TOXICOLOGICAL PROFILE FOR

POLYCYCLIC AROMATIC HYDROCARBONS

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

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UPDATE STATEMENT

A Toxicological Profile for Polycyclic Aromatic Hydrocarbons was released in December 1990. This edition supersedes any previously released draft or final profile.

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

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and 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 being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but 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.

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 protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order 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.

(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.

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 the Agency for Toxic Substances and Disease Registry (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 Environmental Protection Agency (EPA). The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on February 28, 1994 (59 FR 9486). 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); and October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Foreword

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers 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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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. The Green Border review assures consistency with ATSDR policy.

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

3. 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.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for the PAHs. The panel consisted of the following members:

1. Dr. Gail Charnley, Consultant in Toxicology, Arlington, Virginia;

2. Dr. Edmond LaVoie, Professor, Rutgers University College of Pharmacy, Piscataway, New Jersey; and

3. Dr. Alexander Wood, Distinguished Research Leader and Director, Department of Oncology, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about polycyclic aromatic hydrocarbons (PAHs) and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,408 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. PAHs have been found in at least 600 of the sites on the NPL. However, the number of NPL sites evaluated for PAHs is not known. As EPA evaluates more sites, the number of sites at which PAHs are found may increase. This information is important because exposure to PAHs may cause harmful health effects and because these sites are potential or actual sources of human exposure to PAHs.

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

If you are exposed to substances such as PAHs, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT ARE POLYCYCLIC AROMATIC HYDROCARBONS?

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage, or other organic substances, such as tobacco and charbroiled meat. There are more than 100 different PAHs. PAHs generally occur as complex mixtures (for example, as part of combustion products such as soot), not as single compounds. PAHs usually occur

naturally, but they can be manufactured as individual compounds for research purposes; however, not as the mixtures found in combustion products. As pure chemicals, PAHs generally exist as colorless, white, or pale yellow-green solids. They can have a faint, pleasant odor. A few PAHs are used in medicines and to make dyes, plastics, and pesticides. Others are contained in asphalt used in road construction. They can also be found in substances such as crude oil, coal, coal tar pitch, creosote, and roofing tar. They are found throughout the environment in the air, water, and soil. They can occur in the air, either attached to dust particles or as solids in soil or sediment.

Although the health effects of individual PAHs are not exactly alike, the following 17 PAHs are considered as a group in this profile:

- acenaphthene
- acenaphthylene
- anthracene
- benz[a]anthracene
- benzo[a]pyrene
- benzo[e]pyrene
- benzo[b]fluoranthene
- benzo[g,h,i]perylene
- benzo[j]fluoranthene
- benzo[k]fluoranthene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[1,2,3-c,d]pyrene
- phenanthrene
- pyrene

These 17 PAHs were chosen to be included in this profile because (1) more information is available on these than on the others; (2) they are suspected to be more harmful than some of the others, and they exhibit harmful effects that are representative of the PAHs; (3) there is a greater chance that you will be exposed to these PAHs than to the others; and (4) of all the PAHs analyzed, these were the PAHs identified at the highest concentrations at NPL hazardous waste sites.

More information can be found on the chemical and physical properties of PAHs in Chapter 3 and on their use and disposal in Chapter 4.

1.2 WHAT HAPPENS TO POLYCYCLIC AROMATIC HYDROCARBONS WHEN THEY ENTER THE ENVIRONMENT?

PAHs enter the environment mostly as releases to air from volcanoes, forest fires, residential wood burning, and exhaust from automobiles and trucks. They can also enter surface water through discharges from industrial plants and waste water treatment plants, and they can be released to soils at hazardous waste sites if they escape from storage containers. The movement of PAHs in the environment depends on properties such as how easily they dissolve in water, and how easily they evaporate into the air. PAHs in general do not easily dissolve in water. They are present in air as vapors or stuck to the surfaces of small solid particles. They can travel long distances before they return to earth in rainfall or particle settling. Some PAHs evaporate into the atmosphere from surface waters, but most stick to solid particles and settle to the bottoms of rivers or lakes. In soils, PAHs are most likely to stick tightly to particles. Some PAHs evaporate from surface soils to air. Certain PAHs in soils also contaminate underground water. The PAH content of plants and animals living on the land or in water can be many times higher than the content of PAHs in soil or water. PAHs can break down to longer-lasting products by reacting with sunlight and other chemicals in the air, generally over a period of days to weeks. Breakdown in soil and water generally takes weeks to months and is caused primarily by the actions of microorganisms. For more information on what happens to PAHs in the environment see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS?

PAHs are present throughout the environment, and you may be exposed to these substances at home, outside, or at the workplace. Typically, you will not be exposed to an individual PAH, but to a mixture of PAHs.

1. PUBLIC HEALTH STATEMENT

In the environment, you are most likely to be exposed to PAH vapors or PAHs that are attached to dust and other particles in the air. Sources include cigarette smoke, vehicle exhausts, asphalt roads, coal, coal tar, wildfires, agricultural burning, residential wood burning, municipal and industrial waste incineration, and hazardous waste sites. Background levels of some representative PAHs in the air are reported to be 0.02-1.2 nanograms per cubic meter (ng/m^3; a nanogram is one-millionth of a milligram) in rural areas and 0.15-19.3 ng/m^3 in urban areas. You may be exposed to PAHs in soil near areas where coal, wood, gasoline, or other products have been burned. You may be exposed to PAHs in the soil at or near hazardous waste sites, such as former manufactured-gas factory sites and wood-preserving facilities. PAHs have been found in some drinking water supplies in the United States. Background levels of PAHs in drinking water range from 4 to 24 nanograms per liter (ng/L; a liter is slightly more than a quart).

In the home, PAHs are present in tobacco smoke, smoke from wood fires, creosote-treated wood products, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, and contaminated cow's milk or human breast milk. Food grown in contaminated soil or air may also contain PAHs. Cooking meat or other food at high temperatures, which happens during grilling or charring, increases the amount of PAHs in the food. The level of PAHs in the typical U.S. diet is less than 2 parts of total PAHs per billion parts of food (ppb), or less than 2 micrograms per kilogram of food (µg/kg; a microgram is one-thousandth of a milligram).

The primary sources of exposure to PAHs for most of the U.S. population are inhalation of the compounds in tobacco smoke, wood smoke, and ambient air, and consumption of PAHs in foods. For some people, the primary exposure to PAHs occurs in the workplace. PAHs have been found in coal tar production plants, coking plants, bitumen and asphalt production plants, coal-gasification sites, smoke houses, aluminum production plants, coal tarring facilities, and municipal trash incinerators. Workers may be exposed to PAHs by inhaling engine exhaust and by using products that contain PAHs in a variety of industries such as mining, oil refining, metalworking, chemical production, transportation, and the electrical industry. PAHs have also been found in other facilities where petroleum, petroleum products, or coal are used

or where wood, cellulose, corn, or oil are burned. People living near waste sites containing PAHs may be exposed through contact with contaminated air, water, and soil. For more information on human exposure to PAHs, see Chapter 5.

1.4 HOW CAN POLYCYCLIC AROMATIC HYDROCARBONS ENTER AND LEAVE MY BODY?

PAHs can enter your body through your lungs when you breathe air that contains them (usually stuck to particles or dust). Cigarette smoke, wood smoke, coal smoke, and smoke from many industrial sites may contain PAHs. People living near hazardous waste sites can also be exposed by breathing air containing PAHs. However, it is not known how rapidly or completely your lungs absorb PAHs. Drinking water and swallowing food, soil, or dust particles that contain PAHs are other routes for these chemicals to enter your body, but absorption is generally slow when PAHs are swallowed. Under normal conditions of environmental exposure, PAHs could enter your body if your skin comes into contact with soil that contains high levels of PAHs (this could occur near a hazardous waste site) or with used crankcase oil or other products (such as creosote) that contain PAHs. The rate at which PAHs enter your body by eating, drinking, or through the skin can be influenced by the presence of other compounds that you may be exposed to at the same time with PAHs. PAHs can enter all the tissues of your body that contain fat. They tend to be stored mostly in your kidneys, liver, and fat. Smaller amounts are stored in your spleen, adrenal glands, and ovaries. PAHs are changed by all tissues in the body into many different substances. Some of these substances are more harmful and some are less harmful than the original PAHs. Results from animal studies show that PAHs do not tend to be stored in your body for a long time. Most PAHs that enter the body leave within a few days, primarily in the feces and urine. More information on how PAHs enter and leave your body can be found in Chapters 2 and 6.

1.5 HOW CAN POLYCYCLIC AROMATIC HYDROCARBONS AFFECT MY HEALTH?

PAHs can be harmful to your health under some circumstances. Several of the PAHs, including benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno [1,2,3-c,d]pyrene, have caused tumors in laboratory animals when they breathed these substances in the air, when they ate them, or when they had long periods of skin contact with them. Studies of people show that individuals exposed by breathing or skin contact for long periods to mixtures that contain PAHs and other compounds can also develop cancer.

Mice fed high levels of benzo[a]pyrene during pregnancy had difficulty reproducing and so did their offspring. The offspring of pregnant mice fed benzo[a]pyrene also showed other harmful effects, such as birth defects and decreased body weight. Similar effects could occur in people, but we have no information to show that these effects do occur.

Studies in animals have also shown that PAHs can cause harmful effects on skin, body fluids, and the body’s system for fighting disease after both short- and long-term exposure. These effects have not been reported in people.

The Department of Health and Human Services (DHHS) has determined that benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene are known animal carcinogens. The International Agency for Research on Cancer (IARC) has determined the following: benz[a]anthracene and benzo[a]pyrene are probably carcinogenic to humans; benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene are possibly carcinogenic to humans; and anthracene, benzo[g,h,i]perylene, benzo[e]pyrene, chrysene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to their carcinogenicity to humans. EPA has determined that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene are probable human carcinogens and that acenaphthylene, anthracene,

benzo[g,h,i]perylene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to human carcinogenicity. Acenaphthene has not been classified for carcinogenic effects by the DHHS, IARC, or EPA. More information on the health effects associated with exposure to PAHs can be found in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS?

In your body, PAHs are changed into chemicals that can attach to substances within the body. The presence of PAHs attached to these substances can then be measured in body tissues or blood after exposure to PAHs. PAHs or their metabolites can also be measured in urine, blood, or body tissues. Although these tests can show that you have been exposed to PAHs, these tests cannot be used to predict whether any health effects will occur or to determine the extent or source of your exposure to the PAHs. It is not known how effective or informative the tests are after exposure is discontinued. These tests to identify PAHs or their products are not routinely available at a doctor’s office because special equipment is required to detect these chemicals. More information on tests used to determine the presence of PAHs in your body is presented in Chapters 2 and 6.

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

The federal government has set regulations to protect people from the possible health effects of eating, drinking, or breathing PAHs. EPA has suggested that taking into your body each day the following amounts of individual PAHs is not likely to cause any harmful health effects: 0.3 milligrams (mg) of anthracene, 0.06 mg of acenaphthene, 0.04 mg of fluoranthene, 0.04 mg of fluorene, and 0.03 mg of pyrene per kilogram (kg) of your body weight (one kilogram is equal to 2.2 pounds). Actual exposure for most of the United States population occurs from active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and from eating the compounds in foods. Skin contact

with contaminated water, soot, tar, and soil may also occur. Estimates for total exposure in the United States population have been listed as 3 mg/day.

From what is currently known about benzo[a]pyrene, the federal government has developed regulatory standards and guidelines to protect people from the potential health effects of PAHs in drinking water. EPA has provided estimates of levels of total cancer-causing PAHs in lakes and streams associated with a risk of human cancer development. If the following amounts of individual PAHs are released to the environment within a 24-hour period, EPA must be notified: 1 pound of benzo[b]fluoranthene, benzo[a]pyrene, or dibenz[a,h]anthracene; 10 pounds of benz[a]anthracene; 100 pounds of acenaphthene, chrysene, fluoranthene, or indeno[1,2,3-c,d]pyrene; or 5,000 pounds of acenaphthylene, anthracene, benzo[k]fluoranthene, benzo[g,h,i]perylene, fluorene, phenanthrene, or pyrene.

PAHs are generally not produced commercially in the United States except as research chemicals. However, PAHs are found in coal, coal tar, and in the creosote oils, oil mists, and pitches formed from the distillation of coal tars. The National Institute for Occupational Safety and Health (NIOSH) concluded that occupational exposure to coal products can increase the risk of lung and skin cancer in workers. NIOSH established a recommended occupational exposure limit, time-weighted average (REL-TWA) for coal tar products of 0.1 milligram of PAHs per cubic meter of air (0.1 mg/m^3) for a 10-hour workday, within a 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an occupational exposure limit for coal tar products of 0.2 mg/m^3 for an 8-hour workday, within a 40-hour workweek. The Occupational Safety and Health Administration (OSHA) has established a legally enforceable limit of 0.2 mg/m^3 averaged over an 8-hour exposure period.

Mineral oil mists have been given an IARC classification of 1 (sufficient evidence of carcinogenicity). The OSHA Permissible Exposure Limit (PEL) for mineral oil mist is 5 mg/m^3 averaged over an 8-hour exposure period. NIOSH has concurred with this limit, and has established a recommended occupational exposure limit (REL-TWA) for mineral oil mists

of 5 mg/m^3 for a 10-hour work day, 40-hour work week, with a 10 mg/m^3 Short Term Exposure Limit (STEL).

More information on rules and standards for exposure to PAHs can be found in Chapter 7.

1.8 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:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
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This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 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 of the toxicology of polycyclic aromatic hydrocarbons (PAHs). 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.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of PAHs are indicated in Tables 2-1, 2-2, and 2-3 and Figures 2-l and 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for PAHs. 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.

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

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage, or other organic substances, such as tobacco and charbroiled meat. PAHs can either be synthetic or occur naturally. Most of these chemicals as individual compounds (i.e., not as part of a combustion product) have no known use except for research purposes. A few PAHs are used in medicines and to make dyes, plastics, and pesticides. Others are contained in asphalt used in road construction. They are found throughout the environment in the air, water, and soil. There are more than 100 different PAH compounds and the health effects of the individual PAHs are not exactly alike.

Fifty-four PAHs have been identified at one or more NPL hazardous waste sites. These 54 are acenaphthene, acenaphthylene, 2-acetoaminofluorene, anthracene, 9, 10-anthracenedione, benz[a]anthracene, benzo[a]pyrene, benzo[e]pyrene, benzo[a]fluoranthene, benzo[b]fluoranthene, benzo[b]fluorene, benzofluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]fluoranthene, benzoperylene, benzo[g,h,i]perylene, benzophenanthrene, benzopyrene, benzothiophene, benzo[b]thiophene, chrysene, 4H-cyclopenta[d,e,f]phenanthrene, dibenz[a,j]anthracene, dibenz[a,h]anthracene, 7,12-dimethylbenz[a]anthracene, 2,7-dimethylbenzo[b]thiophene, 1,4-dimethoxyanthracene, dimethyl phenanthrene, 2,5dimethyl phenanthrene, dodecachlorodecahydrotrim, fluoranthene, fluorene, indeno[1,2,3-c,d] pyrene, 12-methylbenz[a]anthracene, methyl anthracene, 9-methylanthracene, 3-methylcholanthrene, methylfluorene, methylphenanthrene, 2-methylphenanthrene, 1-methylphenanthrene, 4-methylphenanthrene, methylpyrene, phenanthrene, phenanthridine, phenanthroline, pyrene, perylene, 6,7-tetrahydropyrene, tetramethylphenanthrene, 3,4,5,6-tetramethylphenanthrene, and trimethylphenanthrene.

However, only 17 PAHs are discussed in this profile. These 17 PAHs are:

- acenaphthene
- acenaphthylene
- anthracene

- benz[a]anthracene
- benzo[a]pyrene
- benzo[e]pyrene
- benzo[b]fluoranthene
- benzo[j]fluoranthene
- benzo[g,h,i]perylene
- benzo[k]fluoranthene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[l,2,3-c,d]pyrene
- phenanthrene
- pyrene

These 17 PAHs were selected using the following four criteria:

(1) toxicity
(2) potential for human exposure
(3) frequency of occurrence at NPL hazardous waste sites
(4) extent of information available.

The 17 PAHs were combined into one profile to avoid repetition across multiple profiles on the individual PAHs since these chemicals often occur together in the environment and many have similar toxicological effects, environmental fate, etc. Instances in which it is known that the various PAHs differ with regard to toxicological effects or environmental fate will be pointed out. For example, PAHs can be classified as “alternant” (e.g., benzo[a]pyrene, benz]a]anthracene, chrysene, dibenz[a,h]anthracene) or “nonalternant” (e.g., fluoranthene, benzo[k]fluoranthene, benzol[j]fluoranthene, indeno[1,2,3-c,d]pyrene). This distinction is based on the electron density associated with the molecule. Altemant PAHs have an equally distributed electron density, whereas nonalternant PAHs behave almost as if they were two different molecules because of an uneven distribution of electron density from one portion of the molecule to another. The toxicological significance of this difference is that alternant and nonalternant PAHs appear to behave differently, for example, with regard to how they are metabolized to ultimate carcinogens (see Section 2.3.3, Metabolism).

Reliable health-based and environmental information exists on only a few of the 17 PAHs discussed in this profile, and the potential health effects of the other less well-studied PAHs must be inferred from this information. By combining all 17 PAHs in one profile, these comparisons and inferences can

easily be made. Although a large toxicity database exists on complex mixtures that contain PAHs (such as crude oils, various high boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes), these data generally have not been used in this profile. It is difficult to ascertain the toxicity of the component PAHs in these mixtures because of the potential interactions that could occur and the presence of other toxic substances in the mixtures. Furthermore, ATSDR has developed a profile on one of these complex mixtures, creosote, and the reader is referred to this profile for information on this complex mixture (ATSDR 1994). However, most of the available information on the health effects of PAHs in humans must be inferred from studies that reported the effects of exposure to complex mixtures that contain PAHs. Several epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions, roofing-tar emissions, and cigarette smoke. Each of these mixtures contains benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and co-carcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene to cause cancer in humans. For this reason, and also because of the lack of data on the effects of individual PAHs in humans, such information has been included in this profile on PAHs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to any of the 17 PAHs discussed in this profile. However, a dose-related decrease in survival was noted in hamsters after 60 weeks of inhalation exposure to 46.5 mg/m^3 benzo[a]pyrene for 109 weeks (Thyssen et al. 1981). The authors attributed this reduced survival in part to toxic and carcinogenic effects induced by this PAH (e.g., tumors in the pharynx and larynx that could have inhibited food intake).

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, dermal, or ocular effects in humans or animals following inhalation exposure to any of the 17 PAHs discussed in this profile. The systemic effects observed after inhalation exposure are discussed below.

The highest NOAELs for respiratory and renal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Only one study was located regarding respiratory effects in humans following inhalation exposure to PAHs, specifically, benzo[a]pyrene. The respiratory health of 667 workers in a rubber factory was investigated (Gupta et al. 1993). Respiratory health was evaluated and examined for correlations to length of employment at the factory. In addition, total suspended particulate matter and benzo[a]pyrene concentrations were monitored in various parts of the factory and examined for possible correlation with the respiratory health of the workers in the same area of the factory. Statistically significant decrements in ventilatory function occurred following prolonged exposure as assessed by duration of employment. When different sections of the factory were considered, workers in the compounding section were the most affected, which was associated with the highest exposure to particulate matter and benzo[a]pyrene. Workers in the compounding section exhibited radiographic abnormalities including patch opacities, prominent bronchiovascular markings, and pleural effusions. Other symptoms included bloody vomit, breathing problems, chest pains, chest irritation, throat irritation, and cough. Workers in other areas of the plant exposed to lower levels of particulate matter and benzo[a]pyrene were similarly affected although to a lesser degree and in fewer numbers (Gupta et al. 1993). No attempt was made to separate the effects of exposure to benzo[a]pyrene and particulate matter, or to identify possible simultaneous exposure to other toxic chemicals.

Groups of 40 Fischer-344/Crl rats/sex were exposed nose-only to an aerosol of benzo[a]pyrene (7.7 mg/m^3) 2 hours/day, 5 days/week, for 4 weeks (Wolff et al. 1989a). Nasal and left lung sections were examined histopathologically. No treatment-related lesions were noted in the lungs or nasal cavities of the animals exposed to benzo[a]pyrene. Although this was a well-conducted inhalation toxicity study, it is not appropriate for use in risk assessment because only one concentration was

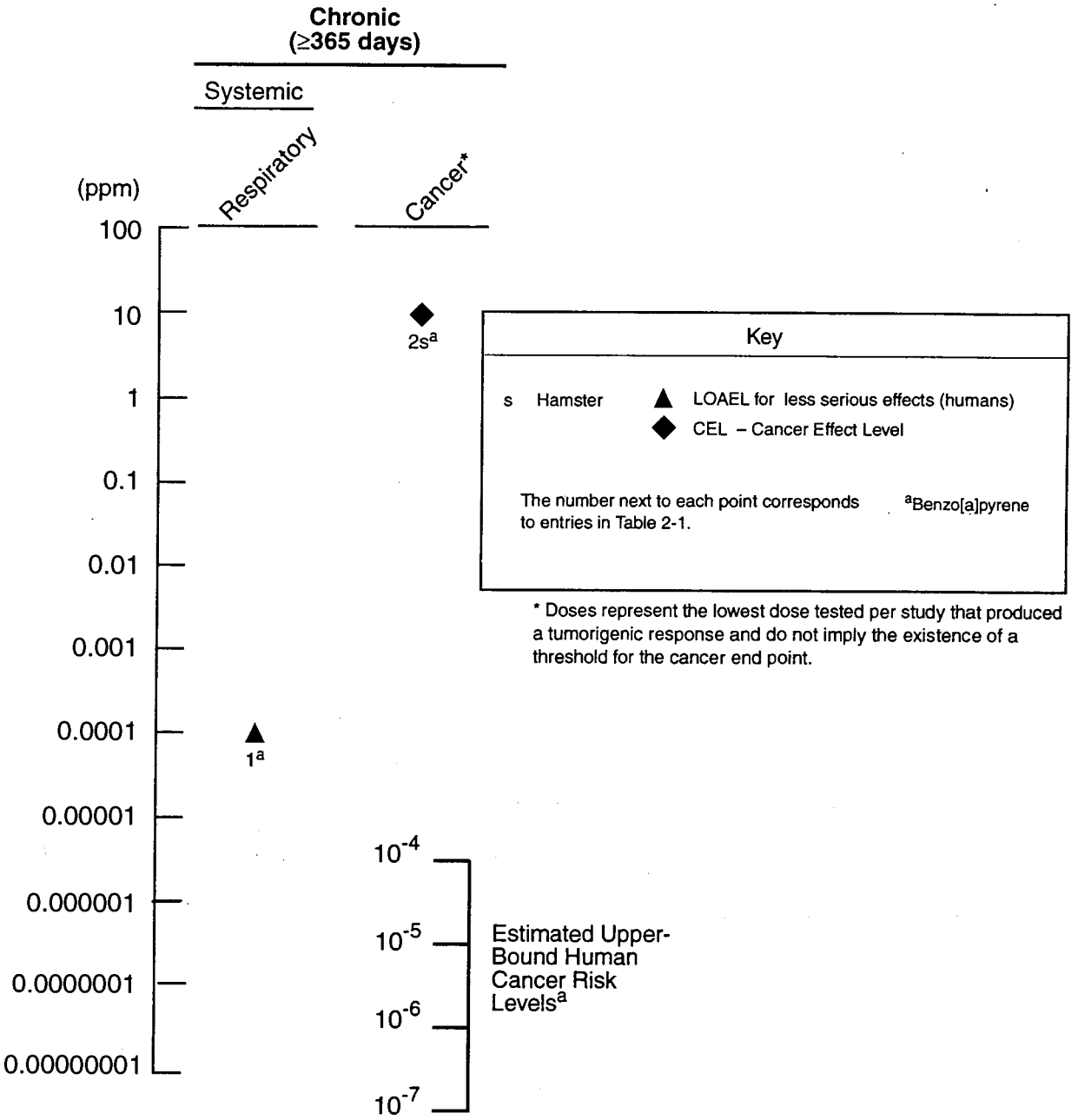
TABLE 2-1. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
CHRONIC EXPOSURE							
Systemic							
1	Human	6 mo - >6 yr	Resp			0.0001 NS (reduced lung function, abnormal chest x-ray, cough, bloody vomit, throat and chest irritation.	Gupta et al. 1993 benzo[a]pyrene
Cancer							
2	Hamster (Syrian golden)	109 wk 7 d/wk 3-4.5 hr/d				9.5 M (CEL: 34.6% increase in respiratory tract tumors; neoplasms of the upper digestive tract in 26.9%)	Thyssen et al. 1981 benzo[a]pyrene

[a]The number corresponds to entries in Figure 2-1.

CEL = cancer effect level; d = day(s); hr = hour; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Inhalation



studied (thereby precluding the assessment of a dose-response relationship); no adverse treatment-related effects were observed; and the only parts of the respiratory tract examined histopathologically were the lungs and nose.

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to any of the 17 PAHs discussed in this profile.

Groups of 40 Fischer-344/Crl rats/sex were exposed nose-only to an aerosol of benzo[a]pyrene 2 hours/day, 5 days/week, for 4 weeks (Wolff et al. 1989a). Kidney sections were examined histopathologically. No treatment-related lesions were noted in the kidneys of the animals exposed to benzo[a]pyrene.

2.2.1.3 Immunological and Lymphoreticular Effects

Humoral immunity was monitored in male iron foundry workers in Poland (Szczeklik et al. 1994). Coke oven workers (199) were compared to cold-rolling mill workers (76). The groups were similar with respect to age, length of employment, and smoking habits. The results showed that coke oven workers, exposed to high concentrations of atmospheric PAHs, including fluoranthene, perylene, pyrene, benzo[a]pyrene, chrysene, benz[a]anthracene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene, had reduced levels of serum immunoglobins. The workers most exposed to PAHs worked at the topside area of the coke ovens. Benzo[a]pyrene exposure was used as a reference point. Coke oven workers, exposed to 0.0002-0.50 mg/m^3 benzo[a]pyrene, were compared to cold-rolling mill workers, whose exposure to benzo[a]pyrene was 3-5 orders of magnitude less. Average length of employment was 15 years. IgG, IgA, IgM, and IgE concentrations were measured. Coke oven workers exhibited a marked depression of mean serum IgG and IgA, compared to mill workers. IgM tended to decrease, whereas IgE tended to increase in the coke oven workers. The biological significance of this finding is unclear and is not addressed by the authors. However, the authors suggest that serum immunoglobulin levels may be a useful biomarker for PAH exposure. The authors note, however, that the coke oven workers were exposed to higher levels of sulfur dioxide and carbon monoxide than were the cold-rolling mill workers, and they suggest that this additional exposure may have potentiated the effects of the PAH exposure. The potential contribution of the smoking habits of the subjects was not investigated.

No studies were located regarding the following effects in humans or animals following inhalation exposure to any of the 17 PAHs discussed in this profile:

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Becher et al. (1984) evaluated urine and blood samples from 15 aluminum plant workers (average age, 29 years; average years employed, 3.8) exposed to an estimated total PAH concentration of 1 mg per 8-hour work shift. The main PAH components identified by air sampling and also detected in the urine samples included phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[e]pyrene, and benzo[a]pyrene. Results of the cytogenetic analysis of peripheral lymphocytes of the exposed workers indicated that the frequency of sister chromatid exchange was not influenced by the presence of large amounts of PAHs. These findings were reported to be consistent with the negligible increase in lung cancer found in epidemiological studies of aluminum workers. The investigators, therefore, questioned the relevance of PAH air monitoring as a measure of the occupational hazards associated with PAH exposure. Alternatively, it is possible that there are no occupational hazards associated with PAH exposure at these levels. Similar results were obtained with iron factory workers (length of employment: 2-46 years) exposed to 0.0005-0.00 mg/m^3 benzo[a]pyrene (Perera et al. 1993), who exhibited an increased rate of mutations in peripheral lymphocytes that were not correlated with PAH exposure. These authors suggest that both biomonitoring and personal monitoring may be necessary to evaluate exposure.

The high lung cancer rate in Xuan Wei, China, is associated with smokey coal use in unvented homes, but not with wood or smokeless coal use (Mumford et al. 1993). Smoky coal combustion emits higher PAH concentrations than wood combustion. This study evaluated PAH-DNA adducts in placentas, and in peripheral and cord white blood cells (WBC) from Xuan Wei women burning smoky coal or wood and from Beijing women using natural gas. Exposures were based on benzo[a]pyrene concentrations determined by personal monitors. Women in Xuan Wei burning smoky coal without a chimney were

exposed to 0.383 mg/m^3 benzo[a]pyrene, those burning smoky coal with chimneys were exposed to 0.184 mg/m^3, and women burning wood or using natural gas (Beijing) had no detectable exposure to benzo[a]pyrene. Positive results (detection of PAH-DNA adducts) were found in 58, 47, and 5% of the placentas from Xuan Wei women burning smoky coal without a chimney, with a chimney, and Beijing women using natural gas, respectively. Positive results were found in 46, 6.5, 56, and 25% of placentas from Xuan Wei women who lived in houses without and with chimneys, Xuan Wei women burning wood, and Beijing controls, respectively. Peripheral WBC samples were positive in 7 of 9, 8 of 9, and 3 of 9 for the Xuan Wei women who lived in houses without and with chimneys and Beijing women, respectively. No dose-response relationship was observed between the air benzo[a]pyrene concentrations and DNA adduct levels or percentage of detectable samples. However, using the fluorescent color assay, there was a significant association between DNA adduct detection in the placenta and cooking methods. Moreover, individual comparisons of the data revealed a significant difference between both smokey coal groups (chimney, no chimney) and natural gas cooking. The results of this study suggest that DNA adducts can be used as a biomarker to assess human exposure to combustion emissions.

Thirty-four workers in an electrode paste plant were monitored for response to exposure (Ovrebo et al. 1994). Exposure to benzo[a]pyrene was 0.9 μg/m^3; exposure to pyrene was 3.5μg/m^3. 1-Hydroxypyrene was measured in the urine, and PAH-DNA adducts were measured in white blood cells to demonstrate their relationship to the exposure. Results from these workers were compared to two reference control groups: research and development (R&D) workers and nickel refinery workers. Mean values of PAH-DNA adducts in the white blood cells from randomly selected participants in the three groups were only marginally different, with the exception of two smokers in the electrode plant, who had the highest levels. Mean PAH-DNA adduct levels were 10.9 adducts per 108 nucleotides for the electrode workers, 10.8 adducts per 10^8 nucleotides for the R&D personnel, and 10.0 adducts per 10^8 nucleotides for nickel plant workers not occupationally exposed to PAHs. No correlation was found between PAH-DNA adducts and 1-hydroxypyrene in the urine.

In an ongoing comprehensive evaluation of biological markers, workers in or near an iron foundry with varying exposures to PAHs were examined for response to exposure (Santella et al. 1993). Exposure to benzo[a]pyrene, determined by personal monitors, was 2-60 ng/m^3, which are the lowest levels yet analyzed in foundry workers. 1-Hydroxypyrene was measured in the urine, and PAH-DNA adducts were measured in white blood cells to demonstrate their relationship to the exposure.

Cigarette smoking, but not age or charbroiled food, influenced the level of 1-hydroxypyrene but not PAH-DNA adducts. When workers were classified into three categories of exposure (low, <.0005 mg/m^3; medium, 0.0005-0.0012 mg/m^3; high, >0.0012 mg/m^3), PAH-DNA adducts showed an increasing trend, with exposure from 5.2 to 6.2-9.6 adducts per 10^8 nucleotides in the low-, medium, and high-exposure groups, respectively. However, the three exposure groups did not differ significantly from each other, and no independent control group was used.

In order to evaluate the correlation between peripheral blood leukocyte DNA adducts as an indicator of exposure to PAHs and the airborne contamination of PAH at the workplaces, a survey of 69 coke oven workers was carried out (Assennato et al. 1993). In each workplace, total PAH and specific (benz[a]anthracene, benzo[a]pyrene, chrysene) PAH airborne concentrations were measured. Job titles included supervisor, door maintenance, machine operator, gas regulators, temperature operators, and top side workers. For the workplaces evaluated, the range of airborne concentrations (μg/m^3) for benz[a]anthracene, benzo[a]pyrene, and chrysene, respectively, were: supervisor (0.41, 0.29, 0.32), door maintenance (4.26-14.79, 2.31-6.37, 2.34-6.53), machine operator (0.11-33.19, 0.08-13.17, 0.03-12.63), gas regulators (0.21-2.10, 0.12-1.61, 0.13-1.60), temperature operators (1.77-10.07, 1.37-5.03, 0.98-4.78), and top side workers (0.45-3.40, 0.47-4.73, 0.23-2.42). Mean values (fmol/μg DNA) for PAH-DNA adducts in leukocytes by job title were: supervisor (0.059), door maintenance (0.174) machine operator (0.065), gas regulators (0.081), and temperature operators (0.071). Levels of exposure were correlated with PAH-DNA adduct formation. However, the differences were not statistically significant. The major limitations of the study included no record of length of exposure, no independent control group, no reporting of expected background levels of adducts, and no estimation of the length of time individual workers were exposed to particular levels of the PAHs. Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans following inhalation exposure to any of the 17 PAHs discussed in this profile. However, epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Each of these mixtures contains benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene as well as other

potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and co-carcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Furthermore, the levels of individual or total PAHs were not quantified in any of these reports. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene to cause cancer in humans.

Several inhalation studies for animals given benzo[a]pyrene were located. Shulte et al. (1993) found a significant increase in all lung tumors and a dose-dependent increase in malignant lung tumors for mice exposed to PAH-enriched exhausts containing 0.05 or 0.09 mg/m^3 benzo[a]pyrene. The chronic study of Thyssen et al. (1981) provides clear-cut evidence of a dose-response relationship between inhaled benzo[a]pyrene particles (99% of the benzo[a]pyrene particles were between 0.2 and 0.54 microns in diameter) and respiratory tract tumorigenesis. Respiratory tract tumors were induced in the nasal cavity, pharynx, larynx, and trachea in a dose-related manner in hamsters exposed to 9.5 mg/m^3 or 46.5 mg/m^3 for 109 weeks. No lung tumors were found, and the reason for the absence of lung tumors is not known. Furthermore, the particle sizes were reported to be within the respirable range (0.2-0.5 microns in diameter). Tumors were also observed following exposure to 46.5 mg/m^3 in the esophagus and forestomach (presumably as a consequence of mucocilliary particle clearance) (Thyssen et al. 1981). These tumor types consisted of papillomas, papillary polyps, and squamous cell carcinomas.

The CEL from the Thyssen et al. (1981) study is recorded in Table 2-1 and plotted in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to any of the 17 PAHs discussed in this profile.

Oral exposure to 120 mg/kg/day benzo[a]pyrene has resulted in decreased survival time in two strains of mice (DBA/2N and AKR/N) whose hepatic aryl hydrocarbon hydroxylase (AHH) activity is not induced by PAHs ("nonresponsive" mice) (Robinson et al. 1975). AHH is a microsomal enzyme believed to be responsible for the metabolism of benzo[a]pyrene. All of the mice in the treatment group died, with at least half the deaths occurring within 15 days of dosing. Only three mice in the control group died. Death appeared to be caused by bone marrow depression (aplastic anemia, pancytopenia), leading to hemorrhage or infection. In contrast, only 6 of 90 (7%) mice with inducible AHH activity ("responsive" mice) similarly exposed to benzo[a]pyrene died over the same period of time. The authors concluded that the decreased survival in the nonresponsive mice was associated with a single gene difference encoding aromatic hydrocarbon responsiveness and was dependent on route of exposure. Benzo[a]pyrene was not as rapidly metabolized by the liver and excreted following oral administration in nonresponsive mice as in responsive mice. Therefore, more benzo[a]pyrene was available to reach the target tissue (i.e., bone marrow) in the nonresponsive mice, resulting in bone marrow depression and death.

A LOAEL for death for intermediate-duration exposure in mice is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, dermal, or ocular effects in humans following oral exposure to any of the 17 PAHs discussed in this profile. The systemic effects observed in humans or animals after oral exposure are discussed below.

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

Respiratory Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of respiratory distress were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Wistar/Af/Ha n/Mol/ Kuo)	4 d 1 x/d (G)	Gastro	150 M			Nouslainen et al. 1984 benz[a]anthracene
			Hepatic	150 M			
			Renal	150 M			
2	Rat (Wistar/Af/Ha n/Mol/ Kuo)	4 d 1 x/d (G)	Gastro	150 M			Nouslainen et al. 1984 benzo[a]pyrene
			Hepatic	150 M			
			Renal	150 M			
	Reproductive						
3	Mouse (CD-1)	10 d Gd 7-16 (G)		40 F		160 F (reduced pregnancy)	Mackenzie and Angevine 1981 benzo[a]pyrene
	Developmental						
4	Mouse (B6AKF1, AKR/J)	8 d Gd 2-10 (F)				120 F (fetal resorption in Ahd/Ahd)	Legraverend et al. 1984 benzo[a]pyrene
5	Mouse (CD-1)	10 d Gd 7-16 (G)		10 F		40 F (reduced pup weight at 20 days)	Mackenzie and Angevine 1981 benzo[a]pyrene
	Cancer						
6	Mouse (CFW Swiss)	1-7 d ad lib (F)		13.3		33.3 (CEL: gastric neoplasms)	Neal and Rigdon 1967 benzo[a]pyrene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Systemic						
7	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	700			EPA 1989c acenaphthene
			Cardio	700			
			Gastro	700			
			Hemato	700			
			Musc/skel	700			
			Hepatic		175[b]	(increased relative liver weight)	
			Renal	700			
			Endocr	700			
			Dermal	700			
			Ocular	700			
			Bd Wt	700			
8	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	1000			EPA 1989d anthracene
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Musc/skel	1000			
			Hepatic	1000[c]			
			Renal	1000			
			Endocr	1000			
			Dermal	1000			
			Ocular	1000			
			Bd Wt	1000			

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Mouse (DBA/2,ARR/N); (C57B1/b, C3H/HeN, BALB/cAnN)	6 mo (F)	Hemato			120 (aplastic anemia)	Robinson et al. 1975 benzo[a]pyrene
			Hepatic		120 (increased liver weight)		
10	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	500			EPA 1988e fluoranthene
			Cardio	500			
			Gastro	500			
			Hemato	125 F 500 M	250 F (decrease in packed cell volume)		
			Musc/skel	500			
			Hepatic		125[d] M (increased relative liver weight)		
				125 F	250 F (increased relative liver weight; centrilobular pigmentation, increased enzymes)		
			Renal	250 M 125 F	500 M (renal tubular 250 F regeneration; interstitial lymphocytic infiltrates and/or fibrosis)		
			Endocr	500			
			Dermal	500			
			Ocular	500			
			Bd Wt	500			

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
11	Mouse (CD-1)	13 wk 1 x/d (GO)	Resp	500			EPA 1989e fluorene
			Cardio	500			
			Gastro	500			
			Hemato	125	250 (decreased PCV and MCHC in males; decreased RBC, PCV, MCH, and MCHC in females)		
			Musc/skel	500			
			Hepatic		125[e] (increased relative liver weight)		
			Renal	250 M 500 F	500 M (increased absolute and relative kidney weight)		
			Endocr	500			
			Dermal	500			
			Ocular	500			
			Bd Wt	500 M 250 F	500 F (increased body weight)		
	Immunological/Lymphoreticular						
12	Mouse (CD-1)	13 wk 1 x/d (GO)		700			EPA 1989c acenaphthene
13	Mouse (CD-1)	13 wk 1 x/d (GO)		1000			EPA 1989d anthracene
14	Mouse (CD-1)	13 wk 1 x/d (GO)		500 F	500 M (increased serum globulin values)		EPA 1988e fluoranthene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Mouse (CD-1)	13 wk 1 x/d (GO)		125	250 M (increased spleen weight)		EPA 1989e fluorene
	Neurological						
16	Mouse (CD-1)	13 wk 1 x/d (GO)		700			EPA 1989e acenaphthene
17	Mouse (CD-1)	13 wk 1 x/d (GO)		1000			EPA 1989d anthracene
18	Mouse (CD-1)	13 wk 1 x/d (GO)		500			EPA 1988 fluoranthene
19	Mouse (CD-1)	13 wk 1 x /d (GO)		500			EPA 1989e fluorene
	Reproductive						
20	Mouse (CD-1)	13 wk 1 x/d (GO)		700 M 350 F	700 F (decreased ovary weights correlated with increased incidence and degree of inactivity of the ovary and uterus)		EPA 1989c acenaphthene
21	Mouse (CD-1)	13 wk 1 x/d (GO)		1000			EPA 1989d anthracene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
22	Mouse (White Swiss)	19-29 d ad lib (F)		133.3 F				Rigdon and Neal 1965 benzo[a]pyrene
23	Mouse (CD-1)	13 wk 1 x/d (GO)		500				EPA 1988 fluoranthene
24	Mouse (CD-1)	13 wk 1 x/d (GO)		500				EPA 1989e fluorene
	Cancer							
25	Mouse (CFW Swiss)	30-197 d ad lib (F)		1.3		2.6	(CEL: gastric tumor)	Neal and Rigdon 1967 benzo[a]pyrene
26	Mouse (Swiss)	23-238 d ad lib (F)				33.3	(CEL: papillomas; squamous cell carcinomas)	Rigdon and Neal 1966 benzo[a]pyrene

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
27	Mouse (Swiss)	80-140 d ad lib (F)					33.3	(CEL: tumors of the forestomach in 69/108)	Rigdon and Neal 1969 benzo[a]pyrene

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.6 mg/kg/day for acenaphthene; dose divided by an uncertainty factor of 300 (3 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability)

[c]Used to derive an intermediate-duration oral MRL of 10 mg/kg/day for anthracene; dose obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans and 10 for human variability)

[d]Used to derive an intermediate-duration oral MRL of 0.4 mg/kg/day for fluoranthene; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability)

[e]Used to derive an intermediate-duration oral MRL of 0.4 mg/kg/day for fluorene; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability)

ad lib = ad libitum; BaP = benzo(a)pyrene; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavage (oil); Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PCV = packed cell volume; RBC = red blood cells; Resp = respiratory; TPA = tetradecanoyl phorbol acetate; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Oral

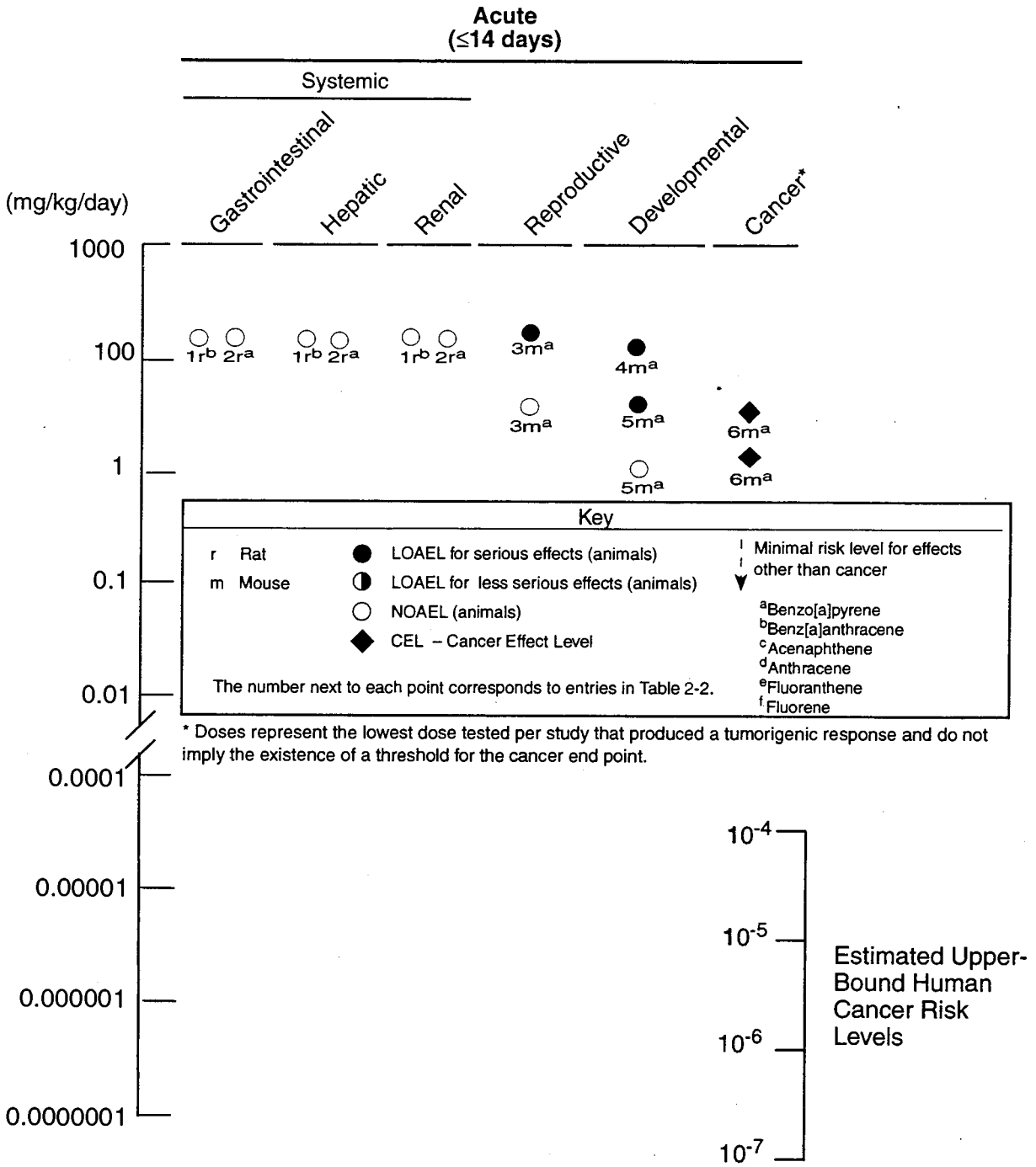


Figure 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Oral (continued)

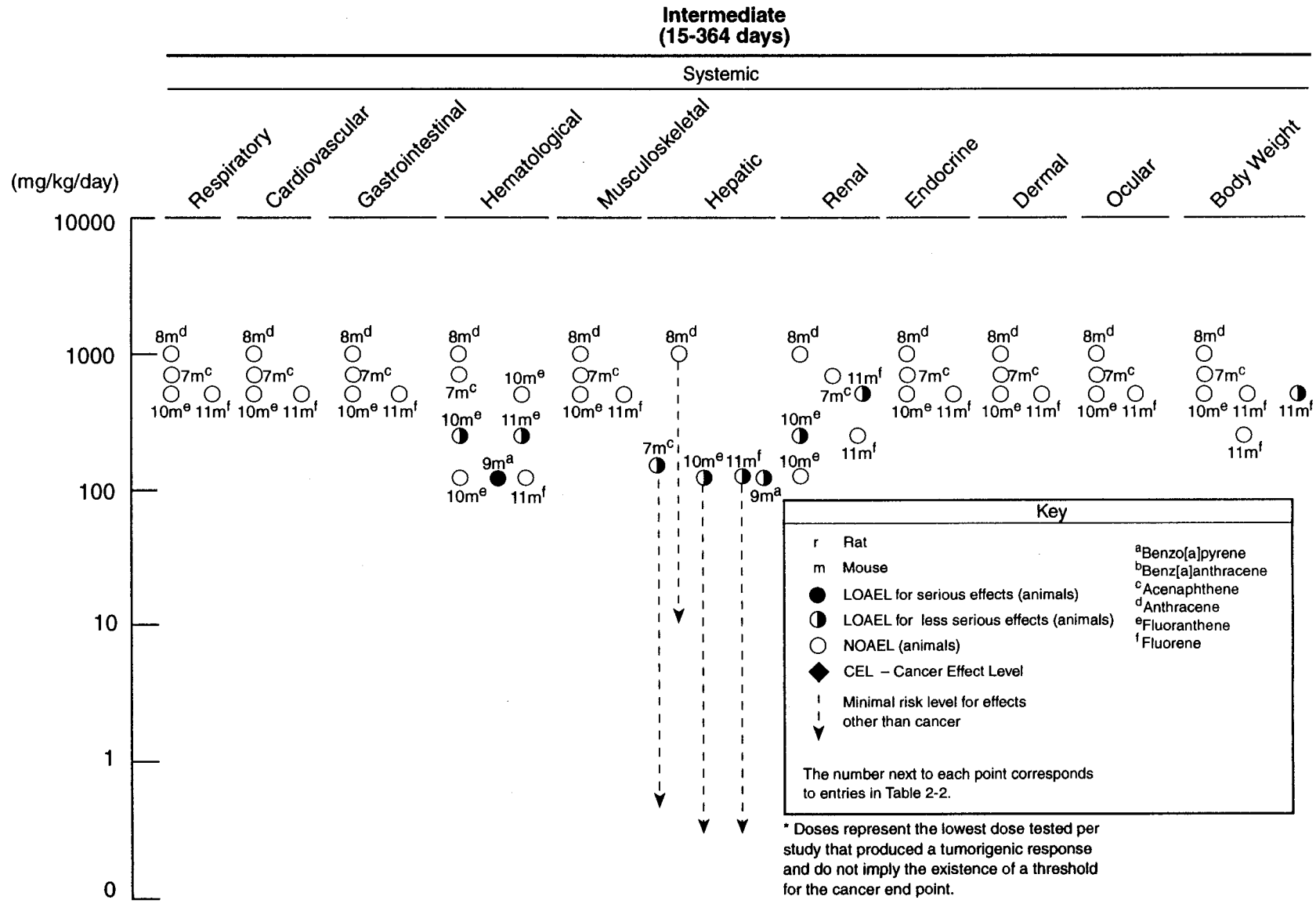
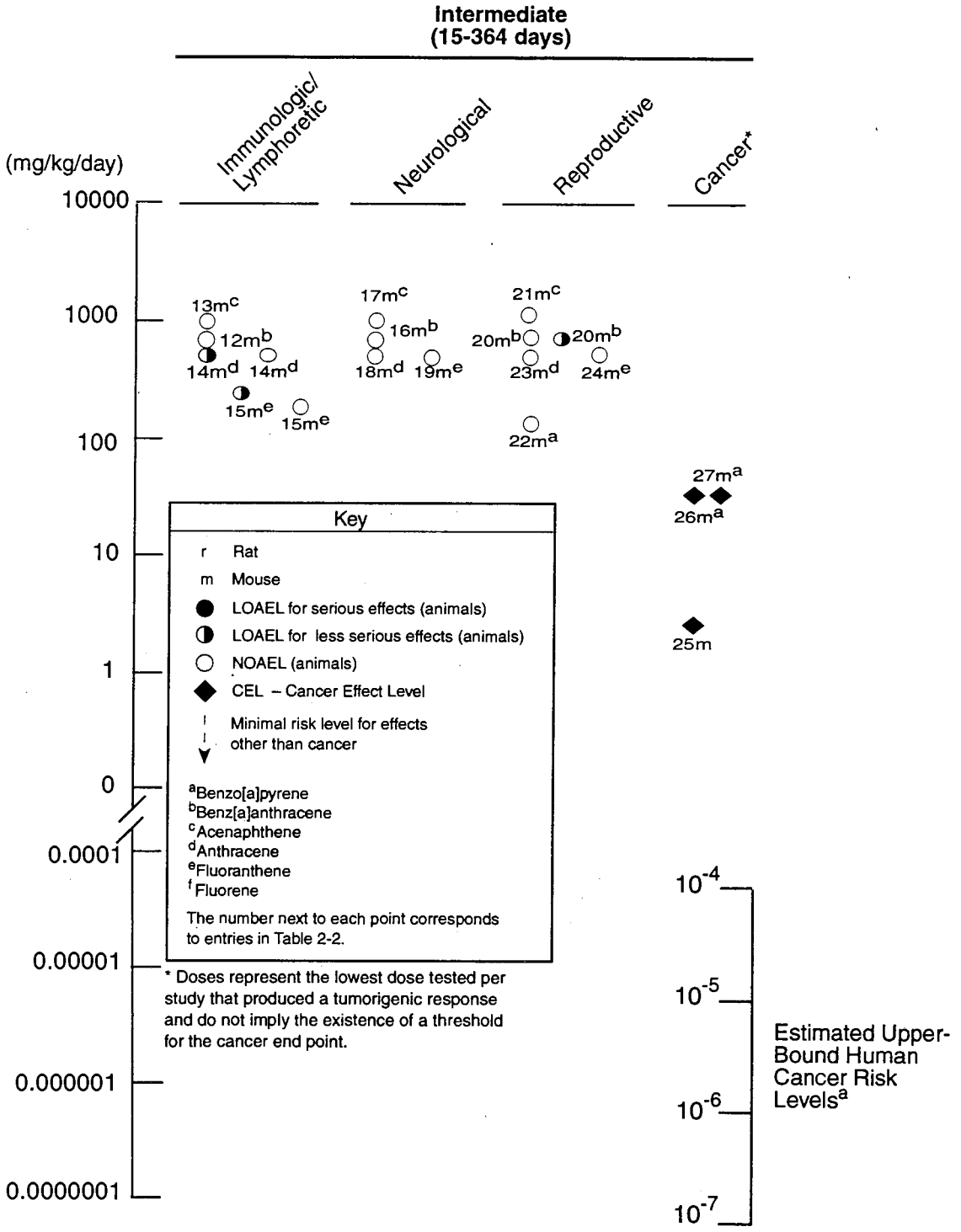


Figure 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons – Oral (continued)



Cardiovascular Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of cardiovascular distress were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Gastrointestinal Effects. Minimal information is available on the gastrointestinal effects of human oral exposure to PAHs. In one study, humans that consumed anthracene-containing laxatives (the anthracene concentration was not specified) for prolonged periods of time were found to have an increased incidence of melanosis of the colon and rectum (i.e., unusual deposits of black pigments in the colon and rectum) compared to patients who did not consume anthracene laxatives. However, no definitive conclusions can be drawn from these results because of study limitations that include possible misclassification of patients with respect to the level of anthracene laxative use over 30 years and no accounting for other factors involved in the pathogenesis of melanosis (Badiali et al. 1985).

