
AZ	1	14	No data		0	0	0	14	0	14
CA	44	13,482	89		0	17,729	439	28,581	3,158	31,739
CO	7	2,106	0		0	0	0	2,106	0	2,106
CT	4	17,579	0		0	0	0	17,579	0	17,579
DE	2	721	0		0	0	0	721	0	721
FL	15	515,776	5		0	0	0	515,781	0	515,781
GA	13	18,576	0		0	9	0	18,576	9	18,585
GU	1	288	No data		0	0	0	288	0	288
HI	2	623	20		0	50	0	643	50	693
IA	11	13,873	0		0	11	0	13,873	11	13,884
IL	42	161,983	88		0	24,504	2,509	162,071	27,013	189,084
IN	35	166,075	526	26,140	29,037		17	221,609	186	221,795
KS	11	6,607	16		0	2	31,587	6,626	31,587	38,213
KY	20	23,003	840		0	323	0	24,103	63	24,166
LA	51	89,494	1,072		3	4,722	0	92,701	2,590	95,291
MA	7	4,948	0		0	5	262	4,948	267	5,215
MD	11	13,018	0		0	0	0	13,018	0	13,018
ME	3	6,208	No data		0	0	17	6,208	17	6,225
MI	26	104,586	0		0	463	2,040	104,836	2,253	107,089
MN	4	5,369	0		0	6	70	5,371	74	5,445
MO	20	59,389	6		0	8	84	59,400	87	59,487
MS	8	46,209	277		0	0	0	46,487	0	46,487
MT	4	1,192	8		0	17	0	1,216	1	1,217
NC	11	5,273	21		0	2,405	32	6,981	750	7,731
ND	4	1,934	2		0	0	893	1,936	893	2,829
NE	1	1,465	No data		0	9,853	0	1,465	9,853	11,318
NJ	21	17,753	629		0	712	5	18,382	717	19,099
NM	11	10,637	5		5	0	1,199	10,647	1,199	11,846
NV	1	8,075	No data		0	0	0	8,075	0	8,075
NY	19	6,141	0		0	0	500	6,141	500	6,641
OH	47	51,153	37		0	12,718	667	51,198	13,376	64,574
OK	10	28,605	299		0	6,801	48	35,327	426	35,753
OR	3	16,276	0		0	0	3	16,276	3	16,279

6. POTENTIAL FOR HUMAN EXPOSURE

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

State ^c	RF ^d	Air ^e	Reported amounts released in pounds per year ^b							On- and off-site
			Water ^f	UI ^g	Land ^h	Other ⁱ	Total release			
							On-site ^j	Off-site ^k		
PA	55	95,520	643	0	9,646	4,065	96,174	13,700	109,874	
PR	12	1,745	0	0	0	0	1,745	0	1,745	
SC	11	37,030	22,000	0	0	0	59,030	0	59,030	
SD	3	52	No data	0	1	0	52	1	53	
TN	6	4,706	No data	0	260	0	4,706	260	4,966	
TX	127	282,582	738	204,570	11,548	9,282	470,932	37,788	508,720	
UT	8	3,999	5	0	250	0	4,003	250	4,253	
VA	11	1,357	8	0	2	0	1,365	2	1,367	
VI	3	1,667	0	0	25	0	1,667	25	1,692	
VT	1	4	No data	0	0	600	4	600	604	
WA	15	4,840	0	0	1,087	0	5,537	390	5,927	
WI	9	15,802	39	0	1,929	9	15,840	1,938	17,778	
WV	10	85,154	63	0	10,983	110,190	85,221	121,169	206,390	
WY	9	676	No data	0	1	250	677	250	927	
Total	781	2,068,353	27,502	230,718	366,742	165,023	2,551,993	306,345	2,858,337	

Source: TRI02 2004 (Data are from 2002)

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

6. POTENTIAL FOR HUMAN EXPOSURE

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 2.1 million pounds of naphthalene, amounting to about 72% of the total environmental release under the TRI program, was discharged to the air from manufacturing and processing facilities in the United States in 2002 (TRI02 2004). 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

Estimated releases of 27.5 thousand pounds (21.5 metric tons) of naphthalene to surface water from 781 domestic manufacturing and processing facilities in 2002, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2004). These releases are summarized in Table 6-1.

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,

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 2004). 1-Methylnaphthalene and 2-methylnaphthalene 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).

6. POTENTIAL FOR HUMAN EXPOSURE

As shown in Table 6-1, an estimated total of 27,502 pounds of naphthalene, amounting to about 1.0% of the total environmental release, was discharged to surface water from manufacturing and processing facilities in the United States in 2002 (TRI02 2004). An additional 230,718 pounds (8.0% 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

Estimated releases of 366 million pounds reported under the TRI program (166.7 metric tons) of naphthalene to soils from 781 domestic manufacturing and processing facilities in 2002, accounted for about 12.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2004). An additional 0.231 million pounds (104.8 metric tons), constituting about 8.0% of the total TRI environmental emissions, were released via underground injection from facilities required to report to the TRI (TRI02 2004). These releases are summarized in Table 6-1.

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.

The residuals produced in gas production by coal carbonization, carbureted water gas production, or oil gas production at manufactured gas plants (MGPs) included PAHs (naphthalene, anthracene, phenanthrene and benzo[1]pyrene). These residuals were deposited on site in tar wells, sewers, nearby pits, or streams resulting in widespread soil and groundwater contamination (Luthy et al. 1994).

As shown in Table 6-1, an estimated 366,742 pounds of naphthalene, amounting to about 8.1% of the total environmental release, was discharged to land from manufacturing and processing facilities producing and using naphthalene in the United States in 2002 (TRI02 2004). 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. POTENTIAL FOR HUMAN EXPOSURE

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 4.6×10^{-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%)

6. POTENTIAL FOR HUMAN EXPOSURE

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 (3.60×10^{-4} and 4.99×10^{-4} atm·m³/mol) for 1-methylnaphthalene and 2-methylnaphthalene are of similar magnitude to these properties for naphthalene (HSDB 2004; 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 2004) 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 2004). 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} cm³/molecule·sec (Atkinson et al. 1987) and the atmospheric half-life for naphthalene based on this reaction is <1 day. The

6. POTENTIAL FOR HUMAN EXPOSURE

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 $5.23 \times 10^{-11} \text{ cm}^3/\text{molecule-sec}$ for 1-methylnaphthalene and 2-methylnaphthalene, respectively. Based on an atmospheric hydroxyl radical concentration of $1 \times 10^6/\text{cm}^3$, 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.

6. POTENTIAL FOR HUMAN EXPOSURE

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).

6. POTENTIAL FOR HUMAN EXPOSURE

In contaminated subsurface soils often found at former MGP sites, naphthalene is present as a component coal tar, a dense nonaqueous-phase liquid (DNAPL). It may exist in the subsurface in the form of trapped pools of organic liquid or as immobilized macroporous ganglia. Slow dissolution of naphthalene and other PAHs from DNAPLs into the aqueous phase causes them to be unavailable to the microorganism, thus resulting in the dissolution of the PAHs being the rate-limiting step in their biodegradation (Thomas et al. 1986). Using phenanthrene as a test substance, Birman and Alexander (1996) showed that the viscosity of the NAPL may reflect a slower diffusion of the aromatic substrate in the more viscous NAPLs and its subsequent slower mass transfer to water. Ghoshal and Luthy (1996) demonstrated that a very large fraction of naphthalene can be biodegraded from an accessible coal-tar-NAPL (free flowing) by microorganisms in bioslurry systems. Metabolically active microflora were detected beneath the water table at a former MGP sites from 2.6 to 30.8 m below the ground surface. The subsurface micorflora appeared to be acclimated to the presence of PAHs and were found to mineralize naphthalene (8–55%) in sediment-water microcosms under aerobic conditions. Naphthalene biodegradation half-lives ranged from 18 to 480 days (Durrant et al. 1994).

Naphthalene remaining in soil for extended periods of time was shown to become less available to bacteria and earthworms (Kelsey and Alexander 1997).

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

Reliable evaluation of the potential for human exposure to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is

6. POTENTIAL FOR HUMAN EXPOSURE

bioavailable. The analytical methods available for monitoring naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in a variety of environmental media are detailed in Chapter 7.

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 $5.19 \mu\text{g}/\text{m}^3$, 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 $0.94 \mu\text{g}/\text{m}^3$ has been reported (Howard 1989). An average naphthalene concentration of $170 \mu\text{g}/\text{m}^3$ 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 $3.3 \mu\text{g}/\text{m}^3$ (Propper 1988). Average naphthalene concentrations ranging from 10 to $888 \text{ ng}/\text{m}^3$ were measured in several sites in Phoenix and Tucson, Arizona from 1994 to 1996 (Zielinska et al. 1998). A mean naphthalene concentration of $0.129 \text{ ng}/\text{m}^3$ 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 $4.6 \mu\text{g}/\text{m}^3$ (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 $1,600 \mu\text{g}/\text{m}^3$ (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 $32 \mu\text{g}/\text{m}^3$, 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 to $1.82 \mu\text{g}/\text{m}^3$ respectively (Chuang et al. 1999). In homes with smokers, indoor and outdoor air concentrations were measured to be 2.2 and $0.3 \mu\text{g}/\text{m}^3$, respectively. Comparable values in homes without smokers were 1.0 and $0.1 \mu\text{g}/\text{m}^3$, respectively (EPA 1991e; IARC 1993). The average reported concentration of naphthalene inside automobiles in commuter traffic is about $4.5 \mu\text{g}/\text{m}^3$ (Lofgren et al. 1991).

Naphthalene has also been detected in air in industrial facilities. Reported naphthalene vapor levels ranged from 11 to $1,100 \mu\text{g}/\text{m}^3$ in a coke plant and from 0.72 to $310 \mu\text{g}/\text{m}^3$ in an aluminum reduction plant

6. POTENTIAL FOR HUMAN EXPOSURE

(Bjorseth et al. 1978a, 1978b). Reported particulate levels for the same facilities ranged from nondetected to $4.4 \mu\text{g}/\text{m}^3$, and from 0.9 to $4 \mu\text{g}/\text{m}^3$, respectively.

Naphthalene has been detected in the emissions from motor vehicles. Mean concentrations of 104.3, 31.9, and $54.1 \mu\text{g}/\text{m}^3$ 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 $162.5 \text{ mg}/\text{m}^3$ 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 $\mu\text{g}/\text{m}^3$ 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 $\mu\text{g}/\text{m}^3$ of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, 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).

Shauer et al. (2002) compared the tailpipe emissions of catalyst- and noncatalyst-converter-equipped motor vehicles. Approximately $1,000 \mu\text{g}/\text{km}^{-1}$ of naphthalene and 2-methylnaphthalene and $500 \mu\text{g}/\text{km}^{-1}$ of 1-methylnaphthalene were detected in the catalyst-equipped vehicles. Approximately $50,000 \mu\text{g}/\text{km}^{-1}$ of naphthalene and 2-methylnaphthalene and $30,000 \mu\text{g}/\text{km}^{-1}$ of 1-methylnaphthalene were detected in the noncatalyst converter-equipped vehicles.

1-Methylnaphthalene and 2-methylnaphthalene have been reported in ambient air at average concentrations of 0.51 and $0.065 \mu\text{g}/\text{m}^3$, 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 $1.5 \mu\text{g}/\text{m}^3$ (EPA 1988g).

6. POTENTIAL FOR HUMAN EXPOSURE

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-methylnaphthalene, 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

6. POTENTIAL FOR HUMAN EXPOSURE

concentrations of naphthalene ranged from 128.9 to 496.6 $\mu\text{g/L}$ (Kinman et al. 1995). Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene have been detected in groundwater at Gas Works Park, Seattle, Washington, in the range of 0.02–12, 0.02–1.1, and 0.03–1.4 mg/L , respectively (Turney and Goerlitz 1990). Gas Works Park is located on the site of a coal and oil gasification plant that ceased operation in 1956.

1-Methylnaphthalene and 2-methylnaphthalene were reported in an urban snow-pack in Michigan at concentrations of <0.05 – 0.177 and <0.05 – 0.251 $\mu\text{g/L}$, 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 $\mu\text{g/kg}$ (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 $\mu\text{g/g}$ 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 $\mu\text{g/kg}$ in sludge-treated soils (Wild et al. 1990). Methylnaphthalenes (isomer not specified) were reported at a concentration of 2.9 $\mu\text{g/g}$ in coal-tar contaminated soil (Yu et al. 1990). Hawthorne et al. have reported concentration of naphthalene to be 48 mg/kg in the soil from an unspecified manufactured gas plant in Midwestern United States (Hawthorne et al. 2001). Naphthalene and 2-methylnaphthalene have been detected in groundwater at Gas Works Park, Seattle, Washington, in the range of 0–46 and 0–6.3 mg/L , respectively (Turney and Goerlitz 1990). Gas Works Park is located on the site of a coal and oil gasification plant that ceased operation in 1956.

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 $\mu\text{g/kg}$ (Staples et al. 1985). Another analysis of STORET data indicated that concentrations in positive sediment samples ranged from 0.02 to 496 $\mu\text{g/kg}$ (EPA 1982d). Naphthalene and methylnaphthalenes (isomers not specified) were

6. POTENTIAL FOR HUMAN EXPOSURE

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 $\mu\text{g}/\text{kg}$, respectively while concentrations of methyl-naphthalenes were 50.4 and 55.3 $\mu\text{g}/\text{kg}$, respectively. Naphthalene and methyl-naphthalenes concentrations in nearby noncontaminated estuarine sediments were 2.1 and 1.9 $\mu\text{g}/\text{kg}$, 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 $\mu\text{g}/\text{kg}$ 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 largest 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 methyl-naphthalene (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 methyl-naphthalenes (isomer not specified) were detected at concentrations of 7.15 and 65.11 $\mu\text{g}/\text{kg}$ of salmon tissue, respectively, and at 12.9 and 17.3 $\mu\text{g}/\text{kg}$ 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). Methyl-naphthalenes have occasionally been detected in fish from polluted waters. 2-Methyl-naphthalene was reported at concentrations ranging from 0.4 to 320 $\mu\text{g}/\text{g}$ in fish from Ohio waters, but neither isomer of methyl-naphthalene was detected in muscle tissue of fish from polluted areas of Puget Sound (GDCH 1992). Methyl-naphthalenes were also detected in oysters in Australia at <0.3–

6. POTENTIAL FOR HUMAN EXPOSURE

2 µg/g. Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were detected at mean concentrations of 1.98, 0.96, and 1.98 ng/g, respectively, in farmed salmon and at 2.15, 1.53, and 2.93 ng/g, respectively, in wild salmon from the Pacific coast (Easton et al. 2002).

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

6. POTENTIAL FOR HUMAN EXPOSURE

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 $\mu\text{g}/\text{cigarette}$, 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 $\mu\text{g}/\text{kg}$ (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).

Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were among the chemicals detected in Lower Manhattan in the aftermath of the destruction of the World Trade Center, New York City, New York on September 11th, 2001. Concentration of naphthalene ranged from 699 ng/m^3 on 9/26–9/27 to 42 ng/m^3 on 10/21–10/22. The concentration of 1-methylnaphthalene ranged from 178 to 100 ng/m^3 and that of 2-methylnaphthylene ranged from 267 to 165 ng/m^3 for the same days (Swartz et al. 2003).

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 $\mu\text{g}/\text{m}^3$ 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

6. POTENTIAL FOR HUMAN EXPOSURE

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/m³ by soxhlet extraction and 1.8 mg/m³ 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 to 1.82 µg/m³, respectively (Chuang et al. 1999). In a study reporting the concentrations of volatile organic compounds (VOCs) in a wide range of environments (i.e., 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/m³ (labs) to 12.1 µg/m³ (heavily trafficked roadside) (Kim et al. 2001). A mean concentration of naphthalene was found to be 2.3 µg/m³ 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/m³) and 1-methylnaphthalene (average concentration 0.08 µg/m³) 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.

6. POTENTIAL FOR HUMAN EXPOSURE

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 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{m}^3$ and from 0 (nondetected) to 44 $\mu\text{g}/\text{m}^3$ for naphthalene-containing particulate in a coke plant. Similar measurements in an aluminum reduction plant yielded somewhat lower levels of 0.72–310 $\mu\text{g}/\text{m}^3$ for vapor and 0.08–4 $\mu\text{g}/\text{m}^3$ 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 $\mu\text{g}/\text{m}^3$ in an area sample and 19.3 $\mu\text{g}/\text{m}^3$ for a personal sample. For 2-methylnaphthalene, 17.6 $\mu\text{g}/\text{m}^3$ was the maximum area concentration reported and 31.9 $\mu\text{g}/\text{m}^3$ 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-methylnaphthalene, respectively (NIOSH 1991). The workers at greatest risk of exposure included mining machine operators, aircraft engine mechanics, and miscellaneous machine operators. The NOES data have become progressively dated, and as a consequence, less representative of current exposure situations. The number of workers exposed to naphthalene during its manufacture and subsequent use is estimated to be 250–500 in the UK and 1,500–2,000 in the European Union (EU). These estimates do not include operators handling creosote treated lumber or brush applicators or users of tar paints/membranes (EU 2002).

6. POTENTIAL FOR HUMAN EXPOSURE

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 Section 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 m³/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

6. POTENTIAL FOR HUMAN EXPOSURE

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 was among the chemicals detected at nine day care centers in Durham, Raleigh, and Chapel Hill, North Carolina (Wilson et al. 1999). Indoor and outdoor air was found to contain naphthalene at concentrations of 205 and 89.6 ng/m³, respectively. The concentrations were 0.011 ppm in soil, 0.008 ppm in dust, 0.94 ppb in liquid food, and 0.25 ppb in solid food samples. The differences in PAH concentrations between day care centers serving low-income clients and those serving middle-income clients were found to be small.

Naphthalene (mothballs) is commonly used as a moth repellent 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

6. POTENTIAL FOR HUMAN EXPOSURE

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-methylnaphthalene are available. Where adequate information is not available, ATSDR, in conjunction with 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 2004). Information that documented the physical and chemical properties of 1-methylnaphthalene and 2-methyl-

6. POTENTIAL FOR HUMAN EXPOSURE

naphthalene are also available (HSDB 2004). 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. 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 2002, became available in May of 2004. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Naphthalene producers, production locations and volumes, uses, releases, and disposal practices are well documented (Lacson et al. 2000; SRI 2004; TRI02 2004). 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.

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.

6. POTENTIAL FOR HUMAN EXPOSURE

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 1991; 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. Reliable monitoring data for the levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in the environment can be used in combination with the known body burden of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

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

6. POTENTIAL FOR HUMAN EXPOSURE

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 Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene were located. These substances are not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. These substances will be considered in the future when chemical selection is made for sub-registries to be established. The information that is

6. POTENTIAL FOR HUMAN EXPOSURE

amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2004) 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.

6. POTENTIAL FOR HUMAN EXPOSURE

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
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
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
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

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Naphthalene^a

Investigator	Affiliation	Research description	Sponsor
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	Observing microbial diversity and horizontal gene transfer in a shallow aquifer	U.S. Department of Agriculture
Hagblom 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
Huang W	Drexel University, Philadelphia, Pennsylvania	Black carbon in soils and sediments and its interactions with organic pollutants	U.S. Department of Agriculture
Huwe JK; Hakk H; Shappell NW; Shlever WL; Larsen GL; Smith DJ	Agricultural Research Service, Fargo, South Dakota	Dioxins and other environmental contaminants in food	U.S. Department of Agriculture
Xing B	University of Massachusetts, Amherst, Massachusetts	Effects of long-term tillage and cover crop systems on soil organic matter and pesticide sorption	U.S. Department of Agriculture
Chorover JD	Pennsylvania State University, University Park, Pennsylvania	Effects of mineral-organic interactions on chemical processes in soils	U.S. Department of Agriculture
Thompson ML; Sandor JA; Burras CL	Iowa State University, Ames, Iowa	Human impacts on soil; a pedogenic perspective	U.S. Department of Agriculture
Hyman MR	North Carolina State university, Raleigh, North Carolina	Physiology, biochemistry, and enzymology of microbial cometabolism	U.S. Department of Agriculture
Larson RA; Sims GK	University of Illinois, Urbana, Illinois	Phytoremediation of agrochemicals with aquatic and terrestrial plants	U.S. Department of Agriculture

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Naphthalene^a

Investigator	Affiliation	Research description	Sponsor
Simkins S	University of Massachusetts, Amherst, Massachusetts	Quantification of pesticide-derived organic carbon in microbial biomass and soil humic substances	U.S. Department of Agriculture
Pignatello JJ	Connecticut Agricultural Experimental Station, New Haven, Connecticut	Reducing the potential for environmental contamination by pesticides and other organic chemicals	U.S. Department of Agriculture
Scow KM	University of California, Davis, California	Reducing the potential for environmental contamination by pesticides and other organic chemicals	U.S. Department of Agriculture
Maier RM; Brusseau ML	University of Arizona, Tucson, Arizona	Reducing the potential for environmental contamination by pesticides and other organic chemicals	U.S. Department of Agriculture
Xing B	University of Massachusetts, Amherst, Massachusetts	Sorption of organic contaminants in soils; mechanisms and implications for desorption and bioavailability	U.S. Department of Agriculture
Rolston DE	University of California, Davis, California	Transport and transformation of trace gases in soil	U.S. Department of Agriculture

^aFEDRIP 2004

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-methylnaphthalene. 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

7. ANALYTICAL METHODS

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-naphthoyleglycine, 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

7. ANALYTICAL METHODS

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	Capillary column GC/PID	20 ng/g	76–202 (naphthalene) 77–82 (1-methylnaphthalene) 75–131 (2-methylnaphthalene)	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

^aData 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

7. ANALYTICAL METHODS

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	APHA 1992e
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

7. ANALYTICAL METHODS

Table 7-2. Analytical Methods for Determining Naphthalene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
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

^aIdentification limit in water. Detection limits for actual samples are several orders of magnitude higher, depending upon the sample matrix and extraction procedure employed.

^bBased 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

7. ANALYTICAL METHODS

Table 7-3. Analytical Methods for Determining 2-Methylnaphthalene in Environmental Samples^a

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

^aEPA 1986c

GC = gas chromatography; MS = mass spectroscopy

7. ANALYTICAL METHODS

limits or accuracy for 1-methylnaphthalene, this compound may be analyzed in environmental media by GC and HPLC methods (HSDB 1995).

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-methylnaphthalene is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and

7. ANALYTICAL METHODS

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-methylnaphthalene, 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.

7. ANALYTICAL METHODS

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-methylnaphthalene 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-methylnaphthalene, and 2-methylnaphthalene in air, water, and other media are summarized in Table 8-1.

As discussed in Chapter 2 and Appendix A, several MRLs for naphthalene (chronic-duration inhalation, acute-duration oral, and intermediate-duration oral) and chronic-duration oral MRLs for 1-methylnaphthalene and 2-methylnaphthalene have been derived.

An MRL of 0.0007 ppm (3×10^{-3} mg/m³) for chronic inhalation exposure to naphthalene is based on a LOAEL for nasal lesions in rats (Abdo et al. 2001; NTP 2000; $LOAEL_{[human\ equivalent\ concentration]} = 0.2$ ppm), and 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). An MRL of 0.6 mg/kg/day for acute oral exposure to naphthalene is based on a minimal LOAEL of 50 mg/kg/day for clinical signs of toxicity in pregnant rats and a total uncertainty factor of 90 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability). The acute-duration oral MRL of 0.6 mg/kg/day is adopted as the intermediate-duration oral MRL for naphthalene.

For chronic-duration oral exposure to 1-methylnaphthalene, an MRL of 0.07 mg/kg/day was derived based on a LOAEL of 71.6 mg/kg/day for pulmonary alveolar proteinosis in female mice exposed to 1-methylnaphthalene in the diet for 81 weeks and an uncertainty factor of 1,000 (10 for using a LOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

For chronic-duration oral exposure to 2-methylnaphthalene, an MRL of 0.04 mg/kg/day was derived based on the lower 95% confidence limit on a benchmark dose associated with 5% extra risk ($BMDL_{05} = 4$ mg/kg/day) for pulmonary alveolar proteinosis in male mice exposed to 2-methylnaphthalene in the diet for 81 weeks and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

The EPA calculated an oral exposure RfD of 2×10^{-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 2005; NTP 1980b). An inhalation RfC of 3×10^{-3} mg/m³ for naphthalene was derived

8. REGULATIONS AND ADVISORIES

based on a LOAEL of 10 ppm ($\text{LOAEL}_{[\text{human equivalent concentration}]}=9.3 \text{ mg/m}^3$) for nasal lesions in mice exposed by inhalation for 2 years (IRIS 2005; NTP 1992a).

The EPA (2003r) calculated an oral exposure RfD of 0.004 mg/kg-day for 2-methylnaphthalene based on a value of 3.5 mg/kg-day for a 95% lower confidence limit on a dose associated with 5% extra risk (BMDL_{05}) for pulmonary alveolar proteinosis in mice exposed to 2-methylnaphthalene in the diet for 81 weeks.

The EPA is currently conducting a comprehensive review of the available environmental and toxicity data of naphthalene as part of its FIFRA re-registration process. The results of this review are expected in March 2008.

8. REGULATIONS AND ADVISORIES

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 2002
WHO	Drinking water guideline	No data	
NATIONAL			
Regulations and Guidelines:			
a. Air:			
ACGIH	TLV (8-hour TWA) Naphthalene ^b	10 ppm	ACGIH 2003
	STEL	15 ppm	
EPA	Hazardous air pollutant	Naphthalene	EPA 2003g 40 CFR 63, Table 1
	National emission standards for hazardous air pollutants		EPA 2003h 40 CFR 61.134
	Naphthalene processing, final coolers, and final-cooler cooling towers at coke by-product recovery plants	No (zero) emissions are allowed	
NIOSH	REL (10-hour TWA) Naphthalene	10 ppm	NIOSH 2003
	STEL	15 ppm	
	IDLH	250 ppm	
OSHA	PEL (8-hour TWA) for general industry Naphthalene	10 ppm	OSHA 2003a 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for construction industry Naphthalene	10 ppm	OSHA 2003c 29 CFR 1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry Naphthalene	10 ppm	OSHA 2003b 29 CFR 1915.1000
USC	Hazardous air pollutant	Naphthalene	USC 2003 42 USC 7412
b. Water			
EPA	Drinking water health advisories		EPA 2002a
	1-day (10-kg child)	0.5 mg/L	
	10-day (10-kg child)	0.5 mg/L	
	DWEL ^c	0.7 mg/L	
	Life-time ^d	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
	Hazardous substance designated in accordance with Section 311 (b)(2)(A) of the Clean Water Act	Naphthalene	EPA 2003p 40 CFR 116.4

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	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 ^e	
EPA	Carcinogenicity classification	Group C ^f	IRIS 2005
	RfD (oral)	2.0x10 ⁻² mg/kg/day	IRIS 2005
	RfC (inhalation)	3.0x10 ⁻³ mg/m ³	IRIS 2005
	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 and 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	
EPA	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	
	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	EPA 2003k 40 CFR 264, Appendix IX
		<u>Method</u>	<u>PQL</u>
	Naphthalene	8100	200 µg/L
		8270	10 µg/L
	2-Methylnaphthalene	8270	10 µg/L

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	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 ^g	10/03/95	
	TSCA health and safety data reporting for naphthalene ^h		EPA 2003o 40 CFR 716.120
	Effective date	08/04/95	
	Sunset date	10/03/95	
NTP	Carcinogenicity classification	Naphthalene is reasonably anticipated to be a human carcinogen (Group 2)	NTP 2005
<u>STATE</u>			
a. Air	No data		
b. Water			
Maine	Drinking water guideline	25 µg/L	HSDB 2004
Minnesota	Drinking water guideline	300 µg/L	HSDB 2004
New Jersey	Drinking water standard	300 µg/L	HSDB 2004
Washington	Drinking water guideline	14 µg/L	HSDB 2004
Wisconsin	Drinking water guideline	40 µg/L	HSDB 2004
Florida	Drinking water guideline	6.8 µg/L	HSDB 2004

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

Agency	Description	Information	Reference
<u>STATE</u> (cont.)			
c. Food	No data		
d. Other	No data		

^aGroup 2B: possibly carcinogenic to humans

^bSkin 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.

^cDWEL: a lifetime exposure concentration protection of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from drinking water.

^dLife-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.

^eA4: not classifiable as a human carcinogen

^fGroup C: a possible human carcinogen

^gReporting 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.

^hTSCATS 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; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; 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

9. REFERENCES

*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.

Abraham BM, Liu TY, Robert A, et al. 1993. Data comparison study between field and laboratory detection of polychlorinated biphenyls and polycyclic aromatic hydrocarbons of Superfund sites. *Haz Waste Haz Mater* 10:461-475.

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ACGIH. 1993. Threshold limit values (TLVs) for chemical substances in the work environment for 1993-1994. Cincinnati, OH: American Conference of Government Industrial Hygienists.

ACGIH. 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Government Industrial Hygienists.

*ACGIH. 2003. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol* 27:532-537.

*Adkins B, Van Stee EW, Simmons JE, et al. 1986. Oncogenic response of strain A/J mice to inhaled chemicals. *J Toxicol Environ Health* 17:311-322.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. *Environ Health Perspect Suppl* 103(7):103-112.

Afolabi OA, Adesulu EA, Oke OL. 1983. Polynuclear aromatic hydrocarbons in some Nigerian preserved freshwater fish species. *J Agric Food Chem* 31:1083-1090.

*Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. *Fed Regist* 54(174):37617-37634.

*Agency for Toxic Substances and Disease Registry. 1995. Toxicological profile for naphthalene, 1-methylnaphthalene, 2-methylnaphthalene. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.
<http://www.atsdr.cdc.gov/toxprofiles/tp67.html>. July 9, 2003.

Ahmad I, Pacheco M, Santos MA, et al. 2003. Naphthalene-induced differential tissue damage association with circulating fish phagocyte induction. *Ecotoxicol Environ Saf* 54:7-15.

* Cited in text

9. REFERENCES

- Ahn IS, Lion TY, Shuler ML. 1999. Validation of a hybrid two-site gamma model for naphthalene desorption kinetics. *Environ Sci Technol* 33:3241-3248.
- Ailsable J, Balks M, Atori N, et al. 1999. Polycyclic aromatic hydrocarbons in fuel-oil contaminated soils, Antarctica. *Chemosphere* 39:2201-2207.
- *Ajao OG, Adenuga MO, Ladipo JK. 1988. Colorectal carcinoma in patients under the age of 30 years: A review of 11 cases. *J Royal College Surgeons of Edinburgh* 33:277-279.
- Aktay G, Cengiz G, Söylemezoğlu T, et al. 2000. Protective effect of nitrendipine on naphthalene-induced oxidative stress. *J Fac Pharm Gazi Univ* 17(1):19-24.
- Alajbeg I, Ivankovic S, Alajbeg IZ, et al. 2002. Antiproliferative effect of non-aromatic oil fractions on squamous cell carcinoma VII: *In vitro* and preliminary *in vivo* results. *Period Biol* 104(1):89-94.
- Albero B, Sanchez-Brunete C, Tadeo J. 2002. Determination of polycyclic aromatic hydrocarbons in honey by matrix solid-phase dispersion and gas chromatography/mass spectrometry. *J AOAC Int* 86(3):576-582.
- *Alexandrov K. 1973. Effect of some derivatives of naphthalene on aryl hydrocarbon (benzo[a]pyrene) hydroxylase *in vitro*. *Experientia* 29:1209-1210.
- Alexandrov K, Frayssinet C. 1973. Brief communication: *In vivo* effect of some naphthalene-related compounds on aryl hydrocarbon (benzo[a]pyrene) hydroxylase. *J Natl Cancer Inst* 51:1067-1069.
- Allen CCR, Boyd DR, Hempenstall F, et al. 1999. Contrasting effects of a nonionic surfactant on the biotransformation of polycyclic aromatic hydrocarbons to *cis*-dihydrodiols by soil bacteria. *Appl Environ Microbiol* 65:1335-1339.
- Allen JO, Dookeran NM, Smith KA, et al. 1996. Measurement of polycyclic aromatic hydrocarbons associated with size-segregated atmospheric aerosols in Massachusetts. *Environ Sci Technol* 30:1023-1031.
- Almgren M, Grieser F, Powell JR, et al. 1979. A correlation between the solubility of aromatic hydrocarbons in water and micellar solutions, with their normal boiling points. *J Chem Eng Data* 24:285-287.
- *Altman PL, Dittmer DS. 1974. In: *Biological handbooks: Biology data book*. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.
- *Ambre J, Ruo TI, Smith-Coggins R. 1986. Mothball composition: Three simple tests for distinguishing paradichlorobenzene from naphthalene. *Ann Emerg Med* 15:724-726.
- American Chemistry Council. 2003. Comments from the Naphthalene Panel of the American Chemistry Council to NTP regarding the nomination of naphthalene for listing in the 11th Report on Carcinogens. Arlington, VA: American Chemistry Council.
- *Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3:272-290.

9. REFERENCES

- *Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 87:185-205.
- *Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. *Animal test alternatives: Refinement, reduction, replacement*. New York: Marcel Dekker, Inc., 9-25.
- *Anziulewicz JA, Dick HJ, Chiarulli EE. 1959. Transplacental naphthalene poisoning. *Am J Obstet Gynecol* 78:519-521.
- *APHA. 1992a. Method 6410 (Extractable base/neutrals and acids). In: *Standard methods for the examination of water and wastewater*. 18th ed. Washington, DC: American Public Health Association.
- *APHA. 1992b. Method 6440B (Liquid-liquid extraction chromatographic method). In: *Standard methods for the examination of water and wastewater*. 18th ed. Washington, DC: American Public Health Association.
- *APHA. 1992c. Method 6440A (Polynuclear aromatic hydrocarbons). In: *Standard methods for the examination of water and wastewater*. 18th ed. Washington, DC: American Public Health Association.
- *APHA. 1992d. Method 6210D (Purge and trap capillary-column gas chromatographic/mass spectrometric method). In: *Standard methods for the examination of water and wastewater*. 18th ed. Washington, DC: American Public Health Association.
- *APHA. 1992e. Method 6220C (Purge and trap gas chromatographic method II). In: *Standard methods for the examination of water and wastewater*. 18th ed. Washington, DC: American Public Health Association.
- *APHA. 1992f. Method 6230D (Purge and trap gas chromatographic method). In: *Standard methods for the examination of water and wastewater*. 18th ed. Washington, DC: American Public Health Association.
- API. 1991. Gasoline vapor exposure assessment at service stations. American Petroleum Institute. Environmental Sciences Department. API Publ No 4553.
- Arena JM. 1970. *Poisoning: Toxicology--symptoms--treatments*. 2nd ed. Springfield, IL: Charles C. Thomas, 73.
- Ares J. 1993. Occupational exposure to PAHs measured with UV derivative spectroscopy corrected for advective and gaseous losses. *Bull Environ Contam Toxicol* 51:203-210.
- *Arfsten DP, Davenport R, Schaeffer DJ. 1994. Reversion of bioluminescent bacteria (Mutatox) to their luminescent state upon exposure to organic compounds, munitions, and metal salts. *Biomed Environ Sci* 7:144-149.
- Athanasious M, Tsantali C, Trachana M, et al. 1995. Hemolytic anemia in a female newborn infant whose mother inhaled naphthalene before delivery. *J Pediatr* 130(4):680-681.
- Atkinson R, Aschmann SM. 1987. Kinetics of the gas-phase reactions of alkylnaphthalenes with O₃, N₂O₅ and OH radicals at 298±2 K. *Atmos Environ* 21:2323-2326.

9. REFERENCES

- *Atkinson R, Arey J, Zielinska B, et al. 1987. Kinetics and products of the gas-phase reactions of OH radicals and N₂O₅ with naphthalene and biphenyl. *Environ Sci Technol* 21:1014-1022.
- *Atkinson R, Aschmann SM, Pitts JN Jr. 1984. Kinetics of the reactions of naphthalene and biphenyl with OH radicals and with O₃ at 294±1 K. *Environ Sci Technol* 18:110-113.
- Baehr AL, Stackelberg PE, Baker RJ. 1999. Evaluation of the atmosphere as a source of volatile organic compounds in shallow groundwater. *Water Resour Res* 35:127-136.
- *Bagchi D, Bagchi M, Balmoori J, et al. 1998a. Induction of oxidative stress and DNA damage by chronic administration of naphthalene to rats. *Res Commun Mol Pathol Pharmacol* 101(3):249-257.
- Bagchi M, Bagchi D, Balmoori J, et al. 1998b. Naphthalene-induced oxidative stress and DNA damage in cultured macrophage J774A.1 cells. *Free Radical Biol Med* 25(2):137-143.
- *Bagchi D, Balmoori J, Bagchi M, et al. 2000. Role of *p53* tumor suppressor gene in the toxicity of TCDD, endrin, naphthalene, and chromium (VI) in liver and brain tissues of mice. *Free Radic Biol Med* 28(6):895-903.
- *Bagchi D, Balmoori J, Bagchi M, et al. 2002. Comparative effect of TCDD, endrin, naphthalene and chromium (VI) on oxidative stress and tissue damage in the liver and brain tissues of mice. *Toxicology* 175:73-82.
- Bagchi M, Balmoori J, Ye X, et al. 2001. Protective effect of melatonin on naphthalene-induced oxidative stress and DNA damage in cultured macrophage J774A.1 cells. *Mol Cell Biochem* 221:49-55.
- *Bahnick DA, Doucette WJ. 1988. Use of molecular connectivity indices to estimate soil sorption coefficients for organic chemicals. *Chemosphere* 17:1703-1715.
- Bakermans C, Hohnstock-Ashe AM, Padmanabhan S, et al. 2002. Geochemical and physiological evidence for mixed aerobic and anaerobic field biodegradation of coal tar waste by subsurface microbial communities. *Microb Ecol* 44(2):107-117.
- *Bakke J, Struble C, Gustafsson JA, et al. 1985. Catabolism of premercapturic acid pathway metabolites of naphthalene to naphthols and methylthio-containing metabolites in rats. *Proc Natl Acad Sci USA* 82:668-671.
- *Bakke JE, Davison KL, Larsen GL. 1990. Evidence for the absence of cysteine S-conjugate N-acetyltransferase activity in the metabolism of propachlor, naphthalene, and dichlobanil in calves. *Xenobiotica* 20:801-807.
- Balch GC, Metcalfe CD, Huestis SY. 1995. Identification of potential fish carcinogens in sediment from Hamilton Harbour, Ontario, Canada. *Environ Toxicol Chem* 14:79-91.
- *Banerjee S, Baughman GL. 1991. Bioconcentration factors and lipid solubility. *Environ Sci Technol* 25:536-539.
- *Barbee GC. 1994. Fate of chlorinated aliphatic hydrocarbons in the vadose zone and ground water. *Ground Water Monit Remed* 14:129-140.

9. REFERENCES

- *Barfknecht TR, Naismith RW, Matthews RJ. 1985. Rat hepatocyte primary culture/DNA repair test. PH 311-TX-008-85. 5601-56-1 (unpublished material). Submitted to U.S. EPA by Texaco, Inc. Office of Toxic Substances microfiche no. OTS0513638.
- *Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. *Regul Toxicol Pharmacol* 8:471-486.
- Baudot PH, Viriot ML, Andre JC, et al. 1991. Analysis of polyaromatic hydrocarbons by synchronous fluorescence spectrometry: Application to occupational health. *Analysis* 19:85-97.
- Bayard R, Barna L, Mahjoub B, et al. 2000. Influence of the presence of PAHs and coal tar on naphthalene sorption in soils. *J Contam Hydrol* 46(1-2):61-80.
- Baynes RE, Brooks JD, Budsaba K, et al. 2001. Mixture effects of JP-8 additives on the dermal disposition of jet fuel components. *Toxicol Appl Pharmacol* 175:269-281.
- Baynes RE, Brooks JD, Riviere JE, et al. 2000. Membrane transport of naphthalene and dodecane in jet fuel mixtures. *Toxicol Ind Health* 16:225-238.
- Beck AJ, Alcock RE, Wilson SC, et al. 1995. Long-term persistence of organic chemicals in sewage sludge-amended agricultural land: A soil quality perspective. *Adv Agron* 55:345-391.
- Beck AJ, Johnson DL, Jones KC. 1996. The form and bioavailability of non-ionic organic chemicals in sewage sludge-amended agricultural soils. *Sci Total Environ* 185:125-129.
- Becker L, Matuschek G, Lenoir D, et al. 2001. Leaching behaviour of wood treated with creosote. *Chemosphere* 42:301-308.
- Bedient PB, Rodgers AC, Bouvette TC, et al. 1984. Ground-water quality at a creosote waste site. *Ground Water* 22:318-329.
- *Bender ME, Huggett RJ. 1989. Polynuclear aromatic hydrocarbon residues in shellfish: Species variations and apparent intraspecific differences. In: Kaiser HE, ed. *Comparative aspects of tumor development*. Dordrecht (Netherlands): Kluwer Academic Publishers, 226-234.
- Bennett ER, Metcalfe TL, Metcalfe CD. 1996. Semi-permeable membrane devices (SPMDS) for monitoring organic contaminants in the Otonabee River, Ontario. *Chemosphere* 33:363-375.
- Benoit FM, LeBel GL, Williams DT. 1979. Polycyclic aromatic hydrocarbon levels in Eastern Ontario drinking waters, 1978. *Bull Environ Contam Toxicol* 23:774-778.
- *Benson WH, Dorough HW. 1984. Comparative ester hydrolysis of carbaryl and ethiofencarb in four mammalian species. *Pestic Biochem Physiol* 21:199-206.
- Berg GL, ed. 1984. *Farm chemicals handbook 1984*. Willoughby, OH: Meister Publishing Co., C159.
- *Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. *Endometriosis: Advanced management and surgical techniques*. New York, NY: Springer-Verlag.
- Bernabei M, Reda R, Galiero R, et al. 2003. Determination of total and polycyclic aromatic hydrocarbons in aviation jet fuel. *J Chromatogr A* 985(1-2):197-203.

9. REFERENCES

- *Berry MR, Johnson LS, Jones JW, et al. 1997. Dietary characterizations in a study of human exposure in the lower Rio Grande valley: I. Foods and beverages. *Environ Int* 23(5):675-692.
- *Bieniek G. 1994. The presence of 1-naphthol in the urine of industrial workers exposed to naphthalene. *Occup Environ Med* 51:357-359.
- Bieniek G. 1997. Urinary naphthols as an indicator of exposure to naphthalene. *Scand J Work Environ Health* 23:414-420.
- Billings RE, Miller NE, Dabbs SE, et al. 1990. Comparison of the toxicity of naphthalene and naphthalene-1,2-dihydrodiol (DIOL). *Biological Reactive Intermediates IV*:681-684.
- Birdsall R, Kikor JJ, Cheney MA. 2001. Uptake of polycyclic aromatic hydrocarbon compounds by the gills of a bivalve mollusk *Elliptio complanata*. *Environ Toxicol Chem* 20:309-316.
- *Birman I, Alexander M. 1996. Effect of viscosity of nonaqueous-phase liquids (NAPLs) on biodegradation of NAPL constituents. *Environ Toxicol Chem* 15(10):1683-1686.
- Birnbaum LS, McKinney JD. 1985. A persistent hexabromonaphthalene isomer is 2,3,4,5,6,7-hexabromonaphthalene. *J Toxicol Environ Health* 16:219-227.
- Birnbaum LS, Darcey DJ, McKinney JD. 1983. Hexabromonaphthalene contaminants of polybrominated biphenyls: Chemical composition and disposition in the rat. *J Toxicol Environ Health* 12:555-573.
- *Bjorseth A, Bjorseth O, Fjeldstad PE. 1978a. Polycyclic aromatic hydrocarbons in the work atmosphere: I. Determination in an aluminum reduction plant. *Scand J Work Environ Health* 4:212-223.
- *Bjorseth A, Bjorseth O, Fjeldstad PE. 1978b. Polycyclic aromatic hydrocarbons in the work environment. II. Determination in a coke plant. *Scand J Work Environ Health* 4:224-236.
- Bjorseth A, Bjorseth O, Fjeldstad PE. 1981. Polycyclic aromatic hydrocarbons in the work atmosphere: Determination of area-specific concentrations and job-specific exposure in a vertical pin Soderberg aluminum plant. *Scand J Work Environ Health* 7:223-232.
- *Blomberg S, Roerade J. 1988. An evaluation and comparison of micro-techniques for concentration of volatile components from dilute solutions. *Chromatographia* 25:21-25.
- Bock KW, van Ackeren G, Lorch F, et al. 1976. Metabolism of naphthalene to naphthalene dihydrodiol glucuronide in isolated hepatocytes and in liver microsomes. *Biochem Pharmacol* 25:2351-2356.
- *Bock KW, von Clausbruch UC, Winne D. 1979. Absorption and metabolism of naphthalene and benzo[a]pyrene in the rat jejunum in situ. *Med Biol* 57:262-264.
- Bohon RL, Claussen WF. 1951. The solubility of aromatic hydrocarbons in water. *J Am Chem Soc* 73:1571-1578.
- Bolton JL. 2000. Role of quinones in toxicology. *Chem Res Toxicol* 13:135-160.

9. REFERENCES

- *Bolton JL, Trush MA, Penning TM, et al. 2000. Role of quinones in toxicology. *Chem Res Toxicol* 13(3):2-17.
- Bond DL, Thodos G. 1960. Vapor pressures of alkyl aromatic hydrocarbons. *J Chem Eng Data* 5:289-292.
- Bond JA, Wallace LA, Ostermon-Golkar S, et al. 1992. Symposium overview. Assessment of exposure to pulmonary toxicants: Use of biological markers. *Fundam Appl Tox* 18:161-174.
- Boogaard PJ, Vansittert NJ. 1994. Exposure to polycyclic aromatic hydrocarbons in petrochemical industries by measurement of urinary 1-hydroxypyrene. *Occup Environ Med* 51:250-258.
- *Boom A, Marsalek J. 1988. Accumulation of polycyclic aromatic hydrocarbons (PAHs) in an urban snowpack. *Sci Total Environ* 74:133-148.
- Booth GM, Bradshaw WS, Carter MW. 1983. Screening of priority chemicals for potential reproductive hazard, contract 210-81-6012. Cincinnati, OH: National Institute for Occupational Safety and Health, PB83213017.
- *Bos RP, Theuws JL, Jongeneelen FJ, et al. 1988. Mutagenicity of bi-, tri- and tetra-cyclic aromatic hydrocarbons in the "taped-plate assay" and in the conventional *Salmonella* mutagenicity assay. *Mutat Res* 204:203-206.
- Bosveld A, de Bie PAF, van den Brink, et al. 2002. *In vitro* EROD induction equivalency factors for the 10 PAHs generally monitored in risk assessment studies in The Netherlands. *Chemosphere* 49:75-83.
- Botello AV, Calva LG. 1998. Polycyclic aromatic hydrocarbons in sediments from Pueblo Viejo, Tamiahua, and Tampamachoco Lagoons in the southern Gulf of Mexico. *Bull Environ Contam Toxicol* 60:96-103.
- Botello AV, Villanueva S, Diaz GG. 1997. Petroleum pollution in the Gulf of Mexico and Caribbean Sea. *Rev Environ Contam Toxicol* 153:91-118.
- Botello AV, Villaneuva SF, Diaz GG, et al. 1998. Polycyclic aromatic hydrocarbons in sediments from Salina Cruz Harbour and coastal areas, Oaxaca, Mexico. *Mar Pollut Bull* 36:554-558.
- *Bourne MC, Young L. 1934. The metabolism of naphthalene in rabbits. *Biochem J* 28:803-808.
- Bouwer EJ, Zhang W, Wilson LP, et al. 1996. Biodegradation of coal tar constituents in aquifer sediments. In: Rubin H, ed. *Soil aquifer pollution*. Berlin: Springer-Verlag, 173-190.
- Bowes RC, Ramos KS. 1994. Assessment of cell-specific cytotoxic responses of the kidney to selected aromatic hydrocarbons. *Toxicol In Vitro* 8:1151-1160.
- Boyd EM, Killham K, Wright J, et al. 1997. Toxicity assessment of xenobiotic contaminated groundwater using lux modified *Pseudomonas fluorescens*. *Chemosphere* 35:1967-1985.
- Boyd MR. 1977. Evidence for the cell as a site of cytochrome P450-dependent mixed-function oxidase activity in lung. *Nature* 269:713-715.

9. REFERENCES

- Boyland E, Sims P. 1958. Metabolism of polycyclic compounds. 12. An acid-labile precursor of 1-naphthylmercapturic acid and naphthol: an N-acetyl-5-(1,2-dihydrohydroxynaphthyl)-L-cysteine. *Biochem J* 68:440-447.
- Boyland E, Sims P. 1960. Metabolism of polycyclic compounds. 16. The metabolism of 1,2-dihydronaphthalene and 1,2-epoxy-1,2,3,4-tetrahydronaphthalene. *Biochem J* 77:175-181.
- Boyland E, Solomon JB. 1955. Metabolism of polycyclic compounds. 8. Acid-labile precursors of naphthalene produced as metabolites of naphthalene. *Biochem J* 59:518-522.
- Boyland E, Weigert F. 1947. Metabolism of carcinogenic compounds. *Br Med Bull* 4:354-359.
- Boyland E, Wiltshire GH. 1953. Metabolism of polycyclic compounds. 7. The metabolism of naphthalene, 1-naphthol and 1,2-dihydroxy-1,2-dihydronaphthalene by animals. *Biochem J* 53:636-641.
- Boyland E, Ramsay GS, Sims P. 1961. Metabolism of polycyclic compounds. 18. The secretion of metabolites of naphthalene. 1,2-dihydronaphthalene and 1,2-epoxy-1,2,3,4-tetrahydronaphthalene in rat bile. *Biochem J* 78:376-384.
- *Bradley LJ, Magee BH, Allen SL. 1994. Background levels of polycyclic aromatic hydrocarbons (PAH) and selected metals in New England urban soils. *J Soil Contam* 3:349-361.
- Bradley RS, Cleasby TG. 1953. The vapour pressure and lattice energy of some aromatic ring compounds. *J Chem Soc (Part II)*: 1690-1692.
- *Breger RK, Franklin RB, Lech JJ. 1981. Metabolism of 2-methylnaphthalene to isomeric dihydrodiols by hepatic microsomes of rat and rainbow trout. *Drug Metab Dispos* 9:88-93.
- *Breger RK, Novak RF, Franklin RB, et al. 1983. Further structural analysis of rat liver microsomal metabolites of 2-methylnaphthalene. *Drug Metab Dispos* 11:319-323.
- *Bregman R. 1954. Mothball poisoning. A case presentation. *Clin Proc Child Hosp Dist Columbia* 9:1-5.
- Brindle ID, Li XF. 1990. Investigation into the factors affecting performance in the determination of polycyclic aromatic hydrocarbons using capillary gas chromatography-mass spectrometry with splitless injection. *J Chromatogr* 498:11-24.
- Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: The C.V. Mosby Company, :103-104.
- *Brooks JM, Kennicutt MC, Wade TL, et al. 1990. Hydrocarbon distributions around a shallow water multiwell platform. *Environ Sci Technol* 24:1079-1085.
- *Brown KW, Donnelly KC. 1988. An estimation of risk associated with the organic constituents of hazardous and municipal waste landfill leachates. *Haz Waste Haz Mater* 5(1):1-30.
- Brown SK, Sim MR, Abramson MJ, et al. 1994. Concentrations of volatile organic compounds in indoor air - A review. *Indoor Air* 4:123-134.

9. REFERENCES

- Brubaker WW, Jr, Hites RA. 1998. OH reaction kinetics of polycyclic aromatic hydrocarbons and polychlorinated dibenzo-p-dioxins and dibenzofurans. *J Phys Chem* 102:915-921.
- Brunson EL, Canfield TJ, Dwyer FJ, et al. 1998. Assessing the bioaccumulation of contaminants from sediments of the upper Mississippi River using field-collected oligochaetes and laboratory-exposed *lumbriculus variegatus*. *Arch Environ Contam Toxicol* 35:191-201.
- *Brusseau ML. 1991a. Cooperative sorption of organic chemicals in systems composed of low organic carbon aquifer materials. *Environ Sci Technol* 25:1747-1752.
- Brusseau ML. 1991b. Nonequilibrium sorption of organic chemicals: Elucidation of rate-limiting processes. *Environ Sci Technol* 25:134-142.
- *Buckpitt AR, Bahnson LS. 1986. Naphthalene metabolism by human lung microsomal enzymes. *Toxicology* 41:333-341.
- *Buckpitt AR, Franklin RB. 1989. Relationship of naphthalene and 2-methylnaphthalene metabolism to pulmonary bronchiolar epithelial cell necrosis. *Pharmacol Ther* 41:393-410.
- *Buckpitt AR, Warren DL. 1983. Evidence of hepatic formation, export and covalent binding of reactive naphthalene metabolites in extrahepatic tissues *in vivo*. *J Pharmacol Exp Ther* 225:8-16.
- *Buckpitt AR, Bahnson LS, Franklin RB. 1984a. Hepatic and pulmonary microsomal metabolism of naphthalene to glutathione adducts: Factors affecting the relative rates of conjugate formation. *J Pharmacol Exp Ther* 231:291-300.
- Buckpitt AR, Bahnson LS, Franklin RB. 1984b. Intermediacy of 1-naphthol in the covalent binding and pulmonary toxicity of naphthalene [abstract]. *Toxicologist* 4:134.
- *Buckpitt AR, Bahnson LS, Franklin RB. 1985. Evidence that 1-naphthol is not an obligate intermediate in the covalent binding and the pulmonary bronchiolar necrosis by naphthalene. *Biochem Biophys Res Commun* 126:1097-1103.
- *Buckpitt AR, Bahnson LS, Franklin RB. 1986. Comparison of the arachidonic acid and NADPH-dependent microsomal metabolism of naphthalene and 2-methylnaphthalene and the effect of indomethacin on the bronchiolar necrosis. *Biochem Pharmacol* 35:645-650.
- *Buckpitt A, Boland B, Isbell M, et al. 2002. Naphthalene-induced respiratory tract toxicity: Metabolic mechanisms of toxicity. *Drug Metab Rev* 34(4):791-820.
- *Buckpitt AR, Buonarati M, Avey LB, et al. 1992. Relationship of cytochrome P450 activity to cell cytotoxicity. II. Comparison of stereo-selectivity of naphthalene epoxidation in lung and nasal mucosa of mouse, hamster, rat and Rhesus monkey. *J Pharmacol Exp Ther* 261:364-372.
- Buckpitt AR, Castagnoli N Jr, Nelson SD, et al. 1987. Stereoselectivity of naphthalene epoxidation by mouse, rat, and hamster pulmonary, hepatic, and renal microsomal enzymes. *Drug Metab Dispos* 15:491-498.
- *Buckpitt A, Chang A-M, Weir A, et al. 1995. Relationship of cytochrome P450 activity to cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. *Molecular Pharmacol* 47:74-81.

9. REFERENCES

Buonarati M, Jones AD, Buckpitt A. 1990. *In vivo* metabolism of isomeric naphthalene oxide glutathione conjugates. *Drug Metab Dispos* 18:183-189.

*Bysshe SE. 1982. Bioconcentration factor in aquatic organisms. In: Lyman WJ, ed. *Handbook of chemical property estimation methods*. New York, NY: McGraw Hill, 5-1-5-30.

Cadle SH, Mulawa PA, Hunsanger EC, et al. 1999. Composition of light-duty motor vehicle exhaust particulate matter in the Denver, Colorado area. *Environ Sci Technol* 35:26-32.

*Calabrese EJ. 1986. Ecogenetics: Historical foundation and current status. *J Occup Med* 28:1096-1102.

Calabrese EJ, Stanek EJ, James RC, et al. 1997. Soil ingestion: A concern for acute toxicity in children. *Environ Health Perspect* 105:1354-1358.

Carmo AM, Hundal LS, Thompson ML. 2000. Sorption of hydrophobic organic compounds by soil materials: Applications of unit equivalent Freundlich coefficients. *Environ Sci Technol* 34:4363-4369.

*Castranova V, Rabovsky J, Tucker JH, et al. 1988. The alveolar type II epithelial cell: A multifunctional pneumocyte. *Toxicol Appl Pharmacol* 93:472-483.

Catallo WJ, Schlenker M, Gambrell RP. 1995. Toxic chemicals and trace metals from urban and rural Louisiana Lakes: recent historical profiles and toxicological significances. *Environ Sci Technol* 29:1436-1445.

CCRIS. 1992. Chemical carcinogenesis research information system. Bethesda, MD: National Library of Medicine, November 2, 1992.

CCTTE. 1988. Computerized listing of chemicals being tested for toxic effects. United Nations Environment Programme, International Programme on Chemical Safety, International Register of Potentially Toxic Chemicals, Geneva, Switzerland.

*CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDC/ATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registry. Summary report, August 27, 1990.

*CEH. 1993. Chemical Economics Handbook. File 359 on DIALOG. DIALOG Information Services, Inc. Palo Alto, CA. January 1993.

Cerniglia CE, Freeman JP, Althaus JR, et al. 1983. Metabolism and toxicity of 1- and 2-methylnaphthalene and their derivatives in cyanobacteria. *Arch Microbiol* 136:177-183.

Cerniglia CE, Gibson DT, Van Baalen C. 1979. Algal oxidation of aromatic hydrocarbons: Formation of 1-naphthol from naphthalene by *Agmenellum quadruplicatum*, strain PR-6. *Biochem Biophys Res Commun* 88:50-58.

Cerniglia CE, Gibson DT, Van Baalen C. 1980. Oxidation of naphthalene by cyanobacteria and microalgae. *J Gen Microbiol* 116:495-500.