Enzyme alterations in the mucosa of the gastrointestinal tract have been observed in animals acutely exposed to anthracene, benz[a]anthracene, benzo[a]pyrene, or phenanthrene. In rats, acute intragastric administration of 50 or 150 mg/kg/day benz[a]anthracene or benzo[a]pyrene, respectively, for 4 days resulted in suppression of carboxylesterase activity in the intestinal mucosa (reduction of activity by 30% and 44%, respectively); rats exposed to 100 mg/kg/day of anthracene or phenanthrene exhibited carboxylesterase activity that was increased by 13% and 30%, respectively (Nousiainen et al. 1984). Enzyme alteration in the absence of other signs of gastrointestinal toxicity is not considered an adverse health effect, but it may precede the onset of more serious effects. Based on this very limited information, it would appear that acute ingestion of anthracene, benz[a]anthracene, benzo[a]pyrene, or phenanthrene at these doses may not adversely affect the gastrointestinal tract of animals; however, exposed animals exhibited biochemical changes and it is possible that more serious effects could occur at high doses.

Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No adverse effects on the gastrointestinal system were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Hematological Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No hematological effects were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene (EPA 1989d). Administration of 250 mg/kg/day fluoranthene by gavage for 13 weeks to mice resulted in decreased packed cell volume in females, but not in males, given doses up to 500 mg/kg/day (EPA 1988e). Both male and female mice exposed to 250 mg/kg/day fluorene exhibited hematologic effects, including decreased packed cell volume and hemoglobin content (EPA 1989e).

Adverse hematopoietic effects (e.g., aplastic anemia, pancytopenia) that ultimately led to death were reported in the Ah-nonresponsive strains of mice, DBA/2N and AKR/N, following oral exposure to 120 mg benzo[a]pyrene/kg/day for 180 days. Death was attributed to hemorrhage or infection that resulted from pancytopenia (Robinson et al. 1975). Similar results were obtained by Legraverend et al. (1983). The Ah gene encodes a cytosolic receptor (Ah receptor) that regulates the induction of the cytochrome P-450 enzymes. Differences in this gene locus determine whether the Ah receptor will be “high-affinity” (i.e., will allow for the induction of the cytochrome P-450 enzymes [more specifically, AHH] and is found in responsive mice) or “low-affinity” (i.e., does not allow for the induction of the AHH and is found in nonresponsive mice). Mice with a high-affinity Ah receptor (i.e., responsive mice) were administered 120 mg/kg/day benzo[a]pyrene in the diet for 3 weeks and exhibited no myelotoxicity. However, all nonresponsive mice that were treated according to the same regimen died from myelotoxic effects within 3 weeks (Legraverend et al. 1983). These results support the results of Robinson et al. (1975).

Musculoskeletal Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of musculoskeletal effects were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Hepatic Effects. The induction of foci of altered hepatocytes is often seen in rats and mice that also develop liver tumors. These foci have altered enzyme activities and higher rates of cell proliferation than normal hepatocytes. A l-day intragastric administration of 200 mg/kg of benzo[a]pyrene or dibenz[a,h]anthracene, or of 180 mg/kg benz[a]anthracene to rats was followed by a

diet containing 2-acetylaminofluorene (2-AAF) and carbon tetrachloride induced gamma-GT foci (Tsuda and Farber 1980). Partially hepatectomized rats and sham hepatectomized rats were used, to provide proliferating and non-proliferating hepatocytes, respectively. Partially hepatectomized rats were more responsive to treatment than the sham-operated animals. For partially hepatectomized rats, benzo[a]pyrene was a more potent foci inducer than either benz[a]anthracene or dibenz[a,h]anthracene. Increased relative liver weight was seen in male mice and increased absolute and relative liver weight was seen in female mice given 175 mg/kg/day acenaphthene daily by gavage for 13 weeks; these effects were unaccompanied by other hepatic effects (EPA 1989c). Increased absolute and relative liver weight correlated with hepatocellular hypertrophy was seen in male and female mice given 350 mg/kg/day acenaphthene daily by gavage for 13 weeks (EPA 1989c). Increased serum cholesterol was also seen in females receiving 350 mg/kg/day acenaphthene (EPA 1989c). Increased liver weight and dose-related centrilobular pigmentation accompanied by an increase in liver enzymes were observed in both male and female mice receiving 250 mg/kg/day fluoranthene by gavage for 13 weeks (EPA 1988e). Male mice exposed to 125 mg/kg/day fluoranthene exhibited a slight increase in centrilobular pigmentation, and an increase in relative liver weight (EPA 1988e). Increased relative liver weight was observed in all treated groups, whereas increased absolute and relative liver weight was observed in the mid- and high-dose animals receiving 0, 125, 250, and 500 mg/kg/day fluorene for 13 weeks (EPA 1989e). However, there were no accompanying histopathological changes. No statistically significant effects of treatment were reported after 13-week administration of 1,000 mg/kg/day anthracene (EPA 1989d)

The ability to induce aldehyde dehydrogenase (ADH) in animals has been correlated with carcinogenic potency. Rats that were intragastrically administered 100 mg/kg/day of benzo[a]pyrene, benz[a]anthracene, anthracene, chrysene, or phenanthrene for 4 days exhibited cytosolic ADH induction (Torronen et al. 1981). However, benzo[a]pyrene and benz[a]anthracene were much more effective than phenanthrene, chrysene, or anthracene. Exposure to benzo[a]pyrene and benz[a]anthracene also increased the relative liver weights by 27% and 19%, respectively (Torronen et al. 1981). The authors concluded that anthracene, phenanthrene, and chrysene, which have been characterized as either noncarcinogens or equivocal carcinogens (see Section 2.2.2.8), are poor ADH inducers (Torronen et al. 1981).

The induction of carboxylesterase activity has also been observed in animals exposed to PAHs (Nousiainen et al. 1984). Benzo[a]pyrene, benz[a]anthracene, and chrysene were moderate inducers of

hepatic carboxylesterase activity in rats that were intragastrically administered 50, 100, and 150 mg/kg/day (100 mg/kg/day for chrysene), respectively, for 4 days. However, rats administered 100 mg/kg/day anthracene or phenanthrene did not exhibit induction of hepatic carboxylesterase activity. Induction of hepatic microsomal enzymes generally results in enhanced biotransformation of other xenobiotics (to either more or less toxic forms).

Increases in liver weight following partial hepatectomy have also been examined following acute oral exposure to various PAHs. Partially hepatectomized rats were fed diets containing various PAHs for 10 days. Administration of 51.4 mg/kg/day acenaphthene or 180 mg/kg/day fluorene resulted in statistically significant increases in liver weight compared to controls, which may have indicated an effect on regeneration, although rates of cell proliferation were not determined. Administration of 15.4 mg/kg/day acenaphthene, 51.4 mg/kg/day benzo[a]pyrene, or 51.4 mg/kg/day pyrene, anthracene, or phenanthracene had no effect. Diets containing 51.4 mg/kg/day acenaphthene or dibenz[a,h]anthracene, 180 mg/kg/day anthracene or phenanthracene, or 437 mg/kg/day pyrene produced no increase in the liver-to-body-weight ratio. Rats that were fed a diet containing 514 mg/kg/day chrysene exhibited equivocal results: in one trial, a significant increase in liver weight gain was noted, while in another trial, no increase in. liver-to-body-weight ratio was observed (Gershbein 1975). Thus, both suspected carcinogenic and noncarcinogenic PAHs can affect liver weights, although much higher doses are required for noncarcinogenic PAHs. The livers of rats administered single doses of ,fluorene by gavage in dimethyl sulfoxide (DMSO) were evaluated for the promotion of growth (i.e., cell proliferation as determined by organ weight and mitotic index) (Danz et al. 1991). The authors claimed that liver weight was increased in a dose-dependent manner to 20% over control values, and that the mitotic index of the hepatocytes was increased by 6-fold after 48 hours. However, the organ weight data were not presented, and the mitotic index data presented graphically in the text do not indicate a 6-fold increase over controls.

Ah-responsive strains of mice (C57BL/6, C3H/HeN, BALB/cAnN) that were orally administered 120 mg benzo[a]pyrene/kg/day in their diet for 180 days exhibited a 13% increase in relative liver weights (Robinson et al. 1975).

The hepatic effects observed in animals following oral exposure to PAHs are generally not considered serious. However, the enzyme alterations, gamma-GT foci induction, liver regeneration, and increased liver weight may precede the onset of more serious hepatic effects.

Renal Effects. The kidney microsomal carboxylesterase activity of rats was moderately induced by 50-150 mg/kg of benzo[a]pyrene following 4 days of intragastric administration; however, rats administered 100 mg/kg/day of anthracene or phenanthrene and 50-150 mg/kg benz[a]anthracene did not exhibit increased activity. The authors conclude that anthracene, phenanthrene, and benz[a]anthracene are not inducers of kidney carboxylesterase activity (Nousiainen et al. 1984). Enzyme induction is considered an adverse effect when observed concurrently with more serious effects such as impaired renal function and/or histopathological changes of the kidney.

Increasing dietary doses of pyrene ranging from 1,000 mg/kg food (127 mg/kg/day) up to 25,000 mg/kg food (917 mg/kg/day) for a mean dose of 426.6 mg/kg/day over a 25-day study produced dilation of the renal tubules in an unspecified number of mice. This effect was not observed until the highest dose was administered (Rigdon and Giannukos 1964). The limitations of this study (e.g., doses changed throughout exposure period and no statistical analyses performed) render these results of questionable toxicological significance.

Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of renal toxicity were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene (EPA 1989d). Increased absolute and relative kidney weight was observed in males, but not females receiving 500 mg/kg/day fluorene for 13 weeks (EPA 1989e). Renal tubular regeneration, and interstitial lymphocytic infiltrates and/or fibrosis were observed after 13-week oral administration of fluoranthene to female mice at 250 mg/kg/day, and male mice at 500 mg/kg/day (EPA 1988e).

Endocrine Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of endocrine imbalance were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Dermal Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of derrnal effects were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings

were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Ocular Effects. Male and female mice were exposed to 0, 17.5, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No signs of ocular toxicity were seen during life for any dose group, and no gross or microscopic damage was seen upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene (EPA 1988e, 1989d, 1989e).

Body Weight Effects. Male and female mice were exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). No adverse effects on body weight were seen during life or upon necropsy. Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene (EPA 1988e, 1989d). After administration of 500 mg/kg/day fluorene for 13 weeks; however, female mice exhibited increased body weight, although male mice showed no effect at the same dose level (EPA 1989e).

Other Systemic Effects. The number of thymic glucocorticoid receptors in 6-week-old rats treated once with 2 mg/kg benzo[a]pyrene was measured (Csaba et al. 1991). It is assumed that administration was by oral gavage, but this was never explicitly stated. The number of these receptors was decreased by 40% in females and unaffected in males relative to the vehicle control animals. The statistical significance of these effects was not indicated, nor was the functional consequences of a decrease in receptor number assessed by examination of functional parameters.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to any of the 17 PAHs discussed in this profile.

A single gavage dose of 150 mg/kg fluorene to male Sprague-Dawley rats had no effect on thymus or spleen weight (Danz and Brauer 1988). Little useful information can be obtained from this study as only one dose was tested (thereby precluding assessment of the validity of the negative response) and no tests of immune function were evaluated. Male and female mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no effect of treatment on splenic weight

or histopathology (EPA 1989c). Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene (EPA 1988e, 1989d). After administration of 2.50 mg/kg/day fluorene for 13 weeks, however, increased absolute and relative spleen weight was seen in both sexes (EPA 1989e).

Lee and Strickland (1993) looked for antibodies specific to PAH-DNA adducts in the serum of BALB/c mice treated orally twice per week for 8 weeks with 0.5 or 5 mg/kg benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, chrysene, dibenz[a,h]anthracene, or fluoranthene. Increased antibody response was noted in animals treated with the low dose of benz[a]anthracene and benzo[b]fluoranthene, but not any of the other PAHs.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to any of the 17 PAHs discussed in this profile.

Male and female mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no effect of treatment on behavior, or histopathologic effects on nerve or brain samples (EPA 1989c). Similar findings were reported after 13-week administration of 1,000 mg/kg/day anthracene, and 500 mg/kg/day fluoranthene (EPA 1988e, 1989d). After administration of 500 mg/kg/day fluorene for 13 weeks, however, increased brain weight was observed in females, but not in males (EPA 1989e). No histopathologic changes were observed.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to the PAHs discussed in this profile. Three animal studies were located that evaluated the reproductive effects of benzo[a]pyrene in animals. The results of two oral studies in mice (Mackenzie and Angevine 1981; Rigdon and Neal 1965) and one in rats (Rigdon and Rennels 1964) indicate that benzo[a]pyrene induces reproductive toxicity in animals. The incidence and severity of these effects depends on the strain, method of administration, and dose levels used. In one study, benzo[a]pyrene administered by gavage to pregnant CD-l mice decreased the percentage of pregnant females that reached parturition and produced a high incidence of sterility in the progeny (Mackenzie and Angevine 1981). In

contrast, benzo[a]pyrene administered in the diet caused no adverse effects on fertility of Swiss mice (Rigdon and Neal 1965) but reduced the incidence of pregnancy in female rats (Rigdon and Rennels 1964). Based on these studies, the LOAEL for benzo[a]pyrene-induced reproductive toxicity in parental mice was 160 mg/kg/day, and the LOAEL for these effects in the progeny of exposed animals was 10 mg/kg/day (Mackenzie and Angevine 1981). Because only the parental doses are quantifiable, these are the only data presented in Table 2-2.

When CD-l mice were administered benzo[a]pyrene by gavage daily for 10 days during gestation, there was a significant reduction in the percentage of pregnant females to reach parturition at 160 mg/kg/day, the highest dose tested (Mackenzie and Angevine 1981). When F_1 progeny were bred with untreated animals, the fertility index decreased significantly in all treatment groups. At 10 mg/kg/day, the lowest dose tested, the reduced fertility noted was associated with significant alterations in gonadal morphology and germ cell development. The treatment at higher doses resulted in total sterility. Contrary to these results, no adverse effects on reproduction were observed in Swiss mice fed benzo[a]pyrene in the diet at ≤133 mg/kg/day over varying time spans during mating, gestation, and parturition (Rigdon and Neal 1965). The apparent discrepancy in the results of the two studies may be attributable to the method of benzo[a]pyrene administration and metabolic differences in the two strains of mice used.

Dietary administration of benzo[a]pyrene for 28 days revealed no treatment-related effects on the estrous cycle of female rats. These rats experienced no significant adverse effects on their fertility when bred to untreated male rats (Rigdon and Rennels 1964). In another series of experiments, when benzo[a]pyrene-fed male and female rats were bred, only two of seven females became pregnant (as compared to 3 of 6 controls); the offspring of one rat were stillborn while those of others were resorbed (Rigdon and Rennels 1964). Although the data suggest that benzo[a]pyrene may induce reproductive toxicity in rats, they are inconclusive because of the use of a single dose level, small number of animals, and inadequate reporting of data.

Male mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no effect of treatment on reproductive organ weight or histology (EPA 1989c). Female mice, however, exhibited decreased ovary weights correlated with an increase of inactivity of the ovary and uterus (EPA 1989c). No adverse effects on reproductive organs were reported after 13-week

administration of 1,000 mg/kg/day anthracene, 500 mg/kg/day fluoranthene, or 500 mg/kg/day fluorene to male and female mice (EPA 1988e, 1989d, 1989e).

The available information from animal studies suggests that benzo[a]pyrene may have the potential to produce adverse reproductive effects in exposed humans. The highest NOAEL and all LOAEL values from each reliable study for reproductive effects following acute- and intermediate-duration exposures are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to PAHs. Three animal studies were reviewed that assessed developmental effects of benzo[a]pyrene in inbred strains of rats and mice. The data from these studies indicate that prenatal exposure to benzo[a]pyrene produced reduced mean pup weight during postnatal development and caused a high incidence of sterility in the F_1 progeny of mice (Mackenzie and Angevine 1981). Using Ah-responsive and Ah-nonresponsive strains of mice, the increased incidences of stillboms, resorptions, and malformations observed correlated with the maternal and/or embryonal genotype (Legraverend et al. 1984). In another study, negative results were obtained when benzo[a]pyrene was administered to Swiss (responsive) mice (Rigdon and Neal 1965).

Benzo[a]pyrene was administered by gavage to pregnant CD-l mice during gestation at doses of 10, 40, and 160 mg/kg/day. The viability of litters at parturition was significantly reduced in the highest dose group (Mackenzie and Angevine 1981). The mean pup weight was significantly reduced in all treatment groups by 42 days of age. The F_1 progeny that were exposed prenatally to benzo[a]pyrene (10, 40, and 160 mg/kg/day) were bred with untreated animals and further studied for postnatal development and reproductive function. The F_1 progeny from the 10-mg/kg/day group experienced decreased fertility with associated alterations in gonadal morphology and germ-cell development. Because only the parental doses are quantifiable, these are the only data presented in Table 2-2. Therefore, the LOAEL of 10 mg/kg/day noted in the F_1 progeny discussed above is not presented in Table 2-2. Higher doses produced total sterility. This study provides good evidence for the occurrence of developmental effects following *in utero* exposure to benzo[a]pyrene.

The effect of genetic differences in metabolism of orally administered benzo[a]pyrene on *in utero* toxicity and teratogenicity was evaluated in mice that either metabolize benzo[a]pyrene readily (Ah-responsive) or not (Ah-nonresponsive) (Legraverend et al. 1984). Pregnant mice, either B6AKFl (Ah-responsive) or AKR/J (Ah-nonresponsive), were fasted prior to a diet containing 120 mg/kg/day benzo[a]pyrene on days 2-10 of gestation. The mice were killed on day 18 of gestation. On day 16 of gestation, intraperitoneal injections of napthoflavone were administered to distinguish between fetuses with different Ah-genotypes (Ahb/Ahd and Ahd/Ahd). Oral administration of benzo[a]pyrene to the pregnant AKR/J mice (non-responsive) caused more stillbirths, decreased weight gain, resorptions, and birth defects among Ahd/Ahd (Ah-nonresponsive) than among Ahb/Ahd (Ah-responsive) embryos. However, no differences in *in utero* toxicity or teratogenicity were observed in Ah-genetically different embryos (Ahd/Ahd and Ahb/Ahd) of B6AKFl mothers (responsive). The authors concluded that differences in *in utero* toxicity and teratogenicity are specific to the route of administration and can be attributed to “first pass” liver metabolism occurring with oral dosing. They also concluded that *in utero* toxicity and teratogenicity are directly related to the maternal and/or embryonal genotype controlled by the Ah-locus; that is, both maternal metabolism as well as target organ metabolism (embryo/fetus) were important in determining susceptibility to developmental toxicity. Specifically, metabolism by a responsive mother reduces *in utero* toxic effects in the fetus. Similarly, responsive fetuses in the uterus of a non-responsive mother show fewer *in utero* toxic effects. Non-responsive fetuses in the uterus of a non-responsive mother show the highest incidence of *in utero* toxic effects. Although the study emphasizes the importance of administrative route in benzo[a]pyrene metabolism and resulting toxicity, it had the following limitations: 1) only one dose was evaluated; 2) no quantitative comparisons between treated groups and corresponding control animals were presented for any of the reported *in utero* toxicity or teratogenic effects; 3) small sample size; 4) purity of benzo[a]pyrene was not specified.

In another study, negative results were obtained when the potential developmental effects of benzo[a]pyrene were studied in mice (Rigdon and Neal 1965). Dietary administration of this chemical to mice at concentrations equivalent to 33.3, 66.7, or 133.3 mg/kg/day at various times before and after mating elicited no adverse effects on the developing embryos. Maternal weight gain was reduced in the mice administered the higher levels of benzo[a]pyrene, but this effect was reversed when the animals were changed to the control ration. Limitations of this study that preclude its inclusion in Table 2-2 consist of the use of an inconsistent protocol, varying number of animals, and varying time of gestation exposure.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in mice for acute-duration exposure is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to any of the 17 PAHs discussed in this profile.

Pregnant *Erythrocebus patas* monkeys were treated once on gestation day (Gd) 50, 100, or 150 (term = 160 days) with 5-50 mg/kg benzo[a]pyrene (Lu et al. 1993). Fetuses were removed by Cesarean section l-50 days after treatment and fetal organs, placentae, and maternal livers were assayed for DNA adducts. Benzo[a]pyrene-DNA adducts were high in fetal organs, placentae, and maternal livers in all three trimesters of gestation. Adduct levels were higher in mid-gestation compared to early or late gestation. dG-N2-BPDE was the major adduct detected. The adduct levels in fetal tissues increased with benzo[a]pyrene dose, but at a much lower rate that placentae or maternal livers. Preference in binding to DNA of various fetal tissues was more apparent in early gestation compared to late gestation, and at lower doses compared to higher doses. During early gestation and at lower doses, benzo[a]pyrene produced a similar level of DNA binding in fetal lung, liver, maternal liver, and placenta. Individual fetal organ adduct levels correlated significantly with placental adduct levels, indicating placental and/or maternal contribution to adduct formation in fetuses. Evidence of fetal contribution to adduct formation was also found. DNA adduct levels in fetal skin were lowest of all fetal organs tested and less affected by gestational stage at time of treatment. In contrast, DNA adduct levels in fetal liver exhibited distinct gestation stage specificity with higher adduct, levels attained during mid-gestation compared to other stages of gestation. Adduct levels decreased at a much faster rate during the first 10-15 days compared to 15-50 days after treatment. However, 10% of the DNA adducts persisted 50 days after treatment in all organs studied. Together, the results suggest that placental adduction accurately indicates fetal exposure.

Male B6C3F_1 mice were fed 0, 0.325, 0.1825, 1.625, 3.25, or 6.5 mg/kg/day benzo[a]pyrene for 21 days (Culp and Beland 1994). Animals were killed and the liver, lung, and forestomach DNA extracted and analyzed for benzo[a]pyrene-DNA adducts. The major adduct, dG-N2-BPDE, was quantified. Adduct levels in liver and lung increased in a linear manner. Adduct levels in the forestomach appeared to plateau at the highest dose. At doses below the highest, adduct levels were in

the order of forestomach > liver > lung, with the values of average slopes being 3.0 + 0.59, 2.1 + 0.17, 1.3 + 0.37 fmol adduct/mg DNA/μg benzo[a]pyrene/day, respectively. At these doses, the lung and the forestomach were not significantly different. At the high dose, liver > forestomach > lung, and each tissue was significantly different from the other.

DNA binding of coal tar components in male mice was investigated following the ingestion of coal tar obtained from a manufactured coal plant (Weyand et al. 1991). One of four different samples (A-D) of coal tar or a mixture of four equal portions of the four samples was administered in a gel diet which contained 0.25% coal tar. The coal tar contained phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, and benzo[g,h,i]perylene, among other PAHs. In addition, a diet containing benzo[a]pyrene at the same level as the 0.25% diet prepared with Sample C was administered; animals consuming this diet ingested 0.01-0.02 mg benzo[a]pyrene per day. The diets were administered for 15 days. Chemical-DNA adduct formation was evaluated in animals following 14 days of treatment. Chemical-DNA adduct formation was also evaluated in animals maintained on a 0.1, 0.2, 0.5, and 1.0% coal tar diet prepared with one of the coal tar samples (C). Chemical-DNA adduct formation in animals dosed with 0.l-1.0% Sample C indicated a dose-related effect in lung DNA adduct formation, but no dose-related effect was observed for forestomach tissue. In addition, overall adduct levels in lung tissue were considerably higher than forestomach levels for animals on the 0.5 or 1% diet. In contrast, adduct levels were highest in the forestomach of animals on diets lower in coal tar content (0.1 or 0.2%). Chemical-DNA adducts of coal tar components evaluated for Samples A-D and the mixture of the four coal tar samples at 0.25% in the diet administered for 15 days indicated adducts in the lung, liver, and spleen of all animals. Adduct patterns were similar, but quantitative differences were observed between coal tar samples and tissue sites. The highest adduct levels were detected in lung DNA. Adduct formation in animals fed the benzo[a]pyrene diet, could not account for the differences in the adduct levels observed in animals given the mixtures. Also, adduct formation in animals fed the coal tar mixtures correlated with benzo[a]pyrene content in the coal tar, indicating the adducts arose from a variety of PAHs in the coal tar mixtures. The levels of 1-hydroxypyrene in the urine of these animals correlated with the pyrene content of these coal tars.

The DNA binding of manufactured gas plant residue (MGP) components in male B6C3Fl mice was investigated following oral administration (Weyand and Wu 1994). Male mice were fed a gel diet containing manufactured gas plant (MGP) residue (coal tar) at 0.3% for 28 days, or the corresponding

control diet. Two mixtures of MGP residue were used: Mix of 3 combining equal amounts of samples from three different MGP plant sites, and Mix of 7 combining equal amounts of samples from seven different MGP plant sites, including those used in the Mix of 3. The mixtures contained pyrene, benz[a]anthracene, chrysene, benzo[b]fluorene, benzo[k]fluorene, benzo[a]pyrene, indeno[l,2,3-cd] pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene. Data was presented in terms of pyrene consumed. Animals were sacrificed on the twenty-ninth day and lung and forestomach were excised and DNA isolated. Chemical-DNA adduct formation was evaluated. Ingestion of the adulterated diets resulted in a relatively low level of DNA adducts in the forestomach in comparison with the lung (one-tenth the level). PAH-DNA adduct levels in the lung of mice maintained on the Mix of 3 (1.4 mg/kg/day pyrene) were two times greater than the level induced by the Mix of 7 (1.2 mg/kg/day pyrene) suggesting that the composition of the MGP residue may have influence PAH absorption or DNA adduct formation.

Oral exposure to a total dose of 10 mg/kg benzo[a]pyrene produced gene mutations in the mouse coat color spot test (Davidson and Dawson 1976, 1977). Dose-related increases in the frequency of micronuclei were seen in bone marrow cells harvested from MS/Ae and CD-l male mice (four mice/strain/dose) 48 hours after administration of a single oral dose of benzo[a]pyrene ranging from 62.5 to 500 mg/kg (Awogi and Sato 1989). Although the response appeared to be stronger in the MS/Ae strain, the reduction in polychromatic erythrocytes, indicative of target cell toxicity at all levels in the CD-1 strain, limited the comparative evaluation of strain specificity.

In another study, a dose of benzo[a]pyrene (150 mg/kg) known to induce a clastogenic response was orally administered to groups of five adult males and females, pregnant females, and fetal ICR mice. An increased incidence of micronuclei in bone marrow cells harvested from the various groups of adult animals and also in the livers of the fetuses was observed (Harper et al. 1989). Genetic damage was most severe in the fetuses. The approximately 7-fold increase in micronuclei in fetal livers as compared to maternal bone marrow suggests that the transplacentally-induced genotoxicity was probably associated with the immature detoxification processes of fetal liver as compared to adult bone marrow. It would, nevertheless, appear that the fetus may be at an increased risk.

Data showing that orally administered benzo[a]pyrene induces micronuclei were confirmed in subsequent studies (Shimada et al. 1990, 1992) using rats (Sprague-Dawley) and mice (CD-l and BDF_1), different dosing regimes (single, double, or triple doses), and different target cells (bone

marrow and peripheral blood reticulocytes). A single oral gavage dose of 63 mg/kg benzo[a]pyrene significantly ($p<0.0l$) increased the yield of chromosomes with abnormal morphology in bone marrow cells collected from hybrid $lC3F_1$ male mice (Adler and Ingwersen 1989).

There is conflicting evidence that the genetic damage induced by benzo[a]pyrene is partially controlled by the expression of structural genes for benzo[a]pyrene-specific cytochromes P-450. In one study, two inbred strains of mice differing in AHH inducibility (AHH-inducible strain C57BL/6 and AHH-noninducible strain DBA/2) received two consecutive daily doses of either 10 or 100 mg/kg of the test material (Wielgosz et al. 1991). Animals were sacrificed 5 days postexposure, and bone marrow and spleen cells were examined for sister chromatid exchange and DNA adducts. Results showed a marked increase in sister chromatid exchange induction and the formation of DNA adducts in bone marrow and spleen cells recovered from the DBA/2 mice (AHH-noninducible) in both dose groups compared to the C57BL/6 (AHH-inducible) mice. However, no clear correlation between AHH inducibility and the positive clastogenic response induced by 150 mg/kg benzo[a]pyrene was found in adult male and female mice with genetically determined differences in AHH induction (Adler et al. 1989). Similarly, the transplacental exposure of 11-day-old homozygous and hybrid embryos (dams received a single oral gavage dose of 150 mg/kg and embryos were sampled 15 hours after treatment) to benzo[a]pyrene showed that the clastogenic response was independent of genetic constitution.

In contrast to the relatively uniform evidence that benzo[a]pyrene is a genotoxin in whole animals, the test material failed to induce unscheduled DNA synthesis (UDS) in the parenchymal liver cells of Brown Norway rats exposed by oral gavage to 12.5 mg/mL (Mullaart et al. 1989). There was, however, a clear increase in single-strand DNA breaks in cells from the two major centers of metabolism (the parenchymal liver and intestinal cells) of the treated animals that was not apparent in the nonparenchymal liver cells.

Significant ($p<0.05$), but marginal, increases in the frequency of abnormal sperm were found in CD-l mice (8-12/group) exposed via oral gavage to benzo[a]pyrene doses ranging from 360 to 432 mg/kg (Salamone et al. 1988). The effect, however, was not clearly dose related, and the wide variation in the background frequency rendered the data inconclusive. Comparable doses produced no adverse effects in $B6C3F_1$ mice. Similarly, the evaluation of pyrene (241-844 mg/kg) in this study yielded uniformly negative results.

Orally administered fluoranthene (400 and 750 mg/kg) did not increase the sister chromatid exchange frequency in mice (Palitti et al. 1986). Gene mutations were not produced in bacteria or yeast in a host-mediated assay in which anthracene, benzo[a]pyrene, chrysene, or fluoranthene were administered to mice by gavage; positive results were produced in bacteria in the same test system in which mice were exposed to benz[a]anthracene and injected intraperitoneally with the bacteria (Simmon et al. 1979). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to the 17 PAHs discussed in this profile. The animal studies discussed in this section are presented first by exposure duration (acute, intermediate, and chronic), and within each duration category the information on individual PAHs is discussed in alphabetical order. PAHs for which no information was available for specified exposure durations were omitted.

Acute-Duration Exposure. Mice acutely administered 1.5 mg/day benz[a]anthracene by oral gavage two times over 3 days exhibited increased incidences of hepatomas and pulmonary adenomas (80% and 85%, respectively) as compared to control incidences (10% and 30% for hepatomas and pulmonary adenomas, respectively) after 568 days of observation (Klein] 1963). No malignant tumors were observed in this study.

Mice fed benzo[a]pyrene in the diet at a concentration equivalent to 33.3 mg/kg/day exhibited forestomach neoplasms following 2 or more days of consumption. However, a lower concentration of benzo[a]pyrene (equivalent to 13.3 mg/kg/day) administered for up to 7 days did not produce forestomach tumors (Neal and Rigdon 1967) (see Table 2-2). Hamsters have also been observed to develop papillomas and carcinomas of the alimentary tract in response to gavage or dietary exposure to benzo[a]pyrene (Chu and Malmgren 1965). A 77% mammary tumor incidence was observed 90 weeks after a single oral dose of 50 mg benzo[a]pyrene (100 mg/kg) was administered to rats, as compared to a 30% incidence in untreated animals (McCormick et al. 1981).

A single dose of 0.05 mg/kg dibenz[a,h]anthracene in polyethylene glycol (PEG)-400 failed to induce tumors in male Swiss mice after 30 weeks. However, forestomach papillomas were found in 10% of mice administered a single dose of 0.05 mg/kg dibenz[a,h]anthracene followed by 30 weekly doses of

PEG alone, and in 21% of the mice when the dibenz[a,h]anthracene dose was followed by 30 weekly doses of PEG plus 3% croton oil (Berenblum and Haran 1955). Treatment with croton oil alone yielded a 14-16% tumor incidence. These results suggest that the carcinogenic activities of croton oil and dibenz[a,h]anthracene are additive in the mouse forestomach.

Intermediate-Duration Exposure. One intermediate-duration study was located that evaluated the carcinogenic potential of acenaphthene. Male and female mice exposed to 0, 175, 350, or 700 mg/kg/day acenaphthene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1989c).

Similarly, only one intermediate-duration study was located that evaluated the carcinogenic potential of anthracene. Male and female mice exposed to 0, 250, 500, 1,000 mg/kg/day anthracene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1989d).

One intermediate-duration study was located that evaluated the carcinogenic potential of benz[a]anthracene. Mice that received intermittent gavage doses of 1.5 mg/kg/day benz[a]anthracene for 5 weeks (Klein 1963). Mice were sacrificed at a median age of 437 or 547 days. The treated mice killed at 437 days exhibited a 95% incidence of pulmonary adenomas at an average of 3 per lung and a 46% incidence of hepatomas, with an average of 2.1 per tumor-bearer. Forestomach papillomas were found in 5% of the mice. Control animals killed after 441 days exhibited a 10% incidence of pulmonary adenomas. Treated mice sacrificed after 547 days exhibited a 95% pulmonary adenoma incidence, as was observed in the group sacrificed earlier, but an increased hepatoma incidence of 100%. Control animals sacrificed after 600 days had 30 and 10% incidences of pulmonary adenomas and hepatomas, respectively. This study was not adequately reported; it did not include complete histopathology, adequate treatment durations, large enough sample sizes, or statistical analysis. Although this study is inconclusive because of methodological limitations, it does provide some qualitative evidence for the potential carcinogenicity of benz[a]anthracene by the oral route.

Intragastric doses of 67-100 mg/kg benzo[a]pyrene have been shown to elicit pulmonary adenomas and forestomach papillomas in mice (Sparnins et al. 1986; Wattenberg and Leong 1970). Intermittent gavage exposure of mice to 67-100 mg/kg benzo[a]pyrene resulted in increased forestomach (100%) and pulmonary tumor incidences relative to controls at 30 weeks of age (Sparnins et al. 1986;

Wattenberg and Leong 1970). The study by Wattenberg and Leong (1970) involved gavage administration of approximately 1.0 mg of benzo[a]pyrene once a week for 8 weeks.

The incidence of forestomach tumors (papillomas and carcinomas) in mice was related to the duration of oral exposure to benzo[a]pyrene following intermediate-duration administration of dietary benzo[a]pyrene at various doses up to 250 ppm (33.3 mg/kg/day) for 30-197 days (Neal and Rigdon 1967, see Table 2-2). The tumor incidence also increased with increasing dose. In the same study, mice fed 250 ppm (33 mg/kg/day) for periods of 1-7 days exhibited increased forestomach tumor incidences following 2 or more days of benzo[a]pyrene exposure (total dose of 2 mg), while mice fed 10 ppm (13.3 mg/kg/day) for 110 days (total dose of 4.48 mg) did not develop tumors. The authors suggest that these findings provide evidence that there are no cumulative carcinogenic effects of benzo[a]pyrene or its metabolites in mice. These data suggest that differences in susceptibility may be strongly influenced by the age of the mice at the time that they were initially exposed. This study provides the best dose-response information available for the oral route of exposure despite the irregular protocol employed, although the relevance of forestomach tumors in rodents to human cancer is the subject of some controversy because humans lack a forestomach.

An association between dietary benzo[a]pyrene and the development of leukemia and tumors of the forestomach and lung has been observed in mice. Tumor incidence was related to both dose and length of exposure (except in the case of leukemia). Mice administered dietary doses of up to 1,000 ppm (up to 133 mg/kg/day) for intermediate lengths of time (23-238 days) exhibited an increased incidence of forestomach tumors (papillomas and carcinomas) (Rigdon and Neal 1966, 1969) (see Table 2-2). Mice administered 250 ppm (33.3 mg/kg/day) benzo[a]pyrene developed papillomas or carcinomas of the forestomach (64%) and all the mice in the 1,000-ppm (133 mg/kg/day) group exhibited forestomach tumors after 86 days of benzo[a]pyrene consumption. A similar relationship was observed for the incidence of lung tumors: mice fed 250 ppm (33.3 mg/kg/day) benzo[a]pyrene exhibited an increased lung adenoma incidence. The occurrence of leukemia was related to the ingestion of 250 ppm (33.3 mg/kg/day) benzo[a]pyrene; 37% of the treated mice developed leukemias (Rigdon and Neal 1969) (see Table 2-2). The lack of consistent protocol in these experiments and the short exposure duration and observation periods preclude the assessment of a dose-response relationship. Furthermore, because tumors were reported as combined papillomas and carcinomas, no distinction between these benign and malignant tumors can be made.

Mammary tumors have also been observed following intermediate-duration exposure to benzo[a]pyrene in rats. Eight weekly oral doses of 6.25 mg benzo[a]pyrene (12.5 mg/kg) administered to rats resulted in a 67% increase in the incidence of mammary tumors in female rats after 90 weeks of observation (McCormick et al. 1981). A 30% incidence of these tumors was observed in the control animals.

Two intermediate-duration studies investigated the carcinogenicity of dibenz[a,h]anthracene in animals following oral exposure. Mammary carcinomas were observed in 5% of the female BALB/c mice dosed with 0.5% dibenz[a,h]anthracene after 15 weeks of dosing; however, no control group was included (Biancifiori and Caschera 1962). In the other study, male and female rats were administered an emulsion of aqueous olive oil and dibenz[a,h]anthracene in place of their drinking water for up to 200 days (Snell and Stewart 1963). Pulmonary adenomatosis, alveologenic carcinoma, mammary carcinoma, and hemangioendotheliomas were observed in the treated rats. These tumors were not observed in the control animals. However, extensive dehydration and emaciation occurred because the animals did not tolerate the vehicle well, which lead to early death and the need to periodically remove the animals from the treatment vehicle. Neither of these studies was adequately reported: they did not perform appropriate histopathologic evaluations, treatment or study durations were inadequate, and the sample size was inadequate. Despite these methodological limitations, these studies do provide some evidence of dibenz[a,h]anthracene's carcinogenicity by the oral route.

One intermediate-duration study was located that evaluated the carcinogenic potential of fluoranthene. Male and female mice exposed to 0, 125, 250, or 500 mg/kg/day fluoranthene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1988e).

Similarly, only one intermediate-duration study was located that evaluated the carcinogenic potential of fluorene. Male and female mice exposed to 0, 125, 250, or 500 mg/kg/day fluorene by gavage for 13 weeks showed no evidence of tumorigenesis at necropsy (EPA 1989e).

Chronic-Duration Exposure. Benzo[a]pyrene was administered in the diet of 32 Sprague-Dawley rats/sex/group either every 9th day or 5 times/week at a dose of 0.15 mg/kg until the animals were either moribund or dead (Brune et al. 1981). An untreated control group consisted of 32 animals/sex. There was no treatment-related effect on survival and no treatment-related increase in tumors at any one site. However, a statistically significant increase in the proportion of animals with tumors of the forestomach, esophagus, and larynx combined was noted among animals receiving treatment

5 times/week (the combined incidence of animals with these tumors was 3/64, 10/64, and 3/64 in the controls, the group fed benzo[a]pyrene 5 times/week, and the group fed benzo[a]pyrene every 9th day). In the same study, groups of 32 Sprague-Dawley rats/sex were administered 0.15 mg/kg benzo[a]pyrene by gavage in a 1.5% caffeine solution either every 9th day (Group 3), every 3rd day (Group 2), or 5 times/week (Group 1) until the animals were moribund or dead, resulting in average annual doses of 6, 18, or 39 mg/kg, respectively. Survival was adversely affected only in Group 3 (mean survival.time = 87 weeks versus 102 weeks in the controls). Treatment with benzo[a]pyrene significantly increased the proportion of animals with tumors of the forestomach, esophagus, and larynx (the combined tumor incidence was 3/64, 6/64, 13/64, 2664, and 14/64 for the untreated controls, the gavage controls, and Groups 3, 2, and 1, respectively).

Summary. These results indicate that benz[a]anthracene, benzo[a]pyrene, dibenz[a,h]anthracene, and possibly other PAHs are carcinogenic to rodents following oral exposure at high doses.

All reliable CELs in mice for acute- and intermediate-duration exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to the 17 PAHs discussed in this profile.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to any of the 17 PAHs discussed in this profile. Other systemic effects observed after dermal exposure are discussed below.

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

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious		Serious	
ACUTE EXPOSURE							
Systemic							
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 anthracene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.001 M mg/c m2	0.005 M mg/cm 2	(induction of melanocytes)	0.025 M (substantial melanocytes)	Iwata et al. 1981 benzo[a]pyrene
Mouse (C34/HeN)	5 d 2 x/5d	Dermal		120 mg F	(contact hypersensitivity)		Klemme et al. 1987 benzo[a]pyrene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal		0.0125 M mg/cm 2	(slight increase melanocytes)		Iwata et al. 1981 chrysene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 fluoranthene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 fluorene
Mouse (C57BL/6)	1-2 d 1 x/d	Dermal	0.05 M mg/c m2				Iwata et al. 1981 pyrene
Immunological/Lymphoreticular							
Mouse (C34/HeN)	5 d 2 x/5d			120 F	(contact hypersensitivity)		Klemme et al. 1987 benzo[a]pyrene

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
Cancer						
Mouse (CD-1)	20 d 10 x				10.1µg F [CEL: 35% (7/20) tumor incidence]	Weyand et al. 1993b benzo[b]fluoranthene
INTERMEDIATE EXPOSURE						
Immunological/Lymphoreticular						
Gn pig (Hartley)	2-3 wk 2 x			0.001% F (slight contact sensitivity)	1.0% F (contact sensitivity)	Old et al. 1963 benzo[a]pyrene
Cancer						
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M (CEL: 1/13 (8%) had a papilloma with coadministration of 0.0005 mg BaP)	Warshawshy et al. 1993 anthracene
Mouse (CD-1)	1 d 1 x/d, then 25 wk 3 d/wk (TPA)		0.09 F mg/kg		0.57 F mg/kg (CEL: 36% skin tumor incidence)	Levin et al. 1984 benz[a]anthracene
Mouse (SENCAR)	once then 23 wk 2 d/wk (TPA)				0.2 mg F (CEL: 6 papillomas/mouse)	Cavalieri et al. 1988b benzo[a]pyrene
Mouse (Swiss)	20 wk 2 x/wk 1 x/d				0.025 F mg (CEL: tumors in 90%)	Cavalieri et al. 1988b benzo[a]pyrene

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious	Serious		
Mouse (Crl:CD-1)	20 d every other day				0.01 mg F	(CEL: 35% developed skin tumors)	LaVoie et al. 1993a benzo[b]fluoranthene
Mouse (CD-1)	20 d every other day				0.006 mg F	(CEL: 5% developed skin tumors)	LaVoie et al. 1993b benzo[j]fluoranthene
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/15 (7%) had a papilloma from chrysene alone; 3/13 (23%) having papillomas or malignancies with coadministration of 0.0005 mg BaP)	Warshawshy et al. 1993 chrysene
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/12 (8%) had papillomas with coadministration of 0.0005 mg BaP)	Warshawsky et al. 1993 fluoranthene
Mouse (CD-1)	20 d 1 x/2d, then 22 wks (TPA)				100 mg F	(CEL: 80% incidnece of tumors)	Rice et al. 1985a indeno(1,2,3-c,d)pyr
Mouse (Swiss)	12 mo 3 x/wk		50 F		100 µg F	(CEL: 6/20 had papillomas, 3/20 had carcinomas)	indeno(1,2,3-cd)pyre

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious	Serious		
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 3/13 (23%) had a tumor (papillomas and malignant) from the mixture alone; 8/17 (47%) with coadministration of 0.0005 mg BaP)	Warshawsky et al. 1993 mix
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/12 (8%) had papillomas from phenanthrene alone; 1/17 (6%) had a malignant tumor with coadministration of 0.0005 mg BaP)	Warshawsky et al. 1993 phenanthrene
Mouse (C3H/HeJ)	6 mo 2 x/wk				0.05 mg M	(CEL: 1/13 (8%) had a papillomas from pyrene alone)	Warshawsky et al. 1993 pyrene
CHRONIC EXPOSURE							
Cancer							
Mouse (NMRI)	17-22 mo 2 d/wk 1 x/d				2 mg F	(CEL: 45% developed skin tumors)	Habs et al. 1984 benzo[a]pyrene
Mouse (C3H/HrJ)	99 wk 2 d/wk 1 x/d				12.5 µg M	(CEL: malignant tumors in 47/50)	Warshawsky and Barkley 1987 benzo[a]pyrene
Mouse (Swiss)	lifetime 3 d/wk 1 x/d				0.01% F	(CEL: papillomas in 5%)	Wynder and Hoffmann 1959b benzo[b]fluoranthene

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Mouse (NMRI)	19-20 mo 2 d/wk 1 x/d				15 µg F (CEL: skin carcinomas in 1/20)	Habs et al. 1984 mix

BaP = benzo(a)pyrene; CEL = cancer effect level; d = day(s); F = female; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; TPA = tetradecanoyl phorbol acetate; wk = week(s); x = time(s)

Dermal Effects. Mixtures of carcinogenic PAHs cause skin disorders in humans and animals; however, specific effects in humans of individual PAHs, except for benzo[a]pyrene, have not been reported. Mixtures of PAHs are also used to treat some skin disorders in humans. From these patients comes much of the data describing dermal effects of PAH exposure.

Regressive verrucae (i.e., warts) was reported following up to 120 dermal applications of 1% benzo[a]pyrene in benzene to human skin over 4 months (Cottini and Mazzone 1939). Although reversible and apparently benign, the changes were thought to represent neoplastic proliferation.

Adverse dermal effects have been noted in humans following intermediate-duration dermal exposure to benzo[a]pyrene in patients with the preexisting dermal conditions of pemphigus vulgaris (acute or chronic disease characterized by occurrence of successive crops of blisters) and xeroderma pigmentosum (a rare disease of the skin marked by disseminated pigment discolorations, ulcers, and cutaneous and muscular atrophy) (Cottini and Mazzone 1939). A 1% benzo[a]pyrene solution topically applied to patients with pemphigus resulted in local bullous eruptions characteristic of the disease. Patients with xeroderma pigmentosum exposed to 1% benzo[a]pyrene slightly longer than the pemphigus patients exhibited only pigmentary and slight verrucous effects. Similarly treated patients with preexisting active skin lesions due to squamous cell cancer showed a general improvement and/or retardation of the lesion. The severity of abnormal skin lesions appeared to be related to age; those in the lowest age range exhibited fewer and less-severe effects than those in the mid-range groups. No such age relationship of effects involving those patients with normal or preexisting skin lesions was noted.

Adverse dermal effects have also been ohserved in animals following both acute- and intermediate-duration dermal exposure to various PAHs. For example, acute topical application of benzo[a]pyrene, benz[a]anthracene, or dibenz[a,h]anthracene applied to the shaved backs of Swiss mice were all reported to suppress sebaceous glands (Bock and Mund 1958). However, controls were not employed; therefore, it is not possible to determine if the effects seen were due to the solvent and/or the application procedures.

Benzo[a]pyrene was applied once weekly to the skin of female ICR/Harlan mice (43-50/group) at doses of 16, 32, or 64 μg per application for 29 weeks (Albert et al. 1991b). Cell cycle kinetics and

morphometrics were evaluated. Evidence of epidermal cytotoxicity and death followed by regeneration was seen in animals administered 64 μg benzo[a]pyrene beginning the first weeks of exposure and later in the lower dose groups. This evidence included dose-related epidermal thickening and vertical nuclei stacking, increased mitotic labeling (2-4-fold with increasing dose), increased incidence of pyknotic and dark cells, and a pronounced inflammatory response in the dermis. The increase in cell proliferation was accompanied by only a minor increase in the size of the epidermal cell population, indicating that the proliferation was a regenerative response.

An acute (96-hour) dermal application of anthracene to the backs of hairless mice followed by ultraviolet radiation exposure for 40 minutes resulted in enhanced dermal inflammation compared to mice exposed exclusively to ultraviolet radiation. However, this effect was reversed within 48 hours (Forbes et al. 1976). Anthracene thus potentiates the skin damage elicited by sunlight exposure and may be considered a photosensitizer in hairless mice.

In animals, dermal application of 1% benzo[a]pyrene to the skin of hairless mice resulted in epidermal cell growth alterations (Elgjo 1968). Increases were observed in mitotic rates, mitotic counts, and mitotic duration and the author suggested that these were indicative of a regenerative reaction. However, concurrent controls were not utilized. The authors concluded that the alterations in the kinetics of epidermal cell growth produced by benzo[a]pyrene were more sustained than after application of croton oil. The study is limited for drawing conclusions concerning the dermal toxicity of benzo[a]pyrene because experimental data were compared with historical controls only, no acetone control was evaluated, and the statistical significance of the increased values was not determined.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following dermal exposure to the 17 PAHs discussed in this profile.

Benzo[a]pyrene can elicit an immune response when applied dermally to the skin of animals. In mice, acute application of 120 μg benzo[a]pyrene elicited an allergic contact hypersensitivity in C3H mice that was antigen specific (Klemme et al. 1987). Slight contact hypersensitivity was also observed in guinea pigs following two dermal applications of 0.001% benzo[a]pyrene given over a period of 2-3 weeks. This response was more severe at a dose of 1.0% benzo[a]pyrene (Old et al. 1963).

In addition to eliciting a contact hypersensitivity response, benzo[a]pyrene has been shown to suppress this response to other sensitizers. The effects of dermally applied benzo[a]pyrene (alone or following dermal pretreatment with the prostaglandin synthetase inhibitor, indomethacin) on contact hypersensitivity (cell-mediated immunity), and production of antibodies to dinitrophenol (DNP) (humoral immunity) were studied in male BALB/c mice treated for 6 weeks to 6 months (Andrews et al. 1991a). A group of mice treated with acetone served as controls. Benzo[a]pyrene alone caused a significant reduction ($p<0.01$) in the contact hypersensitivity response to dinitrofluorobenzene (DNFB) as measured by increases in ear thickness when compared to the vehicle controls. However, indomethacin pretreatment prevented the benzo[a]pyrene-induced contact hypersensitivity response. Benzo[a]pyrene also reduced antibody titres to DNP in treated mice. This suppressive effect on humoral immune function was not restored by pretreatment with indomethacin. These findings led the authors to conclude that the mechanism of benzo[a]pyrene-induced suppression of cell-mediated immunity involved prostaglandins, whereas benzo[a]pyrene-induced suppression of humoral immunity operated via a mechanism independent of prostaglandins. In a subsequent experiment, the effects of dermally applied benzo[a]pyrene (alone or following subcutaneous implantation of the prostaglandin synthetase inhibitor, indomethacin) on Langerhans cells and on skin prostaglandin (PGE_2) levels were studied in male BALB/c mice treated for 3 weeks (Andrews et al. 1991b). Langerhans cells are antigen-presenting cells involved in cell-mediated immunity in skin. A group of mice treated with indomethacin served as controls. Benzo[a]pyrene alone caused a significant increase in the number of skin Langerhans cells, but reduced the percentage of Langerhans cells with dendritic morphology. Skin PGE_2 levels were also significantly increased by benzo[a]pyrene. Indomethacin attenuated the increase in Langerhans cell number and the changes in their morphology, and increased PGE_2 levels, such that all of these parameters were similar to those measured in the control animals. Based on these results, the authors suggested that benzo[a]pyrene induces increases in skin PGE_2 that in turn alter Langerhans cell number and morphology such that the cell-mediated immune response to skin antigens is suppressed.

An earlier study also demonstrated that benzo[a]pyrene affects epidermal Langerhans cells and dermal immunological responses. Female BALB/c mice were administered dermal applications on the dorsal skin of 0.5% benzo[a]pyrene in acetone twice weekly for up to 6 months (Ruby et al. 1989). Animals treated with acetone served as controls. The density, area, perimeter, and morphology of epidermal Langerhans cells were evaluated, along with the contact hypersensitivity response to DNFB. Benzo[a]pyrene treatment caused an increase in the number of epidermal Langerhans cells (as

determined by Ia antigens and B-glucuronidase) from week 2 to week 5 of treatment and after weeks 10 and 18. The area and perimeter of these cells were unaffected by benzo[a]pyrene treatment, but the morphology was altered in that the dendrites appeared shortened. The contact hypersensitivity response to DNFB was significantly reduced in the benzo[a]pyrene-treated mice from 4 to 24 weeks of treatment. The authors propose that benzo[a]pyrene alters Langerhans cell number and morphology such that the cell-mediated immune response to skin antigens is suppressed. Skin tumors appeared in 20% of the benzo[a]pyrene-treated mice after 18 weeks of treatment, and 35% of the mice had l-3 tumors after 24 weeks of treatment. The tumors were squamous papillomas (58%) and squamous cell carcinomas (42%). The changes in Langerhans cell number, distribution, and morphology coincided with the onset of tumors and other nonneoplastic skin lesions that were observed (epidermal hyperplasia and cellular atypia).

All reliable LOAELs from each reliable study for immunological effects for each species and duration category are recorded in Table 2-3.

No studies were located regarding the following health effects in humans or animals following dermal exposure to the 17 PAHs discussed in this profile:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following dermal exposure to the 17 PAHs discussed in this profile. A single topical application of benzo[a]pyrene (0.5-500 μg/mouse) or chrysene (50-1,000 μg/mouse) to groups of HRA/Skh hairless mice (four mice/dose/group) resulted in significantly increased frequencies of micronucleated keratinocytes (He and Baker 1991). In the same study, micronuclei were not induced in the mouse skin cells following application of 2.5-2,500 μg/pyrene per mouse. Male SENCAR mice receiving two topical applications of 20 μg benzo[a]pyrene at 72-hour intervals exhibited increased DNA adduct formation in both epidermal and

lung tissue (Mukhtar et al. 1986). Following a single topical application, 100 μg benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene were reported to bind to DNA in CD-l mouse skin (Weyand et al. 1987). The relative extent of binding was benzo[b]fluoranthene > benzo[j]fluoranthene > benzo[k]fluoranthene > indeno[1,2,3-c,d]pyrene. Covalent binding of chemicals to DNA can result in strand breaks and DNA damage, ultimately leading to mutations.

Benzo[a]pyrene (62.5 or 500 μg) was applied once to the shaved backs of male C57BL/6 mice (Bjelogrlic et al. 1994). Mice were killed at different time intervals after the treatment. DNA was isolated from the skin, purified, and analyzed for benzo[a]pyrene-7,8-diol-9,10-epoxide-DNA adducts. Skin was also evaluated for monoclonal antibody binding to mouse p53 protein, which has been shown to increase in response to DNA damage. Alterations in p53 are the most frequently observed mutations in human cancer. Benzo[a]pyrene-7,8-diol-9,10-epoxide-DNA adducts reached their maximum concentration 24 hours after the treatment, and decreased sharply within 1 week, regardless of the dose. An increase in p53 protein was seen only after treatment with 500 μg benzo[a]pyrene.

Benzo[j]fluoranthene, benzo[j]fluoranthene-4,5-diol, and benzo[j]fluoranthene-9,10-diol were applied to the shaved backs of CD-l mice and the DNA adducts were isolated and separated using multidimensional thin-layer chromatography (TLC) and reverse-phase high performance liquid chromatography (HPLC) (Weyand et al. 1993a). The highest level of adducts was observed with benzohlfluoranthene-4,5-diol, which resulted in the formation of 383 pmol of DNA adducts/mg DNA. This level of DNA modification was more than 2 orders of magnitude greater than that observed with benzo[j]fluoranthene. In contrast, the major DNA adducts detected with benzo[j]fluoranthene-9,10-diol had chromatographic properties distinctly different than the adducts formed from either benzo[j]fluoranthene or B[j]F-4,5-diol. The adducts of the diols corresponded to DNA adducts produced *in vitro* from the respective diolepoxides. In a companion study, benzo[b]fluoranthene, benzo[b]fluoranthene-9,10 diol, 6-hydroxy-benzo[b]fluoranthene-9,10-diol, or 5-hydroxybenzo[b]fluoranthene-9,10-diol were applied to the shaved backs of CD-1 mice and the DNA adducts were isolated and separated using multidimensional TLC and reverse-phase HPLC (Weyand et al. 1993b). Benzo[b]fluoranthene formed one major adduct and 4 minor adducts. The DNA adducts formed from 5-hydroxybenzo[b]fluoranthene-9, l0 diol had identical retention to the major and one of the minor adducts of benzo[b]fluoranthene. These two adducts accounted for 58% of the modified nucleotides produced by benzo[b]fluoranthene application to mouse skin.

The DNA binding of manufactured gas plant residue (MGP) components in male B6C3Fl mice was investigated following topical administration (Weyand and Wu 1994). For topical exposure, male mice were treated with 10 mg MGP residue in 200 μL acetone, and sacrificed 24 hours later. Two mixtures of MGP residue were used: Mix of 3 combining equal amounts of samples from three different MGP plant sites, and Mix of 7 combining equal amounts of samples from seven different MGP plant sites, including those used in the Mix of 3. The mixtures contained pyrene, benz[a]anthracene, chrysene, benzo[b]fluorene, benzo[k]fluorene, benzo[a]pyrene, indeno[l,2,3-cd]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene. Data were presented in terms of pyrene. Animals were sacrificed 24 hours after treatment, and skin and lung were excised and DNA isolated. Chemical-DNA adduct formation was evaluated. Topical application MGP residue in acetone resulted in similar levels of DNA adduct in the skin for both the Mix of 3 and the Mix of 7. The total level of adducts detected in the lung after topical administration was identical to the response after dietary exposure, i.e., the Mix of 3 (1.4 mg/kg/day pyrene) produced adduct levels that were two times greater than the levels induced by the Mix of 7 (1.2 mg/kg/day pyrene). Other genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located that gave evidence of a direct association between human dermal exposure to individual PAHs and cancer induction. However, reports of skin tumors among individuals exposed to mixtures containing PAHs lend some qualitative support to their potential for carcinogenicity in humans. The earliest of these is the report by Pott (1775) of scrotal cancer among chimney sweeps. More recently, skin cancer among those dermally exposed to shale oils has been reported (Purde and Etlin 1980). However, these reports provide only qualitative suggestions pertaining to the human carcinogenic potential of all of the 17 PAHs discussed in this profile, or at least the compounds found in chimneys and shale oils, such as benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, benz[a]anthracene, and benzo[b]fluoranthene. Limitations in these reports include no quantification of exposure to individual PAHs and concurrent exposure to other putative carcinogens in the mixtures.

It has been suggested that an increase in the number of skin melanocytes correlates with the sebaceous gland suppression index, and that the short-term melanocyte-activation test is useful for the detection of skin carcinogens and promoters. Some chemical carcinogens have been shown to induce melanogenesis in melanoblasts in the skin. Anthracene, benzo[a]pyrene, chrysene, fluoranthene,

fluorene, and pyrene were examined for their ability to induce melanocyte activation by topical application to the backs of mice for 1 or 2 consecutive days. Benzo[a]pyrene, an animal skin carcinogen, was a potent melanocyte inducer at doses of 20-100 μg/mouse (0.005-0.025 mg/cm^2) as demonstrated by an increase of up to 19 times over controls in the number of dopa-positive cells, whereas no effects were seen at 4 μg/mouse (0.001 mg/cm^2). Chrysene, a weak skin carcinogen (in animals), increased the number of dopa-positive cells to four times that of controls following an application of 50 μg/mouse (0.0125 mg/cm^2), while larger doses did not cause further increases in the numbers of these cells. Other PAHs such as anthracene, fluoranthene, fluorene, and pyrene (PAHs that are considered to be noncarcinogenic) produced no increases in the number of active melanocytes when applied at a dose of 200 μg/mouse (0.05 mg/cm^2) (Iwata et al. 1981).

Complete Carcinogenesis Studies. Studies in laboratory animals have demonstrated the ability of benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[l,2,3-c,d]pyrene to induce skin tumors (i.e., they are complete carcinogens) following intermediate dermal exposure. Anthracene, fluoranthene, fluorene, phenanthrene, and pyrene do not act as complete carcinogens. The data supporting these conclusions are discussed below by chemical. Only those studies considered adequate and reliable with respect to study design and adequacy of reporting are presented in Table 2-3.

Anthracene. Skin painting experiments were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Anthracene dissolved in toluene was applied to shaved skin twice weekly for six months at a dose of 0.05 mg. Tumor incidence was determined at the end of the study. For anthracene, administration alone produced tumors in 0 of 14 animals. With coadministration of 0.05 mg benzo[a]pyrene, 1 of 13 (8%) had a papilloma, with a mean latency period of 85 weeks. Anthracene was negative as a complete carcinogen following chronic dermal exposure (Habs et al. 1980). Swiss mice receiving 10% anthracene in acetone topically applied to their backs three times a week throughout their lifetime did not develop any skin tumors after 20 months (Wynder and Hoffmann 1959a).

Benz[a]anthracene. Benz[a]anthracene has been shown to cause skin tumors in mice following intermediate-duration dermal application. Graded concentrations of benz[a]anthracene in toluene or *n*-dodecane applied to the backs of mice for 50 weeks resulted in dose-related increases in tumor incidence (Bingham and Falk 1969). This response was enhanced when *n*-dodecane was the solvent

compared with toluene. Malignant tumors were observed at dose levels of about 0.02% benz[a]anthracene (0.15 mg/kg/day) and above when toluene was the solvent; however, when n-dodecane was the solvent, tumors were observed.at much lower concentrations of 0.0002% benz[a]anthracene (0.0015 mg/kg/day). The dose-response relationship reported in this study is extremely shallow (sublinear) over two orders of magnitude. A possible explanation for this is that the tumorigenic potency of certain PAHs is tempered by their cytotoxicity. Thus, the cytotoxic effects to epithelial cells may self-limit their potency as tumorigens. No solvent controls were included for comparison (Bingham and Falk 1969).

Intermediate-duration topical application of benz[a]anthracene to the backs of mice for 30 weeks resulted in a slightly elevated (2.6%) (but not statistically significant) skin tumor incidence. No definitive conclusions can be drawn from this study since only one dose was employed and no statistical analysis was performed.

Benzo[b]fluoranthene. A dose-response relationship for the dermal carcinogenicity of benzo[b]fluoranthene has been demonstrated over a one order-of-magnitude dose range in Swiss mice receiving (0.0l-0.5%) benzo[b]fluoranthene throughout their lifetime. Survival was also dose related. Although this study was designed as a long-term (chronic) bioassay, malignant tumors (90% carcinomas) appeared as early as 4 months in the high-dose group. Papillomas and carcinomas (65% and 85%, respectively) also appeared after 5 months in the mid-dose group. As a result, this study provides evidence that benzo[b]fluoranthene is carcinogenic following intermediate-duration exposure. The lowest dose at which benzo[b]fluoranthene elicited malignant tumors was 0.l%, which is approximately equal to a dose of 2.9 mg/kg received three times weekly, or an average daily dose of 1.2 mg/kg (Wynder and Hoffmann 1959b, see Table 2-3). In another chronic dermal study, benzo[b]fluoranthene produced a significant carcinogenic response of approximately one-third the potency of benzo[a]pyrene. The lowest dose at which tumors appeared was 3.4 μg benzo[b]fluoranthene; however, no distinction was made between papillomas and carcinomas (Habs et al. 1980).

Benzo[j]fluoranthene. Benzofilfluoranthene (0.1% or 0.5%) applied to the skin of female Swiss mice thrice weekly for life induced skin papillomas in 70% and 95% of the animals, respectively, and skin carcinomas in 105% and 95% of the animals, respectively, after 9 months of treatment (Wynder and Hoffmann 1959b).

No statistically significant increase in the incidence of skin tumors was noted in female NMRI mice dermally administered 3.4, 5.6, or 9.2 μg benzo[j]fluoranthene in acetone twice weekly for life (Habs et al. 1980). A total of 4 benzo[j]fluoranthene-treated mice developed skin tumors (application site sarcoma, papillomas, and a carcinoma).

Benzo[k]fluoranthene. Chronic dermal application of benzo[k]fluoranthene to Swiss mice resulted in no tumors, but skin papillomas were observed in 10% of animals when the concentration of benzo[k]fluoranthene was increased. Statistical analyses were not performed (Wynder and Hoffmann 1959b). In another study, no significant increase in tumor incidence was observed in NMRI mice painted with up to 9.2 μg of benzo[k]fluoranthene twice a week for a lifetime; no effect on mortality was noted (Habs et al. 1980).

Benzo[a]pyrene. Benzo[a]pyrene is a potent experimental skin carcinogen, and it is often used as a positive control in bioassays of other agents. Mixtures of PAHs that include benzo[a]pyrene such as coal tar were shown to be dermal carcinogens in animals as early as 1918 (Yamagiwa and Ichikawa 1918). In its role as a positive control, benzo[a]pyrene is usually administered at a single dose level, and thus quantitative evaluation of dose-response relationships is not possible.

Intermediate (19-20 weeks) topical application of a benzo[a]pyrene solution to the backs of mice resulted in a dose-related development of skin papillomas and squamous cell carcinomas (Cavalieri et al. 1988b, see Table 2-3; Shubik and Porta 1957). Benzo[a]pyrene was applied once weekly to the skin of female ICR/Harlan mice (43-50/group) at doses of 16, 32, or 64 μg for 29 weeks (Albert et al. 1991ba). Cell kinetics, morphometrics, and tumor formation were evaluated. Skin tumors were first apparent 12-14 weeks after the start of exposure in the 32- and 64-μg groups and after 18 weeks in the 16-μg group. The overwhelming majority of these tumors were benign. The average time of progression from benign papillomas to malignant carcinomas was 8.1 ± 4.5 weeks. Because there was good correspondence between the dose-response patterns for epidermal damage and the occurrence of skin tumors, and because tumors that initially appear as benign can be the result of tumor promoting agents that increase cell proliferation rates, the authors proposed that the tumors seen after benzo[a]pyrene treatment were the result of promotion related to benzo[a]pyrene-induced tissue damage. However, benign tumors can be formed as a result of genetic damage as well. Because benzo[a]pyrene causes genetic damage in addition to increased rates of cell proliferation, it is likely that genetic damage also played a role. Following a similar protocol in mice (once weekly dermal

applications of benzo[a]pyrene in acetone at doses of 16, 32, and 64 μg/mouse for 34 weeks), tumor development was reported to be best described by a dose-squared response. Quantitative data for tumor incidence were not presented (Albert et al. 1991b).

Carcinogenicity experiments on mouse skin were conducted with groups of 20 female CD-l mice. Benzo[a]pyrene (0.05 mg) dissolved in 50 mL toluene was applied to shaved skin of mice twice weekly for 6 months (Warshawsky et al. 1993). Tumor incidence was determined at the end of the study. Benzo[a]pyrene produced no tumors.

In mice, the tumorigenic dose of benzo[a]pyrene is influenced by the solvent used for delivery. Graded concentrations of benzo[a]pyrene dissolved in decalin or a solution of n-dodecane and decalin were topically administered to the backs of mice for 50 weeks (Bingham and Falk 1969). Use of the n-dodecane and decalin solvent mixture significantly enhanced the potency of benzo[a]pyrene at lower doses in comparison with decalin alone. Malignant tumors appeared in 21% of the animals at 0.00002% (0.0054 mg/kg/day) benzo[a]pyrene in dodecane and decalin solvent. In contrast, a 42% skin tumor incidence was not observed until 0.02% (4.8 mg/kg/day) benzo[a]pyrene in decalin alone was applied. The method of application was not specified, sample sizes were small and no decalin solvent controls were included; however, decalin is not considered to be carcinogenic. In this same study, intermediate (50 weeks) dermal application of benzo[a]pyrene dissolved in the co-carcinogens 1-dodecanol or 1-phenyldodecane produced skin tumors in animals exposed to 0.05% benzo[a]pyrene in either solvent. The tumor incidence varied depending on the solvent concentration; however, the latency period was reduced only when 1-dodecanol was the solvent (Bingham and Falk 1969).

Mice receiving 0.00l-0.01% of benzo[a]pyrene dermally applied to their backs throughout their lifetimes exhibited a dose-response relationship for skin tumors (Wynder and Hoffmann 1959a). A dose of 0.001% benzo[a]pyrene produced skin carcinoma and papilloma incidences of 4% and 45%, respectively. In another study conducted by Wynder and Hoffmann (1959b), higher concentrations of benzo[a]pyrene produced an 85% incidence of combined papillomas and carcinomas. These studies had a number of weaknesses, including no statistical treatment and no solvent control group. Dose quantification is difficult because of the method of application (Wynder and Hoffmann 1959a, 1959b). NMRI mice topically administered 2 μg benzo[a]pyrene throughout their lifetime also developed skin papillomas and carcinomas (45%) (Habs et al. 1984, see Table 2-3). CH3 mice administered a higher dose of 12.5 μg benzo[a]pyrene for 99 weeks exhibited malignant skin tumors (94%) (Warshawsky

and Barkley 1987, see Table 2-3). Increasing malignant carcinoma incidences in these dermal application studies can be correlated to increasing benzo[a]pyrene concentrations.

In mice, the tumorigenic dose of benzo[a]pyrene is dependent on the strain. For example, Habs et al. (1980) tested 1.7-4.6 μg benzo[a]pyrene (0.016-0.04 mg/kg/day) in order to determine its dose-response relationship as a carcinogen when topically applied to the backs of NMRI mice throughout their lifetimes. A clear-cut dose-response relationship was seen for benzo[a]pyrene and the induction of tumors. The lowest dose at which skin tumors appeared was 1.7 μg (0.016 mg/kg/day). This strain of NMRI mice also has a high (70%) background incidence rate of systemic tumors, so an evaluation of the effects of benzo[a]pyrene on any organ other than the site of administration was not possible:

Chrysene. Skin painting experiments with intermediate (6 months) dermal exposure with chrysene were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Chrysene (0.05 mg) dissolved in toluene was applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For chrysene, administration alone produced papillomas in 1 of 15 animals (7%), with a mean latency period of 81 weeks. With coadministration of 0.0005 mg benzo[a]pyrene, 3 of 13 (23%) had tumors (papillomas and malignant), with a mean latency period of 70 weeks.

Chrysene has elicited skin tumors in mice following chronic (68-82 weeks) dermal exposure. Topical application of a chrysene solution in *n*-dodecane/decalin to the skin of mice produced a significant increase in the carcinogenic potency of chrysene compared with the use of decalin alone; 26% and 63% of mice exhibited papillomas and carcinomas, respectively, at 49 weeks (Horton and Christian 1974). Because only one dose level was employed, no dose-response relationship can be inferred, and no solvent control was included. However, in other experiments decalin and *n*-dodecane have been shown to be noncarcinogenic in mice (Bingham and Falk 1969). An average dose of 1.2 mg/kg/day is the lowest dose of chrysene that has been found to elicit malignant tumors in laboratory animals.

In another chronic study, a higher concentration of chrysene applied dermally to the backs of Swiss mice for a lifetime also resulted in increased papilloma and carcinoma incidences (48% and 42%, respectively) compared to controls (Wynder and Hoffmann 1959a). Since only one dose was employed, no dose-response information can be inferred from this study.

Dibenz[a,h]anthracene: Dibenz[a,h]anthracene has also demonstrated a dose-response relationship for skin tumors over a two-orders-of-magnitude dose range following chronic exposure. Swiss mice received concentrations of 0.00l-0.1% dibenz[a,h]anthracene applied to their backs throughout their lifetimes and exhibited dose-related papilloma and carcinoma incidences at the site of application at the two lowest doses. A decreased tumor rate at the highest dose tested probably reflects dibenz[a,h]anthracene's toxicity and the resulting decreased survival observed. The lowest concentration at which dibenz[a,h]anthracene elicited tumors was 0.001% (40% incidence of papillomas and 40% incidence of carcinomas), which is approximately equal to a dose of 0.029 mg/kg (0.012 mg/kg/day) (Wynder and Hoffmann 1959a). In another chronic derrnal study of dibenz[a,h]anthracene, a dose-related increase in skin carcinoma formation was observed, as well as decreased survival time and tumor latency period (Van Duuren et al. 1967).

Groups of 50 female NMRI mice received dermal applications of dibenz[a,h]anthracene in acetone (total doses = 0, 136, 448, or 1,358 nmol) three times a week for a total of 112 weeks (Platt et al. 1990). Papillomas were observed in 6%, 8%, and 32% of the treated animals, respectively.

Fluoranthene. Skin painting experiments with intermediate-duration (6 months) dermal exposure were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Fluoranthene was dissolved in toluene and applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For fluoranthene, administration alone produced tumors in 0 of 15 animals. With coadministration of 0.0005 mg benzo[a]pyrene, 1 of 12 (8%) had papillomas, with a mean latency period of 95 weeks.

Chronic dermal application of up to 1% fluoranthene to the backs of mice did not induce skin tumors following a lifetime of application (Hoffmann et al. 1972; Horton and Christian 1974; Wynder and Hoffmann 1959a).

Fluorene. Fluorene has been reported to be negative as a complete carcinogen (dose not specified) (Kennaway 1924). This information was obtained from an old, secondary source and therefore, its reliability is not known.

Indeno[l,2,3-c,d]pyrene. Indeno[1,2,3-c,d]pyrene was applied to the skin of female Swiss mice three times weekly for 12 months in concentrations of 0.5% (500 μg/application), 0.l%, 0.05%, and 0.01%

(20 mice per group) using acetone as the solvent. A tumor dose-response with 7 papilloma-bearing mice and 5 carcinoma-bearing mice for 0.5%, 6 papilloma-bearing and 3 carcinoma-bearing mice for 0.l%, and no skin tumors for 0.05% and 0.01% solutions was observed (Hoffmann and Wynder 1966). Chronic dermal application of indeno[1,2,3-c,d]pyrene in dioxane to mice did not produce an increased incidence of skin tumors. Similarly, chronic topical application of up to 9.2 μg of indeno[l,2,3-c,d]pyrene in acetone to the backs of mice for a lifetime resulted in no tumor induction (Habs et al. 1980).

Phenanthrene. Phenanthrene tested negative as a complete carcinogen in a mouse study inadequately reported in an old secondary source (Kennaway 1924). Skin painting experiments with intermediate-duration (6 months) dermal exposure were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Phenanthrene dissolved in toluene was applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For phenanthrene, administration alone produced papillomas in 1 of 12 animals (8%), with a mean latency period of 100 weeks. With coadministration of 0.0005 mg benzo[a]pyrene, 1 of 17 (6%) had malignant tumors, with a mean latency period of 53 weeks.

Pyrene. Skin painting experiments with intermediate-duration (6 months) exposure were conducted on groups of 20 male C3H/HeJ mice. Pyrene dissolved in toluene was applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. For pyrene, administration alone produced papillomas in 1 of 13 animals (8%), with a mean latency period of 96 weeks. With coadministration of 0.0005 mg benzo[a]pyrene, 0 of 13 animals had tumors.

Mice chronically administered a 10% pyrene solution throughout their lifetimes did not develop skin tumors (Wynder and Hoffmann 1959a). However, prolonged dermal exposure of mice to 0.5% pyrene in decalin/n-dodecane solvent produced a slightly elevated (15%) skin carcinoma incidence; the level of statistical significance was not provided (Horton and Christian 1974).

Mixtures. Chronic dermal exposure of NMRI mice to a tar condensate that contained several PAHs (pyrene, fluoranthene, chrysene, benz[a]anthracene, benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, benzo[g,h,i]perylene) in addition to other compounds produced a carcinogenic effect as evidenced by an increase in the incidence of skin papillomas and carcinomas (Habs et al. 1984). Because of the

presence of other compounds in the tar condensate, the carcinogenic effect cannot be definitely attributed to the PAHs present in the mixture.

Skin painting experiments of a mixture of anthracene, chrysene, fluoranthene, phenanthrene, and pyrene were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al. 1993). Compounds dissolved in toluene were applied to shaved skin twice weekly for 6 months. Tumor incidence was determined at the end of the study. Treatment included solutions of a mixture of the five noncarcinogenic PAHs at 0.05 mg, or the same compounds in solution with 0.0005 mg benzo[a]pyrene, a dose known to be noncarcinogenic in a similar study design. For the mixture of the 5 PAHs at 0.05 mg each, administration alone produced papillomas and malignant tumors in 3 of 13 animals (23%), with a mean latency period of 73 weeks. With coadministration of benzo[a]pyrene, 8 of 17 (47%) had tumors (papillomas and malignant), with a mean latency period of 66 weeks.

Initiation-Promotion Studies. Carcinogenesis has been demonstrated to be a multistage process in the cells of certain animal tissues, including skin, lung, liver, and bladder. This process is believed to occur in human tumorigenesis as well. The PAHs have been studied extensively for their ability to act as tumor initiators and/or promoters. Following is a brief discussion, by chemical, of the results of the initiation-promotion studies performed with 13 of the 17 PAHs discussed in this profile. Only those studies considered adequate and reliable are presented in Table 2-3.

The difficulty inherent in extrapolating initiation-promotion experiments to human exposure precludes their being used as the basis for human cancer effect levels. Since PAHs occur in complex mixtures of chemicals that may include tumor promoters, their activity as initiating agents is noteworthy. Thus, it is possible that humans dermally exposed to PAHs that are initiating agents, concomitantly with other chemicals that may be active as tumor promoters (including other PAHs) found at nearby hazardous waste sites, may have an increased risk of skin cancer.

Anthracene. Anthracene has been found to be inactive as an initiating agent under a dermal initiation/promotion protocol using tetradecanoyl phorbol acetate (TPA) as the promoter (LaVoie et al. 1983a).

Benz[a]anthracene. Benz[a]anthracene has been observed to be a tumor initiator in an intermediate-duration dermal study. CD-l mice topically administered 2.5 µmol (0.57 mg) benz[a]anthracene

followed by promotion with TPA (for 25 weeks) exhibited an increased skin tumor incidence (36%) as compared to controls (Levin et al. 1984, see Table 2-3).

Benzo[a]pyrene. Benzo[a]pyrene is active as a tumor initiator using initiation/promotion protocols. Topical application of a single initiating dose of benzo[a]pyrene to the backs of mice followed by promotion with TPA or croton oil resulted in an 80-92% incidence of skin papillomas (Cavalieri et al. 1988b, see Table 2-3). Ten doses of benzo[a]pyrene (0.1 mg/dose) topically applied to the backs of Swiss mice followed by promotion with croton oil (for 20 weeks) also resulted in the development of skin tumors (Hoffmann et al. 1972).

In a dermal initiation/promotion assay, groups of 24 female SENCAR mice were administered a single dermal application of benzo[a]pyrene at doses ranging from 4 to 300 nmol (initiating dose), followed 7 days later by twice weekly applications of the promoter TPA, for a total of 24 weeks. Benzo[a]pyrene was active as a skin tumor initiator; the number of tumors per tumor bearing mouse, the percentage of tumor bearing mice, and the number of tumors per mouse were all significantly greater than in acetone controls and increased in a dose-related manner at doses ≥20 nmol (Cavalieri et al. 1991).

In a similar experiment, 24 8-week-old female SENCAR mice were treated dermally with 0.0002 mg (1 nmol) of benzo[a]pyrene in acetone on a shaved portion of dorsal skin (Higginbotham et al. 1993). One week later, tumor promotion was begun with TPA twice weekly for 27 weeks. The number of skin tumors was charted weekly and the mice were killed after experimental weeks. Complete necropsies were performed and tissues were fixed in formalin. Benzo[a]pyrene-treated mice had no skin tumors.

Benzo[e]pyrene. Benzo[e]pyrene is inactive as a skin tumor initiator in mouse skin (Slaga et al. 1980a).

Benzo[b]fluoranthene. The ability of benzo[b]fluoranthene to initiate skin tumor formation has been demonstrated using a standard initiation/promotion protocol with either croton oil or phorbol myristate acetate as a tumor promoter (Amin et al. 1985a; LaVoie et al. 1982). In another study, dermal applications of initiation doses of benzo[b]fluoranthene (10-100 μg) followed by TPA (for 20 weeks)

to the backs of CD-l mice elicited a dose-related skin tumor incidence, predominantly consisting of squamous cell papillomas (LaVoie et al. 1982).

In a dermal initiation/promotion assay, groups of 20 female CD-l mice were administered 10 dermal applications of benzo[b]fluoranthene at total doses of 0, 1, and 4 umol (initiating dose), followed 10 days later by thrice weekly applications of the promoter TPA for a total of 20 weeks (Weyand et al. 1991). Benzo[b]fluoranthene was active as a skin tumor initiator; the number of tumors per tumor-bearing mouse (8.5) and the percentage of tumor-bearing mice (100%) were significantly greater than in acetone controls and were increased in a dose-related manner.

Tumor initiation experiments were conducted with groups of 20 female CD-1 mice. Benzo[b]fluoranthene was applied to the shaved backs of the mice every other day using a total of 10 subdoses (Weyand et al. 1993b). Total doses were 10.1, 30.3, and 100.9 μg in acetone. Negative control mice were treated with acetone. Ten days after the last dose, promotion was begun by applying 2.5 μg TPA thrice weekly for 20 weeks. Tumors were counted weekly. Benzo[b]fluoranthene produced a 35%, 90%, and 95% incidence of tumor-bearing mice with 0.45, 3.70, and 8.65 tumors per mouse for the low, mid and high doses, respectively. No distinction was made between papillomas and carcinomas (Weyand et al. 1993b). Groups of 20 female Crl:CD-1 mice were dermally exposed to a total of 0, 0.01, 0.03, or 0.1 mg of benzo[b]fluoranthene in acetone applied every other day for 20 days in 10 subdoses (LaVoie et al. 1993a). Negative control mice were treated with acetone only. Ten days after the last application of acetone or hydrocarbon, tumor promotion was begun by applying 2.5 μg TPA in acetone three times weekly for 20 weeks. Tumor incidence was recorded after 20 weeks of promotion. The study was repeated for the 0.03 and 0.1 mg doses. Of the mice receiving 0.01 mg benzo[b]fluoranthene, 35% had developed tumors, with an average of 0.45 tumors/mouse. For the 0.03 mg dose, 70-90% of the mice developed tumors with an average of 1.4-3.7 tumors per mouse, whereas the 0.1 mg dose caused 95% of the mice to develop and average of 7.1-8.6 tumors. Of the animals treated with acetone only, 5-15% developed skin tumors. In this study, tumors were not identified as papillomas or carcinomas.

Benzo[j]fluoranthene. Benzo[j]fluoranthene has also been demonstrated to be a tumor initiator in mice, although it is not as potent as benzo[b]fluoranthene. Benzo[j]fluoranthene, however, is more potent than benzo[k]fluoranthene. Mice receiving initiating doses of benzo[j]fluoranthene (30-1,000 μg) followed by TPA promotion exhibited a dose-related increase in tumor incidence

(LaVoie et al. 1982, 1993a; Weyand et al. 1992). Groups of 20 female Crl:CD-1 mice were dermally exposed to a total of 0, 0.006, 0.012, 0.025, or 0.25 mg of benzojjlfluoranthene in acetone applied every other day for 20 days in 10 subdoses (LaVoie et al. 1993b). Negative control mice were treated with acetone only. Ten days after the last application of acetone or hydrocarbon, tumor promotion was begun by applying 2.5 μg TPA in acetone three times weekly for 20 weeks. Tumor incidence was recorded after 20 weeks of promotion. Five percent of the mice receiving 0.006 mg benzo[j]fluoranthene had developed tumors, with an average of 0.4 tumors per mouse. For the 0.012 mg dose, 10% of the mice developed tumors with an average of 0.4 tumors per mouse; 0.025 mg PAH caused 45% of the mice to develop tumors at an average of 0.65 tumors per mouse, whereas the 0.25 mg dose caused 95% of the mice to develop an average of 8.7 tumors. The control animals developed no tumors.

Benzo[k]fluoranthene. Benzo[k]fluoranthene has also been demonstrated to be a tumor initiator in mice, although it too, is not as potent as benzo[b]fluoranthene. Mice receiving initiating doses of benzo[k]fluoranthene (30-1,000 μg) followed by TPA promotion exhibited a dose-related increase in ‘tumor incidence (LaVoie et al. 1982).

Benzo[g,h,i]perylene. Benzo[g,h,i]perylene has been shown to be inactive as an initiating agent when applied at a total dose of 0.25 mg/animal and negative as a complete carcinogen when a 1% solution was applied thrice weekly for 12 months (IARC 1983).

Chrysene. Chrysene is a tumor initiator in classic initiation/promotion bioassays on mouse skin using croton oil or phorbol myristate acetate as promoting agents (Slaga et al. 1980a; Wood et al. 1979a). Initiating doses of chrysene followed by promotion with TPA or croton resin induced a dose-related papilloma incidence in mice (Slaga et al. 1980a; Wood et al. 1979a).

Dibenz[a,h]anthracene. Dibenz[a,h]anthracene has also demonstrated tumor-initiating activity using a standard initiation/promotion protocol (Slaga et al. 1980a). Dibenz[a,h]anthracene has been reported to initiate skin development in a dose-response relationship at doses as low as 0.028 μg followed by promotion with TPA (for 25 weeks) (Buening et al. 1979a).

In a dermal initiation/promotion assay, groups of 50 female NMRI mice were administered a single dermal application of dibenz[a,h]anthracene at doses of 0, 300, or 600 nmol (initiating dose) followed

7 days later by twice weekly applications of the promoter, TPA, for a total of 24 weeks (Platt et al. 1990). Dibenz[a,h]anthracene was active as a skin tumor initiator only at the highest dose tested; 93% of the animals administered 600 nmol dibenz[a,h]anthracene developed skin tumors by 24 weeks.

Fluoranthene. Fluoranthene did not exhibit initiating activity in Swiss mice topically administered 10 doses followed by promotion with croton oil (for 20 weeks) (Hoffmann et al. 1972).

Indeno[l,2,3-c,d]pyrene. A pronounced dose-response relationship has been exhibited by indeno[l,2,3-c,d]pyrene in an initiation-promotion bioassay when TPA was employed as the promoting agent, although it was not as potent an initiator as benzo[b]fluoranthene (Rice et al. 1985a). In another study, 2.83 tumors/mouse were noted after a total initiating dose of 1.0 mg indeno[1,2,3-c,d]pyrene and promotion with TPA for 20 weeks (Rice et al. 1986).

The skin tumor initiating activity of indeno[1,2,3-c,d]pyrene and several of its metabolites generated *in* viva in mouse skin was tested in female Crl:CD/l mice (Rice et al. 1986). Initiating doses of indeno[1,2,3-c,d]pyrene or the metabolites were applied every other day to the shaved skin of groups of 25 mice for a total of 10 doses, which was followed 10 days later by thrice weekly applications of the tumor promotor, TPA, for 20 weeks. None of the metabolites were as active in inducing skin tumors as the parent compound (2.83 tumors/mouse as compared to 0.48-1.68 tumors/mouse at 20 weeks). These findings led the authors to conclude that the principal ultimate mutagenic metabolite, indeno[l,2,3-c,d]pyrene-1,2-oxide, is not the ultimate carcinogenic metabolite of indeno[l,2,3-c,d]pyrene.

Phenanthrene. Phenanthrene was ineffective as an initiator in various mouse strains (LaVoie et al. 1981b; Salaman and Roe 1956; Wood et al. 1979a). CD-1 mice topically administered a single dose of 10 μmol phenanthrene followed by a promoter were observed to have a papilloma incidence 2-4 times that of background; however, the incidences were not statistically significant in comparison to controls because of the small number of animals tested and the high spontaneous tumor incidence (Wood et al. 1979a).

Pyrene. Pyrene has been shown to be inactive as an initiating agent (Salaman and Roe 1956; Van Duuren and Goldschmidt 1976).

Mixtures. Co-administration of pyrene and benzo[a]pyrene to the backs of ICR/Ha mice has produced an enhancement of benzo[a]pyrene tumorigenicity (Van Duuren and Goldschmidt 1976). There is evidence that benzo[g,h,i]perylene is a co-carcinogen with benzo[a]pyrene when both are applied simultaneously to the skin of Swiss mice (Van Duuren et al. 1973). Dermal pretreatment with 100 μg pyrene substantially enhanced benzo[a]pyrene tumor initiation in CD-1 mice, while 100 μg fluoranthene produced a marginal enhancement (Slaga et al. 1979).

2.3 TOXICOKINETICS

Occupational studies provide evidence that inhaled PAHs are absorbed by humans. Animal studies also show that pulmonary absorption of benzo[a]pyrene occurs and may be influenced by carrier particles and solubility of the vehicle; however, the extent of absorption is not known. Absorption of benzo[a]pyrene following ingestion is low in humans, while oral absorption in animals varies among the PAH compounds depending on the lipophilicity. Oral absorption increases with more lipophilic compounds or in the presence of oils in the gastrointestinal tract. Percutaneous absorption of PAHs appears to be rapid for both humans and animals, but the extent of absorption is variable among these compounds and may be affected by the vehicle used for administration. Therefore, absorption of PAHs following inhalation, oral, or dermal exposure may be affected by vehicle of administration.

There was no information available on the distribution of PAHs in humans. PAHs appear to be widely distributed in tissues of animals following oral and inhalation exposure; peak tissue concentrations occurred earlier with higher exposure levels. Placental transfer of PAHs appears to be limited, and therefore, fetal levels are not as high as maternal levels.

Metabolism of PAHs occurs in all tissues and involves several possible pathways. Metabolism of PAHs has been studied extensively *in vitro* and *in vivo.* The metabolism products include epoxide intermediates, dihydrodiols, phenols, quinones, and their various combinations. The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulfate esters; the quinones also form glutathione conjugates.

Quantitative data on the excretion of PAHs in humans are lacking. In general, feces is the major elimination route of PAHs in animals following inhalation exposure. Excretion of benzo[a]pyrene appears to be high following low-level exposure in rats but low in dogs and monkeys. PAHs are

eliminated to a large extent within 2 days following low- and high-level oral exposure in rats. Following dermal exposure, elimination of PAHs occurs rapidly in the urine and feces of guinea pigs and rats.

Absorption of inhaled PAHs appears to occur through the mucous lining of bronchi, while ingested PAHs are taken up by the gastrointestinal tract in fat-soluble compounds. Percutaneous absorption is through passive diffusion. The mechanism of action of most PAHs involves covalent binding to DNA by PAH metabolites. The bay region diol epoxide intermediates of PAHs are currently considered to be the ultimate carcinogen for alternant PAHs. Once the reactive bay region epoxide is formed, it may covalently bind to DNA and other cellular macromolecules and presumably initiate mutagenesis and carcinogenesis.

2.3.1 Absorption

2.3.1.l Inhalation Exposure

Absorption of PAHs in humans following inhalation exposure can be inferred from the presence of urinary metabolites of PAHs in workers exposed to these compounds in an aluminum plant (Becher and Bjorseth 1983). The high concentration of PAHs in the occupational setting did not correspond to the amount of PAHs deposited, metabolized, and excreted in the urine in this study. The authors suggested that PAHs adsorbed to airborne particulate matter may not be bioavailable and that the dose-uptake relationship may not be linear over the entire PAH concentration range.

Twelve workers from a coke plant participated in an intensive skin monitoring program combined with personal air sampling and biological monitoring during 5 consecutive 8-hour shifts (Van Rooij et al. 1993b). The mean concentration of total pyrene in the breathing zone air of the 12 workers ranged from 0.1 to 5.4 μg/m^3. The mean respiratory uptake of pyrene varied between 0.5 and 32.2 μg/day. Based on the estimates of the dermal and respiratory pyrene uptake, it is concluded that an average of 75% of the total absorbed amount of pyrene enters the body through the skin. The total excreted amount of urinary 1-hydroxypyrene as a result of exposure to PAHs during the five consecutive work shifts varied between 36 and 239 nmol. Analysis indicated that dermal absorption was most important in contributing to 1-hydroxypyrene excretion. Of the total dose absorbed by both routes combined,

13-49% is excreted as 1-hydroxypyrene. Variation in excretion is influenced by smoking habits, and consumption of alcohol (see Section 2.3.1.3).

Eleven healthy male smokers and 11 male smokers with lung cancer between the ages of 30-60 years, with a smoking history of 15-25 cigarettes per day for over 10 years were involved in a study (Likhachev et al. 1993). Urinary excretion of benzo[a]pyrene-7,8-diol and 3-hydroxybenzo[a]pyrene was determined. Both benzo[a]pyrene metabolites were detected in the urine, but quantities of 3-hydroxybenzo[a]pyrene were very low. The level of benzo[a]pyrene-7,8-diol in the urine varied considerably both in healthy smokers and smokers with lung cancer. However, the average value of this metabolite in the urine of healthy smokers was significantly higher than in the urine of lung cancer patients who smoked (1.06 mg/kg/day versus 0.56 mg/kg/day).

Animal studies on inhalation absorption of PAHs are limited to benzo[a]pyrene exposure. Rapid absorption was evident following inhalation exposure of low and high levels of benzo[a]pyrene to rats. Acute and intermediate-duration exposure to 4.8 mg/m^3 [^{14}C]-benzo[a]pyrene by nose-only inhalation in rats resulted in elevated levels of radioactivity in tissues and excreta within 3 hours of exposure (Wolff et al. 1989c). High levels of radioactivity were detected in the gastrointestinal tract, which may be due to biliary excretion or mucocilliary clearance of benzo[a]pyrene from the upper respiratory tract. Intratracheal administration of 0.001 mg/kg [^{3}H]-benzo[a]pyrene to rats also resulted in rapid absorption through the lungs. Radioactivity in the liver reached a maximum of 21% of the administered dose within 10 minutes of instillation (Weyand and Bevan 1986, 1988). Presence of radioactivity in other tissues and the bile was also indicative of its absorption in rats. Similar results were also seen in guinea pigs and hamsters following intratracheal exposure to benzo[a]pyrene (Weyand and Bevan 1986, 1987b, 1988).

Pregnant Wistar rats were exposed head-only to 200, 350, 500, 650, or 800 mg/m^3 of [^{14}C]-benzo[a]pyrene aerosol for 95 minutes on gestational day 17 (Withey et al. 1993a). Animals were killed immediately or 6 hours postexposure. Concentration of benzo[a]pyrene and metabolites in maternal blood sampled immediately after exposure were elevated 10-fold over the 4-fold increase in dose. At 6 hours postdosing, the increase was still approximately 10-fold, although the actual concentrations were 2-7-fold less than at 0 hours. Concentrations of benzo[a]pyrene and metabolites in fetal blood sampled immediately after exposure were elevated 5-fold over the 4-fold increase in exposure concentrations. Fetal tissues sampled 6 hours post-dosing had a 9-fold increase in

benzo[a]pyrene and metabolite concentration over the dose range, due to lower concentration in the 200-650 mg/m^3 dose groups at 6 hours compared to 0 hours. Fetal concentrations were 2-10-fold less than maternal concentrations. Benzo[a]pyrene concentrations in blood, lung, liver, and fetal tissues were significantly decreased from 0 to 6 hours postexposure while levels in fat tissue increased. For benzo[a]pyrene sampled immediately postdosing, lung > blood > liver > kidney > fat > fetus. For total metabolites sampled immediately postdosing, lung > blood > liver > kidney > fetus > fat. For benzo[a]pyrene sampled 6 hours postdosing, fat > lung > kidney > liver > blood > fetus. For total metabolites sampled 6 hours postdosing, lung = fat > kidney > liver = blood > fetus.

Twenty male Fisher 344 DuCrj rats were divided into two groups and exposed to diesel exhaust containing 0.151 mg/m^3 pyrene or HEPA-filtered air for 8 weeks, 5 days/week, 7 hours/day (Kanoh et al. 1993). At 2, 4, and 8 weeks during the exposure, the rats from each group were put into a metabolic cage and their urine was collected for 24 hours. Urinary levels of 1-hydroxypyrene in the rats of the exposure group increased remarkably over those of the control group, reaching 2.4 times as much by the end of the 2nd week, and 5.6 times by the 4th and 8th weeks.