9. REFERENCES

- Chaloupka K, Steinber M, Santostefano M, et al. 1995. Induction of *CYP1a-1* and *CYP1a-2* gene expression by a reconstituted mixture of polynuclear aromatic hydrocarbons in B6C3F1 mice. *Chem Biol Interact* 96:207-221
- Chan CH. 1993. St Clair River head and mouth water quality monitoring, 1987-89. *Water Pollut Res J Can* 28:451-471.
- Chapman PM, Downie J, Maynard A, et al. 1996. Coal and deodorizer residues in marine sediments - contaminants or pollutants? *Environ Toxicol Chem* 15:638-642.
- Chapta SC, Boyer JM. 1990. Fate of pollutants. *Research Journal, Water Pollution Control Federation* 62:569-577.
- Chasseaud LF. 1979. The role of glutathione and glutathione S-transferases in the metabolism of chemical carcinogens and other electrophilic agents. *Adv Cancer Res* 29:175-274.
- Chen KC, Dorough HW. 1979. Glutathione and mercapturic acid conjugations in the metabolism of naphthalene and 1-naphthyl N-methylcarbamate (carbaryl). *Drug Chem Toxicol* 2:331-354.
- Chen W, Kan AT, Fu G, et al. 1999. Adsorption-desorption behaviors of hydrophobic organic compounds in sediments of Lake Charles, Louisiana, USA. *Environ Toxicol Chem* 18:1610-1616.
- Chen W, Kan AT, Fu G, et al. 2000. Factors affecting the release of hydrophobic organic contaminants from natural sediments. *Environ Toxicol Chem* 19:2401-2408.
- *Chichester CH, Buckpitt AR, Chang A, et al. 1994. Metabolism and cytotoxicity of naphthalene and its metabolites in isolated murine cells. *Mol Pharmacol* 45:664-672.
- *Childers JW, Witherspoon CL, Smith LB, et al. 2000. Real-time and integrated measurement of potential human exposure to particle-bound polycyclic aromatic hydrocarbons (PAHs) from aircraft exhaust. *Environ Health Perspect* 108:853-862.
- Chin YP, Weber WJ. 1989. Estimating the effects of dispersed organic polymers on the sorption of contaminants by natural solids. 1. A predictive thermodynamic humic substance-organic solute interaction model. *Environ Sci Technol* 23:978-984.
- *Cho M, Chichester C, Morin D, et al. 1994a. Covalent interactions of reactive naphthalene metabolites with proteins. *J Pharmacol Exp Ther* 269:881-889.
- *Cho M, Chichester C, Plopper C, et al. 1995. Biochemical factors important in cell selective toxicity in the lung. *Drug Metab Rev* 27(1-2):369-386.
- *Cho M, Jedrychowski R, Hammock B, et al. 1994b. Reactive metabolite binding to hemoglobin and albumin. *Fundam Appl Toxicol* 22:26-33.
- *Chuang JC, Callahan PJ, Lyu CW, et al. 1999. Polycyclic aromatic hydrocarbon exposures of children in low-income families. *J Exp Anal Environ Epidem* 9(2):85-98.
- *Chuang JC, Callahan PJ, Menton RG, et al. 1995. Monitoring methods for polycyclic aromatic hydrocarbons and their distribution in house dust and track-in soil. *Environ Sci Technol* 29:494-500.

9. REFERENCES

- *Chuang JC, Mack GA, Kuhlman MR, et al. 1991. Polycyclic aromatic hydrocarbons and their derivatives in indoor and outdoor air in an eight-home study. *Atmos Environ* 25B(3):369-380.
- Chugh KS, Singhal PC, Sharma BK, et al. 1977. Acute renal failure due to intravascular hemolysis in the North Indian patients. *Am J Med Sci* 274:139-146.
- Chung HY. 1993. Volatile components in fermented soybean (*Glycine max*) curds. *J Agric Food Chem* 47:2690-2696.
- Chung HY. 1999. Volatile compounds in crabmeats of *Charybdis feriatus*. *J Agric Food Chem* 47:2280-2287.
- Chung TY, Eiserich JP, Shibamoto T. 1993. Volatile compounds isolated from edible Korean chamchwi (*Aster scaber* thunb). *J Agric Food Chem* 41:1693-1697.
- *Chusid E, Fried CT. 1955. Acute hemolytic anemia due to naphthalene ingestion. *AMA Am J Dis Child* 89:612-614.
- Clansky KB, ed. 1986. Chemical guide to the OSHA hazard communication standard. Burlingame, CA: Roytech Publications Inc., 58, 653-657.
- CLC. 1988. Coordinated list of chemicals. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development.
- *Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. *Toxicol Ind Health* 1(4):111-131.
- Clonfero E, Nardini B, Marchioro M. 1996. Mutagenicity and contents of polycyclic aromatic hydrocarbons in used and recycled motor oils. *Mutat Res* 368:283-291.
- Coakley JP, Nagy E, Serodes JB. 1993. Spatial and vertical trends in sediment-phase contaminants in the estuary of the St Lawrence River. *Estuaries* 16:653-669.
- Cock TC. 1957. Acute hemolytic anemia in the neonatal period. *AMA Am J Dis Child* 94:77-79.
- *Colborn T, Clement C. 1992. Chemically induced alterations in sexual and functional development. The wildlife/human connection. In: *Advances in modern environmental toxicology*. Volume XXI. Princeton, NJ: Princeton Scientific Publishing Co.
- *Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. *J Water Pollut Control Fed* 56:898-908.
- Collins MJ, Williams PL, MacIntosh DL. 2001. Ambient air quality at the site of a former manufactured gas plant. *Environ Monit Assess* 68(2):137-152.
- *Connor TH, Thiess JC, Hanna HA, et al. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol Lett* 25:33-40.
- Corchia C, Balata A, Meloni GF, et al. 1995. Favism in a female newborn infant whose mother ingested fava beans before delivery. *J Pediatr* 127(5):807-808.

9. REFERENCES

- *Corner ED, Young L. 1954. Biochemical studies of toxic agents: 7. The metabolism of naphthalene in animals of different species. *Biochem J* 58:647-655.
- Correa M, Venables BJ. 1985. Bioconcentration of naphthalene in tissues of the white mullet (*Mugil curema*). *Environ Toxicol Chem* 4:227-231.
- *Cripps GC. 1992. Baseline levels of hydrocarbons in seawater of the southern ocean. Natural variability and regional patterns. *Mar Pollut Bull* 24:109-114.
- Crump DR. 1995. Volatile organic compounds in indoor air. *Issues Environ Sci Technol* 4:109-124.
- Daly JW, Jerina DM, Witkop B. 1972. Arene oxides and the NIH shift: The metabolism, toxicity and carcinogenicity of aromatic compounds. *Experientia* 28:1129-1149.
- *D'Arcy Doherty DM, Cohen GM, Smith MT. 1984. Mechanisms of toxic injury to isolated hepatocytes by 1-naphthol. *Biochem Pharmacol* 33:543-549.
- Dass C. 1990. Fast atom bombardment combined with mass spectrometry for characterization of polycyclic aromatic hydrocarbons. *J Am Soc Mass Spectrom* 1:405-412.
- *Dawson JP, Thayer WW, Desforges JF. 1958. Acute hemolytic anemia in the newborn infant due to naphthalene poisoning: Report of two cases, with investigations into the mechanism of the disease. *Blood* 13(12):1113-1125.
- *Dean BS, Lopez G, Krenzelok EP. 1992. Environmentally-induced methemoglobinemia in an infant. *Clin Toxicol* 30:127-133.
- DeJonge H, Heimovaara TJ, Verstraten JM. 1999. Naphthalene sorption to organic soil materials studied with continuous stirred flow experiments. *Soil Sci Soc Am J* 63:297-306.
- *Delgado-Rodrigues A, Ortiz-Marttelo R, Graf U, et al. 1995. Genotoxic activity of environmentally important polycyclic aromatic hydrocarbons and their nitro derivatives in the wing spot test of *Drosophila melanogaster*. *Mutat Res* 341:235-247
- Demaagd PGJ, Sinnige TL, Schrap SM, et al. 1998. Sorption coefficients of polycyclic aromatic hydrocarbons for two lake sediments: Influence of the bactericide sodium azide. *Environ Toxicol Chem* 17:1899-1907.
- Deshan Y, Berlin JA, Penning TM, et al. 2002. Reactive oxygen species generated by PAH o-quinones cause change-in-function mutations in p53. *Chem Res Toxicol* 15:832-842.
- Desideri PG, Lepri L, Checchini L, et al. 1994. Organic compounds in surface and deep Antarctic snow. *Int J Environ Anal Chem* 55:33-46.
- Di YP, Yoneda K, Harper R, et al. 2003. Cell signaling of environmental exposure on airway mucin gene expression. *FASEB J* 17(4-5):A829.
- Diamond ML, Gingrich SE, Fertuck K. 2000. Evidence for organic film on an impervious urban surface: Characterization and potential teratogenic effects. *Environ Sci Technol* 34:2900-2908.

9. REFERENCES

- *Dinsdale D, Verschoyle RD. 1987. Pulmonary toxicity of naphthalene derivatives in the rat. *Arch Toxicol (Suppl 11)*: 288-291.
- *Djomo JE, Ferrier V, Gauthier L, et al. 1995. Amphibian micronucleus test *in vivo*: Evaluation of the genotoxicity of some major polycyclic aromatic hydrocarbons found in a crude oil. *Mutagenesis* 10:223-226.
- Doherty MD, Cohen GM. 1984. Metabolic activation of 1-naphthol by rat liver microsomes to 1,4-naphthoquinone and covalent binding species. *Biochem Pharmacol* 33:3201-3208.
- Donohue JM, Moilanen LH. 2003. Regulatory determination for naphthalene in drinking water. *Toxicol Sci* 72(S-1):29.
- Durant ND, Jonkers CA, Wilson LP, et al. 1995. Enhanced biodegradation of naphthalene in MGP aquifer microcosms. In: Hinchee RE, Wilson JT, Downey DC, eds. *Bioremediation*. Columbus, OH: Battelle Press, 189-196.
- *Durant ND, Wilson LP, Bouwer EJ. 1994. Screening for natural subsurface biotransformation of polycyclic aromatic hydrocarbons at a former manufactured gas plant. In: Hinchee RE, Leeson A, Semprini L, et al., eds. *Bioremediation of chlorinated and polycyclic aromatic hydrocarbon compounds*. Boca Raton: CRC Press, Inc., 457-461.
- *Eastmond DA, Booth GM, Lee ML. 1984. Toxicity, accumulation, and elimination of polycyclic aromatic sulfur heterocycles in *Daphnia magna*. *Arch Environ Contam* 13:105-111.
- *Easton MDL, Luszniak D, Von der Geest E. 2002. Preliminary examination of contaminant loadings in farmed salmon, wild salmon and commercial salmon feed. *Chemosphere* 46(7):1053-1074.
- Eckel WP. 1994. Beyond the priority pollutants: Nontarget compounds frequently detected at Superfund sites. *Am Chem Soc Abstr Pap* 34:67-69.
- Efthymiou ML, Gervais P. 1972. [Accidental poisoning in children.] *Cah Med* 13:831-835. (French)
- Eganhouse RP, Cozarelli IM, Scholl MA, et al. 2001. Natural attenuation of volatile organic compounds (VOC's) in the leachate plume of a municipal landfill: Using alkylbenzenes as process probes. *Ground Water* 39:192-202.
- *Ehrlich GG, Goerlitz DF, Godsy EM, et al. 1982. Degradation of phenolic contaminants in ground water by anaerobic bacteria: St. Louis Park, Minnesota. *Ground Water* 20(6):703-710.
- Eickhoff CV, He S-X, Gobas F, et al. 2003. Determination of polycyclic aromatic hydrocarbons in dungeness crabs (*Cancer magister*) near an aluminum smelter in Kitimat Arm, British Columbia, Canada. *Environ Toxicol Chem* 22(1):50-58.
- *Eisele GR. 1985. Naphthalene distribution in tissues of laying pullets, swine, and dairy cattle. *Bull Environ Contam Toxicol* 34:549-556.
- Eitzer BD. 1995. Emissions of volatile organic chemicals from municipal solid waste composting facilities. *Environ Sci Technol* 29:896-902.

9. REFERENCES

- Eldrige JE, Shanmugam K, Bobalek EG, et al. 1983. PAH emissions from paving asphalt in laboratory simulation. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Formation, metabolism, and measurement, proceedings of the seventh international symposium. Columbus, OH: Battelle, 471-482.
- Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier, 904.
- Elovaara E, Heikkila P, Pyy L, et al. 1995. Significance of dermal and respiratory uptake in creosote workers: exposure to polycyclic aromatic hydrocarbons and urinary excretion of 1-hydroxypyrene. *Occup Environ Med* 52:196-203.
- *Emi Y, Konishi Y. 1985. Endogenous lipid pneumonia in B6C3F1 mice. In: Jones TC, Mohr U, Hunt RD, eds. Respiratory system: Monographs on pathology of laboratory animals. New York: Springer-Verlag, 166-168.
- Enzminger JD, Ahlert RC. 1987. Environmental fate of polynuclear aromatic hydrocarbons in coal tar. *Environ Tech Lett* 8:269-278.
- EPA. 1974. 4-HR DOT corrosive test. Mellon Institute. U.S. Environmental Protection Agency. TSCA Section 8D OTS0206434. EPA878213655.
- EPA. 1976. The environmental fate of selected polynuclear aromatic hydrocarbons. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA560575009. PB250948.
- EPA. 1979a. Identification of organic compounds in industrial effluent discharges. Athens, GA: U.S. Environmental Protection Agency, Office of Research and Development. EPA600479016.
- EPA. 1979b. Water-related environmental fate of 129 priority pollutants: Volume I: Introduction and technical background, metals and inorganics, pesticide and PCBs. Washington, DC: U.S. Environmental Protection Agency, Office of Water Planning and Standards. EPA440479029a. PB80204373.
- *EPA. 1980a. Ambient water quality for polynuclear aromatic hydrocarbons. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA440580069.
- *EPA. 1980b. U.S. Environmental Protection Agency. *Fed Regist* 45:33084-33133.
- *EPA. 1980c. Ambient water quality criteria for: Naphthalene. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA440580059. PB82117707.
- EPA. 1980d. Sources of toxic compounds in household wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA600280128. PB81110942.
- *EPA. 1982a. Test method: Polynuclear aromatic hydrocarbons - Method 610. In: Longbottom JE, Lichtenberg JJ, eds. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600482057.

9. REFERENCES

- *EPA. 1982b. Test method: Base/neutrals and acids - method 625. In: Longbottom JE, Lichtenberg JJ, eds. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600482057.
- EPA. 1982c. Acute toxicity and primary irritancy studies peroral, single dose to rats; percutaneous, single dose to rabbits; inhalation, single dose to rats; primary skin irritation, rabbits; primary eye irritation, rabbits. U.S. Environmental Protection Agency. TSCA Section 8D OTS0206434.
- *EPA. 1982d. An exposure and risk assessment for benzo[a]pyrene and other polycyclic aromatic hydrocarbons: Volume II. Naphthalene. Final draft report. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.
- *EPA. 1982e. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA440481014.
- EPA. 1983a. Treatability manual: Volume I. Treatability data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600282001a.
- EPA. 1983b. Volatile organic chemicals in the atmosphere: An assessment of available data. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600383027A.
- EPA. 1984. Health effects assessment for naphthalene. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA540186014.
- EPA. 1985. Notification requirements; Reportable quantity adjustments. U.S. Environmental Protection Agency: Part II. Fed Regist 50(65):13456. 40 CFR Parts 117 and 302.
- *EPA. 1986a. Reference values for risk assessment. Final draft. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Solid Waste. ECAOCIN477.
- *EPA. 1986b. Method 8250: Gas chromatography/mass spectrometry for semivolatile organics: Packed column technique. In: Test methods for evaluating solid waste. SW-846. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.
- *EPA. 1986c. Method 8270: Gas chromatography/mass spectrometry for semivolatile organics: Capillary column technique. In: Test methods for evaluating solid waste. SW-846. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.
- *EPA. 1986d. Method 8410: Capillary column analysis of semivolatile organic compounds by gas chromatography/Fourier transform infrared (GC/FT-IR) spectrometry. In: Test methods for evaluating solid waste. SW-846. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.
- *EPA. 1986e. Guidelines for the health risk assessment of chemical mixtures. U.S. Environmental Protection Agency. Fed Regist 51(185):34014-34025.
- EPA. 1986f. Guidelines for mutagenicity risk assessment. U.S. Environmental Protection Agency. Fed Regist 51(185):34006-34012. EPA630R98003.

9. REFERENCES

*EPA. 1986g. Broad scan analysis of the FY82 national human adipose tissue survey specimens: Volume I - executive summary. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

EPA. 1986h. Health and environmental effects profile for naphthalene. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA600x86241. PB88242383.

*EPA. 1987a. Summary review of health effects associated with naphthalene: Health issue assessment. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600887055F.

EPA. 1987b. National primary drinking water regulations; synthetic organic chemicals; monitoring for unregulated contaminants. U.S. Environmental Protection Agency: Part II. Fed Regist 52(130):25690-25717. 40 CFR Parts 141 and 142.

EPA. 1987c. List (phase 1) of hazardous constituents for ground-water monitoring. U.S. Environmental Protection Agency: Part II. Fed Regist 52(131):25942-25943. 40 CFR Parts 264 and 270.

EPA. 1987d. Reference dose (RfD): Description and use in health risk assessments. Vol. I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600886032a.

EPA. 1987e. Processes, coefficients, and models for simulating toxic organics and heavy metals in surface waters. Athens, GA: U.S. Environmental Protection Agency, Environmental Laboratory. EPA600387015.

*EPA. 1988a. Health effects assessment for naphthalene. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development. EPA600889094.

*EPA. 1988b. Updated health effects assessment for naphthalene. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. Final Draft ECAOCINH014a.

EPA. 1988c. Land disposal restrictions for first third scheduled wastes; final rule. U.S. Environmental Protection Agency: Part II. Fed Regist 53:31138-31222. 40 CFR Parts 264 etc.

*EPA. 1988d. U.S. Environmental Protection Agency: Part II. Fed Regist 53:4500-4539.

EPA. 1988e. Health and safety data reporting period terminations; final rule. U.S. Environmental Protection Agency: Part IV. Fed Regist 53:38642-38654. 40 CFR Parts 716.

EPA. 1988f. Assessment of naphthalene as a potentially toxic air pollutant. Fed Regist 53(54):9138-9141.

*EPA. 1988g. National ambient volatile organic compounds (VOCs) data base update. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Sciences Research Laboratory, Office of Research and Development. EPA600388010a. PB88195631.

EPA. 1988h. Recommendations for and documentation of biological values for use in risk assessment. U.S. Environmental Protection Agency. EPA 600687008. PB88179874.

9. REFERENCES

- *EPA. 1989a. Determination of benzo(a)pyrene [B(a)P] and other polynuclear aromatic hydrocarbons (PAHs) in indoor air. Washington, DC: U.S. Environmental Protection Agency.
- EPA. 1989b. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600890066A.
- *EPA. 1989c. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600888066F.
- *EPA. 1989d. Recognition and management of pesticide poisonings. Washington, DC: U.S. Environmental Protection Agency. EPA540988001. PB91145656.
- EPA. 1989e. Land disposal restrictions for second third scheduled wastes; proposed rule. U.S. Environmental Protection Agency: Part II. Fed Regist 54(7):1056-1119. 40 CFR Parts 148, 268, and 271.
- EPA. 1989f. Reportable quantity adjustments; delisting of ammonium thiosulfate; final rules. U.S. Environmental Protection Agency: Part V. Fed Regist 54(155):33461. 40 CFR Parts 116, 117, and 302.
- *EPA. 1989g. Characteristics of pilot and full-scale hazardous waste incinerator ash. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600D89232.
- *EPA. 1990a. Compendium of methods for the determination of air pollutants in indoor air. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Research and Exposure Assessment Laboratory. EPA600S490010.
- *EPA. 1990b. Interim methods for development of inhalation reference concentrations. Research Triangle Park, NC: U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Office of Research and Development. EPA600890066A.
- *EPA. 1990c. Method 1625 (Containing a codification of documents of general applicability and future effect). U.S. Environmental Protection Agency, Code of Federal Regulations 40 CFR 136.
- *EPA. 1990d. Method 550. Determination of polycyclic aromatic hydrocarbons in drinking water by liquid-liquid extraction and HPLC with coupled ultraviolet and fluorescence detection. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Monitoring Systems Laboratory, 121-142.
- *EPA. 1990e. Method 550.1. Determination of polycyclic aromatic hydrocarbons in drinking water by liquid-solid extraction and HPLC with coupled ultraviolet and fluorescence detection. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Monitoring Systems Laboratory, 143-167.
- EPA. 1990f. U.S. Environmental Protection Agency: Part II. Fed Regist 55:22520-22521, 22583, 22598.
- EPA. 1990g. Treatability of RCRA compounds in bod/nitrification wastewater treatment system with dual media filtration. Cincinnati OH: U.S. Environmental Protection Agency.

9. REFERENCES

*EPA. 1991a. Drinking water criteria document for polycyclic aromatic hydrocarbons (PAHs). Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. ECAOCIND010.

EPA. 1991b. Solid waste disposal facility criteria; final rule. U.S. Environmental Protection Agency: Part II. Fed Regist 56(196):50978, 51033, 51037. 40 CFR Parts 257 and 258.

EPA. 1991c. U.S. Environmental Protection Agency: Part III. Fed Regist 56:7134-7135.

EPA. 1991d. Guidelines for developmental toxicity risk assessment. U.S. Environmental Protection Agency. Fed Regist 56(234):63798-63826.

*EPA. 1991e. Indoor air-assessment; indoor air concentrations of environmental carcinogens. Research Triangle Park, NC: U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Office of Research and Development. EPA600890042.

*EPA. 1991f. Project summary: method for the supercritical fluid extraction of soils/sediments. Washington DC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory. EPA600S490026.

EPA. 1993a. Reference guide to odor thresholds for hazardous air pollutants listed in the clean air act amendments of 1990. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600R92047. PB92239516.

EPA. 1993b. Statistical summary: Emap-estuaries Louisiana province- 1991. Washington, DC: U.S. Environmental Protection Agency. EPA620R93007.

EPA. 1993c. Ambient concentration summaries for Clean Air Act Title III Hazardous air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600R94090.

EPA. 1994a. Interim policy for particle size and limit concentration issues in inhalation toxicity: Notice of availability. U.S. Environmental Protection Agency. Fed Regist 59(206):53799.

*EPA. 1994b. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. U.S. Environmental Protection Agency. EPA600890066F.

EPA. 1994c. Peer review and peer involvement at the U.S. Environmental Protection Agency. Signed by the U.S. EPA Administrator Carol M. Browner, dated June 7, 1994.

EPA. 1994d. Drinking water regulations and health advisories. U.S. Environmental Protection Agency. Office of Water. EPA822R94001.

EPA. 1995. Use of the benchmark dose approach in health risk assessment. U.S. Environmental Protection Agency. EPA630R94007.

*EPA. 1996a. Proposed guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency. Fed Regist 61(79):17960-18011. EPA630R96003.

EPA. 1996b. Guidelines for reproductive toxicity risk assessment. U.S. Environmental Protection Agency. Fed Regist 61(212):56274-56322. EPA630R96009.

9. REFERENCES

- *EPA 1996c. Exposure factors handbook. U.S. Environmental Protection Agency, Office of Research and Development, Washington D.C. EPA600889043. June 6, 2003.
- EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.
- EPA. 1998a. Guidelines for neurotoxicity risk assessment. Fed Regist 63(93):26926-26954.
- EPA. 1998b. Science policy council handbook: Peer review. Washington, DC: Office of Research and Development, U.S. Environmental Protection Agency. EPA100B98001.
- *EPA. 1998c. Toxicological review of naphthalene (CAS No. 91-20-3). In support of Summary Information on the Integrated Risk Information System (IRIS).
- EPA. 1999. Guidelines for carcinogen risk assessment. Washington, DC. U.S. Environmental Protection Agency, Risk Assessment Forum. NCEAF0644.
- EPA. 2000a. Science policy council handbook: peer review. Second edition. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA100B00001.
- *EPA. 2000b. Science policy council handbook: risk characterization. Washington, DC: U.S. Environmental Protection Agency, Office of Science Policy, Office of Research and Development. EPA100B00002.
- EPA. 2000c. Supplemental guidance for conducting for health risk assessment of chemical mixtures. Washington, DC: U.S. Environmental Protection Agency. EPA630R00002. <http://www.epa.gov/cgi-bin/claritw?op-Display&document=clserv:ORD:2103>. June 6, 2003.
- EPA. 2000d. Benchmark dose technical guidance document. External review draft. U.S. Environmental Protection Agency. EPA630R00001.
- *EPA. 2002a. 2002 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822R02038. <http://www.epa.gov/waterscience>. June 6, 2003
- *EPA. 2002b. Health effects support document for naphthalene: External review draft. Alexandria, VA: U.S. Environmental Protection Agency Office of Water. EPA822R02031.
- *EPA. 2003a. Criteria for municipal solid waste landfills. List of hazardous inorganic and organic constituents. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 258, Appendix II. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003b. Designation, reportable quantities, and notification. Designation of hazardous substance. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 302.4. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003c. Effluent guidelines and standards. General provisions. Toxic pollutants. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 401.15. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.

9. REFERENCES

- *EPA. 2003d. Identification and listing of hazardous waste. Hazardous constituents. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 261, Appendix VIII. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003e. Land disposal restrictions. Universal treatment standards. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 268.48. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003f. Landfills point source category. Effluent limitations attainable by the application of the best practicable control technology currently available (BPT). Washington, DC: U.S. Environmental Protection Agency. 40 CFR 445.11. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003g. National emission standards for hazardous air pollutants for source categories. Hazardous air pollutants. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 63, Table 1. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003h. National emission standards for hazardous air pollutants. Standard: naphthalene processing, final coolers, and final-cooler cooling towers. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 61.134. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- EPA. 2003i. Regulation of fuels and fuel additives. Measurement of reformulated gasoline fuel parameters. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 80.46. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003j. Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 117.3. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003k. Standards for owners and operators of hazardous waste treatment, storage, and disposal facilities. Ground-water monitoring list. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 264, Appendix IX. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003l. Standards for the management of specific hazardous wastes and specific types of hazardous waste management facilities. Health-based limits for exclusion of waste-derived residues. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 266, Appendix VII. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003m. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 372.65. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003n. Toxic substances control act. Chemical information rules. Chemical lists and reporting periods. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 712.30. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003o. Toxic substances control act. Health and safety data reporting. Substances and listed mixtures to which this subpart applies. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 716.120. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.

9. REFERENCES

- *EPA. 2003p. Water programs. Designation of hazardous substances. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 116.4. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003q. Water quality guidance for the Great Lakes system. Pollutants of initial focus in the Great Lakes water quality initiative. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 132, Table 6. <http://www.epa.gov/epahome/cfr40.htm>. June 6, 2003.
- *EPA. 2003r. Toxicological review of 2-methylnaphthalene (CAS No. 91-57-6). EPA635R03010. <http://www.epa.gov/iris>. January 2, 2005.
- Epsy, Huston and Associates. 1985. Bioassay testing of sample 5601-56-1 in fresh water with the *Lepomis macrochirus* and *Daphnia magna*: Naphthalene. Report to Texaco, Inc., Glenham, NY by Epsy, Huston and Associates, Inc., Austin, TX. EH&A Job No. 5863.
- Erickson DC, Loehr RC, Neuhauser EF. 1993. PAH loss during bioremediation of manufactured gas plant site soils. *Water Res* 27(5):911-919.
- Eriksson M, Dalhammar G, Borg-Karlson AK. 2000. Biological degradation of selected hydrocarbons in an old PAH/creosote contaminated soil from a gas work site. *Appl Microbiol Biotechnol* 53:619-626.
- Eskinja I, Soljic Z, Svel-Cerovecki S, et al. 1996. Sources and fate of polycyclic aromatic hydrocarbons in ambient air of urban and rural Croatian sites. *Int J Environ Anal Chem* 63:251-268.
- European Union. 2001. European Union risk assessment report: Naphthalene. United Kingdom. EINECS 202-049-5.
- *European Union. 2002. European Union risk assessment report: Naphthalene. United Kingdom. EINECS 202-049-5. http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/naphthalenereport020.pdf. January 12, 2005.
- Evanson M, Van Der Kraak G. 2001. Stimulatory effects of selected PAHs on testosterone production in goldfish and rainbow trout and possible mechanisms of action. *Comp Biochem Physiol C* 130:249-258.
- *Fabacher DL, Hodgson E. 1977. Hepatic mixed-function oxidase activity in mice treated with methylated benzenes and methylated naphthalenes. *J Toxicol Environ Health* 2:1143-1146.
- *Fait DW, Nachreiner RW. 1985. Naphthalene acute inhalation toxicity study. Report to Texaco, Inc., Beacon, NY, by Bushy Run Research Center, Union Carbide, Export, PA. Project No. 48-511.
- *Familusi JB, Dawodu AH. 1985. A survey of neonatal jaundice in association with household drugs and chemicals in Nigeria. *Ann Trop Paediatr* 5:219-222.
- *Fanucchi MV, Buckpitt AR, Murphy ME, et al. 1997. Naphthalene cytotoxicity of differentiating cells in neonatal mice. *Toxicol Appl Pharmacol* 144:96-104.
- Farant J-P, Gariépy M. 1998. Relationship between benzo(A)pyrene and individual polycyclic aromatic hydrocarbons in a Soderberg primary aluminum smelter. *Am Ind Hyg Assoc J* 59:758-765.
- Farkas N, Lorinczy D, Dergez T, et al. 2004. Effect of polycyclic aromatic hydrocarbons on erythrocyte membranes by DSC and EPR. *Environ Toxicol Pharmacol* 16(3):163-168.