Inhalation absorption of benzo[a]pyrene may be affected by the size of particles on which benzo[a]pyrene is adsorbed. The elimination of benzo[a]pyrene from the lungs was studied following intratracheal administration of pure benzo[a]pyrene crystals or benzo[a]pyrene coated on carbon particles in two size ranges (0.5-1.0 μm and 15-30 μm) (Creasia et al. 1976). Fifty percent of the pure benzo[a]pyrene crystals was cleared from the lungs within 1.5 hours and >95% cleared within 24 hours, while only 50% of the benzo[a]pyrene adsorbed to the small carbon particles cleared within 36 hours. Elution of benzo[a]pyrene was even slower with the larger particle size (approximately 4-5 days). These results indicate that the bioavailability of benzo[a]pyrene is altered by the particle size of the carrier. The initial lung deposition of [^{3}H]-benzo[a]pyrene adsorbed onto gallium oxide (Ga_2O_3) particles was 4.9 μg of which 3.1% remained after 30 minutes (Sun et al. 1982). A control study, conducted without the Ga_2O_3 particles at a concentration of 1 mg/m^3, found that 8.2 μg was inhaled, of which 0.9% remained in lungs after 30 minutes. The excretion of hydrocarbon was monitored for over 2 weeks at which time nearly all the initial lung burden was recovered in the excreta, indicating complete absorption of the instilled hydrocarbon. Significant differences in the clearance of benzo[a]pyrene coated with Ga_2O_3 and pure benzo[a]pyrene suggested that a substantial amount of benzo[a]pyrene/Ga_2O_3 particles was removed from the lungs by mucocilliary clearance and subsequent ingestion.

The above results corroborate findings in an *in vitro* experiment by Gerde and Scholander (1989) who developed a model of the bronchial lining layer. These investigators concluded that the release rate of PAHs from carrier particles is the rate-determining step in the transport of PAHs from these particles to the bronchial epithelium.

The absorption of benzo[a]pyrene may also be affected by the solubility of the vehicle used in administration. Approximately 70% of benzo[a]pyrene administered with triethylene glycol was excreted 6 hours following intratracheal instillation (Bevan and Ulman 1991). Excretion rates of benzo[a]pyrene were only 58.4% and 56.2% with ethyl laurate and tricaprylin, respectively, within a 6-hour period. The small volume of benzo[a]pyrene instilled is probably deposited in the bronchial region which allows more water-soluble materials (triethylene glycol) to pass the mucous layer lining than water-insoluble compounds (ethyl laurate and tricaprylin) (Bevan and Ulman 1991).

Nasal instillation of [^{3}H]-benzo[a]pyrene (0.13 mg/kg) to hamsters resulted in the metabolism of [^{3}H]-benzo[a]pyrene in the nasal cavity (Dahl et al. 1985). A large fraction of the metabolites was recovered from the epithelial surface, indicating that benzo[a]pyrene was first absorbed in the mucosa, metabolized, and returned to the mucus. Monkeys and dogs received nasal instillation of [^{14}C]-benzo[a]pyrene at doses of 0.16-0.21 mg/kg (Petridou-Fischer et al. 1988). Radiolabeled metabolites were detected in the nasal cavity, but little or no activity was detected in the blood and excreta of either species during the 48 hours after exposure. These results indicate that absorption of benzo[a]pyrene and/or its metabolites was poor or very slow following nasal instillation in monkeys and dogs.

2.3.1.2 Oral Exposure

There is evidence suggesting that benzopyrene is orally absorbed in humans (Buckley and Lioy 1992; Hecht et al. 1979). Following ingestion of diets containing very low levels of benzo[a]pyrene, the metabolite, 1-hydroxypyrene, was detected in the urine (Buckley and Lioy 1992). No quantitative data on the excretion of the benzo[a]pyrene were provided. The concentration of benzo[a]pyrene in human feces was examined in eight volunteers who ingested broiled meat that contained approximately 9 µg of benzo[a]pyrene (Hecht et al. 1979). The feces of these individuals did not contain detectable levels of benzo[a]pyrene (<0.1 µg/person), which is similar to what was seen following consumption of

control meat that contained undetectable amounts of benzo[a]pyrene by these same volunteers, suggesting that most of the ingested benzo[a]pyrene was absorbed.

Oral absorption of benzo[a]pyrene in rats is incomplete and may be influenced by the presence of oils and fat in the gastrointestinal tract. Oral absorption of benzo[a]pyrene was estimated to be 40%, with a bioavailability of 7.8-11.5%, in Sprague-Dawley rats infused intraduodenally to a total dose of approximately 0.0005 mg/kg for 90 minutes (Foth et al. 1988a). Nearly 80% of a gavage dose of 0.0527 mg/kg [^{14}C]benzo[a]pyrene in peanut oil was detected in the excreta of rats 48 hours after exposure; however, some of the recovered radioactivity may never have been absorbed by the alimentary tract of the rats, but may have passed into the excreta in the peanut oil (Hecht et al. 1979). Radioactivity found in the liver, lungs, kidneys, and testis following a low dose of [^{3}H]-benzo[a]pyrene to Sprague-Dawley rats provides supporting evidence of oral absorption (Yamazaki and Kakiuchi 1989; Yamazaki et al. 1987). The extent of oral absorption in rats is enhanced when benzo[a]pyrene is solubilized in a vehicle (triolein, soybean oils, high-fat diet) that is readily absorbed following low- and high-dose levels (Kawamura et al. 1988; O'Neill et al. 1991).

Oral absorption of benzo[a]pyrene was estimated to be 38-58% following dietary or gavage exposure to high levels in rats (Chang 1943). Anthracene was absorbed to a slightly higher extent (53-74%) than benzo[a]pyrene in rats while phenanthracene was poorly absorbed (4-7%) (Chang 1943). However, the data were limited because an inadequate number of rats was used and study details were lacking.

In general, the oral absorption of chrysene, dibenzanthracene, and pyrene was high following exposure to high doses in rats (Chang 1943; Grimmer et al. 1988; Withey et al. 1991). Following dietary or gavage administration of chrysene in rats, 64-87% of the dose was excreted in the feces (Chang 1943). Recovery of chrysene in excreta of Wistar rats was 74% four days after a single gavage dose of 22 mg/kg chrysene in corn oil (Grimmer et al. 1988). Administration of dibenz[a,h]anthracene in the diet (250 mg) or by stomach tube (200 mg) resulted in more than 90% of the dose being excreted in the feces of white rats (Chang 1943). As with chrysene, absorption of dibenz[a,h]anthracene could not be quantified. Male Wistar rats administered 2-15 mg/kg of [^{14}C]-pyrene recovered 68-92% of the dose in the excreta by 6 days postexposure (Withey et al. 1991). Bioavailability of pyrene and its metabolites was 65-84% over a period of 8 hours following administration.

Blood levels of fluoranthene, pyrene, and benz[a]anthracene after oral administration were examined in rats (Lipniak and Brandys 1993). Fluoranthene, pyrene, or benz[a]anthracene in Tween 80/isotonic saline, was administered orally to rats at a dose of 20 mg/kg. Blood levels after administration indicated that peak concentrations of the three compounds were reached at 1-2 hours after administration. The peak concentration of fluoranthene (≈30 mg/cm^3) was twice as high as that of pyrene, and 5 times higher than benz[a]anthracene.

The effect of diet matrix (gel or powder) on urinary excretion of 1-hydroxypyrene and hydrocarbon binding to DNA was investigated in mice (Wu et al. 1994). Female mice were fed a gel or powder diet containing manufactured gas plant (MGP) residue (coal tar) at 0.1% or 0.3% for 15 days, or the corresponding control diet. Two mixtures of MGP residue were used: Mix of 3 combining equal amounts of samples from three different MGP plant sites, and Mix of 7 combining equal amounts of samples from seven different MGP plant sites, including those used in the Mix of 3. The mixtures contained pyrene, benz[a]anthracene, chrysene, benzo[b]fluorene, benzo[k]fluorene, benzo[a]pyrene, indeno[1,2,3-cd]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene. Data were presented in terms of pyrene consumed and 1-hydroxypyrene excreted. Urine was collected on the first, seventh, and fourteenth day of diet administration. 1-Hydroxypyrene levels in the urine were determined using HPLC and fluorescence. Diet matrix had little effect on the bioavailability of the PAHs.

The intestinal absorption of PAHs is highly dependent on the presence of bile (Rahman et al. 1986). To study the role of bile in the intestinal absorption of PAHs, conscious rats with bile duct and duodenal catheters were given [^{3}H]-benzo[a]pyrene, phenanthrene, anthracene, 2,6-dimethylnaphthalene (DMN), and 7,12-dimethylbenz[a]anthracene (DMBA) with or without exogenous bile. The efficiency of PAH absorption was estimated from the cumulative recovery of radioactivity in the bile and urine over 24 hours. The efficiencies of absorption without bile (as a percentage of absorption with bile) were benzo[a]pyrene, 22.9%; phenanthrene, 96.7%; anthracene, 70.8%; DMN, 91.6%; DMBA, 43.4%. Absorption of the four- or five-membered rings (DMBA and benzo[a]pyrene) was strongly dependent on the presence of bile in the intestinal lumen. The absorption of the tricyclic PAHs (phenanthrene and anthracene) differed with respect to their dependency on bile for efficient absorption. This difference correlated with a difference in water solubility, with anthracene being 18 times less water-soluble than phenanthrene. Those products with low water solubility are dependent on the creation of an intermediate phase of the products of lipolysis and bile salts (Rahman et al. 1986). These reactions occur during the normal process of lipid digestion and absorption in the intestine.

2.3.1.3 Dermal Exposure

Application of 2% crude coal tar to the skin of humans for 8-hour periods on 2 consecutive days yielded evidence of PAH absorption (Storer et al. 1984). Phenanthrene, anthracene, pyrene, and fluoranthene were detected in the blood, but benzo[a]pyrene (which is present in coal tar) was not detected. This difference was attributed to differences in percutaneous absorption, rapid tissue deposition after absorption, or metabolic conjugation with rapid urine excretion. In another study, coal tar ointment was applied to skin of volunteers at various sites (Van Rooij et al. 1993a). The surface disappearance of PAH and the excretion of urinary 1-hydroxy-pyrene were used as parameters for dermal absorption. Surface disappearance measurements showed low but significant differences in dermal PAH absorption between anatomical sites: shoulder > forehead, forearm, groin > ankle, hand (palmar site). An *in vitro* study using human skin revealed that the extent of permeation across viable human skin after 24 hours was estimated to be 3% of the total applied radioactivity from [^{14}C]-benzo[a]pyrene (10 µg/cm^2) (Kao et al. 1985). Using human cadaver skin, it was shown that 23.7±9.7% of the applied benzo[a]pyrene penetrated into the skin (Wester et al. 1990). These results suggest that substantial metabolism and/or binding of benzo[a]pyrene takes place in viable human skin which limits the amount of PAH available to penetrate the skin into the systemic circulation.

Twelve workers from a coke plant participated in an intensive skin monitoring program combined with personal air sampling and biological monitoring during 5 consecutive 8-hour shifts (Van Rooij et al. 1993b). Measurements on exposure pads at six skin sites (jaw/neck, shoulder, upper arm, wrist, groin, ankle) showed that mean total skin contamination of the 12 workers ranged between 21 and 166 µg pyrene per day. The dermal uptake of pyrene ranged between 4 and 34 µg/day, which was about 20% of the pyrene contamination on the skin. The mean concentration of total pyrene in the breathing zone air of the 12 workers ranged from 0.1 to 5.4 µg/m^3. The mean respiratory uptake of pyrene varied between 0.5 and 32.2 µg/day. Based on the estimates of the dermal and respiratory pyrene uptake, it is concluded that an average of 75% of the total absorbed amount of pyrene enters the body through the skin. The total excreted amount of urinary 1-hydroxy-pyrene as a result of exposure to PAHs during the 5 consecutive work shifts varied between 36 and 239 nmol. Analysis indicated that dermal absorption was most important in contributing to 1-hydroxy-pyrene excretion. Of the total dose absorbed by both routes combined, 13-49% is excreted as 1-hydroxy-pyrene. Variation in excretion is influenced by smoking habits, and consumption of alcohol.

Percutaneous absorption of [^{14}C]-benzo[a]pyrene in mice, rats, monkeys, and guinea pigs is rapid and high (Ng et al. 1992; Sanders et al. 1986; Wester et al. 1990; Yang et al. 1989). A single dose of 7 µg/cm^2 [^{14}C]-benzo[a]pyrene in acetone was applied to a 4-cm^2 area of the dorsal skin of female hairless guinea pigs for 24 hours (Ng et al. 1992). Approximately 73% of the administered dose was absorbed dermally by 7 days postexposure; most of the dose was absorbed by day 3. The skin wash at 24 hours of exposure contained about 10.6% of dose (Ng et al. 1992). *In vitro* absorption of benzo[a]pyrene through guinea pig skin demonstrated similar results; 67% absorption in a 24-hour exposure (Ng et al. 1992). Seven days after exposure to 125 µg/cm^2 benzo[a]pyrene, 80% of the total recovered radioactivity was eliminated in the feces of mice (Sanders et al. 1986). The site of application still retained 7% of the recovered radioactivity after 7 days. However, the area of application was not covered to prevent animals from licking the test material which may have lead to ingestion of benzo[a]pyrene.

Groups of 12 male Wistar rats were dosed with 2, 6, or 15 mg/kg of [^{14}C]-pyrene applied to 4 cm^2 of a shaved area of the mid-back (Withey et al. 1993b). Three animals in each dose group were killed at 1,2,4, and 6 days postdosing, and the brain, lungs, heart, liver, spleen, kidneys, testes, muscle, and perirenal fat were removed and analyzed for pyrene and [^{14}C]-pyrene equivalents. Blood, urine, and feces, as well as the skin from the application site were also analyzed. The rate of uptake from the skin was rapid (t1/2 = 0.5-0.8 d) relative to rate processes for the other organs, and about 50% of the applied dose was excreted over the 6 days of the study. Levels of pyrene were highest in the liver, kidneys, and fat. Levels of metabolites were also high in the lung.

Dermal absorption of benzo[a]pyrene in rats and monkeys may be affected by the vehicle of administration (Wester et al. 1990; Yang et al. 1989). Following application of 10 ppm benzo[a]pyrene on the skin of rhesus monkeys, an average absorption of 51 ± 22% was reported with acetone vehicle and 13.2 ± .4% with soil; however, absorption data were based on radioactivity recovered in urine only, and not in feces (Wester et al. 1990). The great variation in the absorption with the acetone vehicle limits these results. This may be related, in part, to the dependence on monitoring radioactivity recovered in urine only as opposed to monitoring radioactivity recovered in urine and feces. Disappearance of the applied dose from the application site was 40% at 24 hours following administration (Wester et al. 1990). Sprague-Dawley rats absorbed 4-5 times more of a 1 ppm dose of benzo[a]pyrene when it was applied dermally alone, compared to a soil-sorbed crude oil mixture (Yang et al. 1989). The greater lipophilicity of the crude oil alone probably increased the

rate of dermal uptake of the test material, since the authors determined that absorption was dependent on the monolayer of soil in contact with the skin, which is comparable to the contact between the skin and oil. Therefore, the soil binding of the PAHs may have slowed absorption. However, no quantitative data were available.

Female Sprague-Dawley rats were exposed dermally to [^{3}H]-benzo[a]pyrene (1 ppm) containing petroleum crude oil alone or in fortified soil matrix for 4 days (Yang et al. 1989). Recovery of radioactivity was 35.3% of the dose applied in oil, as follows: urine (5.3% of dose), feces (27.5%), and tissues (2.5%) 96 hours after beginning of exposure. Recovery was 9.2% of applied dose with benzo[a]pyrene from petroleum crude-fortified soil; recoveries in urine, feces, and tissues were 1.9%, 5.8%, and 1.5%, respectively, at 96 hours. Benzo[a]pyrene (10 ppm) with acetone vehicle or in soil was applied to a 12 cm^{2} area of abdominal skin of female rhesus monkeys for 24 hours (Wester et al. 1990). Urine contained 5l ± 22% of the dose with acetone vehicle and 13.2 ± 3.4% with soil.

The percutaneous absorption of [^{14}C]-anthracene (9.3 µg/cm^{2}) was 52.3% in rats, estimated from radioactivity in urine, feces, and tissues over a 6-day period (Yang et al. 1986). Over time, the permeation of anthracene significantly decreased suggesting that anthracene was dermally absorbed in a dose-dependent manner. Diffusion of anthracene through the skin (stratum corneum) depended on the amount of anthracene on the skin's surface.

When 6.25 µg/cm^{2} [^{14}C]-phenanthrene and pyrene was applied to guinea pigs, dermal absorption was 80% and 94%, respectively (Ng et al. 1991, 1992). *In vitro* absorption of phenanthrene and pyrene in guinea pig skin was about 79-89% and 70%, respectively (Ng et al. 1991, 1992).

Monitoring the removal of compounds from the epidermis is indicative of measuring the compound's dermal absorption. The disappearance of radiolabeled benzo[a]pyrene and its metabolites from the epidermis was monophasic, following first order kinetics with a half-life of approximately 2 hours (Melikian et al. 1987). Recovery of the radiolabel was 99-100% throughout the period of the experiment (8 hours), indicating that volatilization of benzo[a]pyrene from the skin was not a confounding factor (Melikan et al. 1987). In contrast, removal of one of its metabolites, 7,8-dihydroxy-9,10-epoxy-7,8,9,l0-tetrahydrobenzo[a]pyrene (anti-BPDE), from the epidermis was biphasic. The second, slower phase of removal suggested that the stratum comeum, the outermost layer of skin which consists of several layers of inactive, keratinized cells surrounded by extracellular

lipids, may act as a reservoir that can retain and slowly release topically applied lipophilic substances such as benzo[a]pyrene but is penetrated rapidly by more polar compounds such as anti-BPDE.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of PAHs in humans following inhalation exposure. In general, tissue distribution of benzo[a]pyrene following inhalation exposure is qualitatively similar for different species (Bevan and Weyand 1988; Weyand and Bevan 1986, 1987a, 1988; Wolff et al. 1989c). Highest radioactivity was distributed to the cecum, small intestine, trachea, kidneys, and stomach in rats following a 3-hour or 4-week inhalation exposure to 4.8 mg/m^3 [^{14}C]-benzo[a]pyrene (Wolff et al. 1989c). The lungs and liver of rats contained 2.7% and 4.6% of the recovered dose 6 hours after intratracheal administration of 0.001 mg/kg [^{3}H]-benzo[a]pyrene (Bevan and Weyand 1988). [^{3}H]-Benzo[a]pyrene intratracheally administered to rats demonstrated that the highest fractions were distributed to the lung, liver, kidney, gastrointestinal tract, and carcass (Weyand and Bevan 1986, 1987a, 1988). The concentration of benzo[a]pyrene and its metabolites in the intestine increased with time, suggesting the occurrence of biliary excretion and enterohepatic recirculation. Tissue distribution of radioactivity was qualitatively similar in guinea pigs and hamsters (Weyand and Bevan 1987b). Mice that received 2.5 mg/kg benzo[a]pyrene intratracheally also experienced a similar tissue distribution, but Schnizlein et al. (1987) noted that as the lung burden of benzo[a]pyrene diminished, radioactivity continued to increase in the lung-associated lymph nodes for 6 days. This accumulation may eventually affect humoral immunity.

The distribution pattern of benzo[a]pyrene was not significantly affected following aerosol exposure with or without Ga_2O_3 particles (Sun et al. 1982). However, significant differences in the levels of benzo[a]pyrene delivered to the different tissues did exist. Maximum levels were achieved in the liver, esophagus, small intestine, and blood at 30 minutes following exposure. At 12 hours, maximum levels were seen in the lower gastrointestinal tract. Higher tissue levels of hydrocarbon resulted from absorption of benzo[a]pyrene-Ga_2O_3 particles. Inhaled benzo[a]pyrene adsorbed on insoluble Ga_2O_3 particles was cleared predominantly by mucocilliary transport and ingestion. This latter mechanism of

absorption led to the increased levels and longer retention times of benzo[a]pyrene in the stomach, liver, and kidneys (Sun et al. 1982).

Pregnant Wistar rats inhaled head-only high levels of [^{14}C]-pyrene aerosol on gestational day 17 (Withey et al. 1992). Concentrations of pyrene and metabolites in maternal and fetal blood were elevated 8-fold with a fourfold increase in exposure concentrations. However, pyrene levels in fetal blood were about 10 times lower than maternal blood immediately after exposure. In general, radioactivity increased in fat but decreased in blood, lungs, and liver tissues from 0 to 6 hours postexposure. There was only a small increase in the concentration of radioactivity in fetuses over the whole exposure range compared to maternal levels, suggesting placental transfer of pyrene and its metabolites are limited or that metabolism in fetal tissues is limited.

In a similar study, pregnant Wistar rats were exposed head-only to 200, 350, 500, 650, or 800 mg/m^3 of [^{14}C]-benzo[a]pyrene aerosol for 95 minutes on gestational day 17 (Withey et al. 1993a). Animals were killed immediately or 6 hours postexposure. Concentration of benzo[a]pyrene and metabolites in maternal blood sampled immediately after exposure were elevated 10-fold over the 4-fold increase in dose. At 6 hours postdosing, the increase was still approximately 10-fold, although the actual concentrations were 2-7-fold less than at 0 hours. Concentrations of benzo[a]pyrene and metabolites in fetal blood sampled immediately after exposure were elevated 5-fold over the 4-fold increase in exposure concentrations. Fetal tissues sampled 6 hours post-dosing had a 9-fold increase in benzo[a]pyrene and metabolite concentration over the dose range, due to lower concentration in the 200-650 mg/m^3 dose groups at 6 hours compared to 0 hours. Fetal concentrations were 2-10-fold less than maternal concentrations. Benzo[a]pyrene concentrations in blood, lung, liver, and fetal tissues were significantly decreased from 0 to 6 hours postexposure while levels in fat tissue increased. For benzo[a]pyrene sampled immediately postdosing, lung > blood > liver > kidney > fat > fetus. For total metabolites sampled immediately postdosing, lung > blood > liver > kidney > fetus > fat. For benzo[a]pyrene sampled 6 hours postdosing, fat > lung > kidney > liver > blood > fetus. For total metabolites sampled 6 hours postdosing, lung = fat > kidney > liver = blood > fetus.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of PAHs in humans following oral exposure.

Tissue levels of benzo[a]pyrene in Sprague-Dawley rats were highest 2-8 days after initial exposure to multiple doses of 0.0005 mg [^{3}H]-benzo[a]pyrene (Yamazaki and Kakiuchi 1989). The highest radioactivities were found in the kidney and testis. [^{3}H]-Benzo[a]pyrene distributed to the protein fractions of the liver, lung, and kidney (Yamazaki et al. 1987). The radioactivity in the protein fractions of these tissues increased gradually over time. In contrast, the radioactivity in the lipid fractions of these tissues accounted for 70% of the administered dose at 3 hours but decreased rapidly with time. The nucleic acid fraction maintained approximately 10% of the total radioactivity throughout the experiment. The increase in protein binding of radioactivity associated with benzo[a]pyrene and its metabolites, and the persistence of the radioactivity associated with the protein fractions, suggests that protein binding may allow benzo[a]pyrene and its metabolites to accumulate in certain tissues, thus increasing the likelihood of cytotoxicity, mutagenicity, or carcinogenicity of benzo[a]pyrene and its metabolites in these organs. In addition, these organs have low metabolic activity while the liver has a high detoxification potential and can facilitate the excretion of these toxic products (Yamazaki et al. 1987).

Single oral doses of 12 mg/kg [^{14}C]-benzo[a]pyrene were administered by gavage to pregnant NMRI:Han mice on gestational days 11, 12, 13, or 18 (Neubert and Tapken 1988). Distribution of radioactivity was measured at 6, 24, and 48 hours after exposure. Maternal and embryo levels were highest with exposure on gestational day 11. The difference in radioactivity between maternal and embryo liver tissues increased when exposure occurred at later gestation. In another experiment, mice were exposed to 24 mg/kg benzo[a]pyrene for 3 consecutive days during early (gestational days 9-l1) or late gestation (days 15-17) (Neubert and Tapken 1988). Maternal tissue levels were not much different from those observed following the administration of single doses. After multiple dose administration, elimination appeared to be faster in maternal tissues, but slower in embryonic tissues. Placental levels were always higher than those in embryonic tissue. Results suggest that benzo[a]pyrene does not cross the placental barrier readily and, therefore, that levels in embryonic tissues of mice never reach levels found in maternal tissues.

In general, orally absorbed benz[a]anthracene, chrysene, and pyrene were rapidly and widely distributed in the rat (Bartosek et al. 1984; Withey et al. 1991). Maximum concentrations of benz[a]anthracene and chrysene in perfused tissues, like the liver, blood, and brain, were achieved within l-2 hours after administration of high doses (76 and 152 mg/kg) (Bartosek et al. 1984). Maximum levels in lesser perfused tissues, like adipose and mammary tissue, were reached in

3-4 hours. In male Wistar rats receiving a gavage dose of 2-15 mg/kg of [^{14}C]-pyrene, the fat had the highest tissue levels of radioactivity, followed by kidney, liver, and lungs (Withey et al. 1991).

Orally absorbed dibenz[a,h]anthracene in rats was also widely distributed to several tissues (Daniel et al. 1967). However, maximum tissue concentrations were not reached until 10 hours after administration. Highest tissue concentrations were in the liver and kidneys, followed by adrenal glands, ovaries, blood, and fat. Soon after administration, large quantities of dibenz[a,h]anthracene were found in the liver and kidneys. The elimination rate from these organs was rapid. At 3-4 days after administration, dibenz[a,h]anthracene was distributed only in the adrenal glands, ovaries, and fat.

The permeability of the placenta to dimethylbenz[a]anthracene, benzo[a]pyrene, and 3-methylcholanthrene (MC) was compared by Shendrikova and Aleksandrov (1974). Pregnant rats received the PAH orally in sunflower oil at a dose of 200 mg/kg on the 21st day of pregnancy. Within 30 minutes after administration of dimethylbenz[a]anthracene, trace amount of the compound could be detected in the fetus. Maximum levels (1.53-1.6 µg/g) were reached 2-3 hours after administration. Only trace amounts were detected in the fetus at 5 hours after administration. Concentration profiles in the liver and placenta were similar to those seen in the fetus. Benzo[a]pyrene was detected in the fetus at 2.77 µg/g. MC was only present in trace amounts. Concentration differences in the fetus among the various PAHs appeared to be highly dependent on the gastrointestinal absorption of the compound. The difference in fetal concentration of the PAHs did not reflect their ability to permeate the placenta.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of PAHs in humans following dermal exposure. Evidence regarding the distribution of PAHs in animals following dermal exposure is limited. Although PAHs can readily penetrate the skin, there are few data on distribution to tissues. In one published study on this subject, only 1.3% of an applied dose of [^{14}C]-anthracene (9.3 µg/cm^2) was detected in tissues, primarily liver and kidneys, of rats 6 days after administration (Yang et al. 1986). Groups of 12 male Wistar rats were dosed with 2, 6, or 15 mg/kg of [^{14}C]-pyrene applied to 4 cm^2 of a shaved area of the mid back (Withey et al. 1993b). Three animals in each dose group were killed at

1, 2, 4, and 6 days postdosing, and the brain, lungs, heart, liver, spleen, kidneys, testes, muscle, and perirenal fat were removed and analyzed for pyrene and [^{14}C]-pyrene equivalents. Blood, urine, feces, as well as the skin from the application site were also analyzed. The rate of uptake from the skin was rapid (t1/2 = 0.5-0.8 d) relative to rate processes for the other organs, and about 50% of the applied dose was excreted over the 6 days of the study. Levels of pyrene were highest in the liver, kidneys, and fat. Levels of metabolites were also high in the lung.

2.3.3 Metabolism

The lipophilicity of PAHs enables them to readily penetrate cellular membranes and remain in the body indefinitely. However, the metabolism of PAHs renders them more water-soluble and more excretable. Metabolism of PAHs occurs in all tissues. The metabolic process involves several possible pathways with varying degrees of enzyme activities. The activities and affinities of the enzymes in a given tissue determine which metabolic route will prevail.

The metabolism of PAHs has been studied extensively *in vitro* and *in vivo.* The most commonly used system is the rat liver microsomal fraction, although other species are also used. Cells and cultured tissues from human and other animals have also significantly contributed to the elucidation of the PAH metabolic scheme.

The structural similarity of PAHs contributes to the similarities that exist in their biotransformation. Benzo[a]pyrene metabolism has been extensively reviewed and will be used as a model for PAH metabolism. In the many microsomal, cell, and cultured tissue preparations that have been examined, the metabolic profiles are qualitatively similar. However, there are differences in the relative levels and rates of formation of specific metabolites among tissues and cell preparations used from various animal species and strains. These differences are susceptible to change as a result of pretreatment of the animals with either inducers or inhibitors of particular enzymes. Furthermore, it is known that the metabolism of alternant PAHs (such as benzo[a]pyrene, benz[a]anthracene, chrysene, and dibenz[a,h]anthracene) differs from nonalternant PAHs (such as benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, and indeno[1,2,3-c,d]pyrene) (see Section 2.2). Therefore, the metabolism of benzo[b]fluoranthene will also be discussed as a model for nonalternant PAH metabolism.

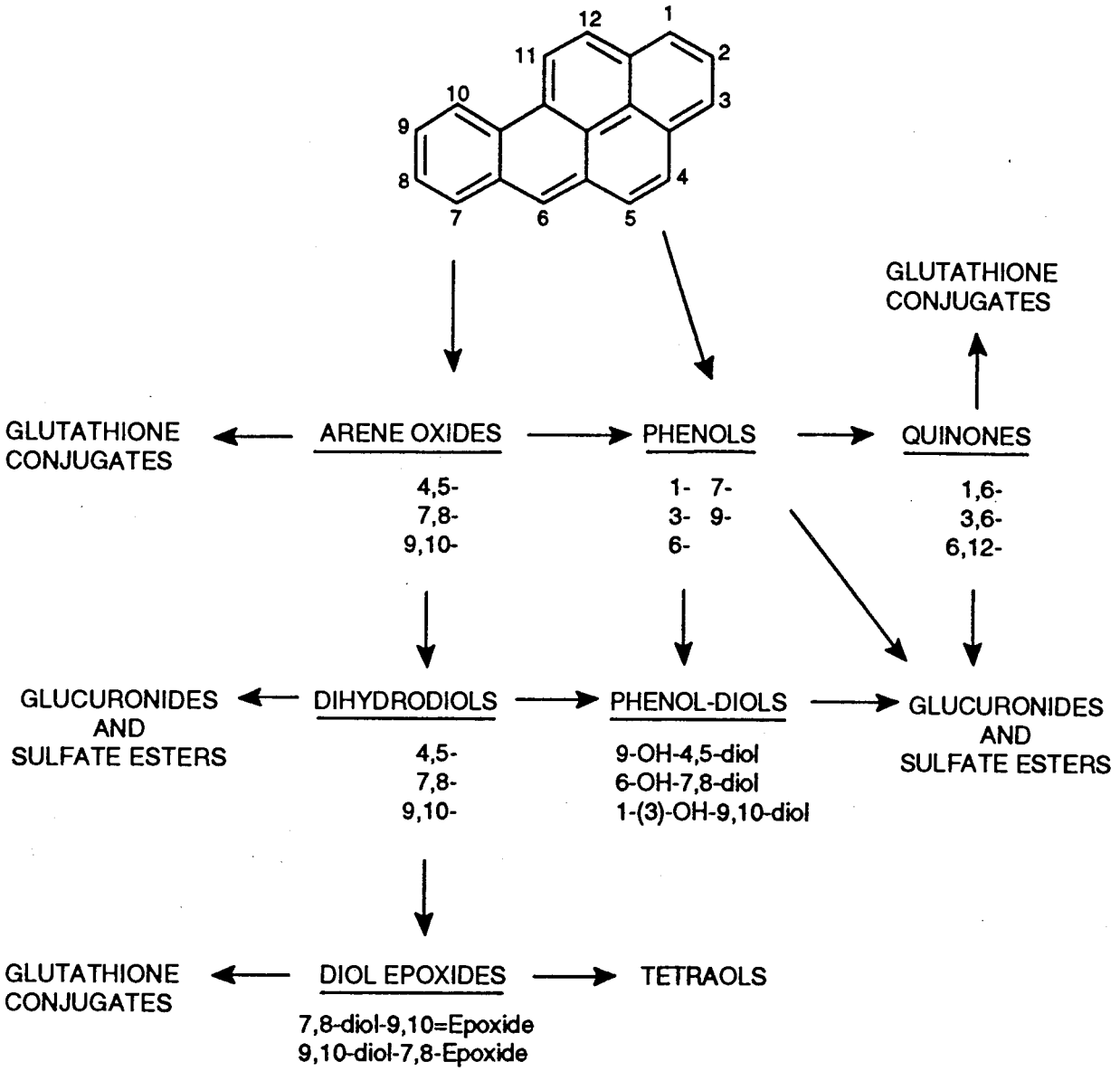
The metabolism of benzo[a]pyrene is summarized in Figure 2-3. Benzo[a]pyrene is metabolized initially by the microsomal cytochrome P-450 systems to several arene oxides. Once formed, these arene oxides may rearrange spontaneously to phenols, undergo hydration to the corresponding trans-dihydrodiols in a reaction catalyzed by microsomal epoxide hydrolase, or react covalently with glutathione, either spontaneously or in a reaction catalyzed by cytosolic glutathione-S-transferases (IARC 1983). Phenols may also be formed by the P-450 system by direct oxygen insertion, although unequivocal proof for this mechanism is lacking. 6-Hydroxybenzo[a]pyrene is further oxidized either spontaneously or metabolically to the 1,6-, 3,6-, or 6,12-quinones. This phenol is also a presumed intermediate in the oxidation of benzo[a]pyrene to the three quinones catalyzed by prostaglandin endoperoxide synthetase (Panthanickal and Marnett 1981). Evidence exists for the further oxidative metabolism to two additional phenols. 3-Hydroxybenzopyrene is metabolized to the 3,6-quinone and 9-hydroxy-benzo[a]pyrene is further oxidized to the K-region 4,5-oxide, which is hydrated to the corresponding 4,5-dihydrodiol (4,5,9-triol). The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulfate esters; the quinones also form glutathione conjugates (Agarwal et al. 1991; IARC 1983).

In addition to being conjugated, the dihydrodiols undergo further oxidative metabolism. The cytochrome P-450 system metabolizes benzo[a]pyrene-4,5-dihydrodiol to a number of uncharacterized metabolites, while the 9,10-dihydrodiol is metabolized predominantly to its l- and/or 3-phenol derivative with only minor quantities of a 9,10-diol-7,8-epoxide being formed. In contrast to the 9,10-diol, benzopyrene-7,8-diol is metabolized to a 7,8-dihydrodiol-9,10-epoxide, and phenol-diol formation is a relatively minor pathway. The diol epoxides can be conjugated with glutathione either spontaneously or by a glutathione-S-transferase catalyzed reaction. They may also hydrolyze spontaneously to tetrols (Hall and Grover 1988).

The route by which PAHs and other xenobiotics enter the body may determine their fate and organ specificity. For example, an inhaled compound may bypass the first-pass effect of the liver and reach peripheral tissues in concentrations higher than one would see after oral exposures. Enzyme activities among tissues are variable.

Benzo[a]pyrene was metabolized *in vitro* by human bronchial epithelial and lung tissue to the 9,10-dihydrodiol, 7,8-dihydrodiol, and small quantities of the 4,5-dihydrodiol and 3-hydroxybenzo[a]pyrene, all of which are extractable into ethyl acetate (Autrup et al. 1978; Cohen et

FIGURE 2-3. Proposed Metabolic Scheme for Benzo(a)pyrene.



al. 1976; Kiefer et al. 1988). These metabolites also conjugated with glutathione and sulfates, but none conjugated with glucuronide. The rate of formation of the dihydrodiols was greater in the bronchial epithelium than in the lung (Autrup et al. 1978; Cohen et al. 1976). This may render some areas of the respiratory tract more sensitive to the effects of carcinogens. One principal difference seen in human lung was the generation of a major ethyl acetate-soluble metabolite that was identified as the sulfate conjugate of 3-hydroxybenzo[a]pyrene, benzo[a]pyrene-3-yl-hydrogen sulfate. This sulfate is very lipid soluble and, thus, would not be readily excreted in the urine (Cohen et al. 1976). Activation of benzo[a]pyrene has also been detected in human fetal esophageal cell culture (Chakradeo et al. 1993).

Intratracheal instillation of benzo[a]pyrene to rats resulted in quinones constituting the highest concentration of metabolites in the lung and the liver within 5 minutes after instillation (Weyand and Bevan 1986, 1988). An *in vitro* study with rat lung demonstrated that the lung tissue has a high capacity to form quinones originating from oxidation at the six position of benzo[a]pyrene to form quinones and subsequently to water-soluble products. Ozone exposure resulted in an increase in the metabolism of benzo[a]pyrene metabolites with the greatest increase observed in the formation of metabolites generated by oxidation at the six position. The proposed retention of quinones following ozone exposure might lead to cytotoxicity associated with superoxide-anion generation by quinone-quinol redox-cycling. However, the high levels of benzo[a]pyrene used in this *in vitro* study may not relate to what occurs *in vivo*. Metabolism of benzo[a]pyrene at carbon six was higher at a lower dose than at the higher dose. Therefore, quinone production and detoxification may represent a major pathway of lung PAH detoxification *in vivo* (Basett et al. 1988).

Approximately 50% of the benzo[a]pyrene that was intratracheally instilled in hamsters was metabolized in the nose (Dahl et al. 1985). The metabolite produced in the hamster nose included tetrols, the 4,5-, 7,8-, and 9,10-dihydrodiol, quinones, and 3-and 9-hydroxybenzo[a]pyrene. Similar metabolites were detected in nasal and lung tissues of rats inhaling benzo[a]pyrene (Wolff et al. 1989b). The prevalence of quinone production was not seen in hamsters as it was in rats (Dahl et al. 1985; Weyand and Bevan 1987a, 1988). In monkeys and dogs, dihydrodiols, phenols, quinones, and tetrols were identified in the nasal mucus following nasal instillation of benzo[a]pyrene (Petridou-Fischer et al. 1988). *In vitro* metabolism of benzo[a]pyrene in the ethmoid turbinates of dogs resulted in a prevalence of phenols (Bond et al. 1988). However, small quantities of .quinones and dihydrodiols were also identified.

Rat lung microsomes facilitated the dissociation of small amounts of benzo[a]pyrene from diesel particles, but only a small fraction of the amount dissociated was metabolized (Leung et al. 1988). The ability to dissociate benzo[a]pyrene was related to the lipid content of the microsomal fraction. Microsomes are able to enhance the slow dissociation of a small amount of benzo[a]pyrene from diesel particles in a form that can be metabolized. Free benzo[a]pyrene was principally and extensively metabolized to the 9,10-dihydrodiol.

A human hepatoma cell line (HepG2) has high benzo[a]pyrene-metabolizing activity and converts benzo[a]pyrene to metabolites (Diamond et al. 1980). When [^{3}H]-benzo[a]pyrene was added to the incubate, a large fraction of the radioactivity was not extractable into chloroform. The extractable fraction contained 9,10-dihydrodiols, 7,8-dihydrodiols, quinones, 3-hydroxybenzo[a]pyrene, and the unchanged parent compound. The cell lysate also consisted of the same metabolites, but the proportions of 3-hydroxybenzo[a]pyrene and the parent compound were much higher than in the medium. Conversely, the proportion of water-soluble metabolites in the cell lysate was lower than in the medium. Treatment of the medium and cell lysate with β-glucuronidase converted only 5-7% of the water-soluble metabolites to chloroform-extractable material. Aryl sulfatase had no effect on radioactivity. These results suggested that this human liver tumor cell line does not extensively utilize the phenol detoxification pathway (Diamond et al. 1980).

Metabolism of benzo[a]pyrene in the primary culture of human hepatocytes primarily resulted in the formation of 3-hydroxybenzo[a]pyrene, 4,5-dihydrodiol, 9,10-dihydrodiol, and 7,8-dihydrodiol (Monteith et al. 1987). As the dose of benzo[a]pyrene increased, the amount of metabolites increased linearly. Binding to DNA was associated with the amount of unconjugated 7,8-dihydrodiol. DNA binding was linear up to a benzo[a]pyrene concentration of 100 μmol. At this concentration, binding increased 64-844 times over the extent of binding at 10 umol. As the concentration of benzo[a]pyrene increased, the ratio of dihydrodiol/phenolic metabolites also increased. Although the capacity to form dihydrodiols was not saturated at 100 umol benzo[a]pyrene, there was a change in the relative proportion of the dihydrodiol metabolites formed as the dose of benzo[a]pyrene increased. As benzo[a]pyrene concentration increased, the 9,10-dihydrodiol was the more prevalent metabolite, but levels of 7,8-dihydrodiol also increased (Monteith et al. 1987).

Epoxide hydrolase is a microsomal enzyme that converts alkene and arene oxides to dihydrodiols. Appreciable enzyme activity was observed in human livers. Comparison of epoxide hydrolase

activities with various substrates revealed that the human liver has a single epoxide hydrolase with broad substrate specificity (Kapitulnik et al. 1977). Epoxide hydrolase activity is also present in other tissues and increases the likelihood for carcinogenic effects in these organs. Ethyl acetate extracts of human and rat bladder cultures contained 9,10-dihydrodiol, 7,8-dihydrodiol, and 3-hydroxybenzo[a]pyrene. Covalent binding of [^{3}H]-benzo[a]pyrene with DNA occurring in both human and rat bladder cultures suggested that benzo[a]pyrene-7,8-diol-9, 10-epoxide is generated. The urothelium of the bladder clearly has the ability to generate the ultimate carcinogen (Moore et al. 1982).

Hepatic microsomes from rats induced with 3-methylcholanthrene convert benzo[a]pyrene to benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE) 10 times faster than untreated microsomes. The rate-limiting step in BPDE formation is the competition for P-450 between benzo[a]pyrene and the 7,8-dihydrodiol. Formation of BPDE is directly correlated with the 3-methylcholanthrene inducible form(s) of P-450 (Keller et al. 1987). Formation of the proximate carcinogen, 7,8-dihydrodiol, is stereoselective. Rabbit hepatic microsomes generated more of the 7R,8R enantiomer with an optical purity of >90% (Hall and Grover 1987). The major stereoisomer formed by rat liver microsomes is (+)-diol-epoxide-2 (R,S,S,R absolute conformation) (Jerina et al. 1976, 1980). This metabolite is highly tumorigenic (Levin et al. 1982) and gives rise to the major adduct formed upon reaction with DNA. The adduct is a diol epoxide-deoxyguanosine formed by alkylation at the exocyclic nitrogen (N-2) of deoxyguanosine. This diol epoxide-deoxyguanosine has been isolated from several animal species (Autrup and Seremet 1986; Horton et al. 1985) and human tissue preparations (Harris et al. 1979).

Studies using rat liver microsomes have shown that hydroxy metabolites of benzo[a]pyrene undergo glucuronidation (Mackenzie et al. 1993). Assays with three different DNA-expressed glucuronidases from human liver indicate preferential glucuronidation for the 2- and 5-hydroxy, 4- and 11-hydroxy, or l-, 2-, and 8-hydroxy derivatives of benzo[a]pyrene. There are differences in preferential activities for the glucuronidation of various benzo[a]pyrene metaboiites among the various DNA-expressed glucuronidases from human liver, with some glucuronidases being relatively or totally inactive toward this class of compounds (Jin et al. 1993). The results of this study suggest that the relative content of particular types of glucuronidases in a cell or tissue may be important for determining the extent to which a particular carcinogen is deactivated.

Several xenobiotics can induce enzymes to influence the rat liver microsomal metabolite profiles of various PAHs. For example, AHH, the cytochrome P-450 isoenzyme believed to be primarily responsible for the metabolism of benzo[a]pyrene and other PAHs, is subject to induction by PAHs. Treatment of pregnant and lactating rats with a single intraperitoneal dose of Aroclor 1245 increased the metabolism of benzo[a]pyrene by liver microsomes from pregnant and fetal rats 9-fold and 2-fold, respectively, and 2-fold in lactating rats (Borlakoglu et al. 1993). The pretreatment enhanced the formation of all metabolites, but the ratio of the 7,8-diol (the proximate carcinogen) was increased 3-fold in lactating rats and 5-fold in pregnant rats. Similar results were observed in rabbit lung microsomes (Ueng and Alvares 1993). Cigarette smoke exposure has been shown to increase PAH metabolism in human placental tissue (Sanyal et al. 1993), and in rat liver microsomes (Kawamoto et al. 1993). In studying benz[a]anthracene metabolism, some xenobiotics were found to be weak or moderate inducers, but even less efficient ones altered the benz[a]anthracene profile significantly. Thiophenes equally enhanced oxidation at the 5,6- and the 8,9-positions. Benzacridines favored K-region oxidation (5,6-oxidation) (Jacob et al. 1983b). Indeno[1,2,3-c,d]pyrene stimulated the bay region oxidation (3,4-oxidation) of benz[a]anthracene (Jacob et al. 1985). Similar xenobiotic effects were observed with chrysene as a substrate (Jacob et al. 1987). While some enzyme activities are being enhanced, alternate enzymatic pathways may be suppressed (Jacob et al. 1983a).

Rat liver microsomes also catalyzed benzo[a]pyrene metabolism in cumene hydroperoxide (CHP)-dependent reactions which ultimately produced 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-quinones (Cavalieri et al. 1987). At low CHP concentrations, 3-hydroxybenzo[a]pyrene was the major metabolite. As CHP concentrations increased, levels of quinones increased and levels of 3-hydroxybenzo[a]pyrene decreased. This effect of varying CHP levels was reversed by preincubating with pyrene. Pyrene inhibited quinone production and increased 3-hydroxybenzo[a]pyrene production. Pretreatment with other PAHs like naphthalene, phenanthrene, and benz[a]anthracene nonspecifically inhibited the overall metabolism. The binding of benzo[a]pyrene to microsomal proteins correlated with quinone formation. This suggested that a reactive intermediate was a common precursor. The effects of pyrene on benzo[a]pyrene metabolism indicated that two distinct microsomal binding sites were responsible for the formation of 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-quinone (Cavalieri et al. 1987).

Rat mammary epithelial cells (RMEC) have been shown to activate PAHs (Christou et al. 1987). Cytochrome-P-450 in RMEC is responsible for the monooxygenation of DMBA. Prior exposure’of

cultured cells to benz[a]anthracene induced DMBA metabolism. The metabolite profile following benz[a]anthracene-induction was significantly different from the profile obtained with purified P-450c, the predominant PAH-inducible enzyme in rat liver. The bay region 3,4-dihydrodiol, which was not formed with P-450c, was clearly detectable in RMEC. Low epoxide hydrolase activity in the benz[a]anthracene-induced RMEC limited the formation of all other DMBA dihydrodiols. The DMBA monooxygenase activity of benz[a]anfhracene-induced RMEC was inhibited by a-naphthaflavone. The study concluded that DMBA metabolism by RMEC depended on the induction of P-450c and at least one additional form of P-450 that is sensitive to α-naphthaflavone (Christou et al. 1987).

As expected from results of other studies, the perfused rat lung can release high quantities of benzo[a]pyrene metabolites and conjugates into the perfusate (Molliere et al. 1987). Addition of a liver to this perfusion system up gradient from the lungs reduces the concentration of parent compound and free metabolites to less than 20% of that seen in the liver's absence. The liver provides a protective effect on the lung to inhibit covalent binding of benzo[a]pyrene metabolites to pulmonary macromolecules.

The effects of various factors that can modify the hepatic clearance of PAHs, specifically benz[a]anthracene and chrysene, were studied by Fiume et al. (1983). The hepatic clearance and rate constants of these PAHs were significantly reduced in the perfused livers of fasted rats relative to those of fed rats. This reduction was attributed to a decrease in aryl hydrocarbon hydroxylase activity. Fasting also accelerated the depletion of cytochrome P-450 and other microsomal enzymes. In contrast, pretreatment of the rats with these PAHs resulted in increased clearance of both hydrocarbons from the perfusion medium when compared to control rats.

It was also noted by Fiume et al. (1983) that the livers of male rats demonstrated a significantly higher hepatic clearance of benz[a]anthracene than female rats, perhaps suggesting a sexual difference with aryl hydrocarbon hydroxylase activity. Similar findings regarding sexual differences in the metabolism of chrysene by rat livers were also reported by Jacob et al. (1985, 1987). Furthermore, Fiume et al. (1983) demonstrated that age can play a role in PAH metabolism. The hepatic clearance of PAHs in older rats (2 years) was significantly less than the hepatic clearance in younger rats (8 weeks). However, activation of benzo[a]pyrene to mutagenic derivatives, as measured by the *Salmonella typhimurium* test, with hepatic microsomes from male rats from 3 weeks to 18 months of age showed no age-dependent changes (Hilali et al. 1993).