9. REFERENCES

- *FEDRIP. 2004. Palo Alto, CA: Federal Research in Progress. Dialog Information Services, Inc.
- Fellin P, Otson R. 1994. Assessment of the influence of climatic factors on concentration levels of volatile organic compounds (VOC's) in Canadian homes. *Atmos Environ* 28:3581-3586.
- Feunekes FD Jr, Jongeneelen FJ, Vanderlaan H, et al. 1997. Uptake of polycyclic aromatic hydrocarbons among trainers in a fire-fighting training facility. *Am Ind Hyg Assoc J* 58:23-48.
- Fitzhugh OG, Buschke WH. 1949. Production of cataract in rats by beta-tetralol and other derivatives of naphthalene. *Arch Ophthalmol* 41:572-582.
- *Florin I, Rutberg L, Curvall M, et al. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. *Toxicology* 18:219-232.
- *Flowers L, Ohnishi T, Penning TM, et al. 1997. DNA strand scission by polycyclic aromatic hydrocarbon *o*-quinones: role of reactive oxygen species, Cu(II)/Cu(I) redox cycling and *o*-semiquinone anion radicals. *Biochemistry* 36:8640-8648.
- *Flowers-Geary L, Bleczinski W, Harvey RG, et al. 1994. Cytotoxicity and mutagenicity of polycyclic aromatic hydrocarbon (PAH) *o*-quinones produced by dihydrodiol dehydrogenase (DD). *Proc Am Assoc Cancer Res* 35:161
- *Flowers-Geary L, Bleczinski W, Harvey RG, et al. 1996. Cytotoxicity and mutagenicity of polycyclic aromatic hydrocarbon *o*-quinones produced by dihydrodiol dehydrogenase. *Chem Bio Int* 99:55-72.
- Flucas BJ, Minor LKM, Harris BW. 1995. Polycyclic aromatic hydrocarbons at selected burning grounds at Los Alamos. *Prepr Pap Natl Meet Am Chem Soc Div Environ Chem* 35:7-10.
- *Fomon SJ. 1966. Body composition of the infant: Part I: The male "reference infant." In: Falkner F, ed. *Human development*. Philadelphia, PA:WB Saunders, 239-246.
- *Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 35:1169-1175.
- *Foster GD, Roberts EC Jr, Gruessner B, et al. 2000. Hydrogeochemistry and transport of organic contaminants in an urban watershed of Chesapeake Bay (USA). *Appl Geochem* 15:901-915.
- Fowler MG, Brooks PW, Northcott M, et al. 1994. Preliminary results from a field experiment investigating the fate of some creosote components in a natural aquifer. *Org Geochem* 22:641-649.
- Franklin RB. 1987. Naphthalene. In: Synder R, ed. *Ethel Browning's toxicity and metabolism of industrial solvents*. 2nd ed. Volume I: Hydrocarbons. New York, NY: Elsevier Science Publications, 153-175.
- *Frantz SW, VanMiller JP, Hengler WC. 1986. Ninety-day (sub-chronic) dermal toxicity study with naphthalene in albino rats. Report to Texaco, Inc., Beacon, NY, by Bushy Run Research Center Union Carbide, Export, PA. Project No. 49-539 revised. Submitted to USEPA under section 8D of TSCA. OTS0513643.

9. REFERENCES

- *Fraser MP, Cass GR, Simoneit BRT. 1998a. Gas-phase and particle-phase organic compounds emitted from motor vehicle traffic in a Los Angeles roadway tunnel. *Environ Sci Technol* 32:2051-2060.
- Fraser MP, Cass GR, Simoneit BRT, et al. 1998b. Air quality model evaluation data for organics C6-C22 nonpolar and semipolar aromatic compounds. *Environ Sci Technol* 32:1760-1770.
- Fraser MP, Kleeman MJ, Schauer JJ, et al. 2000. Modeling the atmospheric concentrations of individual gas-phase and particle-phase organic compounds. *Environ Sci Technol* 34:302-312.
- *Frederick CB, Robian Gentry P, Bush ML, et al. 2001. A hybrid computational fluid dynamics and physiologically based pharmacokinetic model for comparison of predicted tissue concentrations of acrylic acid and other vapors in the rat and human nasal cavities following inhalation exposure. *Inhalation Toxicology* 13:359-376.
- *Freeman AE, Weisburger EK, Weisburger JH, et al. 1973. Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. *J Natl Cancer Inst* 51:799-808.
- Freitag D, Ballhorn L, Geyer H, et al. 1985. Environmental hazard profile of chemicals: An experimental method for the assessment of the behaviour of organic chemicals in the ecosphere by means of simple laboratory tests with ¹⁴C labelled chemicals. *Chemosphere* 14:1589-1616.
- Fries GF. 1996. Ingestion of sludge applied organic chemicals by animals. *Sci Total Environ* 185:93-108.
- *FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.
- Furton KG, Rein J. 1991. Effect of microextractor cell geometry on supercritical fluid extraction recoveries and correlations with supercritical fluid chromatographic data. *Anal Chim Acta* 248:263-270.
- Gadsden RH, Mellette RR, Miller WC Jr. 1958. Scrap-iron intoxication. *J Am Med Assoc* 168:1220-1224.
- Gagne F, Blaise C. 1995. Evaluation of the genotoxicity of environmental contaminants in sediments to rainbow trout hepatocytes. *Environ Toxicol Water Qual* 10:217-229.
- Gagne F, Pardos M, Blaise C, et al. 1999. Toxicity evaluation of organic sediment extracts resolved by size exclusion chromatography using rainbow trout hepatocytes. *Chemosphere* 39:1545-1570.
- *Gaines TB. 1969. Acute toxicity of pesticides. *Toxicol Appl Pharmacol* 14:515-534.
- *Gandy J, Millner GC, Bates HK, et al. 1990. Effects of selected chemicals on the glutathione status in the male reproductive system of rats. *J Toxicol Environ Health* 29:45-57.
- *Gatehouse D. 1980. Mutagenicity of 1,2 ring-fused acenaphthenes against *S. typhimurium* TA1537 and TA1538: structure-activity relationships. *Mutat Res* 78:121-135.
- *GDCH. 1992. Gesellschaft Deutscher Chemiker. Methyl-naphthalenes. In: GDCH-Advisory Committee on existing chemicals of environmental relevance (BUA). BUA Report 47.

9. REFERENCES

- Gerarde HW. 1962. The aromatic hydrocarbons. In: Patty FA, ed. Industrial hygiene and toxicology. 2nd ed. Vol. II. Toxicology. New York, NY: John Wiley and Sons, 1237-1239.
- *Germansky M, Jamall IS. 1988. Organ-specific effects of naphthalene on tissue peroxidation, glutathione peroxidases and superoxide dismutase in the rat. *Arch Toxicol* 61:480-483.
- *Geyer H, Sheehan P, Kotzias D, et al. 1982. Prediction of ecotoxicological behaviour of chemicals: Relationship between physico-chemical properties and bioaccumulation of organic chemicals in the mussel *Mytilus edulis*. *Chemosphere* 11:1121-1134.
- *Ghanem A, Shuler ML. 2000. Combining cell culture analogue reactor designs and PBPK models to probe mechanisms of naphthalene toxicity. *Biotechnol Prog* 16:334-345.
- Ghess MJ, Wilbourn J, Tossavainen A, et al. 1986. Information bulletin on the survey of chemicals being tested for carcinogenicity. Lyon, France: International Agency for Research on Cancer, 250.
- *Ghetti G, Mariani L. 1956. [Eye changes due to naphthalene]. *Med Lav* 47(10):533-538. (Italian)
- *Ghoshal S, Luthy RG. 1996. Bioavailability of hydrophobic organic compounds from nonaqueous-phase liquids: The biodegradation of naphthalene from coal tar. *Environ Toxicol Chem* 15(11):1894-1900.
- Giangureco A, Reynolds SD, Stripp BR, et al. 2002. Terminal bronchioles harbor a unique airway stem cell production that localizes to the bronchoalveolar duct junction. *Am J Pathol* 161(1):173-182.
- *Gidron E, Leurer J. 1956. Naphthalene poisoning. *Lancet* (February 4):228-230.
- Gillan JT, Foster GD, Lippa KA. 1998. Ecotoxicological studies in amphibian populations of southern Ontario. *J Great Lakes Res* 24:45-54.
- *Giwerzman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. *Environ Health Perspect Suppl* 101(2):65-71.
- *Godek EG, Naismith RW, Matthews RJ. 1985. Ames Salmonella/microsome plate test (EPA/OECD) (unpublished material). Pharmakon Research International Inc., Waverly, PA. Submitted to Texaco, Inc., Beacon, NY. Submitted to U.S. EPA by Texaco, Inc. Office of Toxic Substances Microfiche No. OTS0513637.
- Godfrey JT, Foster GD, Lippa KA. 1995. Estimated annual loads of selected organic contaminants to Chesapeake Bay via a major tributary. *Environ Sci Technol* 29:2059-2064.
- Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 1990. Goldfrank's toxicologic emergencies. Fourth edition. Norwalk, CT: Appleton & Lange, 763-767.
- Goldstein LS, Kavuru MS, Curtis-McCarthy P, et al. 1998. Pulmonary alveolar proteinosis. Clinical features and outcomes. *Chest* 114:1357-1362.
- Gollahon LS. 1991. Chromosomal damage to preimplantation mouse embryos *in vitro* by naphthalene and aflatoxin B₁. *Dissert Abs Int* 52:694-B.

9. REFERENCES

- *Gollahon LS, Iyer P, Martin JE, et al. 1990. Chromosomal damage to preimplantation embryos *in vitro* by naphthalene. Vet Anatomy Dept and TEES Engineering Toxicology Division, Texas A&M Univ 274:1094.
- *Gomez E, Ledbetter CA, Hartsell PL. 1993. Volatile compounds in apricot, plum, and their interspecific hybrids. J Agric Food Chem 41:1669-1676.
- *Gosselin RE, Smith RP, Hodge HC, et al. 1984. Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, II-153, III-307-III-311.
- Grant WM. 1974. Toxicology of the eye. 2nd ed. Springfield, IL: Charles C Thomas Publisher, 733-739.
- *Grant WM. 1986. Toxicology of the eye. Springfield, IL: Charles C Thomas Publisher, 650-655.
- Green DR, Le Pape D. 1987. Stability of hydrocarbon sample, on solid-phase extraction columns. Anal Chem 49:699-703.
- *Greene JF, Zheng J, Grant DF, et al. 2000. Cytotoxicity of 1,2-epoxynaphthalene is correlated with protein binding and *in situ* glutathione depletion in cytochrome P4501A1 expressing Sf-21 cells. Toxicol Sci 53:352-360.
- Griffin KA, Franklin RB. 1980. Uptake of naphthalene and 2-methylnaphthalene in rodent lung slices [abstract]. Pharmacologist 22:471.
- Griffin KA, Franklin RB. 1982. The effects of three pulmonary toxic agents, naphthalene, 2-methylnaphthalene and 4-ipomeanol on the *in vivo* irreversible binding of [³H]-benzo[a]pyrene. IRCS J Med Sci 10:373-374.
- *Griffin KA, Johnson CB, Breger RK, et al. 1981. Pulmonary toxicity, hepatic, and extrahepatic metabolism of 2-methylnaphthalene in mice. Toxicol Appl Pharmacol 61:185-196.
- *Griffin KA, Johnson CB, Breger RK, et al. 1982. Effects of inducers and inhibitors of cytochrome P-450-linked monooxygenases on the toxicity, *in vitro* metabolism and *in vivo* irreversible binding of 2-methylnaphthalene in mice. J Pharmacol Exp Ther 221:517-524.
- *Griffin KA, Johnson CB, Breger RK, et al. 1983. Pulmonary toxicity of 2-methylnaphthalene: Lack of a relationship between toxicity, dihydrodiol formation and irreversible binding to cellular macromolecules in DBA/2J mice. Toxicology 26:213-230.
- Grigor WG, Robin H, Harley JD. 1966. An Australian variation of full-moon disease. Med J Aust 2:1229-1230.
- *Grimes AJ, Young L. 1956. The metabolism of 2-methylnaphthalene. Biochem J 62:11.
- Guillen MD, Sopelana P, Partearroyo MA. 2000. Polycyclic aromatic hydrocarbons in liquid smoke flavorings obtained from different types of wood. Effect of storage in polyethylene flasks on their concentrations. J Agric Food Chem 48:5083-5087.
- *Gupta R, Singhal PC, Muthusethupathy MA, et al. 1979. Cerebral oedema and renal failure following naphthalene poisoning. J Assoc Physicians India 27:347-348.

9. REFERENCES

Gustafson KE, Dickhut RM. 1997. Distribution of polycyclic aromatic hydrocarbons in Southern Chesapeake Bay surface water: Evaluation of three methods for determining freely dissolved water concentrations. *Environ Toxicol Chem* 16:452-461.

*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Haddad RI. 1996. Effects of in-reservoir weathering on PAH source characterization parameters. *Prepr Pap Natl Meet Am Chem Soc Div Environ Chem* 36(2):207-208.

*Haggerty RJ. 1956. Toxic hazards: Naphthalene poisoning. *N Engl J Med* 255(19):919-920.

Haitzer M, Hoss S, Traunspurger W, et al. 1998. Effects of dissolved organic matter (DOM) on the bioconcentration of organic chemicals in aquatic organisms - A review. *Chemosphere* 37:1335-1362.

Hall LW, Alden RW. 1997. A review of concurrent ambient water column and sediment toxicity testing in the Chesapeake Bay watershed: 1990-1994. *Environ Toxicol Chem* 16:1606-1617.

*Hansen AM, Olsen IL, Holst E, et al. 1991. Validation of a high-performance liquid chromatography/fluorescence detection method for the simultaneous quantification of fifteen polycyclic aromatic hydrocarbons. *Ann Occup Hyg* 35:603-611.

Hanssler H. 1964. [Life-threatening naphthalene intoxication of an infant through vapor in fumes.] *Dtsch Med Wochenschr* 89:1794-1797. (German)

*Harden RA, Baetjer AM. 1978. Aplastic anemia following exposure to paradichlorobenzene and naphthalene. *J Occup Med* 20:820-822.

*Hardin BD, Bond GP, Sikov MR, et al. 1981. Testing of selected workplace chemicals for teratogenic potential. *Scand J Work Environ Health* 7(Suppl 4):66-75.

Hardin BD, Schuler RL, Burg JR, et al. 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratog Carcinog Mutagen* 7:29-48.

Harkema JR, Morgan KT. 1996. Proliferative and metaplastic lesions in nonolfactory nasal epithelia induced by inhaled chemicals. In: Jones TC, ed. *Respiratory system*. Washington, DC: Springer-Verlag, 18-28.

*Harkov R. 1986. Semivolatile organic compounds in the atmosphere: A review. *J Environ Sci Health* A21:409-433.

Harmon HJ. 1988. Effect of naphthalene on cytochrome oxidase activity. *Bull Environ Contam Toxicol* 40:105-109.

Harmon HJ, Sanborn MR. 1982. Effect of naphthalene on respiration in heart mitochondria and intact cultured cells. *Environ Res* 29:160-173.

*Harper BL, Ramanujam VMS, Gad-El-Karim MM, et al. 1984. The influence of simple aromatics on benzene clastogenicity. *Mutat Res* 128:105-114.

9. REFERENCES

- Harper N, Steinberg M, Safe S. 1996. Immunotoxicity of a reconstituted polynuclear aromatic hydrocarbon mixture in B6C3F1 mice. *Toxicology* 109:31-38.
- Harris RP, Berdugo V, O'Hara SC, et al. 1977. Accumulation of ¹⁴C-1-naphthalene by an oceanic and an estuarine copepod during long-term exposure to low-level concentrations. *Marine Biology* 42:187-195.
- Harvey RG, Halonen M. 1968. Interaction between carcinogenic hydrocarbons and nucleosides. *Cancer Res* 28:2183-2186.
- Harvey RG, Pataki J, Wilke RN, et al. 1976. Polycyclic aryloxiranes: A new class of carcinogens. *Cancer Lett* 1:339-343.
- Hauser TR, Bromberg SM. 1982. EPA's monitoring program at Love Canal 1980. *Environ Monit Assess* 2:249-271.
- *Hawthorne SB. 1988. 1988 workshop on supercritical fluid chromatography. *Am Lab* (August 1988):6-8.
- Hawthorne SB, Grabanski CB. 2000. Correlating selective supercritical fluid extraction with bioremediation behavior of PAHS in a field treatment plot. *Environ Sci Technol* 34:4103-4110.
- Hawthorne SB, Miller DJ. 2003. Evidence for very tight sequestration of BTEX compounds in manufactured gas plant soils based on selective supercritical fluid extraction and soil/water partitioning. *Environ Sci Technol* 37(16):3587-3594.
- Hawthorne SB, Poppendieck DG, Grabanski CB, et al. 2001. PAH release during water desorption, supercritical carbon dioxide extraction, and field bioremediation. *Environ Sci Technol* 35(22):4577-4583.
- Hawthorne SB, Poppendieck DG, Grabanski CB, et al. 2002. Comparing PAH availability from manufactured gas plant soils and sediments with chemical and biological tests. 1. PAH release during water desorption and supercritical carbon dioxide extraction. *Environ Sci Technol* 36(22):4795-4803.
- *HazDat. 2005. Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. www.atsdr.cdc.gov/hazdat.html. March 9, 2005.
- *HEAST. 1992. Health effects assessment summary tables, FY 1991. Washington, DC: U.S. Environmental Protection Agency.
- Heikkila P, Luotamo M, Pyy L, et al. 1995. Urinary 1-naphthol and 1-pyrenol as indicators of exposure to coal tar products. *Int Arch Occup Environ Health* 67:211-217.
- Heikkila PR, Luotamo M, Riihimaki V. 1997. Urinary 1-naphthanol excretion in the assessment of exposure to creosote in a impregnation facility. *Scand J Work Environ Health* 23:199-205.
- *Heitzer A, Malachowsky K, Thonnard JE, et al. 1994. Optical biosensor for environmental on-line monitoring of naphthalene and salicylate bioavailability with an immobilized bioluminescent catabolic reporter bacterium. *Appl Environ Microbiol* 60(5):1487-1494.

9. REFERENCES

- *Heitzer A, Webb OF, Thonnard JE, et al. 1992. Specific and quantitative assessment of naphthalene and salicylate bioavailability by using a bioluminescent catabolic reporter bacterium. *Appl Environ Microbiol* 58:1839-1846.
- Hellou J, Warren WG. 1994. Polycyclic aromatic compounds in Northwest Atlantic Cod (*Gadus morhus*) *Environ Pollut* 84:197-202.
- *Hellou J, Warren WG. 1996. Polycyclic aromatic compounds and saturated hydrocarbons in tissues of flatfish: Insight on environmental exposure. *Mar Environ Res* 43:11-25.
- Hellou J, Payne JF, Upshall C, et al. 1994. Bioaccumulation of aromatic hydrocarbons from sediments: a dose-response study with flounder (*Pseudopleuronectes americanus*). *Arch Environ Contam Toxicol* 27:477-485.
- Hellou J, Upshall C, Payne JF, et al. 1993. Total unsaturated compounds and polycyclic aromatic hydrocarbons in mollusks collected from waters around Newfoundland. *Arch Environ Contam Toxicol* 24:249-257.
- *Herbes SE. 1981. Rates of microbial transformation of polycyclic aromatic hydrocarbons in water and sediments in the vicinity of a coal-coking wastewater discharge. *Appl Environ Microbiol* 41:20-28.
- *Herbes SE, Schwall LR. 1978. Microbial transformation of polycyclic aromatic hydrocarbons in pristine and petroleum contaminated sediments. *Appl Environ Microbiol* 35:306-316.
- *Herbes SE, Southworth GR, Shaeffer DL, et al. 1980. Critical pathways of polycyclic aromatic hydrocarbons in aquatic environments. In: Witschi H, ed. *The scientific basis of toxicity assessment*. Amsterdam: Elsevier/North Holland Biomedical Press, 113-128.
- Herman M. 1981. Synergistic effects of individual polycyclic aromatic hydrocarbons on the mutagenicity of their mixtures. *Mutat Res* 90:399-409.
- Hesse S, Mezger M. 1979. Involvement of phenolic metabolites of [¹⁴C]-naphthalene and [¹⁴C]-naphthol formed by rat liver microsomes. *Mol Pharmacol* 16:667-675.
- Hesse S, Mezger M, Schwarz LR. 1981. Formation of reactive metabolites of ¹⁴C-naphthalene in isolated rat hepatocytes and the effect of decreased glucuronidation and sulfation. *Adv Exp Med Biol* 136 (Pt A):739-744.
- Hiatt MH. 1999. Leaves as an indicator of exposure to airborne volatile organic compounds. *Environ Sci Technol* 33:4126-4133.
- Hites RA, Biemann K. 1972. Water pollution: Organic compounds in the Charles River, Boston. *Science* 178:158-160.
- *Ho JS. 1989. A sequential analysis for volatile organics in water by purge-and-trap capillary column gas chromatography with photoionization and electrolytic conductivity detectors in series. *J Chromatogr Sci* 27:91-98.
- Hockwin O, Laser H, Wegener A. 1986. Investigations on rat eyes with diabetic cataract and naphthalene cataract by Zeiss-Scheimpflug measuring system SLC. *Graefes Arch Clin Exp Ophthalmol* 224:502-506.

9. REFERENCES

- Hoeke H, Zellerhoff R. 1998. Metabolism and toxicity of diisopropylnaphthalene as compared to naphthalene and monoalkyl naphthalenes: A minireview. *Toxicology* 126(1):1-7.
- *Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. *J Natl Cancer Inst* 84(5):313-320.
- *Hoffmann K, Krause C, Seifert B, et al. 2000. The German Environmental Survey 1990/92 (GERES II) Sources of personal exposure to volatile organic compounds. *J Expo Anal Environ Epidemiol* 10:115-125.
- Hofmann VP. 1958. Über den reinnaphthalengehalt des gases. *Gas und Wasserfach* 91:301-304. (German)
- Höke H, Zellerhoff R. 1998. Metabolism and toxicity of disopropylnaphthalene as compared to naphthalene and monoalkyl naphthalenes: A minireview. *Toxicology* 126:1-7.
- Holmen JB, Ekesten B, Lundgren B. 1999. Naphthalene-induced cataract model in rats: A comparative study between slit and retroillumination images, biochemical changes and naphthalene dose and duration. *Curr Eye Res* 19:418-425.
- *Honda T, Kiyozumi M, Kojima S. 1990. Alkylnaphthalene. XI. Pulmonary toxicity of naphthalene, 2-methylnaphthalene, and isopropylnaphthalenes in mice. *Chem Pharm Bull* 38:3130-3135.
- Hong KU, Reynolds SD, Giangreco A, et al. 2001. Cells secretory protein-expressing cells of the airway neuroepithelial body microenvironment include a label-retaining subset and are critical for epithelial renewal after progenitor cell depletion. *Am J Respir Cell Mol Biol* 24(6):671-681.
- Horning MG, Kary CD, Gregory PA, et al. 1976. Recycling of naphthalene and naphthalene metabolites through monooxygenase systems. *Toxicol Appl Pharmacol* 37:118.
- *Horning MG, Stillwell WG, Griffin GW, et al. 1980. Epoxide intermediates in the metabolism of naphthalene by the rat. *Drug Metab Dispos* 8:404-414.
- Horton AW, Denman DT, Trosset RP. 1957. Carcinogenesis of the skin. II. The accelerating properties of aliphatic and related hydrocarbons. *Cancer Res* 17:758-766.
- *Howard PH. 1989. Handbook of environmental fate and exposure data for organic chemicals. Vol. 1. Lewis Publishers, 408-421.
- Howsam M, Jones KC, Ineson P. 2000. PAHs in the soils of a mature, mixed-deciduous (*Quercus-fraxinus*) woodland and the surrounding pasture. *Water Air Soil Pollut* 121:379-398.
- *HSDB. 2004. Naphthalene. Environmental standards and regulations. Bethesda, MD: Hazardous Substances Data Bank. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.htm>. December 31, 2004.
- *Hughes CS, Bakker J, Kamatari O. 1985. CEH product review: Naphthalene. In: Chemical economics handbook. Menlo Park, CA: SRI International, 300.7600 C-Z.
- *Hung IF, Fang HF, Lee TS. 1992. Aliphatic and aromatic hydrocarbons in indoor air. *Bull Environ Contam Toxicol* 48:579-584.

9. REFERENCES

- Hunkeler D, Jorger D, Harberli K, et al. 1998. Petroleum hydrocarbon mineralization in anaerobic laboratory aquifer columns. *J Contam Hydrol* 32:41-61.
- Hunt GT, Maisel BE. 1995. Atmospheric concentrations of PCDDs/PCDFs, PAHs and NO₂-PAHs in Fresno, California during winter months. *Organohalogen Compounds* 24:55-61.
- Huntley S, Bonnevie NL, Wenning RJ, et al. 1993. Distribution of polycyclic aromatic hydrocarbons (PAHS) in three Northern New Jersey waterways. *Bull Environ Contam Toxicol* 51
- Huntley SL, Bonnevie NL, Wenning RJ. 1995. Polycyclic aromatic hydrocarbon and petroleum hydrocarbon contamination in sediment from the Newark Bay estuary, New Jersey. *Arch Environ Contam Toxicol* 28:93-107.
- Hyotylainen T, Oikari A. 1999. The toxicity and concentrations of PAHs in creosote-contaminated lake sediment. *Chemosphere* 38:1135-1144.
- *IARC. 1993. IARC scientific publication on indoor concentrations of environmental carcinogens. Volume 12: Indoor air. International Agency for Research on Cancer, World Health Organization, Lyon, France. Publication no. 109, chapter 5.
- *IARC. 1995. Facsimile communication 2/27/95 to Ann Walker, Sciences International, Inc., regarding the evaluation of the carcinogenicity of naphthalene. International Agency for Research on Cancer, World Health Organization, Lyon, France.
- *IARC. 2002. Naphthalene. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. *IARC Monogr Eval Carcinog Risks Hum* 82:367-435.
- *ICRP. 1975. Report on the task group on reference man. New York, NY: Pergamon Press. International Commission on Radiological Protection.
- Ikemoto F, Iwata S. 1978. Sulfhydryl contents of soluble and insoluble lens proteins in naphthalene and traumatic cataracts in rabbits. *Ophthalmic Res* 10:194-201.
- *IRIS. 2005. Naphthalene. U.S. Environmental Protection Agency. Washington, DC: Integrated Risk Information System. <http://www.epa.gov/iris/>. May 6, 2005.
- Irlle U. 1964. [Acute hemolytic anemia caused by naphthalene inhalation in two premature babies and one neonate.] *Dtsch Med Wochenschr* 89:1798-1800. (German)
- IRPTC. 1989a. IRPTC data profile on: 2-methylnaphthalene. International Register of Potentially Toxic Chemicals, United Nations Programme, Geneva, Switzerland. January 1989.
- IRPTC. 1989b. IRPTC data profile on: Naphthalene. International Register of Potentially Toxic Chemicals, United Nations Programme, Geneva, Switzerland. January 1989.
- *Iyer P, Martin JE, Irvin TR. 1991. Role of biotransformation in the *in vitro* preimplantation embryotoxicity of naphthalene. *Toxicology* 66:257-270.
- Jackson TJ, Wade TL, McDonald T, et al. 1994. Polynuclear aromatic hydrocarbon contaminants in oysters from the Gulf of Mexico. *Environ Pollut* 83:291-298.

9. REFERENCES

- Jaffe R, Leal I, Alvarado J, et al. 1998. Baseline study on the levels of organic pollutants and heavy metals in bivalves from the Morrocoy National Park, Venezuela. *Mar Pollut Bull* 36:925-929.
- Jaffrezo JL, Clain MP, Masclet P. 1994. Polycyclic aromatic hydrocarbons in the polar ice of Greenland. Geochemical use of these atmospheric tracers. *Atmos Environ* 28:1139-1145.
- Jafvert CT. 1991. Sediment- and saturated-soil-associated reactions involving an anionic surfactant (dodecylsulfate). 2. Partition of PAH compounds among phases. *Environ Sci Technol* 25:1039-1045.
- James RC. 1985. Hematotoxicity: Toxic effects in the blood. In: Williams PL, Burson JL, eds. *Industrial toxicology*. New York, NY: Van Nostrand Reinhold Company, 59-77.
- James KJ, Stack MA. 1997. The impact of leachate collection on air quality in landfills. *Chemosphere* 34:1713-1721.
- Jerina DM, Daly JW, Witkop B, et al. 1968. The role of arene oxide-oxepin systems in the metabolism of aromatic substrates, III. Formation of 1,2-naphthalene oxide from naphthalene by liver microsomes. *J Am Chem Soc* 90:6526-6527.
- Jerina DM, Daly JW, Witkop B, et al. 1970. 1,2-Naphthalene oxide as an intermediate in the microsomal hydroxylation naphthalene. *Biochemistry* 9:147-155.
- *Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. *Brain Res* 190:3-16.
- Johnstone RA, Quan PM. 1963. Naphthalenes in cigarette smoke [Abstract]. *Nature* 199:1184.
- Juchau MR, Boutelet-Bochan H, Huang Y. 1998. Cytochrome-P450-dependent biotransformation of xenobiotics in human and rodent embryonic tissues. *Drug Metabolism Reviews* 30(3):541-568.
- Junqueira LC, Carneiro J, Kelley RO. 1995. The respiratory system. In: *Basic histology*. 8th edition. Norwalk, CA: Appleton and Lange, 337-341.
- *Kaden DA, Hites RA, Thilly WG. 1979. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons of *Salmonella typhimurium*. *Cancer Res* 39:4152-4159.
- Kahng H-Y, Nam K, Kukor JJ, et al. 2002. PAH utilization by pseudomonas rhodesiae KK1 isolated from a former manufactured-gas plant site. *Appl Microbiol Biotechnol* 60(4):475-480.
- *Kalow W. 1962. *Pharmacogenetics: Heredity and the response to drugs*. Philadelphia, PA: W.B. Saunders Company, 116-120.
- *Kanekal S, Plopper C, Morin D, et al. 1990. Metabolic activation and bronchiolar cell necrosis from naphthalene in the isolated perfused mouse lung. *J Pharmacol Exp Ther* 252(1):428-437.
- Kanekal S, Plopper C, Morin D, et al. 1991. Metabolism and cytotoxicity of naphthalene oxide in the isolated perfused mouse lung. *J Pharmacol Exp Ther* 256:391-401.
- Kang J-J, Cheng Y-W. 1997. Polycyclic aromatic hydrocarbons-induced vasorelaxation through activation of nitric oxide synthase in endothelium of rat aorta. *Toxicol Lett* 93:39-45.