A proposed metabolic scheme for the metabolism of the nonaltemant PAH, benzo[b]fluoranthene is presented in Figure 2-4. Nonalternant PAHs, in contrast to several alternant PAHs, do not appear to exert their genotoxic effect primarily through the metabolic formation of simple dihydrodiol epoxides. In the case of benzo[b]fluoranthene, there is evidence to suggest that metabolism to the dihydrodiol precursor to its bay-region dihydrodiol does occur. Rather than this metabolite being converted to its dihydrodiol epoxide; however, it appears to be extensively converted to its 5-hydroxy derivative. It is the further metabolism of this phenolic dihydrodiol to 5, 9, 10-trihydroxy- 11,12-epoxy-9,10,11,12-tetra-hydrobenzo[b]fluoranthene that has been linked to the genotoxic activity of benzo[b]fluoranthene in mouse skin (Weyand et al. 1993b). In the case of benzo[j]fluoranthene, two potentially genotoxic metabolites have been identified. These are the trans-4,5- and 9,10-dihydrodiols of benzo[j]fluoranthene. It is the conversion of trans-4,5-dihydro-4,5-dihydroxybenzo[j]fluoranthene to anti-4,5-dihydroxy-5,6a-epoxy-4,5,6,6a-tetrahydrobenzo[j]fluoranthene that is principally associated with DNA adduct formation in mouse skin (LaVoie et al. 1993b; Weyand et al. 1993a). Benzo[k]fluoranthene in rat microsomes was shown to result in the formation of 8,9-dihydrodiol. This dihydrodiol can form a dihydrodiol epoxide that is not within a bay region. This may represent an activation pathway of benzo[k]fluoranthene that may be associated, in part, with its genotoxic activity. In the case of nonalternant PAHs, reactive metabolites, that deviate from classical bay region dihydrodiol epoxides, have been linked to their tumorigenic activity.

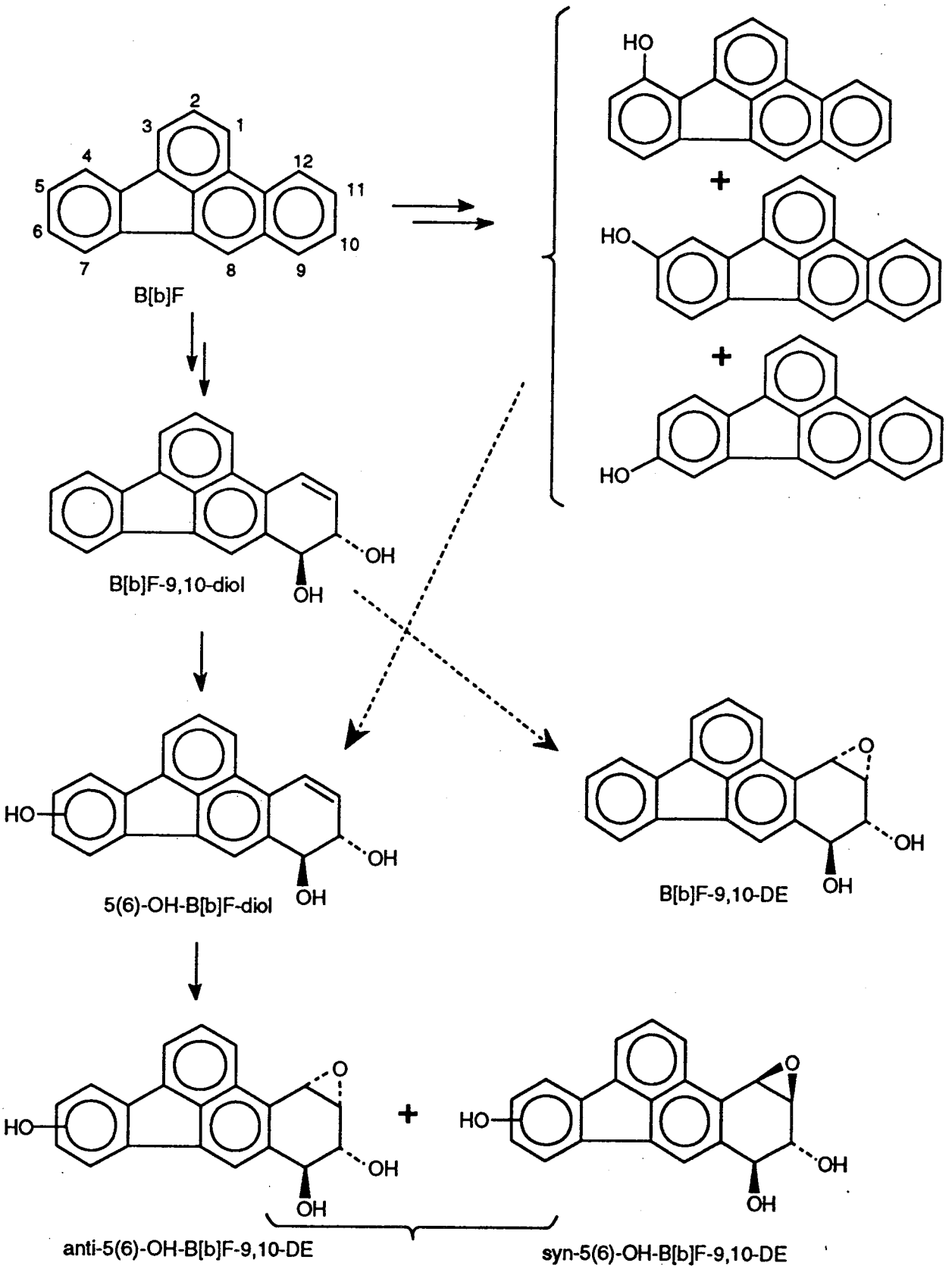
2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Urinary metabolites of PAHs were detected in workers exposed to these compounds in an aluminum plant (Becher and Bjorseth 1983). The ambient levels of PAHs in the workplace (indicated by the authors to exceed 95 mg/m^3, although these data were not presented) did not correspond to the amount of PAHs deposited, metabolized, and excreted in the urine in this study. No quantitative inhalation data were available in humans regarding the excretion of PAHs.

Thirty-four workers in an electrode paste plant were monitored for response to exposure (Ovrebo et al. 1994). Exposure to benzo[a]pyrene was 0.9 µg/m^3; exposure to pyrene was 3.5 µg/m^3. 1-Hydroxypyrene was measured in the urine. Results from these workers were compared to two reference control groups, research and development workers and nickel refinery workers.

FIGURE 2-4. Proposed Metabolic Scheme for Benzo(b)fluoranthene.



Measurements of PAH levels were collected by personal sampling and at two stationary sites. PAH aerosols were collected on filters during the mixing of hot coal tar with carbon. The value of PAHs on the filters varied from 4.3 to 84.6 µg/m^3, with a mean of 14.4 µg/m^3. The PAH particulates were assayed for 8 of 11 PAHs classified as carcinogenic, including benz[a]anthracene, benz[g,h,i]perylene, benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, chrysene, fluoranthene, and indeno[1,2,3-c,d]pyrene, and presented relative to the marker compound, pyrene. Content of these compounds ranged from 30 to 150% of the pyrene content on the filters, which was 1.6 µg/m^3. For example, the benzo[a]pyrene level was 0.8 µg/m^3. Urine analysis indicated a mean urinary value of 1-hydroxypyrene among electrode paste plant workers of 6.98 umol/mol creatinine, compared to 0.08 µmol/mol creatinine for the R&D workers, and 0.14 µmol/mol creatinine for the industrial worker group. Smokers had higher levels of 1-hydroxypyrene compared to non-smokers in all groups. The urinary 1-hydroxypyrene level in the electrode plant workers correlated inversely with age. No correlation was found between frequency of use of a protective mask and the urinary 1-hydroxypyrene concentration.

In an ongoing comprehensive evaluation of biological markers, workers in or near an iron foundry with varying exposures to PAHs were analyzed for response to exposure (Santella et al. 1993). Exposure to benzo[a]pyrene, determined by personal monitors, was 2-60 ng/m^3. 1-Hydroxypyrene was measured in the urine. Cigarette smoking, but not age or charbroiled food, influenced the level of 1-hydroxypyrene. When workers were classified into three categories (low, <.0005 mg/m^3; medium, 0.0005-0.0012 mg/m^3; high, >0.0012 mg/m^3), mean 1-hydroxypyrene levels were 2.7, 1.8, and 3.6 µmol/mol creatinine, respectively. There was a significant difference between the groups after controlling for smoking exposure, but there was no consistent trend. The authors indicate that this study evaluates biological markers of exposure at PAH levels that are very low, compared to other studies.

Workers employed in a graphite electrode producing plant (n=16) and a coke oven (n=33) were compared to a control population of maintenance workers in a blast furnace (n=54) (Van Hummelen et al. 1993). The concentration of PAHs in the environment was measured by personal air samplers, the concentration of hydroxypyrene in urine was measured, and smoking habits were evaluated. The mean age of the workers was 40, and did not differ significantly between the three plants. The proportion of smokers was not different among the three groups. The mean exposure for workers in the graphite electrode producing plant was 11.33 µg/m^3 (0.011 mg/m^3) and was correlated with a urinary

hydroxypyrene concentration of 3.18 µg/g creatinine prior to the shift and 6.25 µg/g creatinine after the shift. For the coke oven workers, airborne PAHs were measured at 23.7 µg/m^3 but this was not illustrative of true exposure, since there were a few very high exposures in the sample: 90.10 µg/m^3 for 7 workers compared to 5.57 µg/m^3 for 26 workers. In accordance with the predominantly low exposure, the urinary hydroxypyrene levels were 0.51 µg/g creatinine before the shift and 0.75 µg/g creatinine after the shift.

The excretion of benzo[a]pyrene following low-level inhalation exposure is rapid and high in rats (Bevan and Weyand 1988; Weyand and Bevan 1986; Wolff et al. 1989c); however, elimination is low in dogs and monkeys (Petridou-Fischer et al. 1988). After nose-only inhalation of 4.8 mg/m^3 [^{14}C]-benzo[a]pyrene for a single exposure or daily for 4 weeks, excretion of radioactivity in the feces of Fischer-344 rats was approximately 96% of the administered concentration (Wolff et al. 1989c). The excretion half-lives in feces and urine were 22 and 28 hours, respectively.

2.3.4.2 Oral Exposure

Five volunteers (21-41 years of age) ingested specially prepared diets high in PAHs, specifically benzo[a]pyrene (from grilled beef), for 2-3 days for an intake of approximately 0.007-0.02 mg/day (Buckley and Lioy 1992). A 100-250-fold increase in ingested benzo[a]pyrene in the high-PAH diet corresponded to a 6-12-fold increase in the elimination of 1-hydroxypyrene. However, benzo[a]pyrene and its other metabolites (not specified) were not measured in excreta, which prevented determination of the total excretion (and an estimate of oral absorption).

Male Sprague-Dawley rats received a low dose of [^{3}H]-benzo[a]pyrene (suspended in 10% ethanolsoybean oil) daily for 3, 5, or 7 days (Yamazaki and Kakiuchi 1989). Highest radioactivity was excreted 2-8 days after first exposure. Polar and phenol metabolites represented approximately 60% and 20% of the radioactivity detected in urine, respectively. The conjugated form accounted for 80% of these urinary metabolites. Only small amounts of unmetabolized benzo[a]pyrene were detected in the urine. Excretion into the feces was not studied.

Male Wistar rats eliminated a large amount of a single gavage dose of 0.22 mg/kg chrysene by 2 days postexposure (Grimmer et al. 1988). The unchanged parent compound represented 0.17% and 13.09% in the urine and feces, respectively. The recovery of the dose in excreta was 74% of dose after 4 days

of which about 61% was represented by hydroxychrysene compounds. The metabolite pattern was similar for urine and feces. The major metabolites identified were 1- and 3-hydroxychrysene, with about 100 times higher amounts in the feces (33.1% and 17.87%, respectively, of administered dose) than urine (0.79% and 0.35%, respectively). Approximately 79% of a large chrysene dose (1,217-2,717 mg/kg in the diet) was eliminated in the feces of rats; however, levels in the urine were not measured (Chang 1943). As the dose of chrysene in the diet increased, the percentage of excreted hydrocarbon also increased.

Male Wistar rats were given single oral doses of 2, 4, 6, 9, or 1.5 mg/kg of [^{14}C]-pyrene (Withey et al. 1991). Recovery of the dose in excreta was 82% for the two low-dose groups and 50-63% for the other groups 2 days postexposure. The urine and feces contained 34-45% and 21-50% of the dose, respectively, at 4 days postexposure. Recovery of radioactivity in the bile was approximately 10% of the dose after 6 hours.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of PAHs in humans following dermal exposure to single PAHs. Excretion patterns of 1-hydroxypyrene in urine were studied in two psoriatic patients, each treated daily with coal tar pitch covering over 50% of their skin for 3 weeks (Hansen et al. 1993). The coal tar contained 1.43 mg/g pyrene. After 1 week of treatment, the urinary concentration of 1-hydroxypyrene increased approximately 100 times. However, the concentration after 3 weeks of treatment was decreased to that observed before treatment was initiated. The authors speculate that the healing of the psoriatic lesions may have rendered the skin less permeable to the PAHs after 3 weeks of treatment and healing.

The urinary excretion of 1-hydroxypyrene was evaluated in 65 automotive repair workers (automobile or diesel truck repair) whose skin was exposed to used mineral oils, and compared to values from non-professionally exposed control males on control diets (Granella and Clonfero 1993). Smoking exposure was equivalent in both groups. Pyrene concentrations were determined in the oily material taken from cloths used to clean various types of engines. Values of urinary 1-hydroxypyrene were determined on Friday at the end of the working week, and again on Monday morning prior to work. Smoking and PAH-rich diets were considered confounding factors. At both the beginning and the end of the working week, the values of urinary 1-hydroxypyrene were slightly higher in exposed subjects

(0.178 + 0.150 and 0.194 + 0.135 µmol creatinine on Monday and Friday, respectively) than in controls ((0.124 + 0.090 µmol/mol creatinine on Monday and Friday, respectively). The urinary 1-hydroxypyrene values were higher in both smoking and non-smoking subjects than controls. The highest values were found in urinary samples of smokers exposed to used mineral oils (0.259 + 0.090 µmol/mol creatinine). In non-smoking workers, post-shift 1-hydroxypyrene values were 0.154 + 0.105 µmol/mol creatinine, compared to 0.083 + 0.042 µmol/mol creatinine for the non-smoking controls. In automobile repair workers, there was no significant difference in the levels of 1-hydroxypyrene at the beginning and end of the work week. Tobacco smoking had more influence on the levels of 1-hydroxypyrene than did occupational exposure in this group. The influence of PAHs in the diet was only detectable when the subjects returned to work after the weekend. No explanation was given for this finding. This data suggests that exposure to PAHs through dermal contact with used engine oil is low.

The elimination of benzo[a]pyrene was rapid and high in mice and guinea pigs following low- and high-level dermal exposure (Ng et al. 1992; Sanders et al. 1986). The percentages of recovered radioactivity in urine and feces were 24.5%, 46.9%, and 25% for Swiss Webster mice dermally exposed to benzo[a]pyrene at 1.25, 12.5, and 125 µg/cm^2, respectively, for 7 days (Sanders et al. 1986). The feces in the high-dose animals had 35%, 58%, and 80% of the total recovered radioactivity after 24 hours, 48 hours, and 7 days, respectively. The amount of radioactivity excreted in urine was about 10% of amount excreted in feces. A elimination half-life of about 30 hours was estimated for benzo[a]pyrene. The data are limited because the exposed area of skin was not reportedly covered or collars were not employed to prevent ingestion of test compound by the animal. In guinea pigs, 73% of the dose was excreted 7 days after low-level (0.28 mg) exposure to benzo[a]pyrene (Ng et al. 1992).

The excretion of dermally absorbed phenanthrene and pyrene was rapid in guinea pigs (Ng et al. 1991, 1992). The presence of [^{14}C]-activity in the urine and feces of rats that received [^{14}C]-anthracene applied to the skin provides evidence of its absorption (Yang et al. 1986). Six days after administration of 9.3 µg/cm^2, the amounts detected in the urine and feces were 29.1% and 21.9% of the dose, respectively.

2.3.4.4 Other Routes of Exposure

No studies were located regarding excretion of PAHs in humans following other routes of exposure.

Three female Beagle dogs were given a bolus of aerosolized crystals of 7.7 mg/kg benzo[a]pyrene or 2.8 mg/kg phenanthrene in a single breath by intratracheal instillation (Gerde et al. 1993a). The blood borne clearance of the PAHs was monitored by repeatedly sampling blood through catheters in the ascending aorta and the right atrium of the dog. Half of the benzo[a]pyrene cleared within 2.4 minutes. Half of the phenanthrene cleared in 1.0 minute. Compared to clearance of phenanthrene, a less lipophilic PAH, the data indicate that the clearance of benzo[a]pyrene was limited by diffusion through the alveolar septa, while clearance of the moderately lipophilic phenanthrene was limited mostly by the rate of perfusion of the blood. The results indicate that inhaled PAHs of sufficient lipophilicity to limit diffusion through cells have a greater potential for toxicity to the lung than less lipophilic PAHs. Because of the thicker epithelia, bronchi should be at greater risk than the alveoli for PAH-induced toxicity exerted at the port of entry. Clearance of PAHs from the respiratory tract follows a biphasic pattern, with a rapid clearance of most of the PAH followed by a slow clearance of a small fraction. Previously published models predict that the rapid phase represents clearance through the thin epithelial barriers in the alveoli, the slow clearance is through the thicker epithelium of the airways, and the rate of clearance from either region will be slowed if the PAH has a high degree of lipophilicity. This study sought to validate model predictions for rates of alveolar clearance of PAHs of different lipophilicities. In a companion study, 3 female Beagle dogs were given doses of 0.00091 g/kg benzo[a]pyrene instilled on the surface of the conducting airways (Gerde et al. 1993b). Sequential lavage of the mucous-retained materials followed the instillations. Benzo[a]pyrene was retained within the mucous lining layer sufficiently to be transported with the mucocilliary escalator. Fractions of benzo[a]pyrene penetrating to the bronchial epithelium had a clearance half-time in the range of 1.4 hours. This long retention indicates a diffusion-limited uptake of benzo[a]pyrene by the airways. Physiological models have predicted that the lipophilicity of solutes such as PAHs will delay clearance from the respiratory tract. This clearance consists of a delayed penetration of the mucous lining layer, allowing mucocilliary clearance, followed by a slow penetration of PAHs through walls of the conducting airways.

Excretion of radioactivity in the urine of rats following intratracheal instillation only accounted for 2.2% of the administered benzo[a]pyrene at 6 hours (Bevan and Weyand 1988; Weyand and Bevan

1986). Amounts of radiolabel in the blood were also very small. However, levels could still be determined in order to derive toxicokinetic parameters. The data obtained by Weyand and Bevan (1986) fit best to a three-compartment model whereby the half-lives for the three phases were 4.3, 31.5, and 277 minutes.

Results obtained by Weyand and Bevan (1986, 1988) revealed that a large fraction of the administered dose was excreted in the bile of rats, therefore suggesting that fecal elimination is the major excretion route. After 6 hours, 53% of the 0.001 mg/kg dose was excreted into the intestine and intestinal contents of rats that were without a bile duct cannula, while cannulated rats excreted 74% in the bile over the same period (Weyand and Bevan 1986). These results indicate the occurrence of enterohepatic recirculation. Metabolites excreted in the bile included thioether conjugates (62.5%), glucuronide conjugates (22.8%), sulfate conjugates (7.4%), and free benzo[a]pyrene (9.8%) (Weyand and Bevan 1988). Radioactivity detected in the gastrointestinal tract of rats following pulmonary exposure to benzo[a]pyrene also suggests that biliary excretion occurs (Weyand and Bevan 1987a; Wolff et al. 1989c). The percentage of benzo[a]pyrene excretion into bile declined as intratracheal doses increased from 0.00016 to 0.35 mg in rats and guinea pigs (Weyand and Bevan 1987b). However, the biliary excretion of benzo[a]pyrene in hamsters remained the same after administration of either dose.

Female Wistar rats received low doses of chrysene (0.002 and 0.004 mg/kg) intratracheally (Grimmer et al. 1988). The major metabolite in the excreta was 1-hydroxychrysene. Hydroxychrysene compounds represented 31.26-48.9% of dose in the feces and about 3% in the urine. The unmetabolized parent compound was 17-19% of the administered dose in feces and only l-2% in urine.

Less than 10% of instilled radioactivity was excreted in the urine and feces of dogs and monkeys 48 hours after intratracheal administration of [^{3}H]-benzo[a]pyrene into the nostril (Petridou-Fischer et al. 1988).

Nineteen outbred male rats were dosed intraperitoneally once with 200 mg/kg benzo[a]pyrene in sunflower oil (Likhachev et al. 1993). Concentrations of benzo[a]pyrene-7,8-diol, a marker metabolite of bioactivation of benzo[a]pyrene, and 3-hydroxy-benzo[a]pyrene, a marker metabolite of deactivation, were measured daily in the urine and feces for 15 days. Levels of these metabolites were

correlated with tumor latency. Another group of- 10 rats was dosed intraperitoneally once with 15 mg/kg benzo[a]pyrene in sunflower oil and urine was collected for 3 days. Five rats were killed on day 3 and the other 5 were killed on day 8. Liver DNA concentrations of benzo[a]pyrene-7,8,9,10-tetrols were determined in animals killed on day 8. Considerable individual variation was observed in the levels of daily and total excretion of benzo[a]pyrene-7,8-diol and 3-hydroxy-benzo[a]pyrene in rats receiving 200 mg/kg benzo[a]pyrene. Both metabolites were excreted primarily in the feces. More than half of the total metabolites excreted were detected during the first five days, and peak concentrations were observed on the second day after benzo[a]pyrene administration. Peritoneal malignant fibrous histiocytomas developed in 10 of the 16 survivors at 15 days. Levels of urinary benzo[a]pyrene-7,8-diol correlated positively with tumor latency. In the animals exposed to 15 mg/kg benzo[a]pyrene, a high correlation was found between excretion of benzo[a]pyrene-7,8-diol and benzo[a]pyrene-DNA adducts in the liver.

[^{14}C]-Benzo[a]pyrene was administered to male germfree rats (Yang et al. 1994). Urine was collected 24 hours before and every 24 hours for 7 days after administration. Urinary metabolites, consisting of 9% of the administered radioactivity, were fractionated by lipophilic ion exchange chromatography, and characterized by reversed-phase HPLC, ultraviolet spectrometry, and gas chromatography/mass spectrometry. About 90% of the administered dose was excreted within 7 days; 80% in the feces and 9% in the urine. About 90% of the radioactivity in the urine was recovered in the methanol eluate. In this eluate, more than 80% of the urinary metabolites were conjugated, while neutral metabolites constituted 13-18%. The neutral metabolites consisted of 7,8,9,10-tetrols (trace), trans-11,12-dihydrodiol (major), trans-7,8-dihydrodiol (trace), three isomer trihydroxy-benzo[a]pyrenes (major), carboxylic methyl ester derivatives of benzo[a]pyrene quinones, and trioxo-benzo[a]pyrenes (major). Most of the urinary radioactivity was excreted within 72 hours of dosing, with a peak excretion of 24-48 hours. A similar time course was observed for excretion in feces (data not shown).

Six hours after intravenous administration of 0.08 mg/kg [^{14}C]-benzo[a]pyrene to rabbits, 30% and 12% of the dose was excreted in the bile and urine, respectively (Chipman et al. 1982). Excretion of activity into the bile was biphasic over a period of 30 hours with apparent half-lives of 0.27 and 4.623 hours for the rapid and slow phases, respectively. Treatment of the bile and urine with β-glucuronidase and aryl sulfatase increased the amount of activity in the bile and urine that was extractable into ethyl acetate indicating the presence of glucuronide and sulfate conjugates.

Intraduodenal administration of the bile resulted in 21% and 14% of the intraduodenal dose being excreted into the bile and urine, respectively. Since biliary metabolites undergo enterohepatic recirculation, the half-life for ^{14}C-activity is expected to be longer in animals without biliary fistulae (Chipman et al. 1982).

The overall elimination of [^{3}H]-benzo[a]pyrene following intravenous administration (0.001 mg/kg) best fits a triexponential model, as after inhalation exposure (Weyand and Bevan 1986). The half-lives for the three phases were 1.5, 22.4, and 178 minutes. These parameters were very similar to those derived from intratracheal instillation.

2.3.5 Mechanisms of Action

PAHs are absorbed through the lungs by transport across the mucus layer lining the bronchi (Bevan and Ulman 1991). In general, PAHs are lipophilic compounds that can cross the lungs through passive diffusion and partitioning into lipids and water of cells (Gerde et al. 1991, 1993a, 1993b). The rapid, blood-bound redistribution of hydrocarbons at low blood concentrations from lungs to other organs indicates that diffusion is the rate-determining step (Gerde et al. 1991). The absorption rates vary among the PAHs, probably depending on the octanol/water partition coefficient. Essentially all of gastrically instilled benzo[a]pyrene is absorbed via uptake of fat-soluble compounds (Busbee et al. 1990). Oral absorption of benzo[a]pyrene is enhanced by some oils (such as corn oil) in the gastrointestinal tract (Kawamura et al. 1988). The mechanism of dermal absorption of PAHs is most likely passive diffusion through the stratum comeum (Yang et al. 1986).

PAHs and their metabolites are distributed to tissues by transport through the blood. Therefore, PAHs reach more-perfused tissues rapidly following exposure and are eliminated more slowly from less-perfused tissues (Bartosek et al. 1984). A large fraction of orally absorbed benzo[a]pyrene is believedto be transported by lipoproteins from the gastrointestinal tract to the blood via the thoracic duct lymph flow (Busbee et al. 1990).

The carcinogenic mechanism of action of altemant PAHs is fairly well elucidated, but it is not as well described for nonaltemant PAHs. Furthermore, it is not known exactly how PAHs affect rapidly proliferating tissues. PAHs express their carcinogenic activity through biotransformation to chemically reactive intermediates that then covalently bind to cellular macromolecules (i.e., DNA) leading to

mutation and tumor initiation. The products of PAH metabolism include epoxide intermediates, dihydrodiols, phenols, quinones, and their various combinations. The bay region (e.g., the sterically hindered, cup-shaped area between carbons 10 and 11 of benzo[a]pyrene or 1 and 12 of benz[a]anthracene) diol epoxide intermediates of PAHs are considered to be the ultimate carcinogen for alternant PAHs (Jerina et al. 1980). These diol epoxides are easily converted into carbonium ions (carbocations) which are alkylating agents and thus mutagens and initiators of carcinogenesis. Therefore, the carcinogenic and toxic potential of PAHs relies on their metabolites. However, several of the tumorigenic PAHs (i.e., the nonaltemant PAHs) discussed in this profile do not have a bay region, or have been shown not to be similarly activated via a simple bay region epoxide (e.g., Amin et al. 1985a, 1985b). This observation has important implications regarding the expression of carcinogenicity for the nonalternant PAHs. If these chemicals are activated to carcinogens via a mechanism that differs from alternant PAHs, then they may also differ with respect to tumor site and species specificity.

A prerequisite for conversion of PAHs into these active bay region diol epoxides is the presence of cytochrome P-450 and associated enzymes.responsible for this conversion. These enzymes can be found primarily in the liver, but they are also present in the lung, intestinal mucosa, and other tissues. Thus, factors such as distribution to the target tissue(s), solubility, and intracellular localization proximate to these enzymes figure prominently in the expression of a PAH's carcinogenicity. In fact, in order to assess whether there was any correlation between carcinogenic potency and the ability to induce P-450 isoenzymes, several indices of P-450 isoenzyme activity (*O*-demethylation of ethoxyresorufin, metabolic activation of 2-amino-6-methyldipyrido [1,2-α:3',2'd]imadazol [Glu-P-I] to mutagens, and immunological detection of polyclonal antibodies against purified rat P-450 I) were measured in microsomal preparations incubated with benzo[a]pyrene and benzo[e]pyrene (Ayrton et al. 1990). While both PAHs increased several parameters of P-450-I activity, benzo[a]pyrene was markedly more potent than benzo[e]pyrene. Based on these results, the authors concluded that the carcinogenic potency of the PAHs tested could be predicted by the degree to which they induced these enzymes.

Changes in the cytochrome P-450 system can affect the carcinogenicity of the PAHs. This system is susceptible to induction by the PAHs themselves as well as other chemicals commonly found in the environment. The degree and specificity (i.e., which enzymes are affected) of induction depend on the tissue and species and strain. The induction of one enzyme particularly important to the metabolism

of PAHs, AHH, is also known to be under genetic control (see discussions in Section 2.2.2 on responsive versus nonresponsive mouse strains). Given the heterogeneity of human genotypes, it is likely that certain human subpopulations exist that are more susceptible to AHH induction and thus more susceptible to the induction of cancer (see Section 2.7).

Once the reactive bay region epoxide is formed, it may covalently bind to DNA and other cellular macromolecules and presumably initiate mutagenesis and carcinogenesis. Indeed, the level of DNA-adduct formation has been found to correlate with tumor induction activity for a number of PAHs in newborn rat liver and lung (Weyand and LaVoie 1988) and in mouse skin (Albert et al. 1991b; Alexandrov and Rojas-Moreno 1990). Furthermore, no benzo[a]pyrene-DNA-adducts were found in rat skin, which is known to be resistant to PAH-induced skin tumor formation (Alexandrov and Rojas-Moreno 1990). The types of adducts formed in various tissues may dictate target organ susceptibility to PAH-induced carcinogenicity. Various metabolites of benzo[a]pyrene were administered to rats intraperitoneally and DNA adducts from lung, liver, and lymphocytes were measured (Ross et al. 1991). The only metabolites that led to DNA binding were 2-, 9-, and 12-hydroxybenzo[a]pyrene and the truns-7,8-dihydrodiol of benzo[a]pyrene. The authors suggested that different DNA adducts resulting from the *in vivo* metabolism of benzo[a]pyrene in different tissues may be related to tissue specificity of benzo[a]pyrene-induced carcinogenicity.

Although the bulk of this work on PAH-induced carcinogenicity has been done in animal models and animal *in vitro* systems, work in human *in vitro* systems indicates that these same mechanisms of activation may be involved in humans. For example, induction of AHH and formation of the reactive intermediate, benzo[a]pyrene 7,8-dihydrodiol, has been observed in the epithelial tissue from human hair follicles (Merk et al. 1987). All the steps necessary for cellular transformation and cancer induction were demonstrated in cultured human skin fibroblasts: inducible AHH activity, altered cellular proliferation kinetics, and DNA damage (Milo et al. 1978). Thus, humans are likely to be susceptible to tumor induction by PAHs by these mechanisms.

Carcinogenic PAHs have been suggested to have an effect on immune function (Luster and Rosenthal 1993; Saboori and Newcombe 1992), thereby allowing the induction of carcinogenesis, while noncarcinogenic PAHs do not affect immune function (see Section 2.4). The effects of dermally applied benzo[a]pyrene alone or following dermal pretreatment with the prostaglandin synthetase inhibitor, indomethacin, on contact hypersensitivity (cell-mediated immunity), production of antibodies

to DNP (humoral immunity), and the induction of skin tumors was studied in male BALBc mice treated for 6 weeks to 6 months (Andrews et al. 1991b). A group of mice treated with acetone served as controls. Skin tumors were observed in the mice treated with benzo[a]pyrene beginning at week 18 of treatment. Pretreatment with indomethacin significantly increased (by 21%) the latency of tumor induction by benzo[a]pyrene and significantly reduced (by 46%) the weight of benzo[a]pyrene-induced skin tumors. Based on these findings, the authors suggested that benzo[a]pyrene-induced skin carcinogenesis may be mediated by a mechanism that involves prostaglandin suppression of cellular immunity. Undoubtedly, several other factors yet to be determined are involved in the ultimate expression of PAH-induced toxicity and carcinogenicity.

2.4 RELEVANCE TO PUBLIC HEALTH

PAHs occur ubiquitously in the environment from both synthetic and natural sources. PAHs occur in the atmosphere most commonly in the products of incomplete combustion. These products include fossil fuels; cigarette smoke; industrial processes (such as coke production and refinement of crude oil); and exhaust emissions from gasoline engines, oil-fired heating, and burnt coals. PAHs are present in groundwater, surface water, drinking water, waste water, and sludge. They are found in foods, particularly charbroiled, broiled, or pickled food items, and refined fats and oils. Individuals living in the vicinity of hazardous waste sites where PAHs have been detected at levels above background may experience exposure to these chemicals via inhalation of contaminated air or ingestion of contaminated food, soil, or water.

Evidence exists to indicate that certain PAHs are carcinogenic in humans and animals. The evidence in humans comes primarily from occupational studies of workers who were exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (e.g., coal tar, coke oven emissions, soot, shale, and crude oil). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lungs and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is probably due to swallowing of particulates containing PAHs subsequent to mucocilliary clearance from the lung. Certain PAHs have also been shown to induce cancer in animals. The site of tumor induction is influenced by route of administration: stomach tumors are observed following ingestion, lung tumors following inhalation, and skin tumors following dermal exposure, although tumors can form at other locations (e.g., lung tumors after dermal exposure).

Noncancer adverse health effects associated with PAH exposure have been observed in animals but generally not in humans (with the exception of adverse hematological and dermal effects). Animal studies demonstrate that PAHs tend to affect proliferating tissues such as bone marrow, lymphoid organs, gonads, and intestinal epithelium.

Minimal Risk Levels (MRLs) for Polycyclic Aromatic Hydrocarbons

Inhalation MRLS

No inhalation MRLs have been derived for PAHs because no adequate dose-response data that identify threshold levels for noncancer health effects are available in humans or animals for any duration of exposure.

Oral MRL.s

No acute, or chronic oral MRLs were derived for PAHs because there are no adequate human or animal dose-response data available that identify threshold levels for appropriate noncancer health effects. Serious reproductive and developmental effects in animals associated with acute oral exposure to PAHs have been reported. These are not appropriate end points for the derivation of an MRL. Noncancer effects noted in longer term oral toxicity studies in animals include increased liver weight (generally not considered to be adverse) and aplastic anemia (a serious effect), neither of which is an appropriate end point for the derivation of an MRL. Intermediate-duration oral MRLs were derived for acenaphthene, anthracene, fluoranthene, and fluorene.

Acenaphthene

- An MRL of 0.6 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to acenaphthene.

The MRL was based on a minimal LOAEL of 175 mg/kg/day for liver weight (EPA 1989c). Four groups of CD-l mice (20/sex/group) were gavaged daily with 0, 175, 350, or 700 mg/kg/day acenaphthene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (including hematology and clinical

chemistry), organ weights and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, clinical signs, body weight changes, total food intake, and ophthalmological alterations. Liver weight changes accompanied by microscopic alterations (cellular hypertrophy) were noted in both the mid- and high-dose groups, and seemed to be dose-dependent. Additionally, high-dose males and mid- and high-dose females showed significant increases in cholesterol levels. Increased relative liver weights in males, and increased absolute and relative liver weight in females, without accompanying microscopic alterations or increased cholesterol levels were also observed at the low dose; in light of the effects seen at higher doses, this change was considered to be a minimum LOAEL. There was no NOAEL. The MRL was obtained by dividing the LOAEL value by 300 (3 for a minimum LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and rounding to one significant figure.

MRLs for acute-duration and chronic-duration have not been derived because suitable NOAEL and LOAEL values have not been identified in the available literature.

Fluoranthene.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluoranthene.

The MRL was based on a minimal LOAEL of 125 mg/kg/day for increased relative liver weight in male mice (EPA 1988e). Four groups of CD-1 mice (20/sex/group) were gavaged daily with 0, 125, 250, or 500 mg/kg/day fluoranthene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (including hematology and clinical chemistry), organ weights, and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, clinical signs, body weight changes, total food intake, or ophthalmological alterations. All treated mice exhibited nephropathy, increased salivation, and increased liver enzyme levels in a dose-dependent manner. However, these effects were either not significant, not dose-related, or not considered adverse at 125 mg/kg/day. Mice exposed to 500 mg/kg/day had increased food consumption throughout the study. Mice exposed to 250 mg/kg/day had statistically increased SGPT values and increased liver weight. Compound-related microscopic liver lesions (indicated by pigmentation) were observed in 65 and 87% of the mid- and high-dose mice, respectively. Male mice exposed to 125 mg/kg/day had increased relative liver

weight. The LOAEL is 125 mg/kg/day, based on-relative liver weight in males. There was no NOAEL. The MRL was obtained by dividing the LOAEL value by 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and rounding to one significant figure.

Fluorene.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluorene.

The MRL was based on a minimal LOAEL of 125 mg/kg/day for relative liver weight (EPA 1989e). Four groups of CD-l mice (20/sex/group) were gavaged daily with 0, 125, 250, or 500 mg/kg/day fluorene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (including hematology and clinical chemistry), organ weights and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, body weight changes, total food intake, or ophthalmological alterations. All treated male mice exhibited increased salivation, hypoactivity, and urine-wet abdomens. A significant decrease in red blood cell count and packed cell volume was observed in females treated with 250 mg/kg/day and in males and females at 500 me/kg/day. Decreased hemoglobin concentration was also observed in the high-dose group. A dose-related increase in relative liver weight was observed in all treated mice, and in absolute liver weight at >250 mg/kg/day. A significant increase in absolute and relative spleen and kidney weight was observed at 250 mg/kg/day.. Increases in absolute and relative liver and spleen weights at the high dose were accompanied by histopathological increases in hemosiderin in the spleen and in the Kupffer cells of the liver. The LOAEL is 125 mg/kg/day based on increased relative liver weight. There was no NOAEL. The MRL was obtained by dividing the LOAEL value by 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and rounding to one significant figure.

Anthracene.

- An MRL of 10 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to anthracene.

The MRL was based on a NOAEL of 1,000 mg/kg/day for liver effects (EPA 1989d). The objective of this study was to evaluate the toxicity of anthracene in a subchronic toxicity study. Four groups of male and female CD-1 mice (20/sex/group) were placed on study, and were dosed with 0, 250, 500, and 1,000 mg/kg/day fluorene in corn oil by gavage for 13 weeks. The mice were observed twice daily for clinical signs. Body weights and food consumption were reported weekly. Hematologic and serum chemistry evaluations were completed at final sacrifice. At final sacrifice, gross post-mortem examinations were completed, organ weights were taken, and histological examinations were subsequently done on the tissues collected from all organ systems. No treatment-related finding were noted in survival, clinical signs, mean body weights, food consumption, and ophthalmological examinations, hematology, clinical chemistry, organ weights , gross pathology, and histopathology. In summary, anthracene produced no discemable effects. This study was conducted under the same laboratory conditions as the 90-day study of acenaphthene (EPA 1989c), and under similar laboratory conditions as the 90-day studies of fluoranthene (EPA 1988e) and fluorene (EPA 1989e), from which intermediate-duration MRLs were derived, based on liver effects. In these studies (EPA 1988e, 1989c, 1989e), many other treatment-related and dose-related effects were observed, including renal, hematological, and splenic, that lent support to the derivation of the MRL for each compound. Thus, although no toxic effects were noted even at the highest dose tested in the study cited for anthracene (EPA 1989d), this free-standing NOAEL has considerable credibility, based on the assumption that toxic effects would have been observed if present, as was seen for the other compounds using the same study design. The NOAEL is 1,000 mg/kg/day based on the absence of liver effects, and any other effects in the organ systems studied. The NOAEL was the highest dose used in the study. The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Dermal MRLs

No acute-, intermediate-, or chronic-duration MRLs were derived for the 17 PAHs because of the lack of appropriate methodology for the development of dermal MRLs.

Death. There have been no reports of death in humans following exposure to any of the PAHs. However, benzo[a]pyrene is fatal to mice following ingestion, and aeath in animals has been reported following parenteral exposure to a number of PAHs. The intraperitoneal LD_{50} values in mice for pyrene, anthracene, and benzo[a]pyrene are 514, >430, and 232 mg/kg, respectively (Salamone 1981).

Reduced survival time in “Ah-responsive” mice (those capable of producing increased levels of cytochrome P-450 enzymes) was observed following a single intraperitoneal dose of 500 mg/kg benzo[a]pyrene (Robinson et al. 1975). In contrast, oral exposure to 120 mg/kg/day benzo[a]pyrene results in reduced survival of “Ah-nonresponsive” mice (those whose P-450 enzymes are not induced by PAHs).

While the results in animal studies indicate that exposure to high doses of PAHs is lethal, the majority of the data are from parenteral exposure. This route is not applicable to exposure routes humans may expect to encounter, so the relevance of these findings to public health is not known. Parenteral administration bypasses the first-pass effect in the liver that occurs following oral exposure (PAHs may be expected to be ultimately biotransformed to inactive metabolites more quickly in the liver than in other tissues). However, because death has been observed in animals following oral exposure as well, it can be assumed that acute exposure to high enough doses of the PAHs can be lethal.

Systemic Effects.

Respiratory Effects. Adverse noncancer respiratory effects, including bloody vomit, breathing problems, chest pains, chest and throat irritation, and abnormalities in chest X-rays have been reported in humans exposed to PAHs and respirable particles in a rubber factory (Gupta et al. 1993). Inhalation is a significant route of exposure to PAHs in humans. *In vitro* studies using human lung tumor cells demonstrate that the benzo[a]pyrene-induced cytotoxicity (as measured by protein incorporation or cloning efficiency) observed was most likely due to formation of such reactive products as the 7,8-diol 9,10-epoxide metabolite of benzo[a]pyrene (Kiefer et al. 1988). Thus, human lung cells are capable of metabolizing PAHs to reactive intermediates. This implies that inhalation exposure to PAHs could result in toxicity in the respiratory tract.

Adverse effects on the respiratory tissue of laboratory animals have also been observed. The effects of benzo[e]pyrene, pyrene, anthracene, benz[a]anthracene, and benzo[a]pyrene on respiratory mucosa were studied in tracheal explants in rats (Topping et al. 1978). The PAHs were incorporated into beeswax pellets that were placed into tracheal grafts that had been transplanted subcutaneously into the subscapular region of isogenic host rats and the pellets remained in place for 4 weeks. Approximately 50-60% of the test substance was delivered to the tracheal tissue by the end of 4 weeks, in most instances. Benzo[e]pyrene induced only mild changes that included slight hyperplasia of the tracheal

epithelium. A more long-lasting epithelial hyperplasia was observed with pyrene, anthracene, and benz[a]anthracene, and tracheas implanted with pyrene also exhibited a more severe mucocilliary hyperplasia. In addition, undifferentiated epithelium and small areas of squamous metaplasia were also seen with these PAHs, effects that persisted at least 8 weeks after exposure. Severe and long-lasting hyperplasia and transitional hyperplasia as well as metaplasia were seen in tracheas exposed to benzo[a]pyrene, and after 8 weeks, 75% of the epithelium was still abnormal. Acute inflammation (edema and/or granulocyte infiltration), subacute inflammation (mononuclear infiltration and an increase in fibroblasts), and fibrosis and hyalinization in the second half of the experiment were seen with all PAHs. The authors concluded that all of the PAHs tested induced pathological changes in the respiratory mucosa of the transplanted tracheas. The effects were different for the noncarcinogenic PAHs (benzo[e]pyrene, pyrene, anthracene, benz[a]anthracene), as compared to the carcinogenic PAH (benzo[a]pyrene); the former induced changes that were short-lived while the latter produced more severe, long-lasting (metaplastic) changes.

Cultured fetal hamster tracheal explants were exposed to two concentrations each of benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[e]pyrene, and pyrene *in vitro* for 4 days, and the effects of these PAHs on the respiratory epithelium were evaluated by scanning electron microscopy (Richter-Reichhelm and Althoff 1986). Exposure to benzo[e]pyrene and pyrene, as well as the lower concentrations of benz[a]anthracene and benzo[b]fluoranthene, resulted in effects similar to those seen in the DMSO controls: up to a 10% incidence of focally slight inhibition of epithelial differentiation and/or metaplasia. When the concentrations of all of the PAHs except benzo[e]pyrene and pyrene were doubled, the frequency of these lesions increased to 50-l00%, and the incidence of dysplasia (including hyperplasia) 1 was also observed to occur in a dose-related manner in explants exposed to benz[a]anthracene, benzo[b]fluoranthene, and benzo[k]fluoranthene. These lesions were not seen in the cultures exposed to benzo[e]pyrene, pyrene, or DMSO. The authors note that these effects on respiratory epithelium seen *in vitro* are similar to the preneoplastic changes seen *in vivo* following exposure to PAHs, and thus, this system may serve as a good screen for assessing risk to the respiratory tract.

These observations, coupled with the fact that the respiratory system appears to be a target for PAH-induced cancer in humans, suggest that the respiratory system may be a target organ for PAH-induced noncancer adverse effects in humans as well.

Cardiovascular Effects. PAHs are contained in cigarette smoke, and smoking is a well-established risk factor in the development of atherosclerosis. Arterial smooth muscle cell proliferation, collagen synthesis, lipid accumulation, and cellular necrosis are all involved in the pathogenesis of the atherosclerotic plaque. *In vitro* studies conducted using bovine, rabbit, and human smooth muscle cells from arteries demonstrated that benzopyrene affects some of the aforementioned processes. Cell proliferation was not affected by benzo[a]pyrene, but a decrease in collagen secretion and an increase in cellular toxicity were noted in both the animal and human cell cultures (Stavenow and Pessah-Rasmussen 1988).

Male White Leghorn chickens (six/group) were given weekly intramuscular injections of benzo[a]pyrene, benzo[e]pyrene, anthracene, and dibenz[a,h]anthracene for 16 weeks prior to removal of the abdominal aorta to investigate the effects of benzo[a]pyrene on the development of arteriosclerotic plaques (Penn and Snyder 1988). Animals injected with DMSO (the vehicle) served as controls. Microscopic plaques were found in the aortas of all treated and control animals. However, the plaque volume index (PVI), which is a measure of both plaque cross-sectional area and plaque length, was nine times larger in the benzo[a]pyrene animals than the controls. Benzo[e]pyrene and dibenz[a,h]anthracene also caused an increase in plaque volume as compared to controls. However, the plaque sizes in the animals treated with anthracene were no different than controls. Therefore, the authors concluded that benzo[a]pyrene, benzo[e]pyrene, and dibenz[a,h]anthracene “promoted” the development of preexisting atherosclerotic plaques in male chickens as opposed to initiating the development of new plaques. The ability to promote plaque development was not correlated with the mutagenicity or carcinogenicity of the PAH tested. Similarly, administration of benzo[a]pyrene or benzo[e]pyrene into atherosclerosis-susceptible or atherosclerosis-resistant pigeons for 3-5 months of treatment indicated that benzo[a]pyrene, but not benzo[e]pyrene, enhanced the formation of arterial lesions in female, but not male, birds (Hough et al. 1993). Female pigeons were also infertile, and showed ovarian abnormalities.

These results, therefore, suggest that PAHs may contribute to the pathogenesis of atherosclerosis in humans. This is a particularly relevant health risk for those individuals who are exposed to high levels of PAHs in the environment and who also smoke cigarettes.

Gastrointestinal Effects. Anthracene has been associated with gastrointestinal toxicity in humans. Humans that consumed laxatives that contained anthracene (anthracene concentration not specified) for

prolonged periods were found to have an increased incidence (73.4%) of melanosis of the colon and rectum as compared to those who did not consume anthracene-containing laxatives (26.6%) (Badiali et al. 1985). The authors suggested that the melanosis observed may be attributed to the consumption of anthracene laxatives and not to intestinal stasis. This study is severely limited because of confounding factors such as the existence of other predisposing factors for melanosis and lack of follow-up.

Several PAHs discussed in this profile have been shown to alter enzyme activity in the intestinal mucosa of animals following oral administration, which could conceivably lead to increased production of reactive intermediates and tissue injury. Given the selectivity of PAHs for rapidly proliferating tissues such as gastrointestinal mucosa and the results discussed above, exposure to PAHs (particularly oral) by humans could lead to adverse gastrointestinal effects.

Hematological Effects. Adverse hematological effects have been observed in animals following exposure to PAHs. For example, administration of a single intraperitoneal dose of benzo[a]pyrene to mice resulted in a small spleen, marked cellular depletion, prominent hemosiderosis, and follicles with large lymphocytes. These pathological lesions were associated with death (Shubik and Porta 1957). Death due to adverse hematological effects (e.g., aplastic anemia and pancytopenia resulting in hemorrhage) has also been observed in mice following intermediate-duration oral exposure to benzo[a]pyrene (Robinson et al. 1975). Fluoranthene and fluorene administered by gavage to male and female mice for 13 weeks caused hematological effects including decreased packed cell volume and decreased hemoglobin content (EPA 1988e, 1989e). In addition, it has been shown that benzo[a]pyrene is toxic to cultured bone marrow cells when applied directly (Legraverend et al. 1983)

PAHs appear to affect other blood elements, as well. The influence of several PAHs on calcium ionophore-induced activation of isolated rabbit platelets was studied (Yamazaki et al. 1990). The activation of the platelets was assessed by measuring thromboxane B_2 synthesis in response to stimulation by the calcium ionophore, A-23 187. The authors reported that thromboxane B_2 synthesis was inhibited by incubation of the stimulated platelets with benz[a]anthracene, chrysene, benzo[a]pyrene, and benzo[g,h,i]perylene, and stimulated by incubation with anthracene and pyrene. However, no statistical analysis was performed on these data, and the changes reported are generally within ±10% of control values. In addition, the effects of the PAHs on thromboxane B_2 synthesis are bidirectional, and in many instances, the same compound induced both inhibition and stimulation at different concentrations.

As discussed above, PAHs tend to exert their adverse effects on rapidly proliferating tissues, such as the bone marrow blood forming elements. It is likely that PAH-induced toxicity in this tissue is due to a specific attack on DNA of cells in the S or synthetic phase of mitosis (EPA 1988a).

Although the human data available on PAH-induced hematological toxicity are flawed by confounding factors, they, together with the animal data and the propensity for PAHs to attack rapidly proliferating tissues, indicate that humans exposed to PAHs may be at risk for developing hematological toxicity.

Hepatic Effects. No adverse hepatic effects have been reported in humans following exposure to PAHs. However, hepatic effects have been observed in animals following acute oral, intraperitoneal, or subcutaneous administration of various PAHs. These effects include the induction of preneoplastic hepatocytes, known as y-glutamyl transpeptidase foci, induction of carboxylesterase and aldehyde dehydrogenase activity, an increase in liver weight, and stimulation of hepatic regeneration (an indication of a proliferative effect) (Danz et al. 1991; Gershbein 1975; Kemena et al. 1988; Robinson et al. 1975; Shubik and Porta 1957; Torronen et al. 1981; Tsuda and Farber 1980). These hepatic changes are not considered serious adverse effects, but their incidence and severity have been shown to correlate with the carcinogenic potency of particular PAHs. Thus, monitoring of liver function and tissue integrity may prove useful in the evaluation of PAH exposure.

More serious effects indicative of hepatic injury have been observed in animals. For example, an acute intraperitoneal injection of phenanthrene to rats resulted in liver congestion with a distinct lobular pattern, and an increase in serum aspartate aminotransferase, gamma-GT, and creatinine (Yoshikawa et al. 1987). Similarly, a single intraperitoneal injection of pyrene resulted in minimal swelling of the liver but no significant alterations in serum chemistry. Longer-term administration of PAHs has also been reported to result in adverse hepatic effects in animals. For example, increased absolute and relative liver weight correlated with hepatocellular hypertrophy was seen in male and female mice given 350 mg/kg/day acenaphthene by gavage for 13 weeks (EPA 1989c). Increased liver weight and dose-related centrilobular pigmentation accompanied by an increase in liver enzymes was observed in both male and female mice receiving 250 mg/kg/day fluoranthene by gavage for 13 weeks (EPA 1988e).

Renal Effects. Adverse renal effects associated with PAHs have not been reported in humans. A single injection of anthracene or fluorene had no adverse effect on the kidneys of mice (Shubik and

Porta 1957). Dilated tubules were observed in the kidneys of mice administered pyrene in the diet for 25 days (Rigdon and Giannukos 1964); the toxicological significance of this effect is not known. Renal tubular regeneration, and interstitial lymphocytic infiltrates and/or fibrosis were observed after 13-week oral administration of fluoranthene to female mice at 250 mg/kg/day, and to male mice at 500 mg/kg/day (EPA 1988e). Given the lack of renal toxicity in humans and the limited value of the observations made in animals, the risk to humans for renal toxicity following exposure to PAHs is not known.

Endocrine Effects. There is suggestive evidence that PAHs may adversely affect endocrine function as well. The number of thymic glucocorticoid receptors in 6-week-old rats treated once with 2 mg/kg benzo[a]pyrene was measured (Csaba et al. 1991). It is assumed that the route of exposure was by oral gavage, but this was never explicitly stated. The number of these receptors was decreased by 40% in females and was unaffected in males relative to the vehicle control animals. The statistical significance of these effects was not indicated, nor was the adversity of a decrease in receptor number assessed by examination of functional parameters.

Dermal Effects. The skin is susceptible to PAH-induced toxicity in both humans and animals. Regressive verrucae were reported following intermediate-duration application of benzo[a]pyrene to human skin (Cottini and Mazzone 1939). Although reversible and apparently benign, these changes were thought to represent neoplastic proliferation. Benzo[a]pyrene application also apparently exacerbated skin lesions in patients with pre-existing skin conditions (pemphigus vulgaris and xeroderma pigmentosum) (Cottini and Mazzone 1939). Workers exposed to substances that contain PAHs (e.g., coal tar) experienced chronic dermatitis and hyperkeratosis (EPA 1988a). Coal tar preparations containing PAHs are used in the therapeutic treatment of some skin disorders. Adverse reactions have been noted in these patients, also.

Adverse dermatological effects have also been noted in animals in conjunction with acute and intermediate-duration dermal exposure to PAHs. These effects include destruction of sebaceous glands, skin ulcerations, hyperplasia, and hyperkeratosis (Bock and Mund 1958), and alterations in epidermal cell growth (Albert et al. 1991b; Elgjo 1968).

The observation that PAHs adversely affected the skin in both humans and animals is not surprising. The skin undergoes rapid cell turnover and is thus a likely target for PAH attack on DNA synthesis.

Given the information discussed above, the ubiquitous nature of PAHs in the environment, and the susceptibility of the skin to PAH-induced toxicity, adverse skin effects may occur in individuals exposed to these chemicals by the dermal route.

Immunological and Lymphoreticular Effects. Humoral immunity was depressed in male iron foundry workers exposed to benzo[a]pyrene (Szczeklik et al. 1994). IgG, and IgA were depressed in those workers exposed to high levels. There are reports in the literature concerning the immunotoxicity of PAHs following dermal and parenteral exposure in animals. The carcinogenic PAHs as a group have an immunosuppressive effect. There are limited data that suggest that the degree of immunosuppression correlates with the carcinogenic potency. For example, using spleen cell cultures from C3H/Anf mice, suppression of humoral immunity (as measured by the plaque-forming cell [PFC] response to sheep red blood cells) and cell-mediated immunity (as measured by the one-way mixed lymphocyte response) were observed following incubation with 10^{-5}-10^{-7} mol benzo[a]pyrene (Urso et al. 1986). There was no loss in cell viability at these concentrations. These immunological responses were unaffected by treatment with equivalent concentrations of benzo[e]pyrene. These findings led the authors to speculate that carcinogenic PAHs alter immune function, thereby allowing the induction of carcinogenesis while noncarcinogenic PAHs do not affect immune function. In addition, benzo[a]pyrene, but not benzo[e]pyrene, in the presence of S9 metabolic activation mix, has been shown to inhibit interferon induction by viruses by 60-70% in cultured LLC-MK_2 cells (Hahon and Booth 1986).

Benzo[a]pyrene has been shown to markedly inhibit the immune system, especially T-cell dependent antibody production by lymphocytes exposed either *in vivo* or *in vitro* (Blanton et al. 1986; Lyte and Bick 1985; White and Holsapple 1984). These effects are generally seen at high dose relative to those that can induce cancer in animals.

The effects of benzo[a]pyrene on several parameters of cell-mediated immune function in isolated and T-cell enriched mononuclear cell populations from three strains of mice (C57, C3H, and DBA) given a single intraperitoneal injection of 10-50 mg/kg benzo[a]pyrene or benzo[e]pyrene following stimulation with phytohemagglutinin (PHA) were studied (Wojdani and Alfred 1984). Neither benzo[a]pyrene nor benzo[e]pyrene had an inhibitory effect on lymphocyte blastogenesis induced by PHA; blastogenesis was slightly stimulated at 2.5 and 10 mg/kg of either PAH. Dose-related suppression of cell-mediated cytotoxicity of allosensitized lymphocytes was observed in all strains of

mice treated with benzo[a]pyrene, but no effect on this parameter was observed following treatment with benzo[e]pyrene. The percentage and adherence of macrophages from benzo[a]pyrene-treated mice were increased. The authors suggest that benzo[a]pyrene, but not benzo[e]pyrene, causes alterations in cell-mediated immune function that could compromise the animal's immune function allowing the development of PAH-induced tumors. A major limitation of this study was the lack of statistical analysis, thereby making it difficult to determine the validity of the changes seen. As mentioned previously, relatively high doses of benzo[a]pyrene were employed in these studies.

Benzo[a]pyrene-induced immune suppression was reported in male $B6C3F_1$ mice (Lyte and Bick 1985) and in the offspring of C3H/Anf mice treated intraperitoneally with benzo[a]pyrene (Urso and Gengozian 1980). Cell-mediated and humoral immune function of the liver, thymus, and spleen were evaluated in both maternal animals and the offspring of C3H mice administered one intraperitoneal dose of benzo[a]pyrene (150 mg/kg) during "mid-pregnancy" (Urso et al. 1992). The offspring were evaluated at 1 week and 18 months of age. Suppression of these various aspects of the immune system was observed in both the mothers and the offspring at these relatively high doses. However, the study lacked sufficient detail to adequately assess either the protocol or the results.

Groups of four $B6C3F_l$ female mice were administered single injections of 0, 50, or 200 mg/kg benzo[a]pyrene in corn oil to study the correlation between DNA adduct formation (as measured by ^{32}P-postlabelling analysis) and the suppression of polyclonal immune responses (^{3}H-TdR incorporation following stimulation by *Escherichia coli* lipopolysaccharide [LPS] and concanavalin A [Con A] and IgM secretion) and decreased cell viability in splenic lymphocytes harvested from the treated mice (Ginsberg et al. 1989). Spleen weight was significantly decreased (18%, $p<0.05$) at 50 mg/kg. The polyclonal response to LPS and Con A was suppressed by 30-45%, and this suppression was statistically significant at 200 mg/kg. IgM secretion was also significantly depressed (42%) at 200 mg/kg. These immunosuppressive effects were accompanied by high levels of benzo[a]pyrene/DNA adducts. The authors speculated that the immunosuppressive effects of benzo[a]pyrene were due to a cytotoxic mechanism (as supported by *in vitro* experiments) that in turn resulted partially from the genotoxic effects of benzo[a]pyrene (i.e., the formation of benzo[a]pyrene/DNA adducts).

Benzo[a]pyrene exerts its inhibitory effects on antibody production through alterations on the normal functioning of macrophages, T cells, and B cells (Blanton et al. 1988; Zhao et al. 1990). In contrast,

benzo[a]pyrene has no effect on most cellular immune responses before the appearance of tumors (Dean et al. 1983b), although benzo[a]pyrene exposure does inhibit IL-2-dependent proliferation (Myers et al. 1988).

Benzo[a]pyrene may also induce autoimmune responses. Groups of eight female Sprague-Dawley rats were administered a single subcutaneous injection of 2 mg benzo[a]pyrene or benzo[e]pyrene (11.1 mg/kg) in sesame oil in the right thigh (Faiderbe et al. 1992). The animals were observed for up to 150 days and blood samples were taken at regular intervals to measure anti-phosphatidylinositol (PtdIns) antibodies. Serum levels of anti-PtdIns in animals treated with benzo[a]pyrene exceeded those of the oil-injected controls after day 10, and the difference became statistically significant ($p<0.05$) after day 40. The levels reached a peak at day 60 after which time they reached a plateau. The anti-PtdIns were of the IgG type and specific to phosphatidylinositol. Malignant sarcomas developed at the injection site in the animals treated with benzo[a]pyrene within 100-120 days. Serum levels of anti-PtdIns in animals treated with benzo[e]pyrene did not differ from those of the oil-injected controls. No malignant sarcomas developed at the injection site in 100% of the animals administered benzo[e]pyrene within 100-120 days. The authors speculated that constant stimulation of lymphocytes reactive for PtdIns by an endogenous antigen, of which PtdIns could be a part, was responsible for the increased serum levels of anti-PtdIns. The authors suggested that PtdIns metabolism is altered in rapidly proliferating malignant cells (the neoplasia being stimulated by benzo[a]pyrene), resulting in the synthesis of the PtdIns-containing antigen. The lack of an autoimmune response to benzo[e]pyrene was due to the fact that benzo[e]pyrene was not carcinogenic; there was no neoplastic transformation occurring that could result in the production of PtdIns-containing antigens such as was seen with benzo[a]pyrene. Therefore, this study provides evidence that benzo[a]pyrene-induced neoplasia may cause an alteration in the metabolism of endogenous substances, resulting in the production of autoimmune antibodies to those substances.

The immunotoxic effects of benzo[a]pyrene have been noted *in vitro* as well (e.g., Ladies et al. 1991), and these studies provide some insight into the mechanism of action of benzo[a]pyrene-induced immunological effects. Splenic lymphocytes from $B6C3F_1$ mice were incubated with various concentrations of benzo[a]pyrene for either 2 hours or the entire culture period (Ginsberg et al. 1989). A dose- and duration-related decrease in splenic lymphocyte viability (as measured by ^{3}H-TdR incorporation) and immune response (as measured by IgM secretion) was observed in the absence of S9 activation. Addition of S9 enhanced this effect after acute-duration exposure. However, there was

very little formation of benzo[a]pyrene/DNA adducts at benzo[a]pyrene concentrations of l-200 μmol in the splenic lymphocytes; this lack of effect was accompanied by a very low level of benzo[a]pyrene metabolism to DNA-adducting metabolites. Benzo[a]pyrene/DNA adducts were measured in liver and lung; however, in the *in vivo* experiment. This led the authors to suggest that benzo[a]pyrene-induced immunotoxicity as expressed by splenic lymphocytes was the result of a cytotoxic effect that was mediated, in part, by a genotoxic mechanism involving the formation of benzo[a]pyrene/DNA adducts remote from the spleen and a direct cytotoxic effect not requiring activation of benzo[a]pyrene to the reactive intermediate.

Incubation of human lymphocytes with 0.1-01.0 μg/mL benzo[a]pyrene resulted in a suppression of lymphokine-activated killer cell (LAK) activity against tumor targets after 3 and 7 days (Lindemann and Park 1989). LAK DNA synthesis was also inhibited after 3 or 7 days of incubation with benzo[a]pyrene. However, benzo[a]pyrene had no effect on LAK binding with tumor targets, and benzo[a]pyrene did not interfere with the cytotoxic effect of natural killer cells added to the incubation medium. Based on these results, the authors concluded that benzo[a]pyrene interferes with the development of the immunological defense killer cells.

Benzo[a]pyrene has also been shown to affect immune responses to viral infection. Benzo[a]pyrene can reversibly inhibit the induction of viral interferon in 32 different mammalian cell lines but only in the presence of S9 metabolic activation (Hahon and Booth 1988). This inhibition must occur at an early level and not affect viral interferon interactions because the activity of exogenous interferon was unaffected. In addition, influenza virus multiplication was also inhibited by activated benzo[a]pyrene. Benzo[e]pyrene had no effect on interferon induction. The authors suggest that benzo[a]pyrene's inhibition of interferon induction may be an early step in compromising the host's immune function, thereby allowing the induction of carcinogenesis.

There is evidence to suggest that PAHs may alter the levels of brain neurotransmitters, which in turn affects the function of the immune system. The levels of two catecholamines, dopamine and norepinephrine, were determined in discrete brain areas in mice in which fibrosarcomas had been induced following a single subcutaneous injection of benzo[a]pyrene (Dasgupta and Lahiri 1992). Both dopamine and norepinephrine levels were significantly decreased in some brain regions (e.g., the corpus striatum and the hypothalamus), and these decreases were evident in both early and late tumor development. The authors state that since immunological function is compromised during

carcinogenesis and certain alterations in brain catecholamines impair immune function, the mechanism by which carcinogens such as benzo[a]pyrene cause immunosuppression and subsequent carcinogenesis may be via depression of brain catecholamines.

Very little information is available on the immunological effects of other PAHs. Mice treated with high doses of dibenz[a,h]anthracene exhibited a reduced serum antibody level in response to antigenic challenge by comparison to controls (Malmgren et al. 1952). The immunosuppressive effects of dibenz[a,h]anthracene were studied in AHH-inducible mice (C57BL/6) and AHH-noninducible mice (DBA/2N) by intraperitoneal and oral administration (Lubet et al. 1984). Immunosuppression occurred in both strains and was more pronounced in the C57BL/6 mice than in the DBA/2N mice, following intraperitoneal administration. However, the DBA/2N mice were more susceptible to immunosuppression following oral administration. These results suggest that PAHs are rapidly metabolized and excreted following oral administration in AHH-inducible mice, whereas in AHH-noninducible mice, the PAHs are absorbed and distributed to target organs. Based on these results, the authors concluded that AHH inducibility plays an important role in the immunosuppressive activity of PAHs.

B-cell lymphopoiesis in mouse bone marrow has been shown to be inhibited by incubation with fluoranthene *in vitro* at concentrations of ≥5 µg/mL (25 µmol). This effect on B-cell precursors may be mediated in part by a stimulation of programmed cell death; as demonstrated by the increase in DNA fragmentation induced by fluoranthene 15-17 hours after addition to the incubation medium. Furthermore, fluoranthene-induced DNA fragmentation always preceded fluoranthene-induced B-cell precursor death. Another mechanism for fluoranthene-induced inhibition of B-cell lymphopoiesis may be alterations in cell growth rates (fluoranthene was shown to slow the rate of B-cell precursor growth at concentrations <5 µg/mL) and/or altered cell survival (Hinoshita et al. 1992).

The lymphoid system, because of its rapidly proliferating tissues, is susceptible to PAH-induced toxicity. The mechanism of action for this effect is most likely inhibition of DNA synthesis. No adverse effects on this system associated with PAH exposure have been reported in humans, but several accounts of lymphoid toxicity in animals are available. A single intraperitoneal injection of benzo[a]pyrene to mice resulted in a small spleen with marked cellular depletion, prominent and edematous trabeculae, and large lymphocytes. These lesions resulted in death (Shubik and Porta 1957). The Shubik and Porta (1957) study was severely limited by the following: the benzo[a]pyrene

was only partly in solution, only one dose was employed, there was a small sample size, the purity of benzo[a]pyrene was not specified, only one sex was tested, and the presence of benzo[a]pyrene in the peritoneal cavity indicates inadequate absorption. No other similar studies were found in the literature.

Even though these effects have not been noted in humans, and the data in animals are contained in only one study, the rapidly proliferating nature of this tissue suggest that humans exposed to PAHs may be a risk for the development of adverse effects on the lymphoid system.

Given the high potential for exposure to PAHs in the vicinity of hazardous waste sites, the evidence from animal studies, and the heterogeneity of human genotypes with regard to enzyme induction capabilities, it would be prudent to consider that PAHs may pose an immunotoxic risk to humans living in areas surrounding hazardous waste sites.

Neurological Effects. No information is available on the short- or long-term neurotoxic effects of exposure to PAHs in humans and animals. Acute-, intermediate-, or chronic-duration studies conducted in animals do not indicate that any of the PAHs tested showed evidence of neurotoxicity, although these tests were not designed to detect subtle neurological changes.

However, there is evidence to suggest that PAHs may alter the levels of brain neurotransmitters. The levels of two catecholamines, dopamine and norepinephrine, were determined in discreet brain areas in mice in which fibrosarcomas had been induced following a single subcutaneous injection of benzo[a]pyrene (Dasgupta and Lahiri 1992). The mice were divided into two groups: early tumor development and late tumor development 3-4 months after administration of the benzo[a]pyrene. Both dopamine and norepinephrine levels were significantly decreased in some brain regions (e.g., the corpus striatum and the hypothalamus), and these decreases were evident in both early and late tumor development. The authors state that because immunological function is compromised during carcinogenesis and because certain alterations in brain catecholamines impair immune function, the mechanism by which carcinogens such as benzo[a]pyrene cause immunosuppression and subsequent carcinogenesis may be via depression of brain catecholamines.

Reproductive Effects. In both prospective and retrospective studies, a decrease in fecundity was observed in women who were exposed prenatally to cigarette smoke (i.e., their mothers smoked when pregnant) (Weinberg et al. 1989; Wilcox et al. 1989). This association was apparent even after

adjustment for age, frequency of intercourse, current smoking status, age at menarche, childhood exposure to cigarette smoking, educational level, reproductive history, body weight, and consumption of alcohol and caffeine. On the other hand, an increase in fecundity was observed in a retrospective study of women who were exposed to cigarette smoke in early childhood. These apparently opposite effects may be partially explained by the fact that when a woman smokes during pregnancy, her fetus is exposed to the components of the cigarette smoke that cross the placenta as well as changes in fetal and placental oxygenation and metabolism that are secondary to changes in maternal metabolism resulting from smoking. However, childhood exposure involves direct inhalation of cigarette smoke. The authors could offer no explanation as to why fecundity should be *increased* as a result of childhood exposure to cigarette smoke (Weinberg et al. 1989; Wilcox et al. 1989).

The testes and ovaries contain rapidly proliferating cells and therefore should be considered susceptible to damage by PAHs. The reproductive toxicity data in animals for the PAHs are limited. The available animal studies exclusively discuss the reproductive effects of benzo[a]pyrene. Adverse effects such as decreased fertility and total sterility in F_1 progeny of CD-1 mice (Mackenzie and Angevine 1981) and decreased incidence of pregnant female rats at parturition (Rigdon and Rennels 1964) were reported following oral exposure to benzo[a]pyrene. However, no adverse reproductive effects were observed in Swiss mice fed benzo[a]pyrene in their diet (Rigdon and Neal 1965). The metabolic differences and method of benzo[a]pyrene administration could account for the differential response to benzo[a]pyrene induced toxicity in these studies. A single intraperitoneal injection of benzo[a]pyrene to female C57BL/6N mice decreased the number of corpora lutea (Swartz and Mattison 1985). The, antiestrogenic effects causing decreased uterine weights in pseudopregnant Sprague-Dawley rats were reported following daily subcutaneous injections of benzo[a]pyrene during days 6-11 of pseudopregnancy (Bui et al. 1986). Similar treatment to pregnant rats during gestation caused resorptions, reduced percentage of viable litters, and decreased uterine weights (Bui et al. 1986; Cervello et al. 1992). Female mice exhibited decreased ovary weights after 13 weeks oral exposure to 700 mg/kg/day acenaphthene (EPA 1989c). The studies conducted on the reproductive effects of benzo[a]pyrene via parenteral routes are briefly discussed below.

Single intraperitoneal injection of benzo[a]pyrene to female C57BL/6N mice at doses as high as 500 mg/kg body weight produced a dose- and time-dependent decrease in the number of corpora lutea (Swartz and Mattison 1985). The NOAEL in this study was 1 mg/kg/day. Groups of 20 C57BL/6N mice were given single intraperitoneal injections of 0-500 mg/kg benzo[a]pyrene (Miller et al. 1992)

and were killed at various intervals after injection. Total ovarian volume, total corpora lutea volume, and total number of corpora lutea per ovary were significantly reduced by doses of benzo[a]pyrene >5 mg/kg in a dose-related manner. These effects resolved in a dose- and time-dependent fashion, so that after 4 weeks, most changes were only evident in the animals treated with the 100 or 500 mg/kg benzo[a]pyrene. Individual corpora lutea volume actually increased in the treated animals, indicating that compensatory hypertrophy was probably occurring. The authors concluded that based on these findings and previous findings, benzo[a]pyrene impairs corpora lutea formation by destroying follicles. In another study, DBA/2N (D2), C57BL/6N (B6), and (DBA/2N x C57BL/6N)F_1 (F_1) mice (7-8/group) were injected with 10 µg of either benzo[a]pyrene or one of three different metabolites of benzo[a]pyrene ([+]7,8-oxide, [-]7,8-dihydrodiol, or [+]-diol-epoxide-2) into the right ovary (Mattison et al. 1989). The left ovary served as a control, and an additional control group injected with the vehicle (DMSO) also served as controls. Ovarian volume, wet weight, and small, growing, and large follicle number were measured in both the treated and contralateral control ovaries. Benzo[a]pyrene and one or more of its'metabolites caused decreases in the treated ovarian weight, the ovarian volume, and the small, growing, and large follicles in one or more strains. In most instances, the contralateral untreated ovary exhibited a compensatory response; ovarian weight and volume increased as compared to the DMSO controls. This study shows that benzo[a]pyrene and some of its metabolites are toxic to the ovaries of mice, and that the ovary is capable of metabolizing benzo[a]pyrene into reactive metabolites. Similarly, administration of benzo[a]pyrene or benzo[e]pyrene into atherosclerosis-susceptible or atherosclerosis-resistant pigeons for 3-5 months of treatment indicated that benzo[a]pyrene, but not benzo[e]pyrene, rendered female pigeons infertile, with ovarian abnormalities (Hough et al. 1993). Cumulatively, these results demonstrate the sensitivity of integrated hypothalamic-pituitary-ovarian function to adverse effects of benzo[a]pyrene.

Daily subcutaneous injection of benzo[a]pyrene beginning on day 6 of gestation for 6 days as opposed to 3 days significantly increased the number of resorptions, and decreased the fetal survival and uterine weights in Sprague-Dawley rats (Bui et al. 1986). In pseudopregnant (i.e., condition occurring following sterile matings in which anatomical and physiological changes occur similar to those of pregnancy) rats, similar benzo[a]pyrene treatment during days 6-l1 of pseudopregnancy significantly decreased the cyclic nucleotide levels and uterine weights suggesting an antiestrogenic effect (Bui et al. 1986). Use of a single dosage level precluded the assessment of dose response in these studies.

Pregnant Sprague-Dawley rats were administered subcutaneous injections of benzo[a]pyrene (in DMSO and corn oil) or the vehicle alone on gestation days 7, 9, 11, 13, and 15 (Cervello et al. 1992). The animals were sacrificed on gestation day 16. There were no maternal deaths or signs of maternal toxicity. However, the number of fetuses per litter and number of live fetuses per litter were significantly decreased in the animals treated with benzo[a]pyrene, and the number of resorptions was significantly increased. In addition, uterine weight, and whole uterine gravid weight were significantly decreased and increased, respectively. These results demonstrate the reproductive toxicity of benzo[a]pyrene, but a dose-response relationship could not be established because only one dose was tested.

These results suggest that the potential for adverse reproductive effects may be increased in humans exposed to benzo[a]pyrene in the workplace or at hazardous waste sites.

Developmental Effects. The developmental toxicity data for PAHs are mostly limited to *in utero* exposure of pregnant animals to benzo[a]pyrene via various routes of exposure. The placental transfer of benzo[a]pyrene has been shown in mice following oral and intravenous exposure of dams (Shendrikova and Aleksandrov 1974) and in rats after intratracheal administration (Srivastava et al. 1986). The available data from oral studies in animals indicate that exposure of pregnant dams to benzo[a]pyrene produced resorptions and malformations in fetuses (Legraverend et al. 1984) and sterility in F_1 mouse progeny (Mackenzie and Angevine 1981). Investigations by Legraverend et al. (1984) suggest that benzo[a]pyrene metabolites generated in the fetus rather than in the maternal tissues are responsible for these adverse effects. Also, the genetic differences observed in this study using the oral route were contrary to those induced by intraperitoneal administration of benzo[a]pyrene (Hoshino et al. 1981; Shum et al. 1979), thus emphasizing the importance of route of administration in benzo[a]pyrene metabolism and resulting toxicity.

The developmental effects of benzo[a]pyrene have also been investigated in animals using the parenteral route of administration. Intraperitoneal injection of benzo[a]pyrene to pregnant mice produced stillbirths, resorptions and malformations at a greater incidence in Ah-responsive mice than in Ah-nonresponsive mice (Shum et al. 1979); testicular changes including atrophy of seminiferous tubules with lack of spermatids and spermatozoa; interstitial cell tumors (Payne 1958); immunosuppression (Urso and Gengozian 1980); and tumor induction (Bulay and Wattenberg 1971; Soyka 1980). Adverse effects observed following subcutaneous injection of benzo[a]pyrene include

increased fetal resorptio'ns in rats (Wolfe and Bryan 1939) and lung tumor induction in mice (Nikonova 1977). Decreased fetal survival (Wolfe and Bryan 1939) and lung tumor development (Rossi et al. 1983) were reported in Swiss mice following direct intra-embryonal injection of benzo[a]pyrene.

Results of *in vitro* studies suggest that benzo[a]pyrene may affect a number of enzyme and hormone activities in the human placenta. The effects of benzo[a]pyrene on the binding of epidermal growth factor (EGF) and receptor autophosphorylation were studied in human placental cell cultures from early and late gestation placentas (Guyda et al. 1990). In a subsequent study, the effects of benzo[a]pyrene on the uptake of aminoisobutyric acid (AIB) by early and late gestational human placental cells was also studied (Guyda 1991). Benzo[a]pyrene decreased binding of EGF (37-60%) to the early gestation placental cells, but not the late gestation placental cells. The decrease in binding was due to a decrease in the number of high-affinity EGF binding sites. This effect was specific for EGF receptor sites and not due to a nonspecific effect of benzo[a]pyrene on the membranes because benzo[a]pyrene had no effect on the binding of ^{125}I-labeled insulin and insulin-like growth factors. The authors concluded that the effects of benzo[a]pyrene on EGF binding were specific and related to gestational age. Benzo[a]pyrene stimulated AIB uptake by both early and late gestational cells and enhanced EGF-stimulated AIB uptake in spite of a decrease in the number of EGF receptors. The implications of these finding are that benzo[a]pyrene could alter EGF-induced secretion of human chorionic gonadotrophin and human placental lactogen secretion as well as metabolic functions, thereby affecting the regulation of cell growth and differentiation in human placentas.

The activity of quinone reductase, a major protective enzyme, was increased 2-3-fold in first trimester human placental extracts *in vitro* when incubated for 6 hours with benz[a]anthracene, dibenz[a,h]anthracene, and chrysene at a concentration of 50 µmol (Avigdor et al. 1992). Based on these results, it can be postulated that the early placenta is capable of metabolizing certain toxic xenobiotics such as PAH quinone metabolites to inactive intermediates thereby protecting the developing embryo.

Benzo[a]pyrene (50 µmol) has been shown to stimulate human gonadotropin release by first trimester human placental explants *in vitro* (Bamea and Shurtz-Swirski 1992). This stimulation was evident following static exposure for 24 hours and also in cultures that were superfused, meaning the benzo[a]pyrene had a delayed effect and did not need to be present for this effect to be expressed.

The implication of these findings is that benzo[a]pyrene can alter human placental endocrine function early in pregnancy.

Results of animal and *in vitro* studies suggest that benzo[a]pyrene may produce adverse effects in the offspring of women exposed during pregnancy. Furthermore, the results of genetic studies conducted via oral and intraperitoneal routes emphasize the importance of route of administration in benzo[a]pyrene metabolism and resulting toxicity and the severity of the effect may vary depending upon the genotype of the individual exposed (see Section 2.7, Populations That Are Unusually Susceptible). Based on these observations, it is therefore prudent to consider that the genetically heterogeneous human population may show variation in response to *in utero* exposure to benzo[a]pyrene.

Other PAHs such as anthracene, benzanthracene, chrysene, and dibenz[a,h]anthracene have also been tested for developmental effects via parenteral routes. Of these compounds, dibenz[a,h]anthracene produced fetolethal effects in rats (Wolfe and Bryan 1939), while chrysene produced liver tumors in the mouse progeny (Buening et al. 1979a; Grover et al. 1975)

Genotoxic Effects. As the results presented in Tables 2-4 and 2-5 indicate, benzo[a]pyrene has been thoroughly studied in genetic toxicology test systems. It induces genetic damage in prokaryotes, eukaryotes, and mammalian cells *in vitro* and produces a wide range of genotoxic effects (gene mutations in somatic cells, chromosome damage in germinal and somatic cells, DNA adduct formation, UDS, sister chromatid exchange, and neoplastic cell transformation). In cultured human cells, benzo[a]pyrene binds to DNA and causes gene mutations, chromosome aberrations, sister chromatid exchange, and UDS.

The results of *in vivo* studies indicate that many of the same types of adverse effects observed *in vitro* were seen in mice, rats, and hamsters exposed to benzo[a]pyrene via the oral, dermal, or intraperitoneal routes. The available data also indicate that benzo[a]pyrene is genotoxic in both somatic and germinal cells of intact animals (Table 2-4). The only study that was found regarding genotoxic effects in humans following exposure to benzo[a]pyrene reported no correlation between aluminum plant workers' exposure to PAHs, including benzo[a]pyrene, and sister chromatid exchange frequency (Becher et al. 1984). The findings from assays using human cells as the target, in

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo*

Species (test system)	End point		Results	Reference
	ANTHRACENE			
Mammalian systems:				
Chinese hamster/bone marrow	Chromosome aberrations	–		Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange		–	Roszinsky-Kocher et al. 1979
Mouse/bone marrow	Micronuclei		–	Salamone et al. 1981
Mouse	Sperm abnormalities	–		Topham 1980
Host-mediated systems:				
Salmonella typhimurium/mouse host-mediated	Gene mutation		(+)[a]	Simmon et al. 1979
Saccharomyces cerevisiae/mouse host-mediated	Gene mutation	–		Simmon et al. 1979
Chinese hamster V79 cells/mouse host-mediated	Sister chromatid exchange	–		Sirianni and Huang 1978
	BENZ(*a*)ANTHRACENE			
Mammalian systems:				
Chinese hamster/bone marrow	Chromosome aberrations	–		Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange		+	Roszinsky-Kocher et al. 1979
Insect systems:				
Drosophila melanogaster/sex-linked recessives	Gene mutation		–	Zijlstra and Vogel 1984
D. melanogaster/somatic mutation	Gene mutation	–		Fahmy and Fahmy 1980
Host-mediated systems:				
S. typhimurium/mouse host-mediated	Gene mutation		+	Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–		Simmon et al. 1979
	BENZO(*b*)FLUORANTHENE			
Mammalian systems:				
Chinese hamster/bone marrow	Chromosome aberrations	–		Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange		–	Roszinsky-Kocher et al. 1979
Mouse skin	DNA binding		+	Weyand et al. 1987, 1992a

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Rat/lung, liver, peripheral blood lymphocytes	DNA binding	+	Ross et al. 1992
Rat peripheral blood lymphocytes	Sister chromatid exchange	+	Ross et al. 1992
New born mice/lung, liver	DNA binding	+	Weyand et al. 1993b
	BENZO(*j*)FLUORANTHENE		
Mammalian systems:			
Mouse skin	DNA binding	+	La Voie et al. 1991a; Weyand et al. 1987, 1993a
	BENZO(*k*)FLUORANTHENE		
Mammalian systems:			
Mouse skin	DNA binding	+	Weyand et al. 1987
	BENZO(*g,h,i*)PERYLENE		
Host-mediated systems:			
Hamster embryos/transplacental exposure	Transformation	–	Quarles et al. 1979
	BENZO(*a*)PYRENE		
Mammalian systems:			
Mouse/dominant lethals	Gene mutation	+	Epstein 1968; Generoso et al. 1982; Russell 1977
Mouse/spot test	Gene mutation	+	Davidson and Dawson 1976, 1977
Rat hepatocytes/unscheduled DNA synthesis	DNA damage	–	Miralis et al. 1982
Rat hepatocytes/unscheduled DNA synthesis	DNA damage	–	Mullaart et al. 1989
Mouse germ cells/unscheduled DNA synthesis	DNA damage	–	Sega 1979
Mouse skin/lung	DNA binding	+	Mukhtar et al. 1986
Mouse skin	DNA binding	+	Morse et al. 1985; Rice et al. 1984; Weyand and Bevan 1987a

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mouse/bone marrow	DNA binding	+	Wielgosz et al. 1991
Mouse/spleen cells	DNA binding	+	Wielgosz et al.1991
Rat liver parenchymal cells	DNA single strand breaks	+	Mullaart et al. 1989
Rat liver nonparenchymal cells	DNA single strand breaks	–	Mullaart et al. 1989
Rat intestinal cells	DNA single strand breaks	+	Mullaart et al. 1989
Mouse/bone marrow	Chromosome aberrations	+	Adler and Ingwersen 1989
Mouse/bone marrow	Chromosome aberrations	+	Adler et al. 1989
Mouse/embryos	Chromosome aberrations	+	Adler et al. 1989
Chinese hamster/bone marrow	Chromosome aberrations	+	Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Chromosome aberrations	(+)	Bayer 1978
Mouse/heritable translocation	Chromosome aberrations	–	Generoso et al. 1982
Mouse/bone marrow	Chromosome aberrations	+	Wielgosz et al. 1991
Mouse/spleen cells	Chromosome aberrations	+	Wielgosz et al. 1991
Chinese hamster/bone marrow	Sister chromatid exchange	+	Bayer 1978; Roszinsky-Kocher et al. 1979
Mouse/bone marrow	Micronuclei	+	Salamone et al. 1981
Mouse/bone marrow	Micronuclei	–	Bruce and Heddle 1979
Mouse/fetal liver	Micronuclei	+	Harper et al. 1989
Mouse/bone marrow	Micronuclei	+	Harper et al. 1989
Mouse/bone marrow	Micronuclei	+	Awogi and Sato 1989
Mouse/keratinocytes	Micronuclei	+	He and Baker 1991
Mouse/bone marrow	Micronuclei	+	Shimada et al. 1990

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mouse/peripheral blood reticulocytes	Micronuclei	+	Shimada et al. 1992
Rat/peripheral blood reticulocytes	Micronuclei	+	Shimada et al. 1992
Chinese hamster/bone marrow	Micronuclei	–	Bayer 1978
Mouse	Sperm abnormalities	+	Bruce and Heddle 1979; Topham 1980
Mouse	Sperm abnormalities	(+)	Salamone et al. 1988
Mouse	Sperm abnormalities	+	Salamone and Logan 1988
Mouse/bone marrow	Micronuclei	+	Balansky et al. 1994
Mouse/bone marrow	Micronuclei	+	Koratkar et al. 1993
Mouse papilloma cells	Gene mutation	+	Colapietro et al. 1993
Human lung	DNA damage	+	Weston et al. 1993a
Mouse papilloma cells	Gene mutation	+	DiGiovanni et al. 1993
Insect systems:			
D. melanogaster/sex-linked recessive	Gene mutation	(+)	Vogel et al. 1983
D. melanogaster/sex-linked recessive	Gene mutation	–	Valencia and Houtchens 1981; Zijlstra and Vogel 1984
D. melanogaster/somatic mutation	Gene mutation	+	Fahmy and Fahmy 1980
D. melanogaster	Chromosome aberration	(+)	Vogel et al. 1983
Host-mediated systems:			
S. typhimurium/mouse host-mediated	Gene mutation	–	Glatt et al. 1985; Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
Chinese hamster V79/mouse host-mediated	Sister chromatid exchange	+	Sirianni and Huang 1978
Hamster embryos/transplacental exposure	Transformation	+	Quarles et al. 1979

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
	BENZO(*e*)PYRENE		
Mammalian systems:			
Chinese hamster/bone marrow	Sister chromatid exchange	(+)	Roszinsky-Kocher et al. 1979
	CHRYSENE		
Mammalian systems:			
Chinese hamster/bone marrow	Chromosome aberrations	–	Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange	+	Roszinsky-Kocher et al. 1979
Host-mediated systems:			
S. typhimurium/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
	DIBENZ(*a,h*)ANTHRACENE		
Mammalian systems:			
Chinese hamster/bone marrow	Chromosome aberrations	–	Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Sister chromatid exchange	+	Roszinsky-Kocher et al. 1979
	FLUORANTHENE		
Mammalian systems:			
Mouse/bone marrow	Sister chromatid exchange	–	Palitti et al. 1986
	INDENO(1,2,3-*c,d*)PYRENE		
Mammalian systems:			
Mouse skin	DNA binding	+	Weyand et al. 1987
	PHENANTHRENE		
Mammalian systems:			
Chinese hamster/bone marrow	Chromosome aberrations	–	Bayer 1978; Roszinsky-Kocher et al. 1979

TABLE 2-4. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Chinese hamster/bone marrow	Sister chromatid exchange	(+)	Bayer 1978; Roszinsky-Kocher et al. 1979
Chinese hamster/bone marrow	Micronuclei	–	Bayer 1978
Host-mediated systems: *S. typhimurium*/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
S. cerevisiae/mouse host-mediated	Gene mutation	–	Simmon et al. 1979
Hamster embryos/transplacental exposure	Transformation	–	Quarles et al. 1979
	PYRENE		
Mammalian systems: Mouse/bone marrow	Micronuclei	–	Salamone et al. 1981
Mouse	Sperm abnormalities	–	Salamone et al. 1988
Mouse	Sperm abnormalities	–	Salamone and Logan 1988
Insect systems: *D. melanogaster*/sex-linked recessive	Gene mutation	–	Valencia and Houtchens 1981
Host-mediated systems Chinese hamster V79/mouse host-mediated	Sister chromatid exchange	–	Sirianni and Huang 1978

[a]A positive result was obtained in one experiment; this result was not reproduced in the same laboratory or in a second laboratory.

DNA = deoxyribonucleic acid; – = negative result; + = positive result; (+) = weakly positive result

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
		ACENAPHTHENE		
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	No data	Pahlman and Pelkonen 1987
Escherichia coli SOS chromotest	Gene mutation	–	No data	Mersch-Sundermann et al. 1992b
		ACENAPHTHYLENE		
Prokaryotic organisms:				
S. typhimurium	Gene mutation	–	No data	Bos et al. 1988
		ANTHRACENE		
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Carver et al. 1986
S. typhimurium	Gene mutation	–	–	LaVoie et al. 1983b; 1985; Rosenkranz and Poirier 1979; Simmon 1979a
S. typhimurium	Gene mutation	–	No data	Bos et al. 1988; LaVoie et al. 1979; Pahlman and Pelkonen 1987
Escherichia coli/Pol A	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli WP2-WP100/rec-assay	DNA damage	–	No data	Mamber et al. 1983
E. coli/differential killing	DNA damage	–	–	Tweats 1981
E. coli SOS chromotest	DNA damage	–	No data	Mersch-Sundermann et al. 1992b
E. coli SOS chromotest	DNA damage	–	–	Mersch-Sundermann et al. 1992a
Eukaryotic organisms:				
Fungi: *Saccharomyces cerevisiae D3*	Miotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Gene conversion	No data	–	Siebert et al. 1981

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mammalian cells:				
Fischer rat embryo cells	Gene mutation	No data	–	Mishra et al. 1978
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	(+)	No data	Amacher and Turner 1980
Mouse lymphoma L5178/TK$^{+/-}$	Gene mutation	–	No data	Amacher et al. 1980
Human lymphoblasts TK6	Gene mutation	–	No data	Barfknecht et al. 1982
Human epithelial cells EUE	Gene mutation	No data	–	Rochhi et al. 1980
HeLa cells/unscheduled DNA synthesis	DNA damage	–	–	Martin et al. 1978
Human skin fibroblasts	DNA damage	No data	–	Milo et al. 1978
Rat liver cells RL1	Chromosome aberrations	No data	–	Dean 1981
Rat liver cells ARL18	Sister chromatid exchange	No data	–	Tong et al. 1981
Hamster BHK21 clone 13	Transformation	–	No data	Greb et al. 1980
Syrian hamster embryo cells	Transformation	No data	–	Dunkel et al. 1981
Mouse C3H/10T1/2 clone 8	Transformation	No data	–	Dunkel et al. 1981
Mouse Balb/3T3 cells	Transformation	No data	–	Lubet et al. 1983b; Peterson et al. 1981
Fischer rat embryo cells	Transformation	No data	–	Mishra et al. 1978
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	–	Dunkel et al. 1981
	BENZ[a]ANTHRACENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Norpoth et al. 1984; Simmon 1979a

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988; Carver et al. 1986; Coombs et al. 1976; Hermann 1981; Pahlman and Pelkonen 1987
S. typhimurium	Gene mutation	+[a]	No data	Phillipson and Ioannides 1989
S. typhimurium	Gene mutation	–[b]	No data	Phillipson and Ioannides 1989
S. typhimurium	Gene mutation	–	–	Rosenkranz and Poirier 1979
E. coli/Pol A	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann 1992a
Eukaryotic organisms: Fungi: *S. cerevisiae* D3	Mitotic recombination	–	–	Simon 1979b
Mammalian cells:				
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	No data	Amacher et al. 1980
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	–	Amacher and Turner 1980; Amacher and Paillet 1982
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	–	–	Amacher and Paillet 1983
Chinese hamster V79	Gene mutation	–	–	Huberman 1975
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Human lymphoblasts TK6	Gene mutation	+	No data	Barfknecht et al. 1982
Human epithelial cells EUE	Gene mutation	No data	–	Rochhi et al. 1980
Human keratinocytes	Gene mutation	No data	–	Allen-Hoffmann and Rheinwald 1984
HeLa cells/unshceduled DNA synthesis	DNA damage	+	No data	Martin et al. 1978

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Rat liver cells ARL18	Sister chromatid exchange	No data	(+)	Tong et al. 1981
Hamster BHK21 clone 13	Transformation	+	No data	Greb et al. 1980
Hamster embryo cells	Transformation	No data	(+)	DiPaolo et al. 1969, 1971
Hamster embryo cells	Transformation	–	No data	Grover et al. 1971
Syrian hamster embryo cells	Transformation	No data	+	Dunkel et al. 1981
Syrian hamster lung cells FSHL	Transformation	No data	+	Emura et al. 1980
Mouse ventral prostate C3H clone G23	Transformation	No data	–	Grover et al. 1971; Marquardt et al. 1972
Mouse Balb/3T3 cells	Transformation	No data	(+)	Dunkel et al. 1981
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	+	Dunkel et al. 1981
	BENZO[b]FLUORANTHENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Amin et al. 1984; Hermann 1981; LaVoie et al. 1979
S. typhimurium	Gene mutation	–	No data	Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	–	No data	Mossanda et al. 1979
E. coli PQ37 SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Chinese hamster V79	Gene mutation	–	–	Huberman 1975
Hamster BHK21 clone 13	Transformation	+	No data	Greb et al. 1980
Syrian hamster lung cells FSHL	Transformation	No data	+	Emura et al. 1980

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
BENZO[j]FLUORANTHENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	LaVoie et al. 1979
S. typhimurium/fluctuation test	DNA binding	+	No data	Marshall et al. 1992; Weyand et al. 1992
S. typhimurium/fluctuation test	Gene mutation	+	+	Marshall et al. 1993
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
BENZO[k]FLUORANTHENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Amin et al. 1985b; LaVoie et al. 1979; LaVoie et al. 1980; Weyand et al. 1988
Mammalian cells:				
Syrian hamster lung cells FSHL	Transformation	No data	–	Emura et al. 1980
BENZO[g,h,i]PERYLENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Andrews et al. 1978; Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Carver et al. 1986; LaVoie et al. 1979; Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	(+)	No data	Mossanda et al. 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
BENZO[a]PYRENE				

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Glatt et al. 1987; Grolier et al. 1989; Prasanna et al. 1987; Rosenkranz and Poirier 1979; Sakai et al. 1985; Simmon 1979a
S. typhimurium	Gene mutation	+	No data	Alfheim and Randahl 1984; Alzieu et al. 1987; Ampy et al. 1988; Andrews et al. 1989; Antignac et al. 1990; Bos et al. 1988; Bruce and Heddle 1979; Carver et al. 1986; Hermann 1981; LaVoie et al. 1979; Lee and Lin 1988; Marino 1987; Norpoth et al. 1984; Pahlman and Pelkonen 1987
S. typhimurium	Gene mutation	+	No data	Phillipson and Ioannides 1989a
S. typhimurium	Gene mutation	–	No data	Gao et al. 1991
S. typhimurium	Gene mutation	–	No data	Phillipson and Ioannides 1989b
S. typhimurium TM677	Gene mutation	+	–	Rastetter et al. 1982
S. typhimurium TM677	Gene mutation	+	No data	Babson et al. 1986
S. typhimurium	Gene mutation	+	No data	Balansky et al. 1994
E. coli WP2-WP100/rec-assay	DNA damage	+	No data	Mamber et al. 1983
E. coli/PoLA		+	–	Rosenkranz and Poirier 1979
E. coli/differential killing	DNA damage	+	–	Tweats 1981
E. coli/SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992b
Eukaryotic organisms:				
Fungi: *S. cerevisiae* D3	Mitotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Animal systems:				
Chinese hamster V79	Gene mutation	+	No data	Arce et al. 1987; Diamond et al. 1980; Huberman 1975
Chinese hamster V79	Gene mutation	+	–	Huberman 1975
Chinese hamster CHO	Gene mutation	+	(+)	Gupta and Singh 1982
Fischer rat embryo cells/OUA®	Gene mutation	No data	+	Mishra et al. 1978
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	–	Amacher and Paillet 1983; Clive et al. 1979
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	+	No data	Amacher et al. 1980; Amacher and Turner 1980; Arce et al. 1987
Mouse lymphoma L5178Y/HGPRT	Gene mutation	(+)	No data	Clive et al. 1979
Human lymphoblasts AHH	Gene mutation	No data	+	Crespi et al. 1985
Human lymphoblasts TK6	Gene mutation	(+)	No data	Crespi et al. 1985
Human lymphoblasts	Gene mutation	+	No data	Danheiser 1989
Human epithelial cells EUE	Gene mutation	No data	+	Barfknecht et al. 1982; Rocchi et al. 1980
Human fibroblasts HSC172	Gene mutation	+	–	Gupta and Goldstein 1981
Human keratinocytes	Gene mutation	No data	+	Allen-Hoffmann and Rheinwald 1984
Rat hepatocytes/DNA repair	DNA damage	No data	+	Williams et al. 1982
Rat tracheal epithelial cells	DNA damage	No data	+	Cosma and Marchock 1988; Cosma et al. 1988
Mouse C3H/10T1/2 clone 8	DNA damage	No data	(+)	Lubet et al. 1983b
HeLa cells/unscheduled DNA synthesis	DNA damage	+	NR	Martin et al. 1978
Human skin fibroblasts	DNA damage	No data	+	Milo et al. 1978
Human mammary cells	DNA damage	No data	+	Leadon et al. 1988

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Human fibroblasts/unscheduled DNA synthesis	DNA damage	+	No data	Agrelo and Amos 1981
Human fibroblasts WI-38/unscheduled DNA synthesis	DNA damage	+	–	Robinson and Mitchell 1981
Human lymphocyte	DNA damage	No data	+	Wienke et al. 1990
Calf thymus DNA	DNA binding	+	No data	Cavalieri et al. 1988a
Chick embryo fibroblasts	DNA binding	No data	+	Liotti et al. 1988
Chick embryo hepatocytes	DNA binding	No data	+	Liotti et al. 1988
Chinese hamster V79	DNA binding	No data	No data	Arce et al. 1987
Mouse lymphoma L5178Y/TK$^{+/-}$	DNA binding	+	No data	Arce et al. 1987
Mouse C3H/10T1/2	DNA binding	+	No data	Arce et al. 1987
Syrian hamster embryo SHE	DNA binding	No data	+	Arce et al. 1987
Rat bladder epithelial cells	DNA binding	No data	+	Moore et al. 1982
Rat mammary epithelial cells	DNA binding	No data	+	Moore et al. 1987
Human liver HepG2 cells	DNA binding	No data	+	Diamond et al. 1980
Human mammary cells	DNA binding	No data	+	Leadon et al. 1988; Moore et al. 1987
Human bladder cells	DNA binding	No data	+	Moore et al. 1982
Human endometrial cells	DNA binding	No data	+	Dorman et al. 1981
Human bronchus cells	DNA binding	No data	+	Harris et al. 1984
Human colon cells	DNA binding	No data	+	Harris et al. 1984
Human lymphocytes	DNA binding	No data	+	Pavanello and Levis 1992