9. REFERENCES

- *Kappeler T, Wuhrmann K. 1978. Microbial degradation of the water-soluble fraction of gas oil - I. *Water Res* 12:327-333.
- *Karickhoff SW. 1981. Semi-empirical estimation of sorption of hydrophobic pollutants on natural sediments and soils. *Chemosphere* 10:833-846.
- *Kawabata TT, White KL. 1990. Effects of naphthalene and naphthalene metabolites on the *in vitro* humoral immune response. *J Toxicol Environ Health* 30:53-67.
- *Keimig SD, Morgan DP. 1986. Urinary 1-naphthol as a biological indicator of naphthalene exposure. *Appl Ind Hyg* 2:61-65.
- Kelly TJ, Muklund R, Spicer CW, et al. 1994. Concentrations and transformations of hazardous air pollutants. *Environ Sci Technol* 28:378-387.
- *Kelsey JW, Alexander M. 1997. Declining bioavailability and inappropriate estimation of risk of persistent compounds. *Environ Toxicol Chem* 16(3):582-585.
- *Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. *Ecotoxicol Environ Safety* 4:26-38.
- Kennicutt MC, McDonald TJ, Denoux GJ, et al. 1992. Hydrocarbon contamination on the Antarctic Peninsula Arthur Harbor - inter and subtidal limpets (*Nacella concinna*) *Mar Pollut Bull* 24:506-511.
- Kennicutt MC, Wade TL, Presley BJ, et al. 1994. Sediment contaminants in Casco Bay, Maine: Inventories, sources, and potential for biological impact. *Environ Sci Technol* 28:1-15.
- Kilanowicz A, Sapota A. 1998. Disposition and metabolism of 1,2-dimethylnaphthalene in rats. *Int J Occup Med Environ Health* 11:305-317.
- Kilanowicz A, Czernski B, Sapota A. 1999. The disposition and metabolism of naphthalene in rats. *Int J Occup Med Environ Health* 12(3):209-219.
- Kilanowicz A, Darago A, Sapota A. 2002a. The role of glutathione in metabolism of selected dimethylnaphthalenes and naphthalene in rat. *Toxicol Lett* 135 (Suppl. 1):15-18.
- Kilanowicz A, Sapota A, Czernski B, et al. 2002b. Disposition and metabolism of 1,6-dimethylnaphthalene in rats. *Toxicol Lett* 134:227-235.
- *Kim YM, Harrad S, Harrison RM. 2001. Concentrations and sources of VOCs in urban domestic and public microenvironments. *Environ Sci Technol* 35:997-1004.
- King MWG, Barker JF. 1999. Migration and natural fate of a coal tar creosote plume. I. Overview and plume development. *J Contam Hydrol* 39:249-279.
- King MWG, Barker JF, Devlin JF, et al. 1999. Migration and natural fate of a coal tar creosote plume 2 Mass balance and biodegradation indicators. *J Contam Hydrol* 39:281-307.

9. REFERENCES

- *Kinman RN, Nutini DL, Carson D. 1995. Evaluation of leachate and gas from sanitary landfills with and without HHW components. 19th Purdue Industrial Waste Conference Proceedings. Chelsea MI: Lewis Publishers, 263-269.
- Kinsey VE, Merriam FC. 1950. Studies on the crystalline lens: II. Synthesis of glutathione in the normal and cataractous rabbit lens. *Arch Ophthalmol* 44:370-380.
- *Kipopoulou AM, Manoli E, Samara C. 1999. Bioconcentration of polycyclic aromatic hydrocarbons in vegetables grown in an industrial area. *Environ Pollut* 106:369-380.
- Kiss G, Varga-Puchony Z, Rohrbacher G, et al. 1998. Distribution of polycyclic aromatic hydrocarbons on atmospheric aerosol particles of different sizes. *Atmos Res* 46:253-261.
- *Kitchin KT, Brown JL, Kulkarni AP. 1992. Predictive assay for rodent carcinogenicity using *in vivo* biochemical parameters: Operational characteristics and complementarity. *Mutat Res* 266:253-272.
- *Kitchin KT, Brown JL, Kulkarni AP. 1994. Predicting rodent carcinogenicity by *in vivo* biochemical parameters. *Environ Carcinog Ecotoxicol C12(1)*:63-88.
- *Kitteringham NR, Davis C, Howard N, Pirmohamed M, et al. 1996. Interindividual and interspecies variation in hepatic microsomal epoxide hydrolase activity: Studies with cis-stilbene oxide, carbamazepine 10,11-epoxide and naphthalene. *J Pharmacol Exp Ther* 278:1018-1027.
- *Klecka GM, Davis JW, Gray DR, et al. 1990. Natural bioremediation of organic contaminants in ground water: Cliff-Dow Superfund site. *Ground Water* 28(4):534-543.
- Kleinfeld M, Messite J, Swencicki R. 1972. Clinical effects of chlorinated naphthalene exposure. *J Occup Med* 14:377-379.
- Knake E. 1956. Uber schwache geschwulsterzeugende wirkung von naphthalin und benzol. *Virchows Arch, Bd* 329:141-176.
- Koch HR, Doldi K. 1975. Naphthalene cataracts in rats of differently pigmented strains [Abstract]. *Exp Eye Res* 20:180.
- Kodama H, Ubuka T, Koyama T, et al. 1974. Effect of naphthalene feeding on the cysteine metabolism in rabbits. *Physiol Chem Phys* 6:107-112.
- Kohler M, Kinniger T, Schmid P, et al. 2000. Inventory and emission factors of creosote, polycyclic aromatic hydrocarbons (PAH) and phenols from railroad ties treated with creosote. *Environ Sci Technol* 34:4766-4772.
- *Kojima M. 1992. Enzymatic distribution patterns of rat lenses and the changes that occur during naphthalene cataract development. *Ophthalmic Res* 24:73-82.
- Kojima S, Hoda T, Babasaki T, et al. 1954. Identification and determination of urinary and biliary metabolites of 2-isopropyl naphthalene in rats. *Eisei Kagaku* 30(2):91-95.
- Kolpin DW, Barbash JE, Gilliom RJ, et al. 1998. Occurrence of pesticides in shallow groundwater of the United States: Initial results from the national water-quality assessment program. *Environ Sci Technol* 32:558-566.

9. REFERENCES

- Kolpin DW, Furlong ET, Meyer MT, et al. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999-2000: A national reconnaissance. *Environ Sci Technol* 36:1202-1211.
- *Kolpin DW, Squillace PJ, Zogorski JS, et al. 1997. Pesticides and volatile organic compounds in shallow urban groundwater of the United States. In: Chilton J, et al. *Groundwater urban environment: Problems, processes and management*. Rotterdam: Balkema.
- *Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. *Biochemistry* 29:4430-4433.
- Kopper Company Inc. 1982. An evaluation of the mutagenic activity of methylnaphthalene fraction in the Ames Salmonella/microsome assay. Submitted to USEPA under section 8D of TSCA. OTS0206434. EPA878213654.
- *Korsak Z, Majcherek W, Rydzynski K. 1998. Toxic effects of acute inhalation exposure to 1-methylnaphthalene and 2-methylnaphthalene in experimental animals. *Int J Occup Med Environ Health* 11:335-342.
- *Kostianen R. 1995. Volatile organic compounds in the indoor air of normal and sick houses. *Atmos Environ* 29:693-702.
- *Kraemer M, Bimboes D, Greim H. 1974. *S. typhimurium* and *E. coli* to detect chemical mutagens. *Arch Pharmacol* 284:R46.
- Krahn MM, Ylitalo GM, Buzitis J, et al. 1993. Comparison of high-performance liquid chromatography/fluorescence screening and gas chromatography/mass spectrometry analysis for aromatic compounds in sediments sampled after the Exxon Valdez oil spill. *Environ Sci Technol* 27:699-708.
- Krause M, Wilcke W, Zech W. 2000a. Polycyclic aromatic hydrocarbons and polychlorinated biphenyls in forest soils: depth distribution as indicator of different fate. *Environ Pollut* 110:79-88.
- Krauss M, Wilcke W, Zech W. 2000b. Availability of polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) to earthworms in urban soil. *Environ Sci Technol* 34:4335-4340.
- *Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. *Principles and methods of toxicology*. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.
- Kroener R, Kleber E, Elstner EF. 1991. Cataract induction by 1,2-naphthoquinone. II. Mechanism of hydrogen peroxide formation and inhibition by iodide. *Z Naturforsch* 46:285-290.
- Krstulovic AM, Rosie DM, Brown PR. 1977. Distribution of some atmospheric polynuclear aromatic hydrocarbons. *Am Lab* 7:11-18.
- *Kulka U, Schmid E, Huber R, et al. 1988. Analysis of the cytogenetic effect in human lymphocytes induced by metabolically activated 1- and 2-methylnaphthalene. *Mutat Res* 208:155-158.
- *Kurz JM. 1987. Naphthalene poisoning: Critical care nursing techniques. *Dimens Crit Care Nurs* 6:264-270.

9. REFERENCES

- *Lacson JG, Cometta S, Kishi A. 2000. Chemical economics handbook [database online]. Menlo Park, CA: SRI International.
- Lagoudi A, Loizidou M, Asimakopoulos D. 1996. Volatile organic compounds in office buildings I Presence of volatile organic compounds in the indoor air. *Indoor Built Environ* 5:341-347.
- Lai DY. 1984. Halogenated benzenes, naphthalenes, biphenyls and terphenyls in the environment: Their carcinogenic, mutagenic and teratogenic potential and toxic effects. *J Environ Sci Health C2*:135-184.
- *Lakritz J, Chang A, Weir A, et al. 1996. Cellular and metabolic basis of cell tolerance to multiple doses of cytochrome P450-activated cytotoxicants. I: Bronchiolar epithelial reorganization and expression of cytochrome P450 monooxygenases in mice exposed to multiple doses of naphthalene. *J Pharmacol Exp Ther* 278(3):1408-1418.
- Lakritz J, Winder BS, Noorous-Zadeh J, et al. 2000. Hepatic and pulmonary enzyme activities in horses. *Am J Vet Res* 61(2):152-157.
- Lamoureux EM, Brownawell BJ. 1999. Chemical and biological availability of sediment-sorbed hydrophobic organic contaminants. *Environ Toxicol Chem* 18:1733-1741.
- Landmeyer JE, Chapelle FH, Petkewich MD, et al. 1998. Assessment of natural attenuation of aromatic hydrocarbons in groundwater near a former manufacturing-gas plant, South Carolina, USA. *Environ Geol* 34:279-292.
- *Lanza DL, Code E, Crespi CL, et al. 1999. Specific dehydrogenation of 3-methylindole and epoxidation of naphthalene by recombinant human CYP2F1 expressed in lymphoblastoid cells. *Drug Metab Dispos* 27(7):798-803.
- *LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. *Environ Prog* 5(1):18-27.
- *Lau OW, Wong SK, Leung KS. 1994. Naphthalene contamination of sterilized milk drinks contained in low-density polyethylene bottles. Part 1. *Analyst* 119(5):1037-1042.
- *Lau OW, Wong SK, Leung KS. 1995. Naphthalene contamination of sterilized milk drinks contained in low-density polyethylene bottles. Part 2. Effect of naphthalene vapour in air. *Analyst* 120(4):1125-1128.
- Lawson GW, Van Winkle L, Toskala E, et al. 2002. Mouse strain modulates the role of the ciliated cell in acute tracheobronchial airway injury-distal airways. *Am J Pathol* 160(1):315-327.
- *Lebo JA, Zajicek JL, Schwartz T, et al. 1991. Determination of monocyclic and polycyclic aromatic hydrocarbons in fish tissue. *J Assoc Off Anal Chem* 74(3):538-544.
- Lee RF, Anderson JW. 1977. Fate and effect of naphthalenes: Controlled ecosystem pollution experiment. *Bull Mar Sci* 27:127-134.
- Lee G, Ray C, Siemers R, et al. 1989. Recent developments in high speed gas chromatography. *Am Lab* (February):108-119.

9. REFERENCES

Lee HJ, Villaume J, Cullen DC, et al. 2003. Monitoring and classification of PAH toxicity using an immobilized bioluminescent bacteria. *Biosensors Bioelectronics* 18(5-6):571-577.

*Lee K-M, Levin DL, Webb R, et al. 1997. Pulmonary alveolar proteinosis. High-resolution CT, chest radiographic, and functional correlations. *Chest* 111:989-995.

Lee W-J, Wang Y-F, Lin T-C, et al. 1995. PAH characteristics in the ambient air of traffic-source. *Sci Total Environ* 159:185-200.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. *Pediatr Clin North Am* 44(1):55-77.

Leguen S, Prost C, Demaimay M. 2000. Critical comparison of three olfactometric methods for the identification of the most potent odorants in cooked mussels (*Mytilus edulis*). *J Agric Food Chem* 48:1307-1314.

*Lehmann I, Thoeke A, Rehwagen M, et al. 2002. The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. *Environ Toxicol* 17(3):203-210.

Lepri L, Desideri P, Cini R, et al. 1995. Transport of organochlorine pesticides across the air/sea interface during the aerosol process. *Anal Chim Acta* 317:149-160.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modelling. In: Ballentine B, Marro T, Turner P, eds. *General and applied toxicology*. Vol. 1. New York, NY: Stockton Press, 153-164.

Levy GN, Weber WW. 1988. High-performance liquid chromatographic analysis of ³²P-postlabeled DNA-aromatic carcinogen adducts. *Anal Biochem* 174:381-392.

*Lezenius A. 1902. [A fall from naphthalene-induced cataracts in masons]. *Klin Monatsbl Augenheilkd.* 40:129. (German)

Li C-T, Mi H-H, Lee W-J. 1999. PAH emission from the industrial boilers. *J Hazard Mater* 69:1-11.

Li H, Christensen ER, VanCamp RP, et al. 1996a. PAHs in dated sediments of Ashtabula River, Ohio, USA. *Environ Sci Technol*

Li H, Otson R, Fellin P. 1996b. Phase distribution of PAH under different atmospheric conditions. In: Jayanty RKM, Fuerst RG, eds. *Measurement of toxic and related air pollutants: An international symposium*. Research Triangle Park, NC: U.S. Environmental Protection Agency's Atmospheric Research and Exposure Assessment Laboratory and the Air & Waste Management Association. EPA600R96096. PB96210323, 3-11.

*Liao W, Smith WD, Chiang TC. 1988. Rapid, low-cost cleanup procedure for determination of semivolatile organic compounds in human and bovine adipose tissues. *J Assoc Off Anal Chem* 71(4):742-747.

Librando V, Fazzino SD. 1993. Quantification of polycyclic aromatic hydrocarbons and their nitro derivatives in atmospheric particulate matter of Augusta City. *Chemosphere* 27:1649-1656.

Lide DR, ed. 1990. *CRC handbook of chemistry and physics*. 71st ed. CRC Press.

9. REFERENCES

- Lin P-H, Kang Y-W, Pan W-C, et al. 2004. Induction of aldehydic DNA lesions by quinonoid derivatives of naphthalene in calf thymus DNA and in the human mammary carcinoma cell line T47D. *Proc Am Assoc Cancer Res* 44:1057.
- *Linick M. 1983. Illness associated with exposure to naphthalene in mothballs - Indiana. *MMWR* 32:34-35.
- Liu K, Xie W, Zhao Z-B, et al. 2000. Investigation of polycyclic aromatic hydrocarbons in fly ash from fluidized bed combustion systems. *Environ Sci Technol* 34:2273-2279.
- *Livingston, AL. 1978. Forage plant estrogens. *J Toxicol Environ Health* 4:301-324.
- Livingstone DR. 1992. Persistent pollutants in marine invertebrates. In: Walker CH, Livingstone DR, eds. *Persistent Pollutants in Marine Ecosystems*, 235-263.
- Lockhart WL, Wilkinson P, Billeck BN, et al. 1993. Polycyclic aromatic hydrocarbons and mercury in sediments from two isolated lakes in Central and Northern Canada. *Water Sci Technol* 28:43-52.
- Loehr RC, Rogers LA, Erickson DC. 1992. Mobility of residues at petroleum industry hazardous waste land treatment sites. *Water Sci Technol* 25:191-196.
- *Lofgren L, Persson K, Stromevall AM, et al. 1991. Exposure of commuters to volatile aromatic hydrocarbons from petrol exhaust. *Sci Total Environ* 108:225-233.
- *Long PH, Herbert RA, Peckham JC, et al. 2003. Morphology of nasal lesions in F344/N rats following chronic inhalation exposure to naphthalene vapors. *Toxicol Pathol* 31:655-664.
- *Lopes TJ, Furlong ET. 2001. Occurrence and potential adverse effects of semivolatile organic compounds in streambed sediment, United States 1992-1995. *Environ Sci Technol* 20:727-737.
- Lopes TJ, Furlong ET, Pritt JW. 1997. Occurrence and distribution of semivolatile organic compounds in stream bed sediments, United States, 1992-1995. In: Little EE, ed. *Toxicology Risk Assessment*. American Society Testing Materials, 105-119.
- *Lorber M. 1972. Hematotoxicity of synergized pyrethrin insecticides and related chemicals in intact, totally and subtotally splenectomized dogs. *Acta Hepato-Gastroenterol* 19:66-78.
- *Luthy RG, Dzombak DA, Peters CA, et al. 1994. Remediating tar-contaminated soils at manufactured gas plant sites. *Environ Sci Technol* 28(6):266A-276A.
- Luthy RG, Ramaswami A, Ghoshal S, et al. 1993. Interfacial films in coal tar nonaqueous-phase liquid-water systems. *Environ Sci Technol* 27(13):2914-2918.
- Luxenhofer O, Ballschmiter K. 1994. C4-C14-alkyl nitrates as organic trace compounds in air. *Fresenius J Anal Chem* 350:395-402.
- *MacGregor RR. 1954. Naphthalene poisoning from the ingestion of moth balls. *Can Med Assoc J* 70:313-314.
- Mackay D, Shiu WY, Sutherland RP. 1979. Determination of air-water Henry's Law constants for hydrophobic pollutants. *Environ Sci Technol* 13:333-336.

9. REFERENCES

- *Mackell JV, Rieders F, Brieger H, et al. 1951. Acute hemolytic anemia due to ingestion of naphthalene moth balls. I. Clinical aspects. *Pediatrics* 71:722-727.
- *Mahvi D, Bank H, Harley R. 1976. Morphology of a naphthalene-induced bronchiolar lesion. *Am J Pathol* 86:559-572.
- Malerba I, Diodovich C, Bowe G, et al. 2004. Naphthalene exposure: effects on apoptosis and gene expression in human cord blood cells. *Toxicol Lett* 144(Supp. 1):s55.
- *Mamber SW, Bryson V, Katz SE. 1983. The *Escherichia coli* WP2/WP100 rec assay for detection of potential chemical carcinogens. *Mutat Res* 119:135-144.
- *Mamber SW, Bryson V, Katz SE. 1984. Evaluation of the *Escherichia coli* K12 inductest for detection of potential chemical carcinogens. *Mutat Res* 130:141-151.
- Manoli LC, Kirchstetter TW, Harley RA, et al. 2000. Polycyclic aromatic hydrocarbons in the bulk precipitation and surface waters of Northern Greece. *Chemosphere* 41:1845-1855.
- Manukovski NS, Teremova MI, Gurevich YL, et al. 1991. Phenol and naphthalene degradation by mixed culture of microorganisms. Institute of Biophysics, USSR Academy of Sciences, 155-163.
- *Marco MP, Nasiri M, Kurth MJ, et al. 1993. Enzyme-linked immunosorbent assay for the specific detection of the mercapturic acid metabolites of naphthalene. *Chem Res Toxicol* 6:284-293.
- Marr LC, Kirchstetter TW, Harley RA, et al. 1999. Characterization of polycyclic aromatic hydrocarbons in motor vehicle fuels and exhaust emissions. *Environ Sci Technol* 33:3091-3099.
- Marsili L, Fossi MC, Casini S, et al. 1997. Fingerprint of polycyclic aromatic hydrocarbons in two populations of southern sea lions (*otaria flavescens*). *Chemosphere* 34:759-770.
- Masclat P, Cachier H, Liousse C, et al. 1995. Emissions of polycyclic aromatic hydrocarbons by Savanna Fires. *J Atmos Chem* 22:41-54.
- *Mason RT. 1995. Naphthalene. In: Kroschwitz JI, Howe-Grant M, eds. *Kirk-Othmer encyclopedia of chemical technology*. New York: John Wiley and Sons, 963-979.
- Mastral AM, Callen MS, Garcia T. 1999. Polycyclic aromatic hydrocarbons and organic matter associated to particulate matter emitted from atmospheric fluidized bed coal combustion. *Environ Sci Technol* 33:3177-3184.
- Mayer KH, Karim SA, Kelly C, et al. 2003. Safety and tolerability of vaginal PRO 2000 gel in sexually active HIV-uninfected and abstinent HIV-infected women. *AIDS* 17(3):321-329.
- *Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. *Toxicology* 74:135-149.
- Mazzerà D, Hayes T, Lowenthal D, et al. 1999. Quantification of polycyclic aromatic hydrocarbons in soil at McMurdo Station, Antarctica. *Sci Total Environ* 229:65-71.

9. REFERENCES

- *Mazzone P, Thomassen MJ, Kavuru M. 2001. Our new understanding of pulmonary alveolar proteinosis: What an internist needs to know. *Cleve Clin J Med* 68:977-985.
- *McCann J, Choi E, Yamasaki E, et al. 1975. Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. *Proc Natl Acad Sci U S A* 72(12):5135-5139.
- McConnell LL, Bidleman TF. 1998. Collection of two-ring aromatic hydrocarbons, chlorinated phenols, guaiacols, and benzenes from ambient air using polyurethane foam/tenax-gc cartridges. *Chemosphere* 37:885-898.
- *McCoull KD, Rindgen D, Blair IA, et al. 1999. Synthesis and characterization of polycyclic aromatic hydrocarbon o-quinone depurinating N7-guanine adducts. *Chem Res Toxicol* 12:237-246.
- McCoy EC, Rosenkranz EJ, Petruzzo LA, et al. 1981. Structural basis of the mutagenicity in bacteria of nitrated naphthalene and derivatives. *Environ Mutagen* 3:499-511.
- McCreary JJ, Jackson JG, Zoltek J. 1983. Toxic chemicals in an abandoned phenolic waste site. *Chemosphere* 12:1619-1632.
- *McDonald JD, Zielinska B, Jujita EM, et al. 2000. Fine particle and gaseous emission rates from residential wood combustion. *Environ Sci Technol* 34:2080-2091.
- McDonald SJ, Kennicutt MC, Liu H, et al. 1995. Assessing aromatic hydrocarbon exposure in Antarctic fish captured near Palmer and McMurdo Stations, Antarctica. *Arch Environ Contam Toxicol* 29:232-240.
- McElroy EA, Buckner JC, Lewis JE, et al. 1998. Chemotherapy for advanced esthesioneuroblastoma: the mayo clinic experience. *Neurosurgery* 42(5):1023-1028.
- *McGilvery RW. 1983. *Biochemistry a functional approach*. 3rd ed. W.B. Saunders Company, 741.
- *McMurray WC. 1977. *Essentials of human metabolism*. 2nd ed. Philadelphia, PA: Harper & Row, 252-254.
- McNally DL, Milhelic JR, Lueking DL. 1999. Biodegradation of mixtures of polycyclic aromatic hydrocarbons under aerobic and nitrate-reducing conditions. *Chemosphere* 38:1313-1321.
- Means JC. 1998. Compound-specific gas chromatographic/mass spectrometric analysis of alkylated and parent polycyclic aromatic hydrocarbons in waters, sediments, and aquatic organisms. *J AOAC Int* 81:657-672.
- Melancon MJ Jr, Lech JJ. 1979. Uptake, biotransformation, disposition, and elimination of 2-methylnaphthalene and naphthalene in several fish species. *Proceedings of the 2nd Annual Symposium on Aquatic Toxicology*, 5-22.
- *Melancon MJ, Rickert DE, Lech JJ. 1982. Metabolism of 2-methylnaphthalene in the rat *in vivo*: I. Identification of 2-naphthoylglycine. *Drug Metab Dispos* 10:128-133.
- *Melancon MJ, Williams DE, Buhler DR, et al. 1985. Metabolism of 2-methylnaphthalene by rat and rainbow trout hepatic microsomes and purified cytochromes P-450. *Drug Metab Dispos* 13:542-547.

9. REFERENCES

- Melcer H, Steel P, Bedford WK. 1995. Removal of polycyclic aromatic hydrocarbons and heterocyclic nitrogen compounds in a municipal treatment plant. *Water Environ Res* 67:926-934.
- *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.
- *Mersch-Sundermann V, Mochayedi S, Kevekordes S, et al. 1993. The genotoxicity of unsubstituted and nitrated polycyclic aromatic hydrocarbons. *Anticancer Res* 13:2037-2044.
- *Michael LC, Pellizzari ED, Wiseman RW. 1988. Development and evaluation of a procedure for determining volatile organics in water. *Environ Sci Technol* 22:565-570.
- Mihelcic JR, Luthy RG. 1991. Sorption and microbial degradation of naphthalene in soil-water suspensions under denitrification conditions. *Environ Sci Technol* 25:169-177.
- *Miles AK, Roster N. 1999. Enhancement of polycyclic aromatic hydrocarbons in estuarine invertebrates by surface runoff at a decommissioned military fuel depot. *Mar Environ Res* 47:49-60.
- *Miles CJ, Delfino JJ. 1999. Priority pollutant polycyclic aromatic hydrocarbons in Florida sediments. *Bull Environ Contam Toxicol* 63:226-234.
- *Minyard JP, Roberts WE. 1991. Chemical contaminants monitoring. State findings on pesticide residues in foods - 1988 and 1989. *Assoc Off Anal Chem* 74:438-452.
- Mitchell AE, Lakritz J, Jones AD. 2000. Quantification of individual glutathione *S*-transferase isozymes in hepatic and pulmonary tissues of naphthalene-tolerant mice. *Arch Toxicol* 74:215-221.
- Miura R, Honmaru S, Nakazaki M. 1968. The absolute configurations of the metabolites of naphthalene and phenanthrene in mammalian systems. *Tetrahedron Lett* 50:5271-5274.
- Mohammed SA, Sorensen DL, Sims RC, et al. 1998. Pentachlorophenol and phenanthrene biodegradation in creosote contaminated material. *Chemosphere* 37:103-111.
- *Moore MM, Harrington-Brock K. 2000. Mutagenicity of trichloroethylene and its metabolites: Implications for the risk assessment of trichloroethylene. *Environ Health Perspect Suppl* 108(Supp 2):215-223.
- Morgan DP. 1982. Pesticide toxicology. In: Tu AT, ed. *Survey of contemporary toxicology*. Vol 2. New York, NY: John Wiley and Sons, 1-36.
- *Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. *Clin Pharmacokin* 5:485-527.
- *Mortelmans K, Haworth S, Lawlor T, et al. 1986. *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen* 8:1-119.
- Mueller M, Klein W. 1993. Fugacity calculations using estimated physico-chemical properties. *SAR QSAR Environ Res* 1:235-262.

9. REFERENCES

- Muhammad F, Baynes RE, Monteiro-Riviera NA, et al. 2003. Absorption through porcine skin exposed to various doses of jet fuel marker components determined with GC-FID using head space SPME fiber. *Toxicol Sci* 72(S-1):383.
- Mulder H, Breure AM, Rulkens WH. 2001. Application of a mechanistic desorption-biodegradation model to describe the behavior of polycyclic aromatic hydrocarbons in peat soil aggregates. *Chemosphere* 42:285-299.
- Mumford JL, Williams RW, Walsh DB, et al. 1991. Indoor air pollutants from unvented kerosene heater emissions in mobile homes: Studies on particles, semivolatile organics, carbon monoxide, and mutagenicity. *Environ Sci Technol* 25:1732-1738.
- *Murano H, Kojima M, Sasaki K. 1993. Differences in naphthalene cataract formation between albino and pigmented rat eyes. *Ophthalmic Res* 25:16-22.
- Murarka I, Neuhauser E, Sherman M, et al. 1992. Organic substances in the subsurface: Delineation, migration, and remediation. *J Hazard Mater* 32(2-3):245-261.
- *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.
- *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.
- *Murata Y, Emi Y, Denda A et al. 1992. Ultrastructural analysis of pulmonary alveolar proteinosis induced by methylnaphthalene in mice. *Exp Toxicol Pathol* 44:47-54.
- *Murray AD, Lockhart WL. 1988. Determination of trace volatile organic compounds in fish tissues by gas chromatography. *J Assoc Off Anal Chem* 71:1086-1089.
- Naes K, Hylland K, Oug E, et al. 1999. Accumulation and effects of aluminum smelter-generated polycyclic aromatic hydrocarbons on soft-bottom invertebrates and fish. *Environ Toxicol Chem* 18:2205-2216.
- Nagata K, Martin BM, Gillette JR, et al. 1990. Isozymes of cytochrome P-450 that metabolize naphthalene in liver and lung of untreated mice. *Drug Metab Dispos* 18:557-564.
- Nagata M, Kojima M, Sasaki K. 1999. Effect of vitamin E eye drops on naphthalene-induced cataract in rats. *J Ocular Pharm and Therapeutics* 15(4):345-351.
- Naiman JL, Kosoy MH. 1964. Red cell glucose-6-phosphate dehydrogenase deficiency - a newly recognized cause of neonatal jaundice and kernicterus in Canada. *Can Med Assoc J* 91:1243-1249.
- *Nakamura S, Oda Y, Shimada T, et al. 1987. SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK1002: Examination with 151 chemicals. *Mutat Res* 192:239-246.
- *Narbonne, JF; Cassand, P; Alzieu, P; et al. 1987. Structure-activity relationships of the N-methylcarbamate series in *Salmonella typhimurium*. *Mutat Res* 191:21-27.

9. REFERENCES

- *NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.
- NATICH. 1988. NATICH database report on state, local and EPA air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality, Planning and Standards, National Air Toxics Information Clearing House.
- NATICH. 1995. NATICH database report on state, local and EPA air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality, Planning and Standards, National Air Toxics Information Clearing House.
- *Neff JM, Burns WA. 1996. Estimation of polycyclic aromatic hydrocarbon concentrations in the water column based on tissue residues in mussels and salmon: An equilibrium partitioning approach. *Environ Toxicol Chem* 15:2240-2253.
- Nerin C, Asensio E. 2004. Behaviour of organic pollutants in paper and board samples intended to be in contact with food. *Anal Chim Acta* 508(2):185-191.
- *NIOSH. 1977. Naphthalene - method S292. In: NIOSH manual of analytical methods. Vol 3. Cincinnati, OH: National Institute for Occupational Safety and Health.
- *NIOSH. 1980. Worker exposure to polyaromatic hydrocarbons at selected petroleum refinery process units of Sun Oil Refinery, Tulsa, Oklahoma. Report to National Institute for Occupational Safety and Health, Cincinnati, OH, by Enviro Control, Inc., Rockville, MD. NTIS No. PB81-236846.
- *NIOSH. 1984a. Hydrocarbons, aromatic - method 1501. In: NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: National Institute for Occupational Safety and Health.
- *NIOSH. 1984b. Polynuclear aromatic hydrocarbons - method 5515-1 to 5515-6. In: NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: National Institute for Occupational Safety and Health.
- NIOSH. 1985. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.
- *NIOSH. 1987. Registry of toxic effects of chemical substances. Vol. 4. 1985-86 ed. Washington, DC U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 3687.
- NIOSH. 1988a. National Occupational Exposure Survey. Cincinnati, OH: National Institute for Occupational Safety and Health, 201-202.
- NIOSH. 1988b. National Occupational Hazard Survey. Cincinnati, OH: National Institute for Occupational Safety and Health, 224, 361.
- *NIOSH. 1991. National Occupational Exposure Survey. Cincinnati, OH: National Institute for Occupational Safety and Health.
- NIOSH. 1992. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. Washington, DC: U.S. Department of Health and Human Services, 28.

9. REFERENCES

- *NIOSH. 2003. Naphthalene. NIOSH pocket guide to chemical hazards. Washington, DC: National Institute for Occupational Safety and Health. <http://www.cdc.gov/niosh/npg/npg.html>. June 6, 2003.
- *NLM. 1995. Chemline. National Library of Medicine, Bethesda, MD.
- *NLM. 2002. Pulmonary alveolar proteinosis. MEDLINEplus Medical encyclopedia. National Library of Medicine. <http://www.nlm.nih.gov/medlineplus/ency/article/000114.htm>. June 18, 2002.
- NRC. 1983. Risk assessment in the federal government: managing the process. National Research Council. Washington, DC: National Academy Press.
- *NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.
- *NTP. 1980a. Subchronic toxicity study: Naphthalene (C52904), B6C3F1 mice. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.
- *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.
- NTP. 1988a. Fiscal year 1988 annual plan. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. National Toxicology Program.
- NTP. 1988b. Review of current DHHS, DOE, and EPA research related to toxicology. Fiscal year 1988. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.
- *NTP. 1989. Chemical status report produced from NTP Chemtrack system. Research Triangle Park, NC: National Toxicology Program, Division of Toxicology Research and Testing, 1-21.
- *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. Final study report and appendix. 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.
- NTP. 1991b. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Laboratory Supplement, sections I-VIII. 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.
- *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. 1992b. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to New Zealand white rabbits on gestational days 6 through 9. 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. TER91021.

9. REFERENCES

- NTP. 1992c. Toxicology and carcinogenesis studies of naphthalene (CAS NO. 91-20-3) in B6C3F1 mice (inhalation studies). National Toxicology Program. TR-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.
- *NTP. 2002a. NTP chemical repository. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html. October 23, 2002.
- NTP. 2002b. Report on Carcinogens Background Document for Naphthalene. Durham, NC: Technology Planning and Management Corporation. <http://ntp-serve.niehs.nih.gov/newhomeroc/rocII/naphthalenePub.pdf>. June 6, 2002.
- *NTP. 2005. Report on carcinogens. 11th edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program. <http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html>. February 15, 2004.
- *O'Brien KA, Smith LL, Cohen GM. 1985. Differences in naphthalene-induced toxicity in the mouse and rat. *Chem Biol Interact* 55:109-122.
- *O'Brien KA, Suverkropp C, Kanekal S, et al. 1989. Tolerance to multiple doses of the pulmonary toxicant, naphthalene. *Toxicol Appl Pharmacol* 99:487-500.
- Oesch F, Daly J. 1972. Conversion of naphthalene to trans-naphthalene dihydrodiol: Evidence for the presence of a coupled aryl monooxygenase-epoxide hydrase system in hepatic microsomes. *Biochem Biophys Res Commun* 46:1713-1720.
- Offenberg JH, Baker JE. 1999. Influence of Baltimore's urban atmosphere on organic contaminants over the Northern Chesapeake Bay. *J Air Waste Manage Assoc* 49:959-965.
- Ogino S, Tojo H, Fujishige I, et al. 1957. Biochemical studies on cataract: IX. Contribution to the histopathology of cataract caused by various guinoid substances. *Am J Ophthalmol* 44:94-105.
- *Ojwang PJ, Ahmed-Jushuf IH, Abdullah MS. 1985. Naphthalene poisoning following ingestion of moth balls: Case report. *East Afr Med J* 62(1):71-73.
- Oman C, Hynning P-A. 1993. Identification of organic compounds in municipal landfill leachates. *Environ Pollut* 80:265-271.
- Orberg J. 1978. Effects of pure chlorobiphenyls (2,4',5-trichlorobiphenyl and 2,2',4,4',5,5'-hexachlorobiphenyl) on the reproductive capacity in female mice. *Acta Pharmacol Toxicol (Copenh)* 42:323-327.
- Ortiz E, Kraatz M, Luthy RG. 1999. Organic phase resistance to dissolution of polycyclic aromatic hydrocarbon compounds. *Environ Sci Technol* 33:235-242.
- *Orzalesi N, Migliavacca L, Miglior S. 1994. Subretinal neovascularization after naphthalene damage to the rabbit retina. *Invest Ophthalmol Vis Sci* 35(2):696-705.

9. REFERENCES

- OSHA. 1995. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000, Table Z-1.
- *OSHA. 2003a. Occupational safety and health standards. Limits for air contaminants. Washington, DC: Occupational Safety and Health Administration. 29 CFR 1910.1000, Table Z-1. <http://www.osha.gov/comp-links.html>. June 6, 2003.
- *OSHA. 2003b. Occupational safety and health standards for shipyard employment. Air contaminants. Washington, DC: Occupational Safety and Health Administration. 29 CFR 1915.1000. <http://www.osha.gov/comp-links.html>. June 6, 2003.
- *OSHA. 2003c. Safety and health regulations for construction. Gases, vapors, fumes, dusts, and mists. Washington, DC: Occupational Safety and Health Administration. 29 CFR 1926.55, Appendix A. <http://www.osha.gov/comp-links.html>. June 6, 2003.
- *OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-436. April 1990.
- *Owa JA. 1989. Relationship between exposure to icterogenic agents, glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Nigeria. *Acta Paediatr Scand* 78(6):848-852.
- *Owa JA, Izedonmwen OE, Ogundaini AO, et al. 1993. Quantitative analysis of 1-naphthol in urine of neonates exposed to mothballs: the value in infants with unexplained anaemia. *Afr J Med Sci* 22:71-76.
- *Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. *Human development*. Philadelphia, PA: WB Saunders, 222-238.
- Paasivirta J, Sinkkonen S, Mikkelsen P. 1999. Estimation of vapor pressures, solubilities and Henry's law constants of selected persistent organic pollutants as functions of temperature. *Chemosphere* 39:811-832.
- Pakdel H, Couture G, Roy C, et al. 1994. Developing methods for the analysis of toxic chemicals in soil and groundwater: The case of Ville Mercier, Quebec, Canada. In: Lesage S, Jackson RE, eds. *Groundwater contamination analysis of hazardous waste sites*. New York: Marcel Dekker, Inc., 381-421.
- *Pakenham G, Lango J, Buonarati M, et al. 2002. Urinary naphthalene mercapturates as biomarkers of exposure and stereoselectivity of naphthalene epoxidation. *Drug Metab Dispos* 30(3):247-253.
- Palmer PT, Martin M, Wentworth G, et al. 2003. Analysis of pesticide residues on museum objects repatriated to the Hupa Tribe of California. *Environ Sci Technol* 37(6):1083-1088.
- Pandya U, Chandra A, Saini M, et al. 2000a. Dietary curcumin delays progression of naphthalene-induced cataract in rats. *Invest Ophthalmol Vis Sci* 41(4):S209.
- Pandya U, Saini MK, Jin GF, et al. 2000b. Dietary curcumin prevents ocular toxicity of naphthalene in rats. *Toxicol Lett* 115:195-204.
- *Pankow JF, Ligocki MP, Rosen ME, et al. 1988. Adsorption/thermal desorption with small cartridges for the determination of trace aqueous semivolatile organic compounds. *Anal Chem* 60:40-47.

9. REFERENCES

- *Papciak RJ, Mallory VT. 1990. Acute toxicological evaluation of naphthalene. *J Am Coll Toxicol Part B: Acute toxicity data* 1(1):17-19.
- *Park KS, Sims RC, Dupont RR, et al. 1990. Fate of PAH compounds in two soil types: Influence of volatilization, abiotic loss and biological activity. *Environ Toxicol Chem* 9:187-195.
- Parkin DM, Wahrendorf J, Demaret E. 1987. *Directory of on-going research in cancer epidemiology*. Lyon, France: International Agency for Research on Cancer, 390, 608.
- Parkinson A. 2001. Biotransformation of xenobiotics. In: Klassen, CD, ed. *Casarett and Doull's toxicology. The basic science of poisons*. 6th ed. New York: McGraw Hill Medical Publishing Division, 133-224.
- Parrish AR, Alejandro NF, Bowes RC, et al. 1998. Cytotoxic response profiles of cultured renal epithelial and mesenchymal cells to selected aromatic hydrocarbons. *Toxicol In Vitro* 12:219-232.
- Patty FA, ed. 1963. *Industrial hygiene and toxicology*. Vol. 2. New York, NY: John Wiley and Sons.
- Peake JL, Reynolds SD, Stripp BR, et al. 2000. Alteration of pulmonary neuroendocrine cells during epithelial repair of naphthalene-induced airway injury. *Am J Pathol* 156(1):279-286.
- Pedersen LM, Cohr K-H. 1984. Biochemical pattern in experimental exposure of humans to white spirit. I. The effects of a 6 hours single dose. *Acta Pharmacol Toxicol* 55:317-324.
- *Pellizzari ED, Hartwell TD, Benjamin SH, et al. 1982. Purgeable organic compounds in mother's milk. *Bull Environ Contam Toxicol* 28:322-328.
- Penning TM, Burczynski ME, Hung CF, et al. 1999. Dihydrodiol dehydrogenases and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active o-quinones. *Chem Res Toxicol* 12(1):1-18.
- *Pereira WE, Domagalski JL, Hostettler FD, et al. 1996. Occurrence and accumulation of pesticides and organic contaminants in river sediment water and clam tissues from the San Joaquin River and tributaries, California. *Environ Toxicol Chem* 15:172-180.
- *Pereira WE, Hostettler FD, Rapp JB. 1996. Distributions and fate of chlorinated pesticides biomarkers and polycyclic aromatic hydrocarbons in sediments along a contamination gradient from a point-source in San Francisco Bay, California. *Mar Environ Res* 41:299-314.
- Pereira WE, Hostettler FD, Luoma SN, et al. 1999. Polycyclic aromatic hydrocarbons. *Mar Chem* 64:99-113.
- Peters CA, Luthy RG. 1993. Coal tar dissolution in water-miscible solvents: experimental evaluation. *Environ Sci Technol* 27:2831-2843.
- Petridou E, Polychronopoulou A, Kouri N, et al. 1997. Unintentional childhood poisoning in Athens: A mirror of consumerism? *Clin Toxicol* 35(6):669-675.
- Petry T, Schmid P, Schlatter C. 1996a. Airborne exposure to polycyclic aromatic hydrocarbons (PAHs) and urinary excretion of 1-hydroxypyrene of carbon anode plant workers. *Ann Occup Hyg* 40:345-357.

9. REFERENCES

- Petry T, Schmid P, Schlatter C. 1996b. The use of toxic equivalency factors in assessing occupational and environmental health risk associated with exposure to airborne mixtures of polycyclic aromatic hydrocarbons (PAHs). *Chemosphere* 32:639-648.
- Pettersson B, Curvall M, Enzell CR. 1980. Effects of tobacco smoke compounds on the noradrenaline induced oxidative metabolism in isolated brown fat cells. *Toxicology* 18:1-15.
- Petty JD, Poulton BC, Charbonneau CS, et al. 1998. Determination of bioavailable contaminants in the lower Missouri River following the flood of 1993. *Environ Sci Technol* 32:837-842.
- Peven CS, Uhler Ad, Querzoli FJ. 1996. Caged mussels and semipermeable membrane devices as indicators of organic contaminant uptake in Dorchester and Duxbury Bays, Massachusetts. *Environ Toxicol Chem* 15:144-149.
- Philpot RM, Wolf CR. 1981. The properties and distribution of the enzymes of pulmonary cytochrome P-450-dependent monooxygenase systems. In: Hodgson E, Bend JR, Philpot RM, eds. *Reviews in biochemical toxicology*. Vol. 3. New York, NY: Elsevier Science Publications, 51-76.
- Phimister A, Plopper CG. Role of glutathione depletion in toxicant induced injury to cells [abstract]. *Toxicologist* 72(S-1):351.
- Piao M, Chu S, Zheng M, et al. 1999. Characterization of the combustion products of polyethylene. *Chemosphere* 39:1497-1512.
- Pichler M, Guggenberger G, Hartmann R, et al. 1996. Polycyclic aromatic hydrocarbons (PAH) in different forest humus types. *Environ Sci Pollut Res* 3:24-31.
- Pinal R, Suresh P, Rao C, et al. 1990. Cosolvency of partially miscible organic solvents on the solubility of hydrophobic organic chemicals. *Environ Sci Technol* 24:639-647.
- Pino MV, Valerio MG, Miller GK, et al. 1999. Toxicological and carcinogenic effects of the Type IV phosphodiesterase inhibitor RP 73401 on the nasal olfactory tissue in rats. *Toxicol Pathol* 27:383-394.
- Pirie A, Van Heyningen R. 1966. *Biochemistry of the eye*. Springfield, IL: Charles C. Thomas, 127-131.
- Plant AL, Pownall HJ, Smith LC. 1983. Transfer of polycyclic aromatic hydrocarbons between model membranes: relation to carcinogenicity. *Chem Biol Interactions* 44:237-246.
- *Plasterer MR, Bradshaw WS, Booth GM, et al. 1985. Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: Naphthalene, *p*-nitrophenol, sodium selenite, dimethyl phthalate, ethylenethiourea and four glycol ether derivatives. *Toxicol Environ Health* 15:25-38.
- Plopper CG, Chang AM, Pang A, et al. 1991. Use of microdissected airways to define metabolism and cytotoxicity in murine bronchiolar epithelium. *Exp Lung Res* 17:197-212.
- *Plopper CG, Macklin J, Nishio SJ, et al. 1992b. Relationship of cytochrome P-450 activity to cell cytotoxicity. III. Morphometric comparison of changes in the epithelial populations of terminal bronchioles and lobar bronchi in mice, hamsters, and rats after parenteral administration of naphthalene. *Lab Invest* 67(5):553-565.

9. REFERENCES

- *Plopper CG, Suverkropp C, Morin D, et al. 1992a. Relationship of cytochrome P-450 activity to cell cytotoxicity. I. Histopathologic comparison of the respiratory tract of mice, rats and hamsters after parenteral administration of naphthalene. *J Pharmacol Exp Ther* 261(1):353-363.
- Plopper CG, Van Winkle LS, Fanucchi MV, et al. 2001. Early events in naphthalene-induced acute cell toxicity. II. Comparison of glutathione depletion and histopathology by airway location. *Am J Respir Cell Mol Biol* 24(3):272-281.
- Poittrast BJ, Keller WC, Elves RG. 1988. Estimation of chemical hazards in breast milk. *Aviat Space Environ Med* 11:87-92.
- Prest HF, Jacobson LA. 1997. Passive water sampling for polynuclear aromatic hydrocarbons using lipid-containing semipermeable membrane devices (SPMDs): Application to contaminant residence times. *Chemosphere* 35:3047-3063.
- Preuss R, Angerer J, Drexler H. 2003. Naphthalene – an environmental and occupational toxicant. *Int Arch Occup Environ Health* 76(8):556-576.
- *PRI. 1985a. Primary dermal irritation study in rabbits (83/EPA): Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 420-TX-013-84.
- *PRI. 1985b. Rabbit eye irritation study (WASH): Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 421 TX-009-84.
- *PRI. 1985c. Delayed contact hypersensitivity in guinea pigs: Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 424-TX-001 84.
- *PRI. 1985d. Micronucleus test (MNT) (OECD): Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 309A-TX-007-85.
- *PRI. 1985e. Rat hepatocyte primary culture/DNA repair test. Waverly, PA: Pharmakon Research International, Inc. PH 311 TX-008-85.
- PRI. 1985f. Acute exposure dermal toxicity (82 EPA/OECD): Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 422-TX-002-84.
- PRI. 1985g. Acute exposure oral toxicity (83 EPA/OECD): Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 402-TX-002-84.
- PRI. 1985h. Ames *Salmonella*/microsome plate test (EPA/OECD): Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 301-TX-020-85.
- *PRI. 1985i. Dose-range-finding-developmental toxicity in rabbits: Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 329DR-TX-001-85.
- PRI. 1985j. Repeated dose dermal toxicity - rat: 28 Day dose range finding study: Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 434-TX-001-85.
- *PRI. 1986. Developmental toxicity study in rabbits: Naphthalene. Waverly, PA: Pharmakon Research International, Inc. PH 329-TX-001 85.

9. REFERENCES

- *Probst GS, McMahon RE, Hill LE, et al. 1981. Chemically induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity tests using 218 compounds. *Environ Mutagen* 3:11-32.
- *Propper R. 1988. Polycyclic aromatic hydrocarbons (PAH). A candidate toxic air contaminant. Air Resources Board. Springfield, VA: National Technical Information Service. TR SS-88-01.
- *Purchase IFH, Longstaf E, Ashby J, et al. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. *Br J Cancer* 37:873-959.
- Pyy L, Makela M, Hakala E, et al. 1997. Ambient and biological monitoring of exposure to polycyclic aromatic hydrocarbons at a cooking plant. *Sci Total Environ* 199:151-158.
- *Quick DJ, Shuler ML. 1999. Use of *in vitro* data for construction of a physiologically based pharmacokinetic model for naphthalene in rats and mice to probe species differences. *Biotechnol Prog* 15:540-555.
- *Rao GS, Pandya KP. 1981. Biochemical changes induced by naphthalene after oral administration in albino rats. *Toxicol Lett* 8:311-315.
- Rao VR, Mitz SV, Hadden CT. 1996. Distribution of contaminants in aquatic organisms from East Fork Poplar Creek. *Ecotoxicol Environ Saf* 33:44-54.
- *Rasmussen RE, Do DH, Kim TS, et al. 1986. Comparative cytotoxicity of naphthalene and its monomethyl- and mononitro-derivatives in the mouse lung. *J Appl Toxicol* 6:13-20.
- Rathbun WB, Holleschau AM, Cohen JF, et al. 1996. Prevention of acetaminophen- and naphthalene-induced cataract and glutathione loss by CySSME. *Invest Ophthalmol Vis Sci* 37(5):923-929
- *Rathbun WB, Holleschau AM, Murray DL, et al. 1990. Glutathione synthesis and glutathione redox pathways in naphthalene cataract of the rat. *Curr Eye Res* 9:45-53.
- Rawlings GD, DeAngelis DG. 1979. Toxicity removal in textile plant waste waters. *Journal American Leather Chemistry Association* 74:404-417.
- Redmond MS, Crocker PA, McKenna KM, et al. 1996. Sediment toxicity testing with the amphipod *Ampelisca abdita* in Calcasieu Estuary, Louisiana. *Arch Environ Contam Toxicol* 30:53-61.
- Reemtsma T, Savric I, Martig C, et al. 1996. LAS, PCB and PAH as indicators for accumulation, biodegradation, and transport processes of wastewater constituents in sewage farm soils. *Prepr Pap Natl Meet Am Chem Soc Div Environ Chem* 36(2):186-188.
- *Rees JR, Pirie A. 1967. Possible reactions of 1,2-naphthaquinone in the eye. *Biochem J* 102:853-863.
- Reeves WR, Bahoumi R, Burghardt RC, et al. 2001. Evaluation of methods for predicting the toxicity of polycyclic aromatic hydrocarbon mixtures. *Environ Sci Technol* 35:1630-1636.
- Reid WD, Ilett KF, Glick JM, et al. 1973. Metabolism and binding of aromatic hydrocarbons in the lung. *Am Rev Respir Dis* 107:539-551.

9. REFERENCES

- *Rhim JS, Park DK, Weisburger EK, et al. 1974. Evaluation of an *in vitro* assay system for carcinogens based on prior infection of rodent cells with nontransforming RNA tumor virus. *J Natl Cancer Inst* 52:1167-1173.
- *Richardson SD, Thruston AD Jr, Collette TW, et al. 1994. Multispectral identification of chlorine dioxide disinfection byproducts in drinking water. *Environ Sci Technol* 28:592-599.
- Richieri PR, Buckpitt AR. 1987. Efflux of naphthalene oxide and reactive naphthalene metabolites from isolated hepatocytes. *J Pharmacol Exp Ther* 242:485-492.
- Richieri PR, Buckpitt AR. 1988. Glutathione depletion by naphthalene in isolated hepatocytes and by naphthalene oxide *in vivo*. *Biochem Pharmacol* 37:2473-2478.
- Ringelberg DB, Talley JW, Perkins EJ, et al. 1994. Succession of phenotypic, genotypic, and metabolic community characteristics during *in vitro* bioslurry treatment of polycyclic aromatic hydrocarbon-contaminated sediments. *Appl Environ Microbiol* 67:542-550.
- Rio J, Manning T. 1988. An investigation of the toxic effects of combustion products-analysis of smoke components. *J Anal Toxicol* 12:274-278.
- *Rittman BE, McCarty PL, Roberts PV. 1980. Trace-organics biodegradation in aquifer recharge. *Ground Water* 18:236-243.
- Riviere JE, Brooks JD, Monteiro-Riviere NA, et al. 1999. Dermal absorption and distribution of topically dosed jet fuels jet-A, JP-8, and JP-8(100) *Toxicol Appl Pharmacol* 160:60-75.
- *Roberts PV, McCarty PL, Reinhard M, et al. 1980. Organic contaminant behavior during groundwater recharge. *J Water Pollut Control Fed* 52:161-172.
- Robinson AG, Dillaman RM. 1985. The effects of naphthalene on the ultrastructure of the hepatopancreas of the fiddler crab, *Uca minax*. *J Invertebr Pathol* 45:311-323.
- Rogers JV, Siegel GL, Pollard DL, et al. 2004a. Cytotoxicity of the JP-8 jet fuel components m-xylene, 1-methylnaphthalene, and n-nonane in keratinocytes. *Toxicologist* 72(S-1):383
- Rogers JV, Siegel GL, Pollard DL, et al. 2004b. The cytotoxicity of volatile JP-8 jet fuel components in keratinocytes. *Toxicology* 197(2):113-121.
- Roony SA, Young SL, Mendelson CR. 1994. Molecular and cellular processing of lung surfactant. *FASEB J* 8:957-967.
- Roper JM, Cherry DS, Simmers JW, et al. 1997. Bioaccumulation of PAHs in the zebra mussel at Times Beach, Buffalo, New York. *Environ Monit Assess* 46:267-277.
- *Rosenfeld JK, Plumb RH. 1991. Ground water contamination at wood treatment facilities. *Ground Water Monitoring Review* II:133-140.
- *Rossa V, Pau H. 1988. Is the experimental naphthalene cataract a model for human senile cataract? *Graefes Arch Clin Exp Ophthalmol* 226:291-293.

9. REFERENCES

- *Rozman K, Summer KH, Rozman T, et al. 1982. Elimination of thioethers following administration of naphthalene and diethylmaleate to the Rhesus monkey. *Drug Chem Toxicol* 5:265-275.
- *RTC. 1999. Naphthalene unscheduled DNA synthesis (UDS) after *in vivo* treatment. Monitored by Rutgers VFT AG; Sponsored by International Tar Assoc. Research Toxicology Center, Rome.
- Rubin ES. 1999. Toxic releases from power plants. *Environ Sci Technol* 33:3062-3067.
- *Rundell JO, Guntakatta M, Matthews EJ. 1983. Criterion development for the application of BALB/c-3T3 cells to routine testing for chemical carcinogenic potential. *Environ Sci Res* 27:309-324.
- Russell P, Yamada T, Xu GT, et al. 1991. Effects of naphthalene metabolites on cultured cells from eye lens. *Free Radic Biol Med* 10:255-261.
- *Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: A review. *Am Ind Hyg Assoc J* 47:142-151.
- Ruzo L, Jones D, Safe S, et al. 1976. Metabolism of chlorinated naphthalenes. *J Agric Food Chem* 24:581-583.
- Sabljić A, Guesten H, Schoenherr J, et al. 1990. Modeling plant uptake of airborne organic chemicals. 1. Plant cuticle/water partitioning and molecular connectivity. *Environ Sci Technol* 24:1321-1326.
- Saeed T, Al-Yakoob S, Al-Hashash H, et al. 1995. Preliminary exposure assessment for Kuwaiti consumers to polycyclic aromatic hydrocarbons in seafood. *Environ Int* 21:255-263.
- *Sakai M, Yoshida D, Mizusaki S. 1985. Mutagenicity of polycyclic aromatic hydrocarbons and quinones on *Salmonella typhimurium* TA97. *Mutat Res* 156:61-67.
- Salmony D. 1960. Some biochemical changes in naphthalene cataract. *Br J Ophthalmol* 44:29-34.
- Sanders G, Hamilton-Taylor J, Jones KC. 1996. PCB and PAH dynamics in a small rural lake. *Environ Sci Technol* 30:2958-2966.
- Sanderson EG, Farant J-P. 2000. Use of benzo[a]pyrene relative abundance ratios to assess exposure to polycyclic aromatic hydrocarbons in the ambient atmosphere in TCH vicinity of a Soderberg aluminum smelter. *J Air Waste Manage Assoc* 50:2085-2092.
- Sandmeyer EE. 1981. Aromatic hydrocarbons. In: Clayton GD, Clayton FE, eds. *Patty's industrial hygiene and toxicology*. 3rd ed. Vol. 2B: Toxicology. New York, NY: John Wiley and Sons, 3256-3258, 3333-3343.
- Sanger DM, Holland AF, Scott GI. 1999. Tidal creek and salt marsh sediments in South Carolina coastal estuaries: II Distribution of organic contaminants. *Arch Environ Contam Toxicol* 37:458-471.
- *Santhanakrishnan BR, Ranganathan G, Balagopala Raju V. 1973. Naphthalene induced haemolytic anaemia with haemoglobinuria. *Indian J Pediatr* 40:195-197.
- Santiago S, Thomas RL, Larbaigt G, et al. 1993. Comparative ecotoxicity of suspended sediment in the lower Rhone River using algal fractionation, microtox and *Daphnia magna* bioassays. *Hydrobiologia* 252:231-244.