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Chinese hamster V79-4	Chromosome aberrations	–	–	Popescu et al. 1977
Chinese hamster CHL	Chromosome aberrations	+	–	Matsuoka et al. 1979
Mouse lymphoma L5178Y/TK$^{+/-}$	Chromosome aberrations	+	No data	Arce et al. 1987
Rat liver cells RL1	Chromosome aberrations	No data	+	Dean 1981
Human fibroblasts WI-38	Chromosome aberrations	+	–	Weinstein et al. 1977
Chinese hamster V79	Sister chromatid exchange	+	No data	Arce et al. 1987; Mane et al. 1990
Chinese hamster V79	Sister chromatid exchange	+	–	Popescu et al. 1977; Wojciechowski et al. 1981
Chinese hamster bone marrow	Sister chromatid exchange	No data	+	Roszinsky-Kocher et al. 1979
Chinese hamster Don-6	Sister chromatid exchange	No data	+	Abe et al. 1983b
Chinese hamster CHO	Sister chromatid exchange	+	–	Husgafvel-Pursiainen et al. 1986
Rat pleural mesothelial cells	Sister chromatid exchange	No data	+	Achard et al. 1987
Rat liver cells ARL18	Sister chromatid exchange	No data	+	Tong et al. 1981
Rat hepatoma Reuber H4-II-E	Sister chromatid exchange	No data	+	Dean et al. 1983a
Rat esophageal tumor R1	Sister chromatid exchange	No data	+	Abe et al. 1983b
Rat ascites hepatoma AH66-B	Sister chromatid exchange	No data	+	Abe et al. 1983b
Human fibroblasts TIG-II	Sister chromatid exchange	+	(+)	Huh et al. 1982
Human hepatoma C-HC-4	Sister chromatid exchange	No data	+	Abe et al. 1983a, 1983b
Human hepatoma C-HC-20	Sister chromatid exchange	No data	+	Abe et al. 1983a, 1983b
Human lymphocyte	Sister chromatid exchange	+	–	Lo Jacono et al. 1992
Human lymphocyte	Sister chromatid exchange	No data	+	Wienke et al. 1990

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Golden hamster embryo cells	Transformation	+	No data	Mager et al. 1977
Hamster BHK21 clone 13	Transformation	+	–	Greb et al. 1980
Hamster embryo cells/SA7 virus transformation	Transformation	No data	+	Casto et al. 1977
Syrian hamster embryo cells	Transformation	No data	+	DiPaolo et al. 1969, 1971; Dunkel et al. 1981
Syrian hamster embryo cells/focus assay	Transformation	No data	+	Casto et al. 1977
Syrian hamster lung FSHL	Transformation	No data	+	Emura et al. 1980, 1987
Syrian hamster SHE/SA7 virus transformation	Transformation	No data	+	Arce et al. 1987
Mouse C3H/10T1/2	Transformation	No data	+	Arce et al. 1987; Lubet et al. 1983b; Peterson et al. 1981
Mouse Balb/3T3	Transformation	No data	+	Dunkel et al. 1981
Mouse Balb/3T3 clone A31-1-1	Transformation	No data	+	Little and Vetroys 1988
Fischer rat embryo cells	Transformation	No data	+	Mishra et al. 1978
Rat embryo cells/SA7 virus transformation	Transformation	No data	+	DiPaolo and Casto 1976
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	+	Dunkel et al. 1981
Human breast cancer cells	Gene expression	+	No data	Moore et al. 1994
Human breast epithelial cells	Transformation	No data	+	Calaf et al. 1993
Rat heptocyte	Sister chromatid exchange	+	No data	Kulka et al. 1993
Chinese hamster cells	Sister chromatid exchange	No data	+	Kulka et al. 1993

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mouse Balb/c-3T3 cells	Transformation	No data	+	Matthews 1994
Hamster tracheal cells	DNA damage	No data	+	Roggeband et al. 1994
Rat tracheal cells	DNA damage	No data	+	Roggeband et all. 1994
	BENZO[e]PYRENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Andrews et al. 1978
S. typhimurium	Gene mutation	(+)	No data	Wood et al. 1979b
S. typhimurium	Gene mutation	+[c]	No data	Wood et al. 1979b
S. typhimurium	Gene mutation	+	No data	LaVoie et al. 1979b
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
E. coli SOS chromotest	DNA damage	(+)	–	Mersch-Sundermann et al. 1992a
Mammalian cells:				
Chinese hamster V79 ovary cells	Sister chromatid exchange	–	No data	Mane et al. 1990
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988; Carver et al. 1986; Hermann 1981; LaVoie et al. 1979; Pahlman and Pelkonen 1987
S. typhimurium	Gene mutation	(+)	No data	Wood et al. 1977
S. typhimurium	Gene mutation	–	–	Rosenkranz and Poirier 1979; Simmon 1979a
E. coli/PolA	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Eukaryotic organisms:				
Fungi:				
S. cerevisiae D3	Mitotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981
Mammalian cells:				
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Human lymphoblasts TK6	Gene mutation	+	No data	Barfknecht et al. 1982
Human ephithelial cells EUE	Gene mutation	No data	–	Rocchi et al. 1980
Hamster BHK21 clone 13	Tranformation	+	No data	Greb et al. 1980
Mouse ventral prostrate C3H clone G23	Transformation	No data	–	Marquardt et al. 1972
	DIBENZ[a,h]ANTHRACENE			
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Andrews et al. 1978; Carver et al. 1986; Hermann 1981; Lecoq et al. 1991b; Pahlman and Pelkonen 1987; Wood et al. 1978
S. typhimurium	Gene mutation	–[a,b]	No data	Phillipson and Ioannides 1989
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
Eukaryotic organisms:				
Fungi:				
Neurospora crassa	Gene mutation	No data	+	Barrat and Tatam 1958
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981
Mammalian cells:				
Chinese hamster V79	Gene mutation	(+)	No data	Huberman 1975
Human epithelial cells EUE	Gene mutation	No data	(+)	Rocchi et al. 1980

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
HeLa cells/unscheduled DNA synthesis	DNA damage	+	NR	Martin et al. 1978
Human bronchus cells	DNA binding	No data	+	Harris et al. 1984
Hamster embryo cells	Transformation	–	No data	Grover et al. 1971
Hamster embryo cells/SA7 virus transformation	Transformation	No data	+	Casto 1973; Casto et al. 1977
Syrian hamster embryo cells	Transformation	No data	+	DiPaolo et al. 1969
Syrian hamster embryo cells/focus assay	Transformation	No data	+	Casto et al. 1977
Hamster BHK21 clone 13	Transformation	+	–	Greb et al. 1980
Mouse ventral prostate C3H clone G23	Transformation	No data	–	Marquardt et al. 1972
Mouse C3H/10T$^{1/2}$ clone 8	Transformation	No data	(+)	Lubet et al. 1983b
Rat embryo cells/SA7 virus transformation	Transformation	No data	+	DiPaolo and Casto 1976
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988; Carver et al. 1986; Hermann 1981; LaVoie et al. 1979
S. typhimurium	Gene mutation	(+)	No data	Bos et al. 1987
S. typhimurium	Gene mutation	–	No data	Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	+	No data	Mossanda et al. 1979
S. typhimurium/fluctuation test	Gene mutation	+	–	Bhatia et al. 1987
S. typhimurium/taped plate assay	Gene mutation	+	–	Bos et al. 1987
S. typhimurium TM 677	Gene mutation	+	–	Rastetter et al. 1982

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
S. typhimurium TM 677	Gene mutation	+	No data	Babson et al. 1986
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Human lymphoblasts AHH1	Gene mutation	No data	–	Crespi et al. 1985
Human lymphoblasts TK6	Gene mutation	+	No data	Barfknecht et al. 1982
Chinese hamster CHO-1	Sister chromatid exchange	+	–	Palitti et al. 1986
Prokaryotic organisms:				
S. typhimurium	Gene mutation	–	–	Sakai et al. 1985
S. typhimurium	Gene mutation	–	No data	Bos et al. 1988; Hermann 1981; LaVoie et al. 1979; Pahlman and Pelkonen 1987
E. coli WP2-WP100/rec-assay	DNA damage	–	No data	Mamber et al. 1983
E. coli SOS chromotest	DNA damage	–	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	–	No data	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Chinese hamster lung cell	Chromosome abberrations	+	–	Matsuoka et al. 1991
IDENO[1,2,3-c,d]PYRENE				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Rice et al. 1985b
S. typhimurium	Gene mutation	+	No data	LaVoie et al. 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mammalian cells:				
Syrian hamster lung cells FSHL	Transformation	No data	+	Emura et al. 1980
		PHENANTHRENE		
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Carver et al. 1986; Oesch et al. 1981
S. typhimurium	Gene mutation	(+)	No data	Bos et al. 1988
S. typhimurium	Gene mutation	–	–	LaVoie et al. 1981b; Rosenkranz and Poirier 1979; Simmon 1979a
S. typhimurium	Gene mutation	–	No data	Hermann 1981; LaVoie et al. 1979; Pahlman and Pelkonen 1987
E. coli/PolA	DNA damage	–	–	Rosenkranz and Poirier 1979
E. coli SOS chromotest	DNA damage	+	–	Mersch-Sundermann et al. 1992a
E. coli SOS chromotest	DNA damage	+	No data	Mersch-Sundermann et al. 1992b
Eukaryotic organisms:				
Fungi: *S. cerevisiae* D3	Mitotic recombination	–	–	Simmon 1979b
S. cerevisiae D4-RDII	Mitotic recombination	No data	–	Siebert et al. 1981
Mammalian cells:				
Fischer rat embryo cells	Gene mutation	No data	–	Mishra et al. 1978
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Human lymphoblasts TK6	Gene mutation	(+)	No data	Barfknecht et al. 1982
Human skin fibroblasts	DNA damage	No data	–	Milo et al. 1978
Chinese hamster V79-4	Chromosome aberrations	–	–	Popescu et al. 1977

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Chinese hamster Don	Chromosome aberrations	No data	–	Abe and Sasaki 1977
Chinese hamster CHL	Chromosome aberrations	No data	–	Ishidate and Odashima 1977
Chinese hamster CHL	Chromosome aberrations	–	–	Matsuoka et al. 1979
Chinese hamster V79-4	Sister chromatid exchange	–	–	Popescu et al. 1977
Chinese hamster Don	Sister chromatid exchange	No data	–	Abe and Sasaki 1977
Syrian hamster embryo cells	Transformation	No data	–	DiPaolo et al. 1969; Dunkel et al. 1981
Hamster BHK21 clone 13	Transformation	–	No data	Greb et al. 1980
Hamster embryo cells/SA7 virus transformation	Transformation	No data	–	Casto et al. 1977
Mouse ventral prostate C3H clone G23	Transformation	No data	–	Marquardt et al. 1972
Mouse C3H/10T$^{1/2}$	Transformation	No data	–	Lubet et al. 1983b; Peterson et al. 1981
Mouse Balb/3T3 cells	Transformation	No data	–	Dunkel et al. 1981
Fischer rat embryo cells	Transformation	No data	–	Mishra et al. 1978
Fischer rat embryo cells/leukemia virus transformation	Transformation	No data	–	Dunkel et al. 1981
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Sakai et al. 1985
S. typhimurium	Gene mutation	+	No data	Bos et al. 1988
S. typhimurium	Gene mutation	–	No data	Carver et al. 1986; Hermann 1981; LaVoie et al. 1979
S. typhimurium/fluctuation test	Gene mutation	+	+	Bhatia et al. 1987
S. typhimurium/taped plate	Gene mutation	+	No data	Bos et al. 1988
E. coli WP2-WP100/rec-assay	DNA damage	–	No data	Mamber et al. 1983

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
E. coli/differential killing	DNA damage	–	–	Tweats 1981
E. coli/SOS chromotest	DNA damage	–	–	Mersch-Sundermann et al. 1992a
E. coli/SOS chromotest	DNA damage	–	No data	Mersch-Sundermann et al. 1992b
Mammalian cells:				
Fisher rat embryo cells	Gene mutation	No data	+	Mishra et al. 1978
Chinese hamster V79	Gene mutation	–	–	Huberman 1975
Chinese hamster V79	Gene mutation	–	No data	Huberman 1975
Mouse lymphoma L5178Y/TK$^{+/-}$	Gene mutation	–	No data	Amacher et al. 1980
Human lymphoblasts TK6	Gene mutation	–	No data	Barfknecht et al. 1982
HeLa cells/unscheduled DNA synthesis	DNA damage	–	–	Martin et al. 1978
Rat hepatocytes/DNA repair	DNA damage	No data	–	Williams et al. 1982
Human skin fibroblasts	DNA damage	No data	–	Milo et al. 1978
Human skin fibroblasts	DNA damage	–	No data	Agrelo and Amos 1981
Human fibroblasts WI-38 unscheduled DNA synthesis	DNA damage	+	–	Robinson and Mitchell 1981
Chinese hamster V79-4	Chromosome aberrations	+	–	Popescu et al. 1977
Human fibroblasts WI-38	Chromosome aberrations	–	–	Weinstein et al. 1977
Rat liver cells RL1	Chromosome aberrations	No data	–	Dean 1981
Chinese hamster V79-4	Sister chromatid exchange	–	–	Popescu et al. 1977
Rat liver cells ARL18	Sister chromatid exchange	No data	–	Tong et al. 1981
Syrian hamster embryo cells	Transformation	No data	–	DiPaolo et al. 1969
Fischer rat embryo cells	Transformation	No data	–	Mishra et al. 1978

TABLE 2-5. Genotoxicity of Polycyclic Aromatic Hydrocarbons *In Vitro (continued)*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Hamster embryo cells/SA7 virus transformation	Transformation	No data	–	Casto et al. 1977
		Chrysene		
Prokaryotic organisms: *S. typhimurium*	Gene mutation	+	No data	Glatt et al. 1993
S. typhimurium	Gene mutation	+	No data	Cheung et al. 1993

[a]Noninduced hamster S9
[b]Noninduced mouse, rat, pig and human S9
[c]Synthetically prepared diol epoxide was strongly mutagenic

AHH = aromatic hydrocarbon hydroxylase; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; FSHL = female sex hormone lutenizing; NR = Not reported; PAHs = polycyclic hydrocarbons; SOS = DNA repair assay; – = negative result; + = positive result; (+) = weakly positive result

conjunction with the data from whole animal experiments, suggest that benzo[a]pyrene would probably have similar deleterious effects on human genetic material.

Because the genotoxic activity of benzo[a]pyrene is well established, it is frequently used as a positive control to demonstrate the sensitivity of various test systems to detect the genotoxic action of unknown compounds. It also serves as the model compound for PAHs, and the available information on the formation of metabolites and structure of benzo[a]pyrene can theoretically be used to predict potential genotoxicity/carcinogenicity of other PAHs that have not been as extensively studied.

Benzo[a]pyrene is generally considered to be biologically inert but can be metabolized by enzyme systems into at least 27 identified metabolites; however, only a few of these metabolites are reactive species that can damage DNA (De Bruin 1976). Benzo[a]pyrene 7,8-diol-9,10-epoxide is thought to be the ultimate mutagenic/carcinogenic metabolite. The primary metabolic pathway leading to the formation of the genotoxic/carcinogenic diol epoxides is assumed to be cytochrome P-450-dependent mixed-function oxidases (MFO), which in the case of PAHs are called AHHs. AHH is an ubiquitous enzyme system and has been found in a variety of tissues including liver, lung, and gastrointestinal tract of rats, mice, hamsters, and monkeys. AHH has also been detected in human liver, lung, placenta, lymphocytes, monocytes, and alveolar macrophages (Singer and Grunberger 1983). The evidence indicating that a variety of human tissues including human lymphocytes (GAO 1991; Wiencke et al. 1990), human lymphoblasts (Danheiser et al. 1989), and human mammary epithelial cells (Mane et al. 1990) can serve as a source of exogenous metabolic activation tends to support the role of AHH systems in initiating the conversion of benzo[a]pyrene to genotoxic forms. However, human erythrocytes, which do not contain an effective cytochrome P-450 system, were more efficient than induced rat liver fractions in converting benzo[a]pyrene to a genotoxin as indicated by higher sister chromatid exchange and micronuclei frequencies observed in human lymphocytes co-cultivated with human erythrocytes (Lo Jacono et al. 1992). The findings, while unconfirmed, suggest that enzymatic systems other than AHH may yield reactive intermediates. Similar evidence that uninduced lung, kidney, or spleen from Sprague-Dawley rats or BALB/c mice did not convert benzo[a]pyrene to a mutagen in *S. typhimurium* was reported by Ampy et al. (1988) who concluded that these tissues may, therefore, not be at risk from exposure. Superficially, the data from the studies conducted by Phillipson and Ioannides (1989) (indicating that neither benzo[a]pyrene nor benz[a]anthracene were mutagenic in *S. typhimurium* TA100 in the presence of noninduced hepatic fractions from rats, mice, pigs, or humans) would tend to support the data reported by Lo Jacono et al. (1992) and Ampy et al.

(1988) (suggesting either that other enzyme systems are involved in the bioactivation of these compounds or that certain tissues are not at risk). However, it is important to note, as pointed out by Phillipson and Ioannides (1989), that the level of P-450 isoenzyme proteins in unexposed animals is relatively low. Support for this statement was provided by the data demonstrating that uninduced hamster liver fractions, which contain high cytochrome P-448 levels, converted both benzo[a]pyrene and benz[a]anthracene to mutagens. By inference, it can reasonably be assumed that repeated exposures are required to induce the requisite enzyme systems to metabolize these promutagens to ultimate mutagenic/carcinogenic forms. It can further be assumed that the tissues of any species, including humans, that contain the appropriate inducible enzyme system are at risk.

The function of other enzyme systems in the biotransformation of benzo[a]pyrene should not be ruled out. However, the evidence that cytochrome P-448 plays a major role in this process was further substantiated by the observation that rat liver enzymes induced by PAHs such as 3-MC or dibenz[a,h]anthracene were more efficient in metabolizing benzo[a]pyrene, dibenz[a,h]anthracene, and benz[a]anthracene to mutagenic metabolites for *S. typhimurium* than was phenobarbital (Teranishi et al. 1975). This finding is consistent with the well-documented observation that various inducing agents such as phenobarbital and 3-MC cause the preferential synthesis of specific forms of cytochrome P-450. In the case of 3-MC, cytochrome P-448 is the principal form of induced cytochrome (Singer and Grunberger 1983).

Epoxidation is thought to be the major pathway for benzo[a]pyrene metabolism pertinent to macromolecular interaction. The metabolic attack consists of the cytochrome P-450/P-448-dependent MFO system converting the benzo[a]pyrene molecule into an epoxide; the epoxide is acted upon by epoxide hydrolase to form a dihydrodiol, and a second cytochrome MFO reaction gives rise to the ultimate mutagenic/carcinogenic form, benzo[a]pyrene 7,8-diol-9,10-epoxide. One of the unique structural features of the diol epoxide is that it appears to form in the area of the PAH molecule referred to as the bay region (i.e., a deep-pocketed area formed when a single benzo ring is joined to the remainder of the multiple ring system to form a phenanthrene nucleus). The location of the bay region(s) for the various PAHs in this profile is depicted in Chapter 3 (Table 3-l).

An additional feature of bay region diol epoxides is the ease of carbonium ion formation, which renders the PAH molecule highly reactive and susceptible to attack by nucleophiles (Jerina 1980; Singer and Grunberger 1983). The carbonium ion is more likely to form in structures where the

epoxide is part of the bay region of a saturated terminal angular ring than in an area where the diol epoxide is not associated with a bay region. Further enhancement of bay region epoxides can occur by the formation of an intramolecular hydrogen bond between the oxygen molecule of the epoxide and an associated hydroxyl group. These metabolites are also more resistant to enzymatic detoxification by epoxide hydrolase and glutathione transferase. The increased reactivity conferred by intramolecular hydrogen bonding and the decreased rate of further metabolism favor the interaction with DNA.

Analysis of the bay region diol epoxides and their contribution to the DNA binding, genotoxicity, and carcinogenicity of various PAHs has provided the basis for the bay region hypothesis (Wood et al. 1979a). For example, DNA adducts formed with non-bay region diol epoxides of benzo[a]pyrene have low mutagenic potential (MacLeod et al. 1994). The hypothesis further predicts that structures with more reactive bay regions would probably be more genotoxic and more carcinogenic. The body of evidence on the mutagenic and tumorigenic activity of the PAHs that form bay region diol epoxides (benzo[a]pyrene, benz[a]anthracene, chrysene, dibenz[a,h]anthracene; benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene) supports this hypothesis.

Based on these considerations, the available genetic toxicology results from studies conducted with the other PAHs in this profile are discussed relative to the bay region hypothesis. It is cautioned, however, that while the use of structural relationships to predict potentially reactive compounds is a powerful tool, it is not infallible, nor does it replace *in vitro* or *in vivo* testing. The formation of bay region epoxides is not an absolute requirement for carcinogenic activity because several PAHs that cannot form bay region epoxides are known to be carcinogens. It can, nevertheless, serve as a warning system to alert regulatory agencies to a potential health hazard and to enable investigators to establish priority lists for testing PAHs.

There is no convincing evidence that the PAHs lacking a bay region structure (acenaphthene, acenaphthylene, and fluorene) are genotoxic; the results for acenaphthene and acenaphthylene are consistently negative. The induction of chromosome aberrations only, at a single dose in Chinese hamster lung cells exposed to fluorene (Matsuoka et al. 1991), is not sufficient to conclude that fluorene is a clastogen. However, none of these compounds have been extensively studied in *in vitro* assays, and they have not been tested *in vivo.*

The majority of the data for anthracene and pyrene were negative. Although isolated positive results were obtained, particularly in microbial systems, neither compound produced consistent genotoxic effects in mammalian cells *in vitro*, and both were negative in the limited *in vivo* studies that have been performed.

The results obtained with fluoranthene, the remaining PAH without a bay region configuration, illustrate the need to apply the bay region hypothesis judiciously. There is ample evidence indicating that fluoranthene induced gene mutations in bacteria and human lymphoblasts and sister chromatid exchange in Chinese hamster ovary cells. Based on the evidence of a powerful response in the *Escherichia coli* PQ37 SOS DNA repair assay (SOS chromotest), Mersch-Sundermann et al. (1992a) predicted that fluoranthene has a relatively high probability of being genotoxic (80%). However, fluoranthene did not induce sister chromatid exchanges in mouse bone marrow cells (Palitti et al. 1986). The work of Busby et al. (1984) in newborn mice, suggests that fluoranthene should be classified as a carcinogen.

The occurrence of a bay region structure on the phenanthrene molecule suggests that this compound is genotoxic. However, the overall findings from the genetic toxicology studies do not support such a prediction. Similarly, the reported observation that the intraperitoneal injection of phenanthrene resulted in sister chromatid exchange induction in Chinese hamster bone marrow cells was not convincing (Bayer 1979; Roszinsky-Kocher et al. 1979). In both studies, the sister chromatid exchange increase over background was less than 1.5 fold and comparable doses did not cause chromosome aberrations. As stated earlier, the occurrence of a bay region on the molecule in conjunction with the reactivity of the bay region appear to be the determinants of genotoxic/carcinogenic activity. It is, therefore, probable that the bay region on phenanthrene is not very reactive, which would account for the lack of genotoxicity and for the low carcinogenicity index (<2) assigned to this compound (Arcos et al. 1968). Similarly, quantum mechanical calculations indicate a low probability of carbonation formation for the bay region diol epoxide of phenanthrene (Jerina 1980).

The lack of genotoxicity for phenanthrene is thought to be related to the metabolism of this substance to its 9,10-dihydrodiol. However, specific methylated phenanthrenes, which direct the metabolic fate of this tricyclic hydrocarbon towards the formation of a classical bay region dihydrodiol epoxide, have exhibited significant genotoxicity (LaVoie et al. 1983a). It was demonstrated that the presence of a

methyl group at or adjacent to the K-region of phenanthrene can inhibit the formation of the 9,10-dihydrodiol and produce powerful mutagens in *Salmonella.* Additionally, the presence of a halogen at the K-region site produced similar results, which further support the association between inhibition of 9,10-dihydrodiol formation and mutagenic potency of substituted phenanthrenes. The study authors concluded that derivatives of phenanthrene that can inhibit metabolism at this site have a greater probability of exerting genotoxic effects. Additionally, methylated derivatives of phenanthrene may act as tumor initiators, as shown on mouse skin (LaVoie et al. 1981b).

The weight of evidence from the *in vitro* and *in vivo* studies conducted with benz[a]anthracene, dibenz[a,h]anthracene, and chrysene indicates that these three agents are genotoxic and that they exert their genotoxic effects through the binding of bay region diol epoxides to cellular DNA. Similarly, there is a substantive body of evidence that confirms the hypothesis implicating the formation of bay region diol epoxides as the major mechanism of action for both the genotoxicity and carcinogenicity induced by these PAHs (Cheung et al. 1993; Fuchs et al. 1993a, 1993b; Glatt et al. 1993; Lecoq et al. 1989, 1991a; Wood 1979). It is also of note that these three compounds, as well as benzo[a]pyrene, induced neoplastic cell transformation in at least one cell line (see Table 2-5).

Both benzo[b]fluoranthene and indeno[1,2,3-c,d]pyrene are known to exhibit mutagenic activity in *S. typhimurium* TA100 in the presence of rat liver homogenate (Amin et al. 1984; Hermann 1981; LaVoie et al. 1979; Rice et al. 1985b). Both of these agents were positive for *in vitro* cell transformation (Emura et al. 1980; Greb et al. 1980) and were shown to bind to mouse skin DNA *in vivo* (Hughes et al. 1993; Weyand 1989; Weyand et al. 1987). In addition, benzo[b]fluoranthene formed DNA adducts in the lungs and livers of adult rats (Ross et al. 1992) and newborn mice (Weyand et al. 1993b) and formed DNA adducts as well as induced sister chromatid exchange in peripheral blood lymphocytes of treated rats (Ross et al. 1992). These data are consistent with reports on the tumorigenic activity of these PAHs in rodents and their potential to act as carcinogens in humans.

Studies on the mutagenic activity of benzofilfluoranthene and benzo[k]fluoranthene have also indicated that these nonalternant PAHs are mutagenic in *S. typhimurium* TAl00 (Amin et al. 1985b; LaVoie et al. 1979, 1980a; Weyand et al. 1988, 1992). There is also evidence that application of either of these PAHs to mouse skin results in DNA adduct formation (Hughes et al. 1993; LaVoie et al. 1991a, 1991b; Weyand et al. 1987, 1993a). The relative extent of binding to mouse skin DNA (i.e.,

benzo[j]fluoranthene > benzo[k]fluoranthene) parallels the relative tumorigenic potency of these hydrocarbons on mouse skin (i.e., benzo[j]fluoranthene is more potent than benzo[k]fluoranthene as a tumor initiator) (LaVoie et al. 1982).

Benzo[g,h,i]perylene has been reported to be mutagenic in *S. typhimurium* and to cause DNA damage in *E. coli.* Benzo[g,h,i]perylene has been shown to be responsible for the formation of DNA adducts isolated after topical application of pharmaceutical grade coal tar to the skin of mice (Hughes et al. 1993). However, the few studies that were found were insufficient to draw meaningful conclusions.

The final compound in this group, benzo[e]pyrene, contains two equivalent bay regions. *In vivo,* benzo[e]pyrene induced a marginal increase in sister chromatid exchanges but did not cause structural chromosome aberrations in bone marrow cells harvested from Chinese hamsters receiving two daily intraperitoneal doses of 450 mg/kg (Roszinsky-Kocher et al. 1979). Similarly, sister chromatid exchange frequencies were not increased in V-79 cells co-cultivated with rat mammary epithelial cells as the source of exogenous metabolic activation (Mane et al. 1990). Benzo[e]pyrene was, however, reported to be weakly mutagenic in *S. typhimurium* (Andrews et al. 1978) and weakly genotoxic in the *E. coli* SOS chromotest (Mersch-Sundermann et al. 1992a, 1992b).

The weak genotoxicity and the very weak carcinogenicity of benzo[e]pyrene appear to contradict the bay region diol epoxide hypothesis. Quantum mechanical analysis of the ringed structure strongly suggests the likelihood of carbonium ion formation and an associated chemical reactivity equivalent to the bay region diol epoxide of dibenz[a,h]anthracene (Wood et al. 1979a). Similarly, synthetically prepared bay region tetrahydro-epoxides of benzo[e]pyrene were found to be highly mutagenic in bacteria and mammalian cells, suggesting that bay region diol epoxide(s), if formed, would also be mutagenic. However, the parent compound was not metabolized to a reactive state by Aroclor 1254 S9 or by purified cytochrome P-450 derived from rat livers induced with Aroclor 1254. From these results, Wood et al. (1979a) concluded that the lack of mutagenicity for benzo[e]pyrene may be associated with the failure of the cytochrome P-450-dependent monooxygenase system to catalyze the critical oxidations necessary to form the bay region diol. Specifically, there was very little formation of the bay region 9,10-dihydrodiol and low conversion of authentic 9,10-dihydrodiol to the bay region diol epoxide. Subsequent studies with authentic bay region diol epoxides of benzo[e]pyrene showed that they had relatively low mutagenic and tumorigenic activity as a result of the diaxial conformation of the diol. The diaxial conformation of the 9,10-dihydrodiol also provides an explanation for the low

formation of the bay region diol epoxide since metabolism is shifted away from the adjacent isolated double bond (Chang et al. 1981; Wood et al. 1980). Since structural-activity analysis suggests that the bay region diol epoxides would have biological activity, Wood et al. (1979a) caution that extrapolation of these findings to *in vivo* metabolic events in species other than rats should be approached with caution. It is conceivable that benzo[e]pyrene would be genotoxic in species capable of carrying out the appropriate enzymatic steps.

In summary, several general conclusions can be reached for the unsubstituted PAHs evaluated in this profile. The formation of diol epoxides that covalently bind to DNA appears to be the primary mechanism of action for both genotoxicity and carcinogenicity of several of the unsubstituted PAHs that are genotoxins (benzo[a]pyrene, benz[a]anthracene, dibenz[a,h]anthracene, chrysene, benzo[b]fluoranthene, benzo[j]fluoranthene). There was insufficient evidence to draw meaningful conclusions regarding the genotoxic potential of benzo[g,h,i]perylene, although some evidence does exist.

With regard to the unsubstituted PAHs that either lack a bay region configuration (acenaphthene, acenaphthylene, anthracene, fluorene, and pyrene) or appear to have a weakly reactive bay region (phenanthrene), there is no compelling evidence to suggest that they interact with or damage DNA. The five PAHs that appear to be exceptions to the bay region diol epoxide hypothesis are fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, and indeno[1,2,3-cd]pyrene (no bay region), and benzo[e]pyrene (two bay regions). The evidence does suggest, however, that fluoranthene possesses genotoxic properties while benzo[e]pyrene is either weakly mutagenic or nonmutagenic.

Cancer. Evidence exists to indicate that mixtures of PAHs are carcinogenic in humans. The evidence in humans comes primarily from occupational studies of workers exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (e.g., coal tar, roofing tar, soot, coke oven emissions, soot, crude oil) (Hammond et al. 1976; Lloyd 1971; Maclure and MacMahon 1980; Mazumdar et al. 1975; Redmond et al. 1976; Wynder and Hoffmann 1967). PAHs, however, have not been clearly identified as the causative agent. Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is likely because of swallowing of particles containing PAHs subsequent to mucocilliary clearance of these particulates from the lung.

Certain PAHs are carcinogenic to animals by the oral route (e.g., benz[a]anthracene, benzo[a]pyrene, and dibenz[a,h]anthracene) (Berenblum and Haran 1955; Chu and Malmgren 1965; Klein 1963; McCormick et al. 1981; Neal and Rigdon 1967; Rigdon and Neal 1966; Snell and Stewart 1963; Spamins et al. 1986; Wattenberg and Leong 1970). The results of dermal studies indicate that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[l,2,3-c,d]pyrene are tumorigenic in mice following dermal exposure (Albert et al. 1991b; Cavalieri 1988b; Habs et al. 1984; Levin et al. 1984; Warshawsky and Barkley 1987; Wilson and Holland 1988; Wynder and Hoffmann 1959b). The sensitivity of mouse skin to PAH tumorigenesis forms the basis for the extensive studies performed using dermal administration. This tumorigenicity can be enhanced or modified with concomitant exposure to more than one PAH, long straight-chain hydrocarbons (i.e., dodecane), or similar organic compounds commonly found at hazardous waste sites. Thus, humans exposed to PAHs in combination with these substances could be at risk for developing skin cancer.

For many of the carcinogenic PAHs discussed in this profile, it appears that the site of tumor induction is influenced by the route of administration and site of absorption, i.e., forestomach tumors are observed following ingestion, lung tumors following inhalation, and skin tumors following dermal exposure. However, the observations (discussed below) that (1) mammary tumors are induced following intravenous injection in Sprague-Dawley rats, (2) the susceptibility to tumor development on the skin after dermal application is not similar in rats and mice, and (3) oral cavity tumors are not observed when benzo[a]pyrene is administered in the diet, suggest that the point of first contact may not always be the site of PAH-induced tumors. The results of carcinogenicity studies conducted with the 17 PAHs discussed in this profile by parenteral routes of exposure are summarized in Table 2-6.

TABLE 2-6. Summary of Carcinogenicity Studies with Polycyclic Aromatic Hydrocarbons Using Parenteral Routes of Exposure

Chemical	Species	Route	Duration	Result/Site	Reference
Anthracene	Rat	Lung implantation	1 dose, 55-week observation	–	Stanton et al. 1972
	Newborn mouse	Subcutaneous	Single dose	–/lung	Platt et al. 1990
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Benz[a]anthracene	Mouse	Subcutaneous	10 weeks	+/injection site	Boyland and Sims 1967
		Intramuscular	No data	+/fibrosarcomas, hemangioendotheliomas	Klein 1952
	Newborn mouse	Intraperitoneal	3 days	+/lung	Levin et al. 1984
	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
Benzo[a]pyrene	Mouse	Subcutaneous	Single dose	+/injection site sarcomas	Pfeiffer 1977
	Newborn mouse	Intraperitoneal	Single dose	+/liver	LeVoie et al. 1987
	Newborn mouse	Intraperitoneal	No data	+/lung	Busby et al. 1984
	Rat	Intramammary	Single dose	+/mammary gland	Cavalieri et al. 1988b, 1988c
	Mouse	Intravaginal	5 months	+/cervix	Naslund et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
	Hamster	Intratracheal	Chronic	–	Kunstler 1983
	Rat	Tracheal implant	Intermediate	+/tracheal	Nettesheim et al. 1977
	Rat	Intrapulmonary	Single dose	+/lung	Iwagawa et al. 1989
	Newborn mouse	Subcutaneous	15 days	+/lung	Busby et al. 1989
	Rat	Intramammary	Single dose	+/mammary gland	Cavalieri et al. 1991
	Mouse	*In utero*	2 days	+/lung	Turusov et al. 1990
	Rat	Tracheal explant	Single dose	+/lung	Topping et al. 1981
	Rat	Intrapulmonary	Single dose	+/lung	Wenzel-Hartung et al. 1990
	Mouse	Intraperitoneal	Single dose	+/lung	Mass et all. 1993
	Hamster	Silastic implant	170 d	+/lung	Hammond and Benfield 1993
	Hamster	Intratracheal	1 time, for 6 weeks	+/lung	Kimizuka et al. 1993
Benzo[b]fluoranthene	Newborn mouse	Intraperitoneal	Single dose	+/liver	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
Benzo[e]pyrene	Rat	Tracheal explant	Single dose	–/trachea	Topping et al. 1981
	Rat	Intrapulmonary	Single dose	–/lung	Deutsch-Wenzel et al. 1983
Benzo[j]fluoranthene	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Benzo[g,h,i]perylene	Mouse	Subcutaneous	Single dose	–	IARC 1983
	Rat	Intrapulmonary	Single dose	+	Deutsch-Wenzel et al. 1983
Benzo[k]fluoranthene	Newborn mouse	Intraperitoneal	Single dose	–	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983

TABLE 2-6. Summary of Carcinogenicity Studies with Polycyclic Aromatic Hydrocarbons Using Parenteral Routes of Exposure (continued)

Chemical	Species	Route	Duration	Result/Site	Reference
Anthracene	Rat	Lung implantation	1 dose, 55-week observation	–	Stanton et al. 1972
Chrysene	Newborn mouse	Intraperitoneal	No data	–	Buening et al. 1979a
	Newborn mouse	Intraperitoneal	Single dose, 70-week, week observation	+/liver	Grover et al. 1975
	Mouse	Subcutaneous	10 weeks	+/injection site tumors	Boyland and Sims 1967
	Rat	Intrapulmonary	Single dose	+/lung	Wenzel-Hartung et al. 1990
Dibenz[a,h]anthracene	Newborn mouse	Intraperitoneal	No data	+/lung	Buening et al. 1979b
	Mouse	Subcutaneous	10 weeks	+/injection site tumors	Boyland and Sims 1967
	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
	Newborn mouse	Subcutaneous	Single dose	+/lung	Platt et al. 1990
	Newborn mouse	Subcutaneous	Single dose	+/injection site sarcoma	O'Gara et al. 1965
	Rat	Intrapulmonary	Single dose	+/lung	Wenzel-Hartung et al. 1990
Fluoranthene	Mouse	Intraperitoneal	15 days	+/lung	Busby et al. 1984
	Mouse	Intraperitoneal	3 doses in 15 days, 9-month observation	+/lung	Wang and Busby 1993
Fluorene	Mouse	Subcutaneous	Single dose	–	Roe 1962; Shear and Luter 1941; Steiner 1955
Ideno[1,2,3-c,d]pyrene	Newborn mouse	Intraperitoneal	Single dose	–	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Phenanthrene	Newborn mouse	Intraperitoneal	No data	–	Buening et al. 1979a
	Rat	Intrapulmonary	Single dose	–/lung	Wenzel-Hartung et al. 1990
Pyrene	Hamster	Intratracheal	30 weeks	–	Sellakumar and Shubik 1974
	Newborn mouse	Subcutaneous	Single dose	–/lung	Busby et al. 1989

+ = increased incidence of tumors; – = no increase in tumor incidence

EPA has performed weight-of-evidence evaluations of several of the PAHs discussed in this profile. The carcinogenicity classifications currently verified by EPA's Carcinogenicity Risk Assessment Verification Endeavor Work Group (EPA 1994) are listed below:

PAH	EPA Classification
Acenaphthylene	D (not classifiable as to human carcinogenicity)
Anthracene	D
Benz[a]anthracene	B2 (probable human carcinogen)
Benzo[b]fluoranthene	B2
Benzo[k]fluoranthene	B2
Benzo[g,h,i]perylene	D
Benzo[a]pyrene	B2
Chrysene	B2
Dibenz[a,h]anthracene	B2
Fluoranthene	D
Fluorene	D
Indeno[1,2,3-c,d]pyrene	B2
Phenanthrene	D
Pyrene	D

A quantitative cancer risk estimate (i.e., cancer potency factor) has thus far been developed for benzo[a]pyrene only (EPA 1992). This cancer potency factor (q_1^*) is 7.3 per (mg/kg)/day and is based on the geometric mean of risk estimates calculated from the Neal and Rigdon (1967) and Brune et al. (1981) studies.

EPA and others have developed a relative potency estimate approach for the PAHs (EPA 1993a; Nisbet and LaGoy 1992). By using this approach, the cancer potency of the other carcinogenic PAHs can be estimated based on their relative potency to benzo[a]pyrene. Following are the toxicity equivalence factors (based on carcinogenicity) calculated for PAHs discussed in this profile considered by the authors of one of these approaches to be of most concern at hazardous waste sites (Nisbet and LaGoy 1992):

Compound	Toxicity Equivalency Factor (TEF)
Dibenz[a,h]anthracene	5
Benzo[a]pyrene	1
Benz[a]anthracene	0.1
Benzo[b]fluoranthene	0.1
Benzo[k]fluoranthene	0.1
Indeno[1,2,3-c,d]pyrene	0.1
Anthracene	0.01
Benzo[g,h,i]perylene	0.01
Chrysene	0.01
Acenaphthene	0.001
Acenaphthylene	0.001
Fluoranthene	0.001
Fluorene	0.001
Phenanthrene	0.001
Pyrene	0.001

EPA (1993) has derived the following relative potency estimates based on mouse skin carcinogenesis:

Compound	Relative Potency[a]
Benzo[a]pyrene	1.0
Benz[a]anthracene	0.145
Benzo[b]fluoranthene	0.167
Benzo[k]fluoranthene	0.020
Chrysene	0.0044
Dibenz[a,h]anthracene	1.11
Indeno[1,2,3-c,d]pyrene	0.055[b]

[a]Model was $P(d)=1-\exp[-a(1+bd)^2]$ for all but indeno[1,2,3-c,d]pyrene

[b]Simple mean of relative potencies (0.021 and 0.089); the latter derived using the one-hit model

2.5 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).

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 (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 PAHs are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by PAHs are discussed in Section 2.5.2.

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 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Polycyclic Aromatic Hydrocarbons

PAHs and their metabolites can be measured in the urine of exposed individuals. In workers exposed to PAHs and dermatology patients treated with coal tar, the PAH metabolite 1-hydroxypyrene has been detected in the urine at concentrations of 0-40 µg/g creatinine or 290 ng/g creatinine, respectively (Jongeneelen et al. 1985). The amount of 1-hydroxypyrene detected in urine samples taken during the weekend was less than that detected during the weekdays, when the exposure was presumably higher than on the weekends. No correlation was found between occupational exposure levels and urine levels, so it is not known whether urinary metabolites could be detected following exposure to low levels of PAHs (as might be expected to occur in individuals living in the vicinity of hazardous waste sites). The presence of 1-hydroxypyrene in urine has also been demonstrated in workers exposed to PAHs in several different environments (creosote-impregnating plant, road workers laying asphalt, and workers exposed to diesel exhaust fumes) (Jongeneelen et al. 1988). In another study, the levels of urinary 1-hydroxypyrene significantly correlated with the environmental levels of pyrene and benzo[a]pyrene in coke plants, steel plants, and several Chinese cities where coal burning occurs (Zhao et al. 1990). The usefulness of monitoring urinary 1-hydroxypyrene concentration by liquid chromatography in occupationally exposed individuals as a biomarker for exposure to environmental PAHs was assessed. Postshift 1-hydroxypyrene urinary levels were significantly increased over preshift 1-hydroxypyrene levels in exposed workers as compared to nonexposed controls (the net mean change was 17-fold higher in the exposed workers as opposed to the nonexposed controls), and smoking status did not affect this result. In addition, in this work setting (an aluminum production plant), environmental levels of pyrene were strongly correlated with the environmental levels of total PAHs, indicating that pyrene is an appropriate environmental PAH marker in this situation. Thus, 1-Hydroxypyrene levels in urine may be used as a biomarker of exposure to PAHs in certain situations (Tolos et al. 1990). Additional studies have evaluated the usefulness of determining PAH or metabolite levels in human urine as a measure of exposure in industrial and environmental exposure settings (Granella and Clonfero 1993; Hansen et al. 1993; Herikstad et al. 1993; Kanoh et al. 1993; Likhachev et al. 1993; Ovrebo et al. 1994; Santella et al. 1993; Strickland et al. 1994; Van Hummelen et al. 1993; Van Rooij et al. 1993a, 1993b; Viau et al. 1993). Based on these results, the identification

of PAH metabolites in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where PAHs have been detected although it would be very difficult to distinguish exposures resulting from hazardous waste sites form those resulting from normal human activities.

Autopsies performed on cancer-free patients found PAH levels of 1l-2,700 ppt in fat samples. Several PAHs were detected, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, with pyrene being detected in the highest concentrations (Obana et al. 1981). A similar study done on livers from cancer-free patients found levels of 6-500 ppt of all of the same PAHs except benzo[e]pyrene, which was not detected in the liver. As in the fat samples studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat (Obana et al. 1981). However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to PAHs from hazardous waste sites. In addition, it is impossible to determine from these biological media whether exposure was to high or low levels of PAHs or if the exposure duration was acute, intermediate, or chronic. Benzo[a]pyrene and 1-nitropyrene were determined in excised lung samples from Chinese and Japanese cancer patients (Tokiwa et al. 1993). Exposure to the two marker compounds was from burning coal (Chinese, benzo[a]pyrene) or oil (Japanese, 1-nitropyrene). Compound levels in the lung correlated with individual exposure history. Using a large sample population, total PAH levels in lung tissue has also been shown to correlate to cancer incidence (Seto et al. 1993).

PAHs form DNA adducts that can be measured in body tissues or blood in both humans and laboratory animals following exposure to PAHs or mixtures containing PAHs (e.g., Assennato et al. 1993; Bjelogrlic et al. 1994; Chou et al. 1993; Culp and Beland 1994; Day et al. 1990; Fuchs et al. 1993a, 1993b; Garg et al. 1993; Garner et al. 1988; Gallagher et al. 1993; Herberg et al. 1990; Hughes and Phillips 1990; Hughes et al. 1993; Jones et al. 1993; Khanduja and Majid 1993; Lee et al. 1993; Lewtas et al. 1993; Likhachev et al. 1993; Lu et al. 1993; Mass et al. 1993; Mumford et al. 1993; Newman et al. 1988, 1990; Nowak et al. 1992; Oueslati et al. 1992; Roggeband et al. 1994; Ross et al. 1990, 1991; Shamshuddin and Gan 1988; Van Schooten et al. 1991, 1992; Weston et al. 1988, 1993a; Weyand et al. 1993a, 1993b). PAHs also form adducts with other cellular macromolecules, such as hemoglobin, globin, and other large serum proteins (e.g., Bechtold et al. 1991; Sherson et al. 1990; Weston et al. 1988). Again, these PAH-DNA and PAH-protein adducts are not specific for any

particular source of PAHs, and the adducts measured could have been from exposure to other sources of PAHs, such as complex mixtures that contain PAHs (e.g., crude oils, various high-boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes), as well as vehicle exhausts, wild fires, agricultural burning, tobacco smoke, smoke from home heating of wood, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, beverages, and grilled meats. It is impossible to determine from these adducts whether exposure was to high or low levels of PAHs or if the exposure duration was short or long.

In another study, an evaluation of mutations in peripheral lymphocytes was conducted in workers in or near an iron foundry; data were examined for correlations to benzo[a]pyrene exposure determined by personal monitors. Exposure levels for benzo[a]pyrene were 2-60 ng/m^3, which are the lowest levels yet analyzed in foundry workers. Mutations at the hypoxanthine guanine phosphoribosyl transferase (HPRT) and glycophorin A (GPA) loci, which are measures of molecular effects in lymphocytes and erythrocytes, respectively, were assessed to demonstrate their relationship to external exposure at these low levels. The rate of mutation was also compared to PAH-DNA adducts in the blood (Santella et al. 1993). Workers were classified into three exposure categories, low (<5), medium (5-12), and high (>12). HPRT mutant frequencies for these groups were 1.04, 1.13, and 1 .82x10^{-6} cells, respectively, and demonstrated an upward trend that was marginally significant. In contrast, HPRT mutations were highly correlated with PAH-DNA adducts (Santella et al. 1993). GPA variants were not correlated with PAH exposure. These results support the use of both biomonitoring and personal environmental monitoring in the determination of exposure.

Three methods were evaluated for their usefulness as biomarkers of exposure to benzo[a]pyrene in Wistar rats administered a single dose of l-200 mg/kg (Willems et al. 1991). These three methods were mutagenicity observed in urine and fecal extracts, chromosome aberrations and sister chromatid exchanges in peripheral blood lymphocytes, and DNA adduct formation in peripheral blood lymphocytes and liver. Mutagens were measured in urine and feces at levels of 10 and 1 mg/kg, respectively. DNA adduct formation (measured by ^{32}P-postlabelling) could be detected at doses of ≥10 mg in lymphocytes and ≥100 mg in liver, and the levels were twice as high in the lymphocytes as in the liver. Only a slight increase in sister chromatid exchanges and no enhanced frequency of chromosomal aberrations were seen. These results indicate that mutagenicity observed in excreta and DNA adducts in lymphocytes are both useful biomarkers of exposure in the rat, with mutagenic activity in feces being the more sensitive.

The ability of phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, indeno[l,2,3-c,d]pyrene, and dibenz[a]anthracene to bind to mouse hemoglobin and serum proteins after tail vein injection was investigated (Singh and Weyand 1994). Urinary excretion of these compounds was also investigated. A direct correlation between urinary excretion and hydrocarbon molecular weight was observed. Binding to both globin and serum proteins was detectable, with binding to serum proteins 10-fold higher than to globin. These results provide an assessment of the potential usefulness of various PAHs as biomarkers of exposure to complex mixtures.

2.5.2 Biomarkers Used to Characterize Effects Caused by Polycyclic Aromatic Hydrocarbons

The available genotoxicity data indicate that several of the 17 PAHs discussed in this profile are genotoxic in both nonmammalian and mammalian systems and are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system). There were no tests reported for humans exposed to benzo[a]pyrene (the most widely tested PAH) *in vivo*, but several types of cultured human tissue cells demonstrated positive results for benzo[a]pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange) and binding of benzo[a]pyrene to DNA. The measurement of DNA adduct formation as well as the induction of sister chromatid exchange in human lymphocytes has been proposed as a biomarker of benzo[a]pyrene-induced effects for human monitoring programs (Wiencke et al. 1990). It is probable, however, that the analysis of DNA adducts would be the more sensitive diagnostic tool since hundreds of benzo[a]pyrene-DNA adducts per nucleus would be required to yield a detectable increase in the sister chromatid exchange frequency for an exposed population. Although these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote (a complex mixture containing PAHs) have been negative, the genotoxic effects observed in human tissue cells, particularly DNA adduct formation, may serve as a biomarker of effects for at least one of the PAHs, benzo[a]pyrene. It would not be possible to identify the source.of the benzo[a]pyrene, however.