9. REFERENCES

- *Santucci K, Shah M. 2000. Association of naphthalene with acute hemolytic anemia. *Acad Emerg Med* 7(1):42-47.
- *Sasaki JC, Arey J, Eastmond DA, et al. 1997. Genotoxicity induced in human lymphoblasts by atmospheric reaction products of naphthalene and phenanthrene. *Mutat Res* 393(1-2):23-35.
- *Sax NI, Lewis RJ Sr. 1987. *Hawley's condensed chemical dictionary*. New York, NY: Van Nostrand Reinhold Company, 775, 806.
- *Sax NI, Lewis RJ. 1989. *Dangerous properties of industrial materials*. 7th ed. New York, NY: Van Nostrand Reinhold Company, 2341-2342, 2451-2452.
- Sayles GD, Acheson CM, Kupferle MJ, et al. 1999. Land treatment of PAH-contaminated soil: Performance measured by chemical and toxicity assays. *Environ Sci Technol* 33:4310-4317.
- *Schafer WB. 1951. Acute hemolytic anemia related to naphthalene: Report of a case in a newborn infant. *Pediatrics* 7:172-174.
- *Schauer JJ, Kleeman MJ, Cass GR, et al. 1999a. Measurement of emissions from air pollution sources. 1. C₁ through C₂₉ organic compounds from meat charbroiling. *Environ Sci Technol* 33(10):1566-1577.
- Schauer J, Kleeman MJ, Cass GR, et al. 1999b. Measurement of emissions from air pollution sources 2. C₁ through C₂₉ organic compounds from medium duty diesel trucks. *Environ Sci Technol* 33:1578-1587.
- *Schauer JJ, Kleeman MJ, Cass GR, et al. 2001. Measurement of emissions from air pollution sources. 3. C₁-C₂₉ organic compounds from fireplace combustion of wood. *Environ Sci Technol* 35:1716-1728.
- Schlotzhauer WS, Chortyk OT. 1987. Recent advances in studies on the pyrosynthesis of cigarette smoke constituents. *J Anal Appl Pyrolysis* 12:193-222.
- *Schmahl D. 1955. [The testing of naphthalene and anthracene for a carcinogenic effect on rats.] *Z Krebsforsch* 60:697-710. (German)
- *Schmeltz I, Tosk J, Hilfrich J, et al. 1978. Bioassays of naphthalene and alkyl naphthalenes for co-carcinogenic activity. Relation to tobacco carcinogenesis. *Carcinogenesis* 3:47-60.
- *Schmeltz I, Tosk J, Hoffman D. 1976. Formation and determination of naphthalene in cigarette smoke. *Anal Chem* 48:645-650.
- Schnelle J, Jansch T, Wolf K, et al. 1995. Particle size dependent concentrations of polycyclic aromatic hydrocarbons (PAH) in the outdoor air. *Chemosphere* 31:3119-3127.
- *Schreiner CA. 2003. Genetic toxicity of naphthalene: A review. *J Toxicol Environ Health Part B Crit Rev* 6:161-183.
- Schultz TW, Moulton MP. 1985. Structure-toxicity relationships of selected naphthalene derivatives. II. Principal components analysis. *Bull Environ Contam Toxicol* 34:1-9.

9. REFERENCES

Schutz LF, Young TM, Higashi RM. 1999. Sorption-desorption behavior of phenanthrene elucidated by pyrolysis-gas chromatography-mass spectrometry studies of soil organic matter. *Environ Toxicol Chem* 18:1710-1719.

Schwarz FP, Wasik SP. 1976. Fluorescence measurements of benzene, naphthalene, anthracene, pyrene, fluoranthene, and benzo[e]pyrene in water. *Anal Chem* 48:524-528.

Schwarz LR, Mezger M, Hesse S. 1980. Effect of decreased glucuronidation and sulfation on covalent binding of naphthalene in isolated rat hepatocytes. *Toxicology* 17:119-122.

*Schwarzenbach RP, Westall, J. 1981. Transport of nonpolar organic compounds from surface water to groundwater. Laboratory sorption studies. *Environ Sci Technol* 15(11):1360-1367.

*Schwarzenbach RP, Giger W, Hoehn E, et al. 1983. Behavior of organic compounds during infiltration of river water to groundwater. *Environ Sci Technol* 17:472-479.

Sears GW, Hopke ER. 1949. Vapor pressures of naphthalene, anthracene and hexachlorobenzene in a low pressure region. *J Am Chem Soc* 71:1632-1634.

*Seitz LM, Ram MS, Rengarajan R. 1999. Volatiles obtained from whole and ground grain samples by supercritical carbon dioxide and direct helium purge methods: Observations on 2,3-butanediols and halogenated anisoles. *J Agric Food Chem* 1999:1051-1061.

*Seixas GM, Andon BM, Hollingshead PG, et al. 1982. The aza-arenes as mutagens for *Salmonella typhimurium*. *Mutat Res* 102:201-212.

Selzer M, Wegener A, Hockwin O. 1991. Regional enzyme profiles in rabbit lenses with early stages of naphthalene cataract. *Lens and Eye Toxicity Research* 8:415-430.

*Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. *Handbook of physiology: Endocrinology V*. Washington, DC: American Physiological Society.

*Shane BS, Henry CB, Hotchkiss JH, et al. 1990. Organic toxicants and mutagens in ashes from eighteen municipal refuse incinerators. *Arch Environ Toxicol* 19:665-673.

Shank RC, Barrows LP, Buckpitt AR. 1980. Comparative metabolism of hydrazine and naphthalene. Wright-Patterson Air Force Base, OH: Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratory. AMRL-TR-80-103.

*Shannon K, Buchanan GR. 1982. Severe hemolytic anemia in black children with glucose-6-phosphate dehydrogenase deficiency. *Pediatrics* 70:364-369.

*Shauer JJ, Kleeman MJ, Cass GR, et al. 2002. Measurement of emissions from air pollution sources. 5. C₁-C₃₂ organic compounds from gasoline-powered motor vehicles. *Environ Sci Technol* 36(6):1169-1180.

Shepard TH. 1986. *Catalog of teratogenic agents*. 5th ed. Johns Hopkins University Press.

*Shichi H, Tanaka M, Jensen NM, et al. 1980. Genetic differences in cataract and other ocular abnormalities induced by paracetamol and naphthalene. *Pharmacology* 20:229-241.

9. REFERENCES

- *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.
- *Shultz MA, Choudary PV, Buckpitt A. 1999. Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. *J Pharmacol Exp Ther* 290(1):281-288.
- Shultz MA, Morin D, Chang AM, et al. 2001. Metabolic capabilities of CYP2F2 with various pulmonary toxicants and its relative abundance in mouse lung subcompartments. *J Pharmacol Exp Ther* 286(2):510-519.
- *Siegel E, Wason S. 1986. Mothball toxicity. *Pediatr Clin North Am* 33:369-374.
- Simcik MF, Eisenreich SJ, Golden KA, et al. 1996. Atmospheric loading of polycyclic aromatic hydrocarbons to Lake Michigan as recorded in the sediments. *Environ Sci Technol* 30:3039-3046.
- Simpson CD, Harrington CF, Cullen WR, et al. 1998. Polycyclic aromatic hydrocarbon contamination in marine sediments near Kitimat, British Columbia. *Environ Sci Technol* 32:3266-3272.
- *Sina JF, Bean CL, Dysart GR, et al. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat Res* 113:357-391.
- Sittig M. 1985. *Handbook of toxic and hazardous chemicals and carcinogens*. 2nd ed. Park Ridge, NJ: Noyes Publications, 630-632.
- Smart G, Buckpitt AR. 1983. Formation of reactive naphthalene metabolites by target vs non-target tissue microsomes: Methods for the separation of three glutathione adducts. *Biochem Pharmacol* 32:943-946.
- Smith JA, Sievers M, Huang S, et al. 2000. Occurrence and phase distribution of polycyclic aromatic hydrocarbons in urban storm-water runoff. *Water Sci Technol* 42:383-388.
- Smith RM. 1988. *Supercritical fluid chromatography*. Letchworth, England: Royal Society of Chemistry.
- Sollmann T. 1957. *A manual of pharmacology and its applications to therapeutics and toxicology*. 8th ed. Philadelphia, PA: W.B. Saunders Company, 821.
- *Sorg RM, Naismith RW, Matthews RJ. 1985. Micronucleus test (MNT) OECD (unpublished material). Submitted to USEPA under section 8D of TSCA. OTS0513639.
- Soucek P. 2000. Expression of cytochrome P450 2A6 in *Escherichia coli*. *Toxicol Lett* 116(Suppl.1):24-25.
- *Southworth GR, Beauchamp JJ, Schmieder PK. 1978. Bioaccumulation potential of polycyclic aromatic hydrocarbons in *Daphnia pulex*. *Water Res* 12:973-977.
- Spicer CW, Miller DF, Levy A. 1974. Inhibition of photochemical smog reactions by free radical scavengers. *Environ Sci Technol* 8:1028-1030.
- *Squillace PJ, Moran MJ, Lapham WW, et al. 1999. Volatile organic compounds in untreated ambient groundwater of the United States. *Environ Sci Technol* 33:4176-4187.

9. REFERENCES

- SRI. 1985. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute, 537, 633, 720, 728.
- SRI. 1986. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute, 605, 713, 812, 821.
- SRI. 1987. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute, 589, 697, 799, 808.
- SRI. 1988. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute, 578, 684, 784, 793.
- SRI. 1990. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute, 580, 694, 795, 805.
- *SRI. 1992. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute, 580, 695, 792, 801.
- *SRI. 2002. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute.
- *SRI. 2003. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute.
- SRI. 2004. 2004 Directory of Chemical Producers. Menlo Park, CA: SRI Consulting, 3, 160, 161, 226, 733, 741.
- *Srivastava SK, Nath R. 1969. Metabolic alterations in experimental cataract. Part I. Inhibition of lactate dehydrogenase and appearance of o-diphenol oxidase in cataractous lens of naphthalene fed rabbits. *Indian J Med Res* 57:225-227.
- *Staples CA, Werner AF, Hoogheem TJ. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. *Environ Toxicol Chem* 4:131-142.
- Stefaniak AB, Breyse PN, Murray MPM, et al. 2000. An evaluation of employee exposure to volatile organic compounds in three photocopy centers. *Environ Res* 83:162-173.
- Steiber RS. 1993. Organic combustion fingerprints of three common home heating fuels. *J Air Waste Manage Assoc* 43:859-863.
- Stevens TP, McBride JT, Peake JL, et al. 1997. Cell proliferation contributes to PNEC hyperplasia after acute airway injury. *Am J Physiol Lung Cell Mol Physiol* 272(16):L486-L493.
- Stillwell WG, Bouwsma OJ, Thenot JP, et al. 1978. Methylthio metabolites of naphthalene excreted by the rat. *Res Commun Chem Pathol Pharmacol* 20:509-530.
- *Stillwell WG, Horning MG, Griffin GW, et al. 1982. Identification of new sulfur-containing metabolites of naphthalene in mouse urine. *Drug Metab Dispos* 10:624-631.

9. REFERENCES

- Stohs SJ, Ohia S, Bagchi D. 2002. Naphthalene toxicity and antioxidant nutrients. *Toxicology* 180:97-105.
- Stout SA, Uhler AD, Emsbo-Mattingly SD. 2003. Characterization of PAH sources in sediments of the Thea Foss/Wheeler Osgood Waterways, Tacoma, Washington. *Soil Sediment Contam* 12(6):815-834.
- Stripp BR, Maxson K, Mera R, et al. 1995. Plasticity of airway cell proliferation and gene expression after acute naphthalene injury. *Am J Physiol* 269(6):L791-799.
- *Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation.
- *Sugiyama K, Wang T-CL, Simpson JT, et al. 1999. Aldose reductase catalyzes the oxidation of naphthalene-1,2-dihydrodiol for the formation of orth-naphthoquinone. *Drug Metab Dispos* 27(1):60-67.
- *Summer KH, Rozman K, Coulston F, et al. 1979. Urinary excretion of mercapturic acids in chimpanzees and rats. *Toxicol Appl Pharmacol* 50:207-212.
- Suter MJF, Riediker S, Giger W. 1999. Selective determination of aromatic sulfonates in landfill leachates and groundwater using microbore liquid chromatography coupled with mass spectrometry. *Anal Chem* 71:897-904.
- *Swartz E, Stockburger L, Vallero DA. 2003. Polycyclic aromatic hydrocarbons and other semivolatile organic compounds collected in New York City in response to the events of 9/11. *Environ Sci Technol* 37:3537-3546.
- *Sweeney LM, Shuler ML, Quick DJ, et al. 1996. A preliminary physiologically based pharmacokinetic model for naphthalene and naphthalene oxide in mice and rats. *Ann Biomed Eng* 24:305-329.
- *Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. *J Water Pollut Control Fed* 53(10):1503-1518.
- Taki T, Nakazima T, Emi Y, et al. 1986. Accumulation of surfactant phospholipids in lipid pneumonia induced with methylnaphthalene. *Lipids* 21(9):548-552.
- Tancrede M, Wilson R, Zeise L, et al. 1987. The carcinogenic risk of some organic vapors indoors: A theoretical survey. *Atmos Environ* 21:2187-2205.
- *Tao RV, Holleschau AM, Rathbun WB. 1991. Naphthalene-induced cataract in the rat. *Ophthalmic Res* 23:272-283.
- *Tarshis IB. 1981. Uptake and depuration of petroleum hydrocarbons by crayfish. *Arch Environ Contam Toxicol* 10:79-86.
- Tenhulscher TEM, Vrind BA, Vandenheuvel H, et al. 1999. Triphasic desorption of highly resistant chlorobenzenes, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons in field contaminated sediment. *Environ Sci Technol* 33:126-132.
- Teschke K, Hertzman C, Van Netten C, et al. 1989. Potential exposure of cooks to airborne mutagens and carcinogens. *Environ Res* 50:296-308.

9. REFERENCES

- *Teshima R, Nagamatsu K, Ikebuchi H, et al. 1983. *In vivo* and *in vitro* metabolism of 2-methylnaphthalene in the guinea pig. *Drug Metab Dispos* 11(2):152-157.
- Thibodeaux LJ. 1979. *Chemodynamics: Environmental movement of chemicals in air, water and soil*. New York, NY: John Wiley and Sons, 456-457.
- Thienes CH, Haley TJ. 1964. Acacia, halogenated hydrocarbons, milk sickness, phosphorus and miscellaneous liver poisons. In: *Clinical toxicology*, 4th ed. Philadelphia, PA: Lea & Febiger.
- Thijssse TR, Vanoss RF, Lenschow P. 1999. Determination of source contributions to ambient volatile organic compound concentrations in Berlin. *J Air Waste Manage Assoc* 49:1394-1404.
- *Thomann RV. 1989. Bioaccumulation model of organic chemical distribution in aquatic food chains. *Environ Sci Technol* 23:699-707.
- *Thomann RV, Mueller JA. 1987. *Principles of surface water quality modeling and control*. New York, NY: Harper and Row, Publishers, 508-509.
- *Thomas JM, Yordy JR, Amador JA, et al. 1986. Rates of dissolution and biodegradation of water-insoluble organic compounds. *Appl Environ Microbiol* 52(2):290-296.
- Thomas RG. 1982. Volatilization from water. In: Lyman WJ, Reehl WJ, Rosenblatt DH, eds. *Handbook of chemical property estimation methods*. New York, NY: McGraw-Hill, 15-1-15-34.
- *Thornton-Manning JR, Dahl AR. 1997. Metabolic capacity of nasal tissue interspecies comparisons of xenobiotic-metabolizing enzymes. *Mutat Res* 380:43-59.
- Till M, Riebinger D, Schmitz H-J, et al. 1999. Potency of various polycyclic aromatic hydrocarbons as inducers of CYP1A1 in rat hepatocyte cultures. *Chem Biol Interact* 117:135-150.
- *Tingle MD, Pirmohamed M, Templeton E, et al. 1993. An investigation of the formation of cytotoxic, genotoxic, protein-reactive and stable metabolites from naphthalene by human liver microsomes. *Biochem Pharmacol* 46:1529-1538.
- *Tonelli QJ, Custer RP, Sorof S. 1979. Transformation of cultured mouse mammary glands by aromatic amines and amides and their derivatives. *Cancer Res* 39:1784-1792.
- *Tong SS, Hirokata Y, Trush MA, et al. 1981. Clara cell damage and inhibition of pulmonary mixed-function oxidase activity by naphthalene. *Biochem Biophys Res Commun* 100:944-950.
- *Tong SS, Lowe MC, Trush MA, et al. 1982. Bronchiolar epithelial damage and impairment of pulmonary microsomal monooxygenase activity in mice by naphthalene. *Exp Mol Pathol* 37:358-369.
- TPCDB. 1988. *Testing Priority Committee Data Base*. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC.
- *Traynor GW, Apte MG, Sokol HA. 1990. Selected organic pollutant emissions from unvented kerosene space heaters. *Environ Sci Technol* 24:1265-1270.
- *Trevisan A, Rossi di Schio M, Pieno M, et al. 2001. Haemolytic anaemia after oral self-giving of naphthalene-containing oil. *J Appl Toxicol* 21:393-395.

9. REFERENCES

- *TRI02. 2004. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Offices of Environmental Information. U.S. Environmental Protection Agency. Toxic Release Inventory. <http://www.epa.gov/triexplorer/> December 15, 2004.
- *Troester MA, Lindstrom AB, Waidyanatha S, et al. 2002. Stability of hemoglobin and albumin adducts of naphthalene oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone. *Toxicol Sci* 68:314-321.
- Trust Hammer B, Kelley CA, Coffin RB, et al. 1998. Delta-13c values of polycyclic aromatic hydrocarbons collected from two creosote-contaminated sites. *Chem Geol* 152:43-58.
- *Tsuda H, Lee G, Farber E. 1980. Induction of resistant hepatocytes as a new principle for a possible short-term *in vivo* test for carcinogens. *Cancer Res* 40:1157-1164.
- Tsuruda LS, Lame MW, Jones AD, et al. 1995. Metabolism of (¹⁴C) naphthalene in the B6C3F1 murine isolated perfused liver. *Drug Metab Dispos* 23(1):129-136.
- *Turkall RM, Skowronski GA, Kadry AM, et al. 1994. A comparative study of the kinetics and bioavailability of pure and soil-adsorbed naphthalene in dermally exposed male rats. *Arch Environ Contam Toxicol* 26:504-509.
- *Turney GL, Goerlitz DF. 1990. Organic contamination of ground water at Gas Works Park, Seattle, Washington. *Ground Water Monit Rev* 10(3):187-198.
- *USAF. 1984. Comparative biochemistry and metabolism: Part 2. Naphthalene lung toxicity. Wright-Patterson Air Force Base, OH: Air Force Systems Command, Aerospace Medical Division, Air Force Aerospace Medical Research Laboratory. United States Air force. AFAMRL-TR-84-058.
- USAF. 1985. Comparative biochemistry and metabolism. Part 2. Naphthalene lung toxicity. Wright-Patterson Air Force Base, OH: U.S. Air Force. Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratory. AMRL-TR-85-069.
- *USC. 2003. Hazardous air pollutants. Washington, DC: United States Code. 42 USC 7412. <http://www4.law.cornell.edu/uscode/>. June 6, 2003.
- USDA. 1978. Food consumption, prices and expenditures. Washington, DC: U.S. Department of Agriculture. Agriculture Economic Report No. 138.
- USITC. 1988. Synthetic organic chemicals: United States production and sales, 1987. Washington, DC: United States International Trade Commission. USITC Publication 2118.
- USITC. 1991. United States International Trade Commission. Synthetic organic chemicals, United States production and sales, 1990. Washington, DC. December 1991. USITC Publication No. 2470.
- *USITC. 2003. Synthetic organic chemicals. United States production and sales. Washington, DC: U.S. International Trade Commission. <http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Exports/27/270740.html>. June 6, 2003.

9. REFERENCES

- *Uyama Y, Ogino S, Ichihara T. 1955. Biochemical study on the genesis of naphthalene cataract: I. The cataractogenic substance excreted in the urine of rabbit treated with naphthalene. *Med J Osaka Univ* 6:229-239.
- *Valaes T, Doxiadis SA, Fessas P. 1963. Acute hemolysis due to naphthalene inhalation. *J Pediatr* 63:904-915.
- Van Bladeren PJ, Vyas KP, Sayer JM, et al. 1984. Stereoselectivity of cytochrome P-450C in the formation of naphthalene- and anthracene-1,2-oxides. *J Biol Chem* 259:8966-8973.
- Van Den Akker E, Lutgerink JT, Lafleur MVM, et al. 1994. The formation of one-G deletions as a consequence of singlet-oxygen-induced DNA damage. *Mutat Res* 309:45-52.
- *Van der Hoeve J. 1906. [Chorioretinitis in humans from the effects of naphthalene.] *Arch Augenheilkd* 56:259-262. (German)
- Vanhattum B, Curtopons MD, Cidmontanes JF. 1998. Polycyclic aromatic hydrocarbons in freshwater isopods and field-partitioning between abiotic phases. *Arch Environ Contam Toxicol* 35:257-267.
- *Van Heyningen R. 1970. Ascorbic acid in the lens of the naphthalene-fed rabbit. *Exp Eye Res* 9:38-48.
- *Van Heyningen R. 1976. Experimental studies on cataract. *Invest Ophthalmol Vis Sci* 15:685-697.
- *Van Heyningen R. 1979. Naphthalene cataract in rats and rabbits: A resume. *Exp Eye Res* 28:435-439.
- *Van Heyningen R, Pirie A. 1967. The metabolism of naphthalene and its toxic effect on the eye. *Biochem J* 102:842-852.
- *Van Heyningen R, Pirie A. 1976. Naphthalene cataract in pigmented and albino rabbits. *Exp Eye Res* 22:393-394.
- Van Winkle LS, Buckpitt AR, Nishio SJ, et al. 1995. Cellular response in naphthalene-induced cell injury and bronchiolar epithelial repair in mice. *Am J Anat* 269(6):L800-L818.
- Van Winkle LS, Evans MJ, Brown CD, et al. 2001. Prior exposure to aged and diluted sidestream cigarette smoke impairs bronchiolar injury and repair. *Toxicol Sci* 60(1):152-164.
- *Van Winkle LS, Gunderson AD, Shimizu JA, et al. 2002. Gender differences in naphthalene metabolism and naphthalene-induced acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 282(5):L1122-L1134.
- *Van Winkle LS, Isaac JM, Plopper CG. 1996. Repair of naphthalene-injured microdissected airways *in vitro*. *Am J Respir Cell Mol Biol* 15:1-8.
- Van Winkle LS, Isaac JM, Plopper CG. 1997. Distribution of epidermal growth factor receptor and ligands during bronchiolar epithelial repair from naphthalene-induced cell injury in the mouse. *Am J Pathol* 151(2):443-459.
- *Van Winkle LS, Johnson A, Nishio SJ, et al. 1999. Early events in naphthalene-induced acute cell toxicity. *Am J Respir Cell Mol Biol* 21:44-53.

9. REFERENCES

- Vanwijnen JH, Slob R, Jongmans-Liedekerken G, et al. 1996. Exposure to polycyclic aromatic hydrocarbons among Dutch children. *Environ Health Perspect* 104:530-534.
- Veigl ML, Nidel JE, Sedwick Wd. 1984. Induction of myeloid differentiation with naphthalene sulfonamide calmodulin antagonists [Abstract]. *Proceedings of the American Association for Cancer Research* 25:44.
- *Veith GD, DeFoe DL, Bergstedt BV et al. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. *J Fish Res Board Can* 36:1040-1048.
- Verschoye RD, Martin J, Dinsdale D. 1997. Selective inhibition and induction of CYP activity discriminates between the isoforms responsible for the activation of butylated hydroxytoluene and naphthalene in mouse lung. *Xenobiotica* 27(8):853-864.
- *Verschueren K. 1983. *Handbook of environmental data on organic chemicals*. 2nd ed. New York, NY: Van Nostrand Reinhold Company, 862-865, 890-899.
- *Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of *CYP2E1* in the human liver: Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem* 238:476-483.
- Villanueva J, Rosell A, Grimalt JO, et al. 1991. Chemical characterization of polycyclic aromatic hydrocarbon mixtures in uncontrolled hazardous waste dumps. *Chemosphere* 22:317-326.
- *Waidyanatha S, Troester MA, Lindstrom AB, et al. 2002. Measurement of hemoglobin and albumin adducts of naphthalene-1,2-oxide, 1,2-naphthoquinone after administration of naphthalene to F344 rats. *Chem Biol Interact* 141(3):189-210.
- Waidyanatha S, Zheng Y, Serder B, et al. 2004. Albumin adducts of naphthalene metabolites as biomarkers of exposure to polycyclic aromatic hydrocarbons. *Cancer Epidemiol Biomarkers Prev* 13(1):117-124.
- *Wakeham SG, Davis AC, Karas IL. 1983. Mesocosm experiments to determine the fate and persistence of volatile organic compounds in coastal seawater. *Environ Sci Technol* 17:611-617.
- *Walters SM. 1986. Cleanup of samples. In: Zweig G, Sherma J, eds. *Analytical methods for pesticides and plant growth regulators*. Vol. 15. Principles, statistics, and applications. New York, NY: Academic Press, Inc., 67-110.
- *Wang BM, Stern EJ, Schmidt RA, et al. 1997. Diagnostic pulmonary alveolar proteinosis. A review and an update. *Chest* 111:460-466.
- Wang D, Piao M, Chu S, et al. 2001. Chlorinated polycyclic aromatic hydrocarbons from polyvinylchloride combustion. *Bull Environ Contam Toxicol* 66:326-333.
- Wang H, Lanza DL, Yost GS. 1998. Cloning and expression of CYP2F3, a cytochrome P450 that bioactivates the selective pneumotoxins 3-methylindole and naphthalene. *Arch Biochem Biophys* 349(2):329-340.

9. REFERENCES

- Wang Y, Wang Z, Na M, et al. 2001. Monitoring priority pollutants in a sewage treatment process by dichloromethane extraction and triolein-semipermeable membrane device (SPMD) *Chemosphere* 43:339-346.
- Wang Z, Fingas M, Shu YY, et al. 1999. Quantitative characterization of PAHs in burn residue and soot samples and differentiation of pyrogenic PAHs from petrogenic PAHs- The 1994 Mobile Burn Study. *Environ Sci Technol* 33:3100-3109.
- *Warren DL, Brown DL Jr, Buckpitt AR. 1982. Evidence for cytochrome P-450 mediated metabolism in the bronchiolar damage of naphthalene. *Chem Biol Interact* 40:287-303.
- Warshawsky D. 2001. Polycyclic and heterocyclic aromatic hydrocarbons. In: Bingham E, Cochrane B, Powell CH, eds. *Patty's toxicology*, 5th ed., Vol. 4. New York, NY: John Wiley & Sons, Inc.
- *Weast RC, Astle MJ, Beyer WH, eds. 1985. *CRC handbook of chemistry and physics: A ready-reference book of chemical and physical data*. Boca Raton, FL: CRC Press, Inc., C-357, C-361.
- Webber MD, Pietz RI, Granato TC, et al. 1994. Organic chemicals in the environment: Plant uptake of PCBs and other organic contaminants from sludge-treated coal refuse. *J Environ Qual* 23:1019-1026.
- Weis LM, Rummel AM, Masten SJ, et al. 1998. Bay or baylike regions of polycyclic aromatic hydrocarbons were potent inhibitors of gap junctional intercellular communication. *Environ Health Perspect* 106:17-22.
- Weisburger JH, Mantel N, Weisburger EK, et al. 1967. New carcinogenic naphthalene and biphenyl derivatives. *Nature* 213:930-931.
- *Weissenfels WD, Klewer HJ, Langhoff J. 1992. Adsorption of polycyclic aromatic hydrocarbons (PAHs) by soil particles: influence on biodegradability and biotoxicity. *Appl Microbiol Biotechnol* 36:689-696.
- *Wells PG, Wilson B, Lubek BM. 1989. *In vivo* murine studies on the biochemical mechanism of naphthalene cataractogenesis. *Toxicol Appl Pharmacol* 99:466-473.
- *West JAA, Buckpitt AR, Plopper CG. 2000a. Elevated airway GSH resynthesis confers protection to cells from naphthalene injury in mice made tolerant by repeated exposures. *J Pharmacol Exp Ther* 294(2):516-523.
- West JAA, Chichester CH, Buckpitt AR, et al. 2000b. Heterogeneity of cell glutathione: A possible basis for differences in cellular responses to pulmonary cytotoxicants. *Am J Respir Cell Mol Biol* 23:27-36.
- West JAA, Williams KJ, Toskala E, et al. 2002. Induction of tolerance to naphthalene in cells is dependent on a stable phenotypic adaptation favoring maintenance of the glutathione pool. *Am J Pathol* 160(3):1115-1127.
- *West JAA, Pakeham G, Morin D, et al. 2001. Inhaled naphthalene causes dose dependent cell cytotoxicity in mice but not in rats. *Toxicol Appl Pharmacol* 173(2):114-119.
- *West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. *J Pediatr* 32:10-18.

9. REFERENCES

- Westberg HB, Selden AL, Bellander T. 2001. Exposure to chemical agents in Swedish aluminum foundries and aluminum remelting plants- a comprehensive survey. *Appl Occup Environ Hyg* 16:66-77.
- Westendorf RG. 1989. Automatic sampler concepts for purge and trap GC. *Am Lab* (February 1989):56-60.
- *White DH, Hardy JW. 1994. Ambient air concentrations of PCDDs, PCDFs, coplanar PCBs and PAHs at the Mississippi Sandhill Crane National Wildlife Refuge, Jackson County, Mississippi. *Environ Monit Assess* 33:247-256.
- White JC, Triplett T. 2002. Polycyclic aromatic hydrocarbons (PAHs) in the sediments and fish of the Mill River, New Haven, Connecticut, USA. *Bull Environ Contam Toxicol* 68:104-110.
- Widdows J, Moore SL, Clarke KR, et al. 1983. Uptake, tissue distribution and elimination of [$1-^{14}\text{C}$]naphthalene in the mussel *Mytilus edulis*. *Mar Biol* (Berlin) 76:109-114.
- *Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. *Mineral metabolism: An advanced treatise. Volume II: The elements Part A.* New York: Academic Press.
- *Wild SR, Waterhouse KS, McGrath SP, et al. 1990. Organic contaminants in an agricultural soil with a known history of sewage sludge amendments: Polynuclear aromatic hydrocarbons. *Environ Sci Technol* 24:1706-1711.
- Wildlife International. 1985a. A dietary LC50 study in the bobwhite with naphthalene: Final report. Report to W.R. Landis Associates, Inc., Valdosta, GA, by Wildlife International Ltd., St. Michaels, MD. Project No. 190-105.
- Wildlife International. 1985b. An acute oral toxicity study in the bobwhite with naphthalene: Final report. Report to W.R. Landis Associates, Inc., Valdosta, GA, by Wildlife International Ltd., St. Michaels, MD. Project No. 190-106.
- *Willems BAT, Melnick RL, Kohn MC, et al. 2001. A physiologically based pharmacokinetic model for inhalation and intravenous administration of naphthalene in rats and mice. *Toxicol Appl Pharmacol* 176(2):81-91.
- Williams KJ, Cruikshank MK, Plopper CG. 2003. Pulmonary heat shock protein expression after exposure to a metabolically activated Clara cell toxicant: Relationship to protein adduct formation. *Toxicol Appl Pharmacol* 192(2):107-118.
- *Williamson DG, Loehr RC, Kimura Y. 1998. Release of chemicals from contaminated soils. *J Soil Contam* 7(5):543-558.
- *Wilson AS, Davis CD, Williams DP, et al. 1996. Characterisation of the toxic metabolite(s) of naphthalene. *Toxicology* 114:233-242.
- *Wilson AS, Tingle MD, Kelly MD, et al. 1995. Evaluation of the generation of genotoxic and cytotoxic metabolites of benzo[a]pyrene, aflatoxin B1, naphthalene and tamoxifen using human liver microsomes and human lymphocytes. *Hum Exp Toxicol* 14:507-515.

9. REFERENCES

- *Wilson NK, Chuang JC, Lyu C. 1999. Multimedia concentrations of PAH in several day care centers. *Polycyclic Aromat Compd* 17:255-265.
- *Wilson NK, Kuhlman MR, Chuang JC. 1989. A quiet sampler for the collection of semivolatile organic pollutants in indoor air. *Environ Sci Technol* 23:1112-1116.
- Windholz M, Budavari S, Blumetti RF, et al., eds. 1983. *The Merck index: An encyclopedia of chemicals, drugs, and biologicals*. 10th ed. Rahway, NJ: Merck and Company, 914.
- *Wolf O. 1976. Krebserkrankungen bei chemiearbeitern einer ehemaligen naphthalinreinigung. *Dt Gesundh-Wesen* 31:996-999.
- *Wolf O. 1978. Arbeitshygiene und arbeitsschutz. *Z Ges Hyg* 24:737-739
- *Woolf AD, Saperstien A, Zarwin J, et al. 1993. Radiopacity of household deodorizers, air fresheners, and moth repellents. *J Toxicol Clin Toxicol* 31:415-428.
- *Xu GT, Zigler JS, Lou MF. 1992a. Establishment of a naphthalene cataract model *in vitro*. *Exp Eye Res* 54:73-81.
- *Xu GT, Zigler JS, Lou MF. 1992b. The possible mechanism of naphthalene cataract in rat and its prevention by an aldose reductase inhibitor (AL01576). *Exp Eye Res* 54:63-72.
- *Yamauchi T, Komura S, Yagi K. 1986. Serum lipid peroxide levels of albino rats administered naphthalene. *Biochem Int* 13:1-6.
- Yang M, Koga M, Katoh T, et al. 1999. A study for the proper application of urinary naphthols, new biomarkers for airborne polycyclic aromatic hydrocarbons. *Arch Environ Contam Toxicol* 36(1):99-108.
- Yang Y, Sharma R, Cheng JZ, et al. 2002. Protection of HLE B-3 cells against hydrogen peroxide-and naphthalene-induced lipid peroxidation and apoptosis by transfection with hGSTA1 and hGSTA2. *Invest Ophthalmol Vis Sci* 43(2):434-445.
- *Yaws C, Yang HC, Pan X. 1991. Henry's law constants for 362 organic compounds in water. *Chem Eng (November)*:179-185.
- Yeom IT, Ghosh MM, Cox CD, et al. 1995. Micellar solubilization of polynuclear aromatic hydrocarbons in coal tar-contaminated soils. *Environ Sci Technol* 29:3015-3021.
- Yost GS, Buckpitt AR, Roth RA, et al. 1989. Contemporary issues in toxicology. Mechanisms of lung injury by systemically administered chemicals. *Toxicol Appl Pharmacol* 101:179-195.
- Young L. 1947. The metabolic conversion of naphthalene to 1,2-dihydronaphthalene-1,2-diol. *Biochem J* 41:417-422.
- Yrjanheikki E, Pye L, Hakala E, et al. 1995. Exposure to polycyclic aromatic hydrocarbons in new coking plant. *Am Ind Hyg Assoc J* 56:782-787.
- Yu D, Berlin JA, Penning TM, et al. 2002. Reactive oxygen species generated by PAH o-quinones cause change-in-function mutations in p53. *Chem Res Toxicol* 15:832-842.

9. REFERENCES

- *Yu X, Wang X, Bartha R, et al. 1990. Supercritical fluid extraction of coal tar contaminated soil. *Environ Sci Technol* 24:1732-1738.
- Zelano V. 1998. Volatile organic compounds in drinking water. *Ann Chim (Rome)* 88:449-460.
- *Zepp RG, Schlotzhauer PF. 1979. Photoreactivity of selected aromatic hydrocarbons in water. In: Jones PW, Leber P, eds. Polynuclear aromatic hydrocarbons. Ann Arbor, MI: Ann Arbor Science, 141-157.
- Zhang XJ. 1998. Emissions of volatile organic compounds from large-scale incinerator plants. *J Environ Sci Health Part A* 33:279-306.
- *Zhao W, Ramos JS. 1998. Cytotoxic response profiles of cultured rat hepatocytes to selected aromatic hydrocarbons. *Toxicol In Vitro* 12:175-182.
- *Zheng J, Cho M, Jones AD, et al. 1997. Evidence of quinone metabolites of naphthalene covalently bound to sulfur nucleophiles of proteins of Murine cells after exposure to naphthalene. *Chem Res Toxicol* 10(9):1008-1014.
- *Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. *Pediatr Res* 12:29-34.
- *Zielinska B, Fung KK. 1994. The composition and concentration of hydrocarbons in the range of C2 to C18 emitted from motor vehicles. *Sci Total Environ* 146/147:281-288.
- *Zielinska B, Fujita E, Sagebiel J, et al. 1998. Arizona hazardous air pollutants monitoring program. *J Air Waste Manage Assoc* 48:1038-1050.
- *Zielinska B, Sagebiel JC, Harshfield G, et al. 1996. Volatile organic compounds up to C20 emitted from motor vehicles: measurement methods. *Atmos Environ* 30:2269-2286.
- *Zinkham WH, Childs B. 1957. Effect of vitamin K and naphthalene metabolites on glutathione metabolism of erythrocytes from normal newborns and patients with naphthalene hemolytic anemia. *Am J Dis Child* 94(6):420-423.
- *Zinkham WH, Childs B. 1958. A defect of glutathione metabolism of erythrocytes from patients with naphthalene-induced hemolytic anemia. *Pediatrics* 22:461-471.
- *Zitko V, Stenson G, Hellou J. 1998. Levels of organochlorine and polycyclic aromatic compounds in harp seal beaters (*phoca groenlandica*). *Sci Total Environ* 221:11-29.
- *Zlatkis A, Kim K. 1976. Column elution and concentration of volatile compounds in biological fluids. *J Chromatogr* 126:475-485.
- *Zoeteman BC, Harmsen K, Linders JB, et al. 1980. Persistent organic pollutants in river water and ground water of the Netherlands. *Chemosphere* 9:231-249.
- *Zuelzer WW, Apt L. 1949. Acute hemolytic anemia due to naphthalene poisoning: A clinical and experimental study. *J Am Med Assoc* 141(3):185-190.

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 (K_d)—The amount of a chemical adsorbed by 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 that 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.

10. GLOSSARY

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 of people that 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.

10. GLOSSARY

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.

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.

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 that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—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₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—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.

10. GLOSSARY

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) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

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 dynamic behavior of a material in the body, used to predict 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, whereas 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 that 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.

10. GLOSSARY

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 $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration 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.

10. GLOSSARY

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 group.

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₎ (TD₅₀)—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 absorption, distribution, and elimination of toxic compounds in the living organism.

10. GLOSSARY

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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 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.

APPENDIX A

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 100-fold 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 F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: June 2005
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 6
Species: Rat

Minimal Risk Level: 0.0007 mg/kg/day 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 B6C3F1 mice 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. Benchmark dose analyses were not conducted on the incidence data for nonneoplastic nasal lesions, because the data provided insufficient information on the shape of the dose-response relationship. The lowest exposure level in the principal study induced nasal lesions in essentially all of the rats.

NOAEL LOAEL

APPENDIX A

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

Lesion	Concentration (ppm)							
	0		10		30		60	
	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 = $10 \times 3 \times 10 = 300$

[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:
 $10 \text{ ppm} \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 1.8 \text{ ppm}$ (duration-adjusted LOAEL for nasal effects in rats or mice)

$1.8 \text{ ppm} \times 128.18/24.45 = 9.4 \text{ mg}/\text{m}^3$

APPENDIX A

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: $HEC = \text{Animal Concentration} \times RGDR_{ET}$;

$RGDR_{ET} = \text{regional gas dose ratio in the extrathoracic (ET) region}$
 $= (\text{Dose}_{ET})_A / (\text{Dose}_{ET})_H = [\text{minute volume}/\text{ET surface area}]_A \div [\text{minute volume}/\text{ET surface area}]_H$;

Reference minute volumes (L/min): 13.8 human, 0.137 rat, 0.0368 mouse;

Reference ET surface area (cm²): 200 human, 15 rat, 3 mouse;

$RGDR_{ET}(\text{Rat to Human}) = [0.137/15] \div [13.8/200] = 0.132$;

$LOAEL_{HEC} = \text{duration-adjusted LOAEL} \times 0.132 = 1.8 \text{ ppm} \times 0.132 = 0.2 \text{ ppm}$

$RGDR_{ET}(\text{Mouse to Human}) = [0.0368/3] \div [13.8/200] = 0.178$;

$LOAEL_{HEC} = \text{duration-adjusted LOAEL} \times 0.132 = 1.8 \text{ ppm} \times 0.178 = 0.3 \text{ ppm}$

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.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: June 2005
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.6 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 toxicity in pregnant rat dams.

NOAEL minimal LOAEL

APPENDIX A

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor= $3 \times 10 \times 3 = 90$

- [x] 3 for use of a minimal 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 maternal toxicity, 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 and decreased body weight gain) than nonpregnant rats. In 13-week gavage studies with nonpregnant rats (NTP 1980b), similar persistent clinical signs 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 have been reported 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.

APPENDIX A

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 clinical signs of toxicity in pregnant rats.

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: June 2005
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.6 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 toxicity in pregnant rat dams.

NOAEL minimal LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor = $3 \times 10 \times 3 = 90$

3 for use of a minimal LOAEL
 10 for extrapolation from animals to humans
 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

APPENDIX A

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

APPENDIX A

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 \geq 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

APPENDIX A

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 ($100 \times 5 \text{ days} / 7 \text{ days} = 71 \text{ mg/kg/day}$). 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.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Methylnaphthalene
CAS Number: 90-12-0
Date: June 2005
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 0.07 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: Because the lowest exposure level was a LOAEL for increased incidence of alveolar proteinosis in male and female mice, benchmark dose analyses of the incidence data were conducted to determine a point of departure (POD) for the chronic-duration oral MRL. Available models in the EPA Benchmark Dose Software were fit to the incidence data for males and females, separately. None of the models provided adequate fit of the incidence data for females or for males, as assessed by chi-square goodness of fit statistics (p-values were <0.1). These results indicate that the data provide insufficient information to model the shape of the dose-response relationship. The lack of fit of the models to the data appears to be due to the apparent plateau of the response between the low- and high-dose levels. Thus, the LOAEL of 71.6 mg/kg/day for increased incidence of alveolar proteinosis in male mice was selected as the POD for the MRL.

NOAEL LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor=10x10x10=1,000

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

APPENDIX A

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).

Goodness-of-fit statistics [p-values for chi-square goodness of fit and the Akaike Information Criteria (AIC)] from the benchmark dose analyses of the incidence data for pulmonary alveolar proteinosis are summarized in the table below.

Table A-2. Goodness-of-fit Statistics From Benchmark Dose Analyses of Incidence Data for Male and Female Mice Exposed to 1-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1993).

Model	Male mouse data		Female mouse data	
	chi-square p-value	AIC	chi-square p-value	AIC
Log-logistic ^b	0.024	172.13	0.014	174.71
Gamma ^a	0.01	173.57	0.007	175.88
Multi-stage ^c	0.01	173.57	0.007	175.88
Quantal linear	0.01	173.57	0.007	175.88
Weibull ^a	0.01	173.57	0.007	175.88
Log-probit ^b	0.002	176.68	0.001	179.07
Probit	0.002	177.06	0.002	178.42
Logistic	0.001	177.45	0.002	178.71
Quantal quadratic	0.0002	181.03	0.0002	182.00

^a = Restrict power ≥ 1 ; ^b = Slope restricted to > 1 ; ^c = Restrict betas ≥ 0 , Degree of polynomial = 1

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2-Methylnaphthalene
CAS Number: 91-57-6
Date: June 2005
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 47
Species: Mouse

Minimal Risk Level: 0.04 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 22/48 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: Because the lowest exposure level was a LOAEL for increased incidence of alveolar proteinosis in male and female mice, benchmark dose (BMD) analyses of the incidence data were conducted to determine a point of departure (POD) for the chronic-duration oral MRL. Available models in the EPA Benchmark Dose Software were fit to the incidence data for males and females, separately. None of the models provided adequate fit of the incidence data for females, as assessed by chi-square goodness of fit statistics (p-values were <0.1). These results indicate that the female data provide insufficient information to model the shape of the dose-response relationship. The apparent plateau of the response between the low- and high-dose levels appears to contribute to the lack of fit of the models to the data. In contrast, the log-logistic and multi-stage models provided marginally adequate fits (p-values >0.1) to the male data, showing p-values of 0.23 and 0.11, respectively, for the chi-square goodness-of-fit statistic (Table A-3). The fitting algorithms for the gamma, quantal-linear, and

APPENDIX A

Weibull models provided identical model parameters and fit statistics as the multi-stage model. The Akaike Information Criteria (AIC) for the log-logistic model was lower than that for the multi-stage model indicating a better fit; thus the log-logistic model of the male data was selected to calculate the BMD POD for the MRL.

A benchmark response of 5% extra risk was selected over a default value of 10% extra risk in order to provide protection for children who may develop pulmonary alveolar proteinosis. This selection is supported by reports that children with pulmonary alveolar proteinosis (albeit of unknown etiology) experience more severe symptoms of respiratory dysfunction than do adults (EPA 2003r; Mazzone et al. 2001).

To derive the MRL of 0.04 mg/kg/day, the BMDL₀₅ of 4.3 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from mice to humans and 10 for human variability).

An alternative NOAEL/LOAEL approach arrives at a similar value for the MRL. In the alternative approach, the LOAEL of 50.3 mg/kg/day for pulmonary alveolar proteinosis in female mice would be divided by an uncertainty factor of 1000 (10 for extrapolation from mice to humans, 10 for human variability, and 10 for extrapolation from a LOAEL to a NOAEL), arriving at a value of 0.05 mg/kg/day.

Table A-3. Benchmark Doses and Goodness-of-Fit Statistics from Modeling of Incidence Data for Pulmonary Alveolar Proteinosis in Male Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1997)

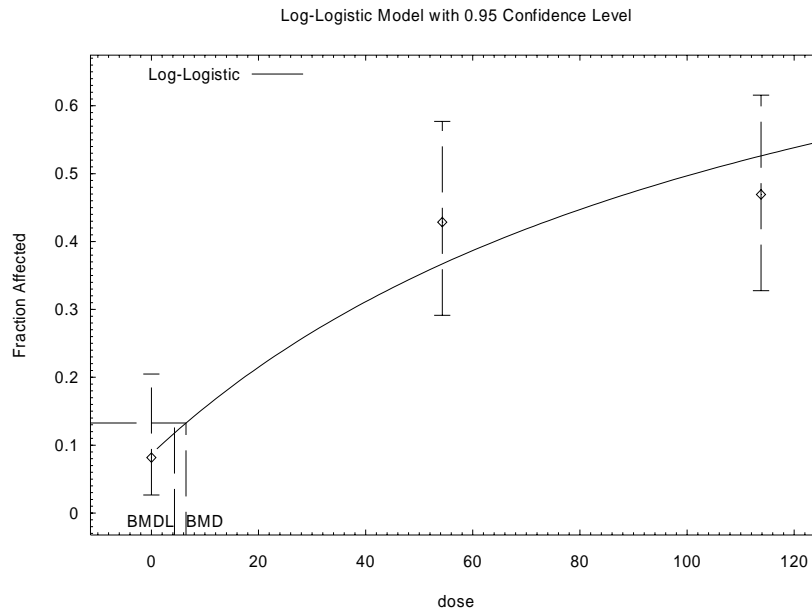
Model	Benchmark doses (mg/kg/day)		Goodness-of-fit statistics	
	BMD (ED05)	BMDL (LED05)	chi-square p-value	AIC
Log-logistic ^b	6.47	4.30	0.23	167.81
Gamma ^a	8.76	6.4	0.11	168.93
Multi-stage ^c	8.76	6.4	0.11	168.93
Quantal linear	8.76	6.4	0.11	168.93
Weibull ^a	8.76	6.4	0.11	168.93
Log-probit ^b	20.92	15.95	0.03	170.99
Probit	17.23	13.8	0.01	172.4
Logistic	18.43	14.62	0.01	172.84
Quantal quadratic	32.73	26.51	0.001	175.87

^a = Restrict power ≥ 1 ; ^b = Slope restricted to > 1 ; ^c = Restrict betas ≥ 0 , Degree of polynomial = 1

BMD(ED05) = predicted benchmark dose associated with 5% extra risk; BMDL (LED05) = 95% lower confidence limit on benchmark dose associated with 5% extra risk

APPENDIX A

**Figure A-1. Observed and Predicted Incidence of Pulmonary Alveolar Proteinosis in Male Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1997): Log-Logistic Model
BMD=ED₀₅; BMDL=LED₀₅**



Observed and predicted incidences of olfactory epithelial neuroblastomas in male rats exposed to naphthalene: Weibull model. BMD=EC₁₀; BMDL=LEC₁₀; dose unit= ppm.

NOAEL LOAEL BMDL =

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor=10x10=100

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 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).

APPENDIX A

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.

The EPA (2003r) Toxicological Review of 2-Methylnaphthalene calculated an oral exposure RfD of 0.004 mg/kg-day for 2-methylnaphthalene based on a value of 3.5 mg/kg-day for a 95% lower confidence limit on a benchmark dose associated with 5% extra risk (BMDL₀₅) for pulmonary alveolar proteinosis in mice exposed to 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1992). The combined incidence data for this lesion in male and female mice in the control and low-dose groups were modeled with the quantal-linear model algorithm in the BMDS software (the high-dose data were excluded from the analysis, because when they were included adequate fit of models to the data were not obtained). A total uncertainty factor of 1,000 was used to derive the RfD: 10 for interspecies variability, 10 for interindividual variability, and 10 for database deficiencies.

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

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 that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

APPENDIX B

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.

MRLs 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment 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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, 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.

APPENDIX B

LEGEND**See Sample LSE Table 3-1 (page B-6)**

- (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. Typically when sufficient data exist, 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 Tables 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 two "18r" data points in sample 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 regimens 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 "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A 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,

APPENDIX B

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

- (9) **LOAEL.** A 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 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate 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/m³ 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

APPENDIX B

- (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 (ppm)	Serious (ppm)	
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)		Nitschke et al. 1981
	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

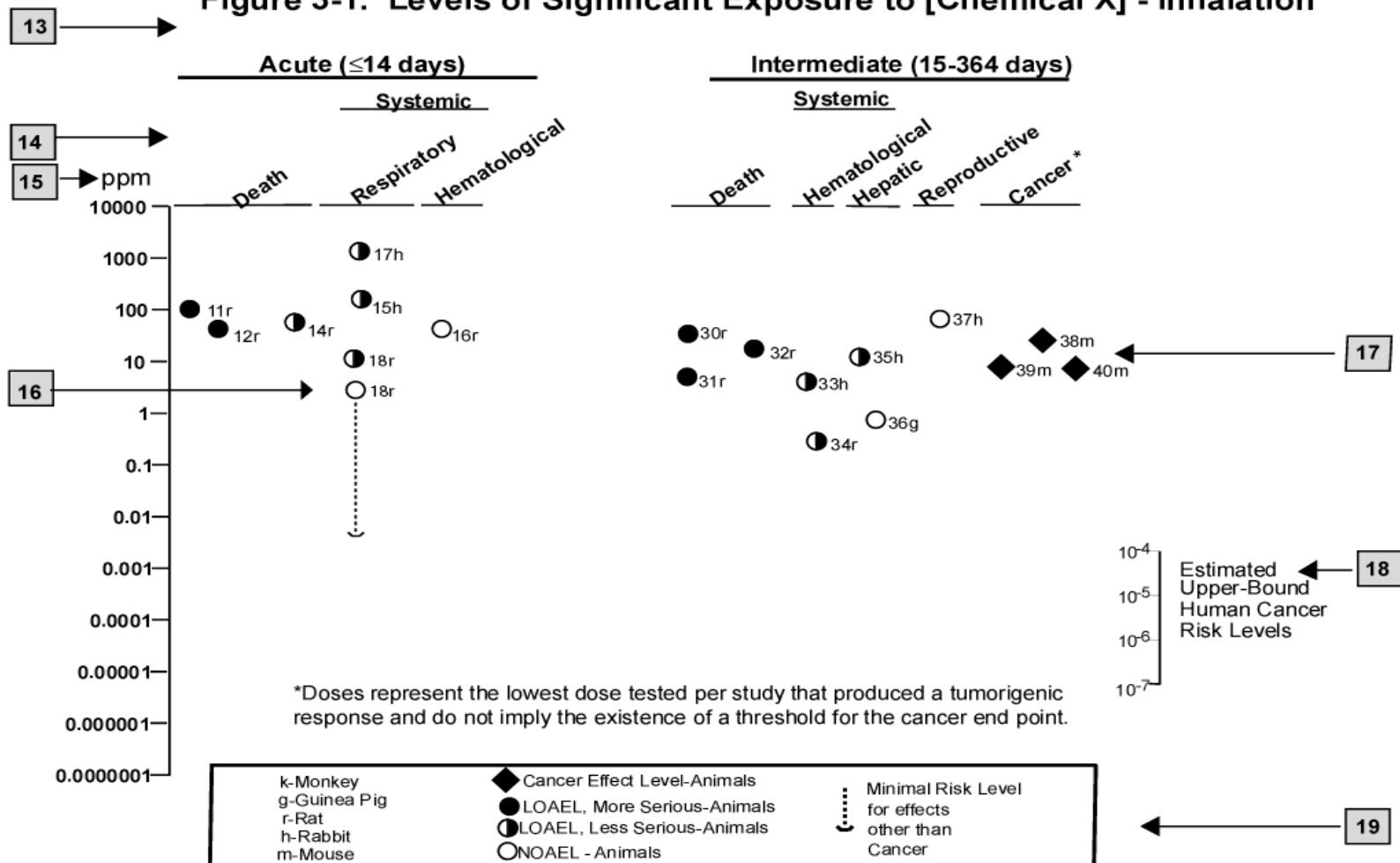
12 →

^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

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
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
AOEC	Association of Occupational and Environmental Clinics
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
BMD	benchmark dose
BMR	benchmark response
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

APPENDIX C

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
K _d	adsorption ratio
kg	kilogram
kgg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

APPENDIX C

MCLG	maximum contaminant level goal
MF	modifying factor
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
NHANES	National Health and Nutrition Examination Survey
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
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

APPENDIX C

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
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
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

APPENDIX C

>	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

APPENDIX D. INDEX

absorbed dose	139
adenocarcinomas	26, 81
adipose tissue	103, 104, 140, 145, 162, 203, 209, 222
adrenals	26
adsorbed	116, 122, 163, 190, 209
adsorption	116, 190, 193, 217
aerobic	193, 194, 211
ambient air	13, 183, 195, 196, 201, 202
anaerobic	193
anemia	43, 44, 70, 71, 87, 104, 136, 141, 143, 161, 162, 166
aspartate aminotransferase	71
bioaccumulation	191, 215
bioavailability	193, 207, 208, 211, 213
biodegradation	192, 193, 194, 207, 211, 215
biomarker	138, 139, 140, 141
biomarkers	138, 139, 140, 162, 215
blood cell count	44, 71, 87
blood cell counts	44, 71
body weight effects	16, 75
breast milk	5, 136, 203, 204, 205
cancer	6, 7, 14, 20, 129, 135, 151, 156, 161, 230
carcinogen	7, 19, 20, 230
carcinogenic	7, 18, 19, 20, 21, 22, 29, 30, 48, 49, 81, 230
carcinogenicity	7, 15, 19, 20, 21, 22, 49, 81, 129, 151, 156, 157, 161
carcinoma	14, 16, 42, 48, 156
carcinomas	21
cardiovascular	43, 69, 87
cardiovascular effects	43, 69, 87
cataract	46, 89, 110, 124, 125, 126, 142, 161
chromosomal aberrations	18, 97, 98, 158
clearance	68, 131
death	29, 46, 78, 97, 98, 101
dermal effects	31, 50, 88
DNA	18, 77, 90, 93, 94, 95, 96, 97, 127, 139, 158
enantiomer	107, 109, 127
endocrine	133, 134
erythema	88
fetus	15, 80, 134, 152
gastrointestinal effects	43, 69, 87
general population	138, 140, 162, 201, 202, 206, 209
genotoxic	18, 29, 90, 98, 129, 158
genotoxicity	18, 19, 129, 130, 158, 159
groundwater	14, 188, 189, 190, 197, 198, 204, 207, 229
half-life	105, 106, 114, 126, 139, 179, 190, 191, 192, 193, 194
hematological effects	43, 70, 87
hemolytic anemia	6, 7, 8, 14, 15, 43, 70, 80, 82, 102, 136, 143, 151, 153, 159, 162, 165
hepatic effects	45, 71, 88
hydroxyl radical	127, 179, 192, 207
immune system	24
immunological	29, 46, 77, 89, 90, 216
K_{ow}	171, 190, 191
LD_{50}	49, 50, 68, 70, 82, 95

APPENDIX D

lymphoreticular.....	46, 77, 78, 89, 90
mass spectroscopy	219, 220
micronuclei	19, 98, 158
milk.....	3, 7, 10, 103, 104, 136, 191, 200, 205, 209, 217
musculoskeletal effects.....	45, 82
neonatal	80, 137, 166, 167
neoplastic.....	15, 16, 17, 18, 20, 31, 42, 121, 123, 127, 128, 129, 133, 151, 156, 158
neurobehavioral	134
nuclear	143
octanol-water partition coefficient.....	120
ocular effects	102, 125, 151
odds ratio	137
olfactory epithelial neuroblastoma.....	17, 18, 20, 22, 42, 48
olfactory epithelium.....	16, 17, 22, 42, 48, 109, 122, 156
partition coefficients.....	190
passive transport	163
pharmacodynamic.....	117
pharmacokinetic.....	117, 118, 119, 135
photolysis.....	192
placenta.....	104
placental barrier	136, 159, 166
pulmonary alveolar proteinosis.....	8, 20, 21, 25, 26, 27, 68, 69, 77, 123, 130, 131, 132, 138, 155, 157, 162, 165, 225, 226
rate constant.....	120, 192
rate constants	120, 192
renal effects	45, 72, 88
respiratory epithelial adenoma.....	17, 18, 20, 22, 42, 48
SGOT.....	72
SGPT	72
solubility	190, 191, 215
toxicokinetic	29, 98, 99, 118, 136, 137, 164, 165, 166
tumors.....	7, 8, 16, 19, 20, 22, 25, 42, 48, 49, 81, 118, 120, 121, 129, 138, 141, 161, 163, 164, 166
vapor phase.....	190, 221
vapor pressure.....	190, 191
volatilization.....	13, 184, 190, 191, 207