PAHs have been shown to cause noncancer adverse effects on rapidly proliferating tissues such as the hematopoietic system, the lymphoid system, and the skin in both humans and animals. The skin is susceptible to PAH-induced toxicity in both humans and animals. Regressive verrucae were reported following intermediate-duration application of benzo[a]pyrene to human skin (Cottini and Mazzone

1939). Although reversible and apparently benign, these changes were thought to represent neoplastic proliferation. Benzo[a]pyrene application also apparently exacerbated skin lesions in patients with pre-existing skin conditions (pemphigus vulgaris and xeroderma pigmentosum) (Cottini and Mazzone 1939). Workers exposed to substances that contain PAHs (e.g., coal tar) experienced chronic dermatitis and hyperkeratosis (EPA 1988a). However, none of these end points is specific to PAHs, and all can be seen with other agents. No other biomarkers of effect (specific or otherwise) have been identified following exposure to PAHs.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990). Additional information can be found in a series of reports on biomarkers issued by the National Research Council (NRC 1989, 1992).

2.6 INTERACTIONS WITH OTHER SUBSTANCES

Because humans are usually exposed to PAHs in complex mixtures rather than to individual PAHs, it is important to understand the potential interactions between the PAHs and other components of the mixture. Interactions may occur among chemicals in a mixture prior to exposure, or may occur after exposure as a result of differing effects of the mixture components on the body. Synergistic and/or antagonistic interactions with regard to the development of health effects, particularly carcinogenesis, may occur.

The extent of human exposures to PAH mixtures in occupational settings is generally not known in quantitative terms. However, exposures to complex chemical mixtures that include PAHs, such as use of tobacco products and exposure to roofing tar emissions, coke oven emissions, coal tar, and shale oils, have been associated with adverse health effects in humans. The biological consequences of human exposure to complex mixtures of PAHs depend on the interaction of the various strongly carcinogenic, weakly carcinogenic, or noncarcinogenic PAHs. For example, there is evidence to suggest that PAHs in cigarette smoke require other components in the smoke in order to exert their tumorigenic effect (Akin et al. 1976).

The interaction between noncarcinogenic and carcinogenic PAHs has been extensively examined in animals. Noncarcinogenic PAHs exhibit co-carcinogenic potential and tumor-initiating and promoting

activity when applied with benzo[a]pyrene to the skin of mice. Simultaneous administration of weakly carcinogenic or noncarcinogenic PAHs including benzo[e]pyrene, benzo[g,h,i]perylene, fluoranthene, or pyrene significantly elevated the benzo[a]pyrene-induced tumor incidence. Benzo[e]pyrene, fluoranthene, and pyrene were more potent co-carcinogens than benzo[g,h,i]perylene (Van, Duuren and Goldschmidt 1976; Van Duuren et al. 1973). Benzo[e]pyrene, fluoranthene, and pyrene have also demonstrated weak tumor-promoting activity following initiation with benzo[a]pyrene, and these compounds increased benzo[a]pyrene-DNA adduct formation (Di Giovanni et al. 1982; Lau and Baird 1992; Rice et al. 1984, 1988; Slaga et al. 1979; Smolarek et al. 1987; Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973).

Interactions between selected noncarcinogenic PAHs and carcinogenic benzo[a]pyrene have also been documented to reduce the carcinogenic potential of benzo[a]pyrene in animals. Benzo[a]fluoranthene, benzo[k]fluoranthene, chrysene, perylene, and a mixture of anthracene, phenanthracene, and pyrene significantly inhibited benzo[a]pyrene-induced injection-site sarcomas. However, other PAHs including anthracene, benzo[g,h,i]perylene, fluorene, and indeno[1,2,3-c,d]pyrene had no antagonistic effects (Falk et al. 1964). Coexposure of tracheal explants to benzo[e]pyrene and benzo[a]pyrene resulted in an increased incidence of tracheal epithelial sarcomas over that seen with either PAH alone (Topping et al. 1981). Phenanthrene administration with benzo[a]pyrene decreased the DNA adduct formation in mice (Rice et al. 1984).

There is evidence to suggest that benz[a]anthracene may serve as an anticarcinogen when administered with benzo[a]pyrene. Coadministration of benz[a]anthracene and benzo[a]pyrene decreased benzo[a]pyrene metabolism, benzo[a]pyrene-DNA adduct formation, and reduced the mutagenic activity of benzo[a]pyrene on hamster embryo cells. It has been postulated that the antimutagenic effect of benz[a]anthracene results from competition with benzo[a]pyrene for MFO enzymes, rather than the induction of detoxifying enzymes (Smolarek et al. 1986).

The synergistic effect of individual PAHs on the mutagenicity of benzo[a]pyrene has also been demonstrated. Anthracene and benzo[e]pyrene enhanced the mutagenicity of benzo[a]pyrene, the maximal increase being obtained with anthracene. Benzo[e]pyrene (at a ratio of 2:l) had no effect on benzo[a]pyrene-induced mutation frequencies in V79 cells, but at a ratio of 15:1, benzo[e]pyrene inhibited the benzo[a]pyrene-induced mutations by approximately 10-fold. Benzo[e]pyrene inhibited the metabolism of benzo[a]pyrene by cultured hamster embryo only at high doses, but at both low and

high doses, the proportion of metabolites formed was altered by benzo[e]pyrene (Baird et al. 1984). The percentage of water-soluble metabolites was decreased, whereas the percentage of diols was increased. The authors postulated that benzo[e]pyrene alters the activity of other PAHs by inhibiting the conversion of the proximate carcinogenic diol of a particular PAH to a diol epoxide.

Benzo[a]pyrene and dibenz[a,h]anthracene in combination with 10 noncarcinogenic PAHs were less potent tumor-inducers than was dibenz[a,h]anthracene alone or in combination with benzo[a]pyrene. The noncarcinogenic or weakly carcinogenic PAHs include benzo[e]pyrene, phenanthrene, anthracene, pyrene, fluoranthene, chrysene, perylene, benzo[g,h,i]pyrene, and coronene. Dose-response relationships for tumor incidences were observed for benzo[a]pyrene and dibenz[a,h]anthracene either alone or in combination with the 10 noncarcinogenic PAHs; however, no treatment-related sarcoma incidences were observed for any of the 10 noncarcinogenic PAHs (Pfeiffer 1977).

Phenanthrene, a noncarcinogenic PAH, demonstrated a dose-related inhibition of dibenz[a,h]anthracene-induced carcinogenicity in mice. Phenanthrene significantly reduced the incidence of injection-site sarcomas elicited by dibenz[a,h]anthracene, especially at low doses. However, when triethylene glycol was the vehicle administered in combination with phenanthrene and dibenz[a,h]anthracene, a substantial increase (50%) in the rate of tumor induction was observed (Falk et al. 1964).

Several experiments have shown that most PAH mixtures are considerably less potent than individual PAHs. Various combustion emissions and benzo[a]pyrene have been examined for carcinogenic potency and tumor initiation activity on mouse skin. In all cases, PAH mixtures were much less potent than benzo[a]pyrene. The authors calculated relative potency estimates that ranged from 0.007 for coke oven emissions extract to less than 0.002 for diesel engine exhaust extract, using papillomas per mouse per milligram of the mixture as the end point (Slaga et al. 1980b). Another study demonstrated that the relative tumorigenicities, as compared to benzo[a]pyrene, of automobile exhaust .condensate (AEC), diesel emission condensate, and a representative mixture of carcinogenic PAHs were 0.0053, 0.00011, and 0.36, respectively, following chronic application to mouse skin (Misfeld 1980). AEC has also exhibited an antagonistic influence on benzo[a]pyrene carcinogenicity when subcutaneously administered to mice; this effect was particularly augmented at higher benzo[a]pyrene concentrations (Pott et al. 1977).

Carcinogenic and noncarcinogenic PAHs, comprising a quantitative fraction of automobile exhaust gas condensate, were selected for carcinogenicity testing via dermal exposure of female NMRI mice. The purpose was to identify interactions between mixtures of the carcinogenic and noncarcinogenic PAHs (Schmahl et al. 1977). The carcinogenic PAHs were benzo[a]pyrene, dibenz[a,h]anthracene, benz[a]anthracene, benzo[b]fluoranthene; and the noncarcinogenic PAHs were phenanthrene, anthracene, fluoranthene, pyrene, chrysene, benzo[e]pyrene, and benzo[g,h,i]perylene. Treatment was carried out twice a week, for the natural lifetime of the animals. Although the carcinogenic action observed could be attributed almost entirely to the action of the carcinogenic PAHs, in relatively small doses, addition of the noncarcinogenic PAHs did not inhibit carcinogenesis, but had an additive effect.

Predicting the toxicity of a complex mixture on the basis of one of several of its components may be misleading, because the interactions among the components may modify toxicity. Since PAHs require metabolic activation by monoxygenases to elicit carcinogenic effects, any alteration in these metabolic pathways will influence the observed toxicity. There are two primary mechanisms by which chemicals interact with PAHs to influence toxicity. A compound may compete for the same metabolic activating enzymes and thereby reduce the toxicity of carcinogenic PAHs, or it may induce the metabolizing enzyme levels to result in a more rapid detoxification of the carcinogenic PAHs (Levin et al. 1982). Chaloupka et al. (1993) showed that a mixture of PAHs, produced as by-products from a manufactured gas plant, was 706 times more potent than expected, based on its benzo[a]pyrene content (0.17%) at inducing mouse hepatic microsomal ethoxyresorufin O-deethylase. Alternatively, compounds may compete for a deactivating pathway, thereby increasing the toxicity of PAHs (Furman et al. 1991). Many monooxygenase inducers are ubiquitous in the environment, and they may have an effect on the toxicity of PAHs. For example, environmental contaminants such as tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphenyls (PCBs) and 3,3’,4,4’-tetrachlorobiphenyl (TCBP) can increase microsomal enzyme activity and consequently affect PAH toxicity (Jacob et al. 1987; Kouri et al. 1978). The dermal absorption of benzo[a]pyrene was measured in the presence or absence of complex organic mixtures derived from coal liquefaction processes (Dankovic et al. 1989). The dermal half-life of benzo[a]pyrene was 3.0 hours when applied alone, 6.7 hours when measured as a component of a mixture, and ranged from 7.8 to 29.7 hours in the presence of different mixtures. The authors proposed that these mixtures inhibit the dermal absorption of benzo[a]pyrene by inhibiting the metabolism of benzo[a]pyrene at the application site. Interactions. can thus play important modulatory roles in the expression of PAH toxicity that may not be adequately reflected based on the toxicity of a single PAH.

The majority of human exposures to PAHs occur in the presence of particles that affect the pharmacokinetics of PAHs in a manner that can enhance their carcinogenicity. Coadministration of benzo[a]pyrene and particulate material, such as hematite (Fe_2O_3) and arsenic trioxide (As_2O_3), greatly increases respiratory tract tumor yields in laboratory animals following intratracheal instillation (Pershagen et al. 1984; Saffiotti et al. 1972; Stenback and Rowland 1979; Stenback et al. 1976). The effects of particles on the potential human carcinogenicity of PAHs are likely to be similar. When benzo[a]pyrene is particle-bound, clearance from hamster lungs is slower than that of pure benzo[a]pyrene aerosol, increasing the length of time the lungs are exposed and increasing the dose to the gastrointestinal tract as a result of mucocilliary clearance. Respirable benzo[a]pyrene-containing particulates such as diesel exhaust, when coated with the phospholipid component of a pulmonary surfactant, are genotoxic (Wallace et al. 1987). Dusts can increase the rates of pulmonary cell proliferation (Harris et al. 1971; Stenback and Rowland 1979; Stenback et al. 1976), which in turn increases the cells' susceptibility to an initiation event in the presence of a carcinogen.

Environmental exposure to PAHs can also occur along with exposure to other environmental pollutants. The effects of exposure to SO_2 (either by inhalation or systemically with endogenous sulfite/bisulfite anions that accumulated as a result of induced sulfite oxidase deficiency) on benzo[a]pyrene-induced lung tumors were studied in male Sprague-Dawley rats (Gunnison et al. 1988). The animals, were administered benzo[a]pyrene (1 mg) by weekly intratracheal instillation for 15 weeks during which time they were exposed daily by inhalation to 30 or 60 ppm SO_2 or were maintained on a high tungsten to molybdenum diet. There were no statistically significant differences between the benzo[a]pyrene only and the benzo[a]pyrene + SO_2 or benzo[a]pyrene + sulfite/bisulfite groups with respect to the incidence of squamous cell carcinomas of the lung, latency for tumor development, or rate of appearance. Although benzo[a]pyrene alone induced almost 100% tumor incidence leaving little room for an SO_2-induced enhanced response, a shortened latency or increased rate of appearance would have suggested that SO_2 potentiates the carcinogenicity of benzo[a]pyrene, and this did not occur. Therefore, the authors concluded that SO_2 does not potentiate the carcinogenicity of benzo[a]pyrene in the lung.

Concomitant exposure to solvents may also occur, particularly in an occupational setting. It has been demonstrated that pretreatment of rats with toluene (1 g/kg intraperitoneally) inhibits the total cytochrome P-450 content in microsomes isolated from the lungs (Furman et al. 1991). In addition, formation of 3-hydroxybenzo[a]pyrene (a nontoxic metabolite) was inhibited by 36% by the

microsomes *in vitro* whereas the formation of several diols (reactive intermediates) was unaffected by toluene pretreatment. These results indicate that toluene alters the balance between toxification and detoxification of benzo[a]pyrene by cytochrome P-450 in the lung, favoring the formation of reactive genotoxic/carcinogenic intermediates. Therefore, the authors suggested that concomitant exposure to solvents, such as toluene, and PAHs may result in an increased risk for lung cancer.

Asbestos exerts a synergistic influence on cigarette smoke (which contains several PAHs) in the development of bronchopulmonary cancers. This has important implications for workers occupationally exposed to asbestos, who also smoke. The interaction between cigarette smoke and asbestos may be explained partly by differences in the kinetics of PAH cell uptake when PAHs are preadsorbed on asbestos (Foumier and Pezerat 1986). Plutonium oxide (PuO_2) has also been shown to enhance benzo[a]pyrene-induced lung carcinogenesis following simultaneous inhalation of both compounds (Metivier et al. 1984).

Another component of cigarette smoke, nicotine, may also affect the toxicokinetics of PAHs. When introduced in the perfusion medium with benzo[a]pyrene, nicotine inhibited the elimination of benzo[a]pyrene from the lung (Foth et al. 1988a).

Naturally occurring compounds have been found to induce the enzymes that metabolize PAHs, leading to either increased or decreased toxicity. Compounds that exert a protective effect against the carcinogenicity of PAHs and are enzyme inducers include plant flavonoids, plant phenols, antioxidants, retinoids (vitamin A), garlic oil, selenium, molybdenum, turmeric extracts, nitrates, soy sauce, and Chinese herbs. Plant flavonoids can induce microsomal monooxygenases and reduce the carcinogenicity of benzo[a]pyrene (Weibel 1980). Flavones administered orally or dermally increased benzo[a]pyrene hydroxylase activity in the small intestine and skin, respectively, and prevented the formation of pulmonary adenomas and forestomach and skin tumors initiated by benzo[a]pyrene (Rahimtula et al. 1977; Wattenberg and Leong 1970). A series of flavonoids and isoflavonoids, compounds that are found in fruits and vegetables, were tested for their ability to inhibit metabolism of benzo[a]pyrene in cultured hamster embryo cells (Chae et al. 1992). The results indicated that the flavonoids are generally more active than the isoflavonoids, and that two hydroxyl, two methoxyl, or methyl and hydroxyl substituents at the 5- and 7-positions and a 2,3-double bond are the structural characteristics required for inhibition of benzo[a]pyrene metabolism to reactive intermediates. Two of these compounds, acacetin and kaempferide also inhibited benzo[a]pyrene-induced mutation in Chinese

hamster V79 cells. Therefore, the authors proposed that the protective effect of these compounds may be due to their ability to inhibit metabolism of benzo[a]pyrene to reactive intermediates. Similar results have been obtained with pine cone extracts, tested in the *Salmonella typhimurium* assay (Lee et al. 1993). These results suggest that these compounds may be useful as potential chemopreventive agents in individuals exposed to genotoxic/carcinogenic PAHs.

Dietary plant phenols, such as tannic acid, quercetin, myricetin, and anthraflavic acid exhibit a protective effect against the tumorigenicity of benzo[a]pyrene and other PAHs by altering the metabolic pathways that detoxify and activate PAHs to their ultimate carcinogenic metabolites, thus suppressing PAH metabolism and subsequent PAH-DNA adduct formation. It has been suggested that the possible mechanism for the anticarcinogenic effect of these plant phenols may be an inhibitory effect on the binding of the ultimate carcinogen to the target tissue DNA (Mukhtar et al. 1988). Oral administration of these compounds has been associated with a decrease in tumorigenesis induced by benzo[a]pyrene in mouse forestomach (Katiyar et al. 1993a, 1993b; Zheng et al. 1993). Antioxidants also affect benzo[a]pyrene hydroxylation by rat liver microsomal MFOs, and reduce the bacterial mutagenicity of benzo[a]pyrene in the presence of rat liver microsomes and cofactors (Rahimtula et al. 1977). Antioxidants such as BHA, BHT, phenothiazine, phenothiazine methosulfate, and ethoxyquin all can reduce the quantitative yield of benzo[a]pyrene metabolites in incubations with rat liver microsomes (Sullivan et al. 1978).

Retinoids, of which vitamin A is a member, have demonstrated an antagonistic effect on benzo[a]pyrene-induced carcinogenicity. (Vitamin A has been shown to prevent and/or reverse the genetic damage caused by benzo[a]pyrene.) Similarly, the ability of benzo[a]pyrene (75 mg/kg, oral administration) to induce micronuclei *in vivo* was completely inhibited in Swiss mice orally administered doses of vitamin A ranging from 750 to 1,500 mg/kg 1 hour prior to benzo[a]pyrene treatment (Rao and Nandan 1990). Although the protective mechanism has not been fully elucidated, it has been suggested that vitamin A interferes with the activation of benzo[a]pyrene to its reactive metabolites, thus reducing the amount of benzo[a]pyrene-DNA binding in rat liver and target tissues (i.e., stomach) to prevent the mutagenic action of benzo[a]pyrene. It has also been suggested that vitamin A can enhance DNA repair (McCarthy et al. 1987; Rao et al. 1986). Conversely, vitamin A deficiency enhances the mutagenicity and carcinogenic effect of cigarette smoke and benzo[a]pyrene. This activity is related to a decreased level of free radical scavengers like ascorbic acid and glutathione in the liver (Alzieu et al. 1987). Another study observed that vitamin A deficient animals exposed to

cigarette smoke via inhalation exhibited enhanced benzo[a]pyrene-DNA adduct formation (Gupta et al. 1987, 1990). This has important implications for humans who smoke and consume diets deficient in vitamin A. Mammary tumor incidence was reduced by 27% (from 67% to 40%) in female rats receiving retinyl acetate before, during, and after the administration of either a single dose or eight weekly doses of benzo[a]pyrene. These results demonstrate that retinyl acetate is capable of inhibiting benzo[a]pyrene-induced mammary tumor formation in rats when given before, during, and after carcinogen treatment (McCormick et al. 1981).

The oral gavage administration of 25 mg/kg *n*-acetylcysteine (NAC) prevented the formation of benzo[a]pyrene-diol-epoxide-DNA adducts in rats receiving benzo[a]pyrene by intratracheal instillation for 3 consecutive days (25 mg/kg in 2% Tween 80) (De Flora et al. 1991). Inhibition of DNA adduct formation was more efficient in the liver than in the lungs. Similarly, micronuclei induction in the benzo[a]pyrene-treated rats was completely reversed by NAC. These results suggest that NAC, which is a glutathione precursor, may be effective in preventing or reversing the binding of the reactive intermediates of PAHs to cellular macromolecules and, therefore, may prevent the subsequent toxic effects of PAHs.

Coumarin, also known to be anticarcinogenic, inhibited benzo[a]pyrene-induced micronuclei in male ICR mice pretreated with 65 or 130 mg/kg/day coumarin for 6 days prior to the intraperitoneal administration of 150 mg/kg benzo[a]pyrene (Morris and Ward 1992). However, pretreatment with either dose of coumarin did not alter the genotoxicity of benzo[a]pyrene when females were included in the study.

Garlic oil also exhibits an antagonistic effect on benzo[a]pyrene by inhibiting benzo[a]pyrene-induced skin carcinogenesis in Swiss mice during the initiation phase (Sadhana et al. 1988). A primary constituent of garlic oil, allyl methyl trisulfide (ATM), has also demonstrated an inhibitory effect on benzo[a]pyrene induced neoplasia of the forestomach in mice (Spamins et al. 1986).

Selenium has been shown to reduce the mutagenicity of benzo[a]pyrene as well as AHH activity (Lee and Lin 1988). Selenium also inhibits the metabolism of benzo[a]pyrene *in vitro* (Bompart and Clements 1990). Several different salts of molybdenum inhibited the formation of certain metabolites of benzo[a]pyrene by lung and liver microsomes *in vitro* obtained from rats pretreated with 3-methylcholanthrene (Bompart et al. 1989). In a later study, it was demonstrated that benzo[a]pyrene

metabolism *in vitro* by lung and liver microsomes isolated from rats that were exposed to 40 or 80 mg/kg of ammonium heptamolybdate for 8 weeks was inhibited (Bompart 1990). These results suggest that molybdenum interferes with the cytochrome P-450 enzymes responsible for the activation of benzo[a]pyrene, and thus may have a protective effect against benzo[a]pyrene-induced toxicity/carcinogenicity.

Ferric oxide has been shown to increase the metabolism of benzo[a]pyrene by hamster alveolar macrophages (Greife and Warshawsky 1993). Alveolar macrophages, the primary lung defense cell, have been shown to metabolize benzo[a]pyrene to a more biologically active form, and then release the metabolites. Concurrent exposure of hamster alveolar macrophages to benzo[a]pyrene-coated ferric oxide resulted in a significant increase in the amount of benzo[a]pyrene metabolites and superoxide anions, which have been shown to produce localized lipid peroxidation and edema *in vivo.*

Lindane, an isomer of hexachlorocyclohexane, is an organochlorine pesticide which is extensively used in agricultural and public health programs in developing countries (Khan et al. 1993). Pretreatment of rat lungs with lindane by intratracheal injection inhibited benzo[a]pyrene hydoxlase activity in the lungs. Reduced elimination of intravenously administered benzo[a]pyrene from the lungs of rats after lindane pretreatment was also observed, suggesting that lindane may alter the clearance of benzo[a]pyrene from the lungs.

Prostacyclin has been shown to significantly reduce genetic damage caused by benzo[a]pyrene to mouse bone marrow cells, using the micronucleus test (Koratkar et al. 1993).

Chinese herbs commonly used in anti-cancer drugs have also been demonstrated to inh.ibit the mutagenicity of benzo[a]pyrene (Lee and Lin 1988).

Aqueous extracts of turmeric, curcumin-free aqueous turmeric extract, and curcumin were tested for their ability to inhibit benzo[a]pyrene-induced mutagenicity in the *S. typhimurium* assay and the bone marrow micronucleus test in Swiss mice (Azuine et al. 1992). A dose-dependent inhibition of benzo[a]pyrene-induced mutagenicity was observed in two strains of *Salmonella* in the presence of Aroclor-1254-induced rat liver homogenate, and 3 mg/kg of these three extracts also significantly inhibited benzo[a]pyrene-induced bone marrow micronuclei formation by 43%, 76%, and 65%. Female Swiss mice were treated with either aqueous turmeric extract (3 mg/day), curcumin-free

aqueous tumeric extract (1 mg/day), or curcumin (1 mg/day) 5 days/week for 2 weeks prior to receiving twice weekly gavage administrations of 20 mg/kg benzo[a]pyrene for 4 weeks. The treatment with the turmeric extracts continued for another 2 weeks after the cessation of benzopyrene treatment, and the animals were observed until they were 180 days old. A group receiving just benzo[a]pyrene served as a control. The benzo[a]pyrene-only animals exhibited 100% tumor incidence with 9.1±0.6 papillomas/mouse. All three extracts significantly ($p<0.00l$) inhibited the formation of forestomach papillomas by benzo[a]pyrene by 53%, and the average numbers of papillomas per mouse was also significantly decreased. The authors suggested that turmeric extracts may be useful as chemopreventive agents, but that there are probably several mechanisms of action for these inhibitory effects.

Pumark, a mixture of solvent extracts of tumeric, betel leaf, and catechu, was tested for its chemopreventative activity against benzo[a]pyrene-induced DNA damage (Ghaisas and Bhide 1994) Sister chromatid exchange and micronuclei formation in human lymphocyte culture were used as markers to assess the protective effect of Pumark. Pumark gave 50-60% protection against benzo[a]pyrene-induced chromosomal damage.

Other environmentally ubiquitous substances, such as nitrites and nitrates, have been shown to interact with PAHs. Pyrene is not mutagenic in the *Salmonella typhimurium* assay. However, when injected intraperitoneally into mice at doses of 10-200 mg/kg in combination with inhalation exposure to 50 or 100 ppm nitrous oxide (NO_2) mutagenic metabolites of pyrene were recovered from the urine (Kanoh et al. 1990). In addition, 1-hydroxypyrene (the major urinary metabolite of pyrene) administration in combination with NO_2 exposure also produced mutagenic metabolites. These results suggest that combined exposure to pyrene, a prevalent environmental PAH, and nitrogen compounds could result in the formation of nitrogenated mutagenic metabolites of pyrene. The effects of nitrite (in drinking water) and/or soy sauce (in food) on the forestomach tumors induced by twice weekly gavage administration of eight total doses of benzo[a]pyrene were studied in mice (Benjamin et al. 1988). The combination of nitrite and soy sauce resulted primarily in a significant reduction in the number of tumors per animal induced by benzo[a]pyrene, and also a reduction in tumor incidence. Neither substance alone had much effect on the carcinogenicity of benzo[a]pyrene alone. The mechanism for this protective effect of the combination of nitrite and soy sauce is not known.

The fungicide (prochloraz), the topical antifungal agent (miconazole) and 7,8-benzoflavone (a strong inhibitor of cytochrome P-450) limited the conversion of benzo[a]pyrene to a mutagen in S. *typhimurium.* The order of inhibitory action was 7,8-benzoflavone ≥ prochloraz ≥ miconazole (Antignac et al. 1990).

Diet (i.e., dietary fat levels) can also have an effect on the disposition and toxicity of PAHs. The metabolism of benzo[a]pyrene in hepatocytes *in vitro* from rats fed high-fat (as corn oil) diets was decreased (Zaleski et al. 1991). This effect was not due to a decrease in the activity of AHH. The authors postulated that the high-fat diets allowed benzo[a]pyrene, which is highly lipophilic, to become sequestered in lipid droplets and, therefore, become inaccessible to the P-450 enzymes. Another study suggests that caloric restriction, per se, can reduce the metabolic activation capacity of the liver, thereby reducing the production of mutagenic metabolites from PAHs (Xiao et al. 1993).

Organosulphur compounds, e.g., S-methyl cysteine sulphoxide (SMCSO) and its metabolite methyl methane thiosulphinate, both naturally occurring compounds present in Brassica vegetables (broccoli, cabbage) were found to inhibit benzo[a]pyrene-induced micronucleus formation in mouse bone marrow by 31 and 33%, respectively, after oral administration (Marks et al. 1993).

o-Cresol, often found in conjunction with PAHs in industrial waste from coking, oil processing, shale processing, and other industries, was found to protect mice from benzo[a]pyrene-induced forestomach tumors after oral administration, when o-cresol was administered before or after benzo[a]pyrene (Yanysheva et al. 1993).

Topical application of 1% croton oil twice weekly at 4 weeks of age had an inhibitory effect on tumor formation in offspring of ICF/Ha female mice treated with intraperitoneal injections of benzo[a]pyrene in sesame oil on the llth, 13th and 15th days of pregnancy (Bulay and Wattenberg 1971).

Administration of a diet containing 3% myo-inositol to mice beginning one week after oral benzo[a]pyrene administration reduced the number of pulmonary adenomas by 40% but did not prevent forestomach tumors (Estensen and Wattenberg 1993). Under the same conditions, administration of 0.5% dexamethasone in the diet inhibited pulmonary adenomas by 57% and also inhibited forestomach tumor formation to a similar degree. A combination of the two compounds resulted in additive chemoprevention.

The ubiquitous nature of PAHs in the environment, particularly as constituents of complex mixtures such as automobile emissions, coal tar, coke oven emissions, and combustion products of tobacco, increases the likelihood that the type of interactions discussed will occur. Thus, interactions may play a decisive role in the expression of toxicity and the development of cancer in exposed populations.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to PAHs than will most persons exposed to the same level of PAHs in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Data suggest that specific subsections of the population may be susceptible to the toxic effects produced by exposure to PAHs. These include people with various conditions, such as aryl hydrocarbon hydroxylase (AHH) that is particularly susceptible to induction, nutritional deficiencies, genetic diseases that influence the efficiency of DNA repair, and imrnunodeficiency due to age or disease. Other subsections of the population that may be susceptible to the toxic effects of PAHs are people who smoke, people with a history of excessive sun exposure, people with liver and skin diseases, and women, especially of child-bearing age. Human fetuses may also be particularly susceptible to the toxic effects produced by exposure to PAHs. Data also indicate that the general population may be at increased risk of developing lung cancer following prolonged inhalation of PAH-contaminated air, and skin cancer following concurrent dermal exposure to PAHs and sunlight. There is some limited evidence that indicates that all people could be sensitive at some point to the toxic effects of environmental contaminants, such as PAHs, as a result of stress and/or circadian rhythms.

Pre- and post-natal exposure to PAHs could produce adverse reproductive and developmental effects in human fetuses. Most PAHs and their metabolites cross the placenta because of their lipid solubility (Calabrese 1978; Shendrikova and Aleksandrov 1974). Fetuses are susceptible to the toxic effects produced by maternal exposure to PAHs, such as benzo[a]pyrene, because of an increased permeability of the embryonic and fetal blood-brain barrier and a decreased liver-enzyme conjugating function (Calabrese 1978; Shendrikova and Aleksandrov 1974). Because of PAH exposure, higher incidences of embryo- and fetolethality, stillbirths, resorptions, and malformations of the kidney and bladder have been observed in animals (Legraverend et al. 1984; Urso and Gengozian 1980; Urso and Johnson 1987). Delayed effects have been observed in the progeny of mothers exposed to PAHs, such as benzo[a]pyrene (Urso and Gengozian 1980). These .delayed effects include sterility of progeny, immune suppression, possible alteration of endocrine function, and cancer in rodents (Csaba and Inczefi-Gonda 1992; Csaba et al. 1991; Legraverend et al. 1984; Mackenzie and Angevine 1981). Tobacco smoke contains both PAHs and particulate matter. These could interact synergistically in pregnant women who smoke to produce decreased birth weight, increased perinatal morbidity and mortality, and other diseases of the newborn (NRC 1983). PAHs in cigarette smoke, such as benzo[a]pyrene, have been associated with the induction of AHH activity in human placental tissue and a decrease in placental size (NRC 1983). Results of *in vitro* studies indicate that benzo[a]pyrene alters human placental endocrine and metabolic function (Avigdor et al. 1992; Bamea and Shurtz-Swirski 1992; Guyda 1991; Guyda et al. 1990).

People with AHH that is particularly susceptible to induction may also be susceptible to the possible carcinogenic effect of exposure to PAHs. This enzyme is mixed function oxidase (MFO) that is involved in the metabolism of PAHs to certain reactive intermediates that can cause cell transformation, mutagenicity, and cytotoxicity. The incidence of this inducible genetic trait is low in 53%, intermediate in 37%, and high in 10% of the white population in the United States (Calabrese 1978). It has been proposed that genetically expressed AHH inducibility is related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. On the other hand, individuals with a greater ability to induce AHH may be able to rapidly detoxify PAHs and eliminate them, thus making them less susceptible to the toxic effects of PAHs. Based on the population frequency of genetically controlled AHH induction, some scientists predict that approximately 45% of the general population are considered to be at high risk, and 9% of the 45% are considered to be at very high risk, of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978).

Certain nutritional deficiencies have been associated with an increased cancer incidence in PAH-exposed animals. These include deficiencies in vitamins A and C, iron, and riboflavin (Calabrese 1978). It is estimated that at least 25% of all children between the ages of 7 and 12 years and all children of low-income families consume less than the recommended dietary allowance (RDA) of vitamin A. It has also been estimated that between 10% and 30% of the infants, children, and adults of low-income groups consume less than the RDA for vitamin C, 98% of all children consume less than the RDA for iron, and 30% of women and 10% of men between the ages of 30 and 60 years consume less than two-thirds of the RDA for riboflavin (Calabrese 1978). Other nutrients such as vitamin D, selenium, and protein can also influence the cancer incidence in animals exposed to PAHs (NRC 1983; Prasanna et al. 1987). Several studies have been conducted to investigate the interaction between nutrition and PAH exposure by administering benzo[a]pyrene to laboratory animals. The nutritional factors listed above either reduced the amount of benzo[a]pyrene binding to DNA in rat liver or forestomach tissue (McCarthy et al. 1987), prevented or reversed genetic damage (Rao et al. 1986), or reduced the activity of AHH (Prasanna et al. 1987). It has also been observed that fasted rats showed altered toxicokinetics of PAHs resulting from benz[a]anthracene and chrysene exposure. This altered toxicokinetics included reduced hepatic clearance because of decreased AHH activity and the acceleration of the depletion of cytochrome P-450 and other microsomal enzymes required to metabolize PAHs (Fiume et al. 1983).

Individuals who undergo a rapid reduction in body fat may be at risk from increased toxicity because of the systemic release and activation of PAHs that had been stored in fat. The metabolism of benzo[a]pyrene in hepatocytes *in vitro* from rats fed high-fat (as corn oil) diets was decreased (Zaleski et al. 1991). This effect was not due to a decrease in the activity of AHH. The authors postulated that the high-fat diets allowed benzo[a]pyrene, which is highly lipophilic, to become sequestered in lipid droplets and, therefore, become inaccessible to the P-450 enzymes.

People exposed to PAHs in conjunction with particulates from tobacco smoke, fossil-fuel combustion, coal fly ash, and asbestos fibers are at increased risk of developing toxic effects, primarily cancer. Even people not susceptible to the toxic effects of PAHs may become affected when exposure occurs in conjunction with exposure to particulates (NRC 1983). This enhanced effect results from the adsorption of PAHs onto the particulates. They are vacuolized into cells, and distributed differently in tissues depending on the size and type of particulate matter. This increased PAH uptake may result in more efficient induction of AHH activity at low PAH concentrations. This activity also increases the

dose to the gastrointestinal tract as a result of mucocilliary clearance (NRC 1983). This synergistic action between PAHs and particulate matter in air pollution has been associated with the occurrence of stomach cancer in humans (Fraumeni 1975).

Immunocompetence is an important factor in decreasing or preventing human susceptibility to toxicity and disease after exposure to environmental contaminants. Small children have an immature immune system, and the elderly may have a deficient immune system due to age, genetic factors, or disease (Calabrese 1978; NRC 1983). It is possible that individuals whose immune systems are compromised could be at an increased risk of carcinogenesis, including that produced by PAHs. Some genetic diseases that may predispose a person to immune deficiency include ataxia telangiectasia, Wiskott-Aldrich syndrome, Bloom's syndrome, common variable immunodeficiency, selective IgA deficiency, Bruton's agammaglobulinemia, severe combined immunodeficiency, selective IgM deficiency, AIDS, and immunodeficiency with normal or increased immunoglobulins (NRC 1983).

Genetic diseases that reduce DNA-repair capabilities also increase an individual's susceptibility to PAH-related malignancy by reducing the efficiency of DNA repair. In fact, the level of benzo[a]pyrene/DNA adducts in peripheral lymphocytes was slightly but significantly higher in 22 lung cancer patients who had at least one "first-degree" relative with lung cancer than in 30 healthy controls (Nowak et al. 1992). This finding led the authors to speculate that altered metabolic activation and deactivation and increased formation of adducts may indicate a genetic predisposition for lung cancer. Some of the diseases that reduce DNA repair capability are also associated with an abnormality of the immune system (NRC 1983). Diseases that may be associated with DNA-repair deficiencies are classical and variant xeroderma pigmentosum, ataxia telangiectasia, Bloom's syndrome, Fanconi's anemia, familial retinoblastoma, D-deletion retinoblastoma, progeria (Hutchinson-Gilford) syndrome, Down's syndrome, dyskeratosis congenita, Cockayne's syndrome, actinia keratosis, and cutaneous malignant melanoma (NRC 1983).

Women may be at increased risk of reproductive dysfunction following exposure to high levels of PAHs. Data from animal studies indicate that oocyte and follicle destruction occurs following dosing with PAHs (Mattison et al. 1989; Miller et al. 1992; Urso and Gengozian 1980; Urso and Johnson 1987). Benzo[a]pyrene exposure may reduce fertility and the ability to bear children (Mackenzie and Angevine 1981; Rigdon and Rennels 1964). Exposure may also reduce fertility of exposed women by

causing ovarian dysfunction (Swartz and Mattison 1985). However, the doses that produced the effects discussed above are high relative to expected environmental exposures to PAHs.

Subsections of the population that suffer from liver and skin diseases may be at increased risk of developing adverse effects from exposure to PAHs. People with pre-existing skin conditions, such as pemphigus vulgaris and xeroderma pigmentosum, and those with normal skin may be at increased risk of developing adverse dermal effects ranging from rashes to cancer following exposure to some PAHs, such as benzo[a]pyrene, anthracene, benz[a]anthracene, and pyrene (Bingham and Falk 1969; Cavalieri et al. 1977, 1988b; Cottini and Mazzone 1939; Forbes et al. 1976; Habs et al. 1980; Shubik and Porta 1957). Exposure to more than one PAH may enhance or reduce tumor development (Slaga et al. 1979; Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973). Skin cancer induction in laboratory animals has been associated with exposure to benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzohlfluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene.

People with significant exposure to ultraviolet radiation, such as from sunlight, may also be at increased risk of developing skin cancer due to PAH exposure. Ultraviolet radiation has a synergistic influence on PAH-induced skin cancer following dermal exposure. It enhances benzo[a]pyreneinduced skin carcinogenesis in the mouse, which is dependent on the dose of benzo[a]pyrene (Gensler 1988). Combined exposure to anthracene and sunlight could produce mutagenic lesions (Blackbum and Taussig 1975; Forbes et al. 1976). Laboratory animals exposed concurrently to chronic ultraviolet irradiation and to PAHs were at a higher risk of skin tumor induction (Mukhtar et al. 1986).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to PAHs. 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 PAHs. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

General recommendations to reduce absorption follo.wing acute exposure to PAHs include removing the individual from the source of exposure, removing contaminated clothing, and decontaminating exposed areas of the body. It has been suggested that contaminated skin should be washed with soap and water, and eyes exposed to PAHs should be flushed with water or saline (Stutz and Janusz 1988). Administration of activated charcoal following ingestion of PAHs is recommended; however, it has not been proven to reduce absorption of PAHs in the gastrointestinal system (Stutz and Janusz 1988). The use of emetics as a means of gastrointestinal decontamination of PAHs is not recommended (Bronstein and Currance 1988). There is a risk of causing chemical pneumonitis in the patient by the aspiration of the PAHs.

2.8.2 Reducing Body Burden

There are no known methods currently available for reducing the body burden of PAHs. Evidence from acute-duration studies in experimental animals indicates that PAHs are rapidly metabolized and conjugated to form water-soluble metabolites that are essentially completely eliminated in the urine and feces within a matter of days (see Sections 2.3.3 and 2.3.4). No data are available on the kinetics of PAHs following chronic exposure, so it is not known if PAHs or their metabolites bioaccumulate in these exposure situations. Given the relatively rapid and complete excretion observed following short-term exposures, it is not likely that PAHs bioaccumulate to an appreciable degree. However, PAHs are lipophilic, so it is conceivable that unmetabolized parent compound could accumulate in tissue fat stores. In fact, diet (i.e., dietary fat levels) may have an effect on the disposition and toxicity of PAHs. The metabolism of benzo[a]pyrene in hepatocytes *in vitro* from rats fed high-fat (as corn oil) diets was decreased (Zaleski et al. 1991). This effect was not due to a decrease in the activity of AHH. The authors postulated that the high-fat diets allowed benzo[a]pyrene, which is highly lipophilic, to become sequestered in lipid droplets and, therefore, become inaccessible to the P-450 enzymes. Therefore, high-fat diets may favor the accumulation of parent PAHs in lipids so that they are not metabolized to reactive intermediates or water-soluble conjugates. Alternatively, rapid fat loss may result in the release of sequestered parent PAHs, making them available to the P-450 enzymes to be metabolized to reactive intermediates as well as water-soluble conjugates that can be easily excreted. Thus, modulating body fat content may reduce body burden of PAHs by hastening

their metabolism to water-soluble conjugates. However, the result may also be an increase in toxicity due to increased metabolism to reactive intermediates.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

As discussed in Sections 2.3.5 and 2.4, it is currently believed that the toxic and carcinogenic effects of PAHs are mediated by reactive diol-epoxide intermediates that interact directly with DNA and RNA, producing adducts. The formation of these adducts leads to neoplastic transformation as well as interfering with the normal functioning of rapidly proliferating tissues. As discussed above, these reactive intermediates are formed when PAHs are biotransformed by the P-450 enzymes. Interference with these metabolic pathways, by inactivation of the activated diol epoxides, reduction in tissue levels of cytochrome P-450, and direct inhibition of the cytochrome P-450 enzymes responsible for the formation of the reactive intermediates, could reduce the toxic and carcinogenic effects of PAHs. A number of drugs, such as cobaltous chloride, SKF-525-A, and 6-nitro- 1,2,3-benzothioadiazole, have been reported to inhibit P-450 enzymes. In addition, as discussed in Section 2.7, other compounds that exert a protective effect against the carcinogenicity of PAHs by interfering with cytochrome P-450 enzymes include plant flavonoids, plant phenols, antioxidants (such as BHA, BHT, phenothiazine, phenothiazine methosulfate, and ethoxyquin), retinoids (vitamin A), garlic oil, selenium, organosulphur compounds, o-cresol, myo-inositol, lindane, and molybdenum (Bompart 1990; Bompart et al. 1989; Chae et al. 1992; Estensen and Wattenberg 1993; Ghaisas and Bhide 1994; Katiyar et al. 1993a, 1993b; Khan et al. 1993; Lee and Lin 1988; Lee et al. 1993; Marks et al. 1993; Mukhtar et al. 1988; Rahimtula et al. 1977; Rao and Nandan 1990; Sullivan et al. 1978; Weibel 1980, Yanysheva et al. 1994; Zheng et .al. 1993). Reduced caloric intake has also been shown to cause decreased metabolism of PAHs by liver microsomes, thus protecting against genotoxic effects (Xiao et al. 1993). P-450 metabolism also results in products that can be more readily eliminated than can the parent compound. Hence, any side products of the drugs or substances listed above, along with their potential to increase the biological half-life of the PAHs, would also need to be considered in any protocol. Further research to determine which cytochrome P-450 isozymes are involved in the metabolism to the reactive intermediates, as well as which isozymes are involved in enhancing the elimination of PAHs, could lead to the development of strategies to selectively inhibit specific isozymes and, thus, reduce the toxic effects of PAHs.

It has also been suggested that some of these compounds may act at other points in the activation, macromolecular binding sequence described above. For instance, vitamin A can also enhance DNA repair (McCarthy et al. 1987; Rao et al. 1986).

Because PAHs are detoxified by conjugation with substances such as glutathione (see Sections 2.3.3 and 2.3.4), sufficient glutathione stores in the body may reduce the chances of toxic effects following acute exposure to PAHs. For example, the oral gavage administration of NAC prevented the formation of benzo[a]pyrene-diol-epoxide-DNA adducts in rats receiving benzo[a]pyrene (De Flora et al. 1991). Inhibition of DNA adduct formation was more efficient in the liver than in the lungs. Similarly, micronuclei induction in the benzo[a]pyrene-treated rats was completely reversed by NAC. These results suggest that NAC, which is a glutathione precursor, may be effective in preventing or reversing the binding of the reactive intermediates of PAHs to cellular macromolecules and, therefore, may prevent the subsequent toxic effects of PAHs.

2.9 ADEQUACY OF THE DATABASE

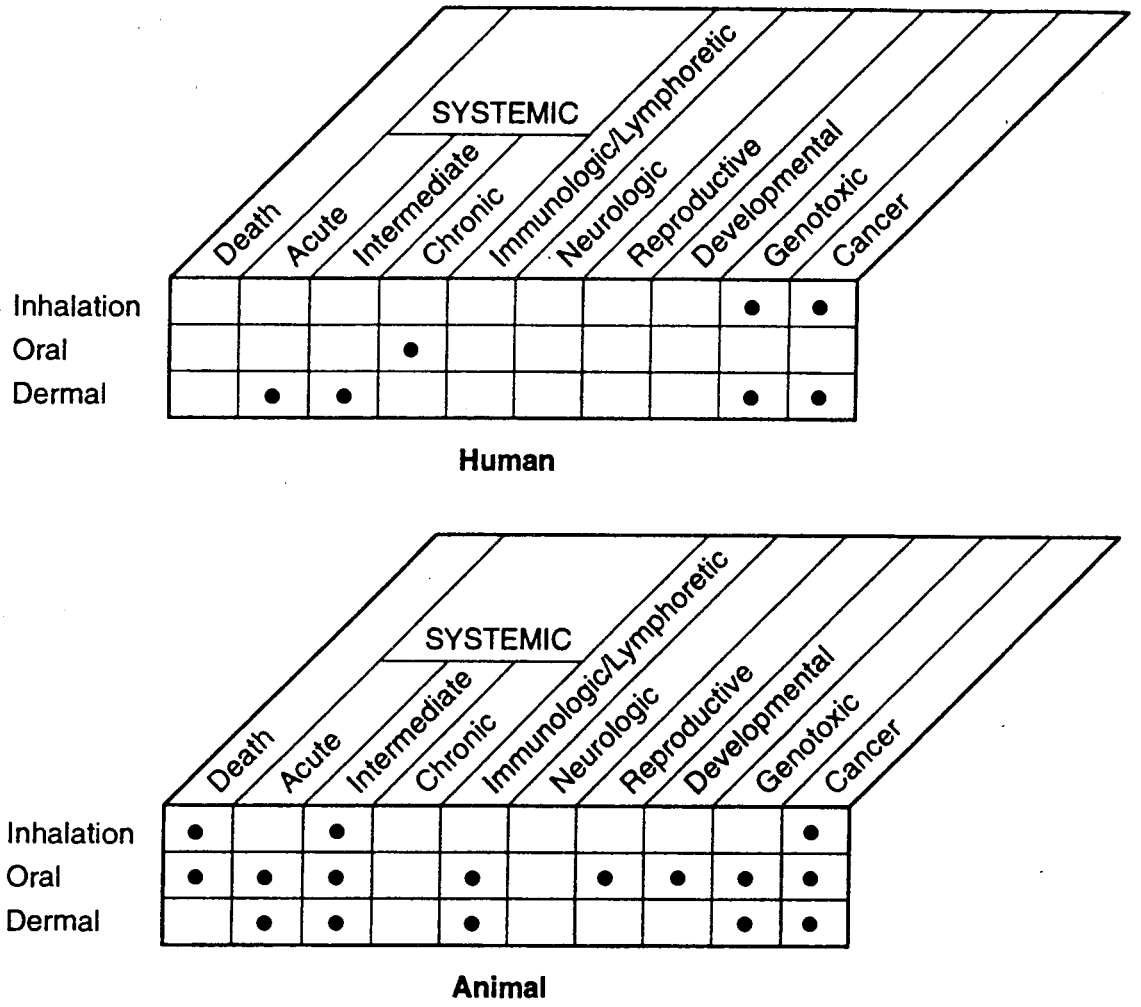
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, 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 PAHs.

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.

2.9.1 Existing Information on Health Effects of Polycyclic Aromatic Hydrocarbons

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PAHs are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing

FIGURE 2-5. Existing Information on Health Effects of Polycyclic Aromatic Hydrocarbons



● Existing Studies

information concerning the health effects of PAHs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 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.

The vast majority of literature reviewed concerning the health effects of PAHs in humans described case reports and chronic-duration studies in workers linking the occurrence of lung and skin cancer and adverse noncancer skin effects with exposure to PAH-containing mixtures such as coke oven emissions, roofing-tar emissions, shale oils, and soot, and exposure to cigarette smoke. The predominant routes of exposure in the studies are inhalation and dermal, but the possibility of some degree of oral exposure cannot be ruled out, especially in light of muco-cilliary clearance and ingestion following inhalation exposure. Because of the lack of quantitative exposure information and the presence of other potentially carcinogenic substances in these mixtures, it is impossible to evaluate the contribution of an individual PAH or even the PAHs as a class to the effects observed.

The database for the health effects of PAHs in experimental animals consists primarily of older animal studies that would be considered inadequate by current standards, and two-stage dermal carcinogenesis studies. As can be seen in Figure 2-5, very little information is available on the effects of inhalation exposure to PAHs in animals. However, oral and dermal exposures to relatively high doses of PAHs have been shown in numerous studies to induce skin, lung, and forestomach tumors in animals, and noncancer adverse effects in rapidly proliferating tissues such as bone marrow, lymphoid organs, gonads, and intestinal epithelium. Benzo[a]pyrene is by far the most extensively studied of the PAHs; therefore, the adverse effects of other less-studied PAHs must generally be inferred from the results obtained with benzo[a]pyrene. This may over- or underestimate the health risk associated with the various PAHs.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Little is known regarding the adverse health effects associated with acute-duration inhalation exposure to any of the PAHs in either humans or animals. Limited

information is available on the effects of acute-duration oral and dermal exposures to PAHs in animals; the skin and the liver have been identified as target organs of PAH toxicity in animals (Iwata et al. 1981; Nousiainen et al. 1984). Available information is insufficient to derive an acute inhalation or oral MRL. Identification of target organs (other than the developing fetus) from acute-duration animal studies following inhalation and oral exposures would be helpful in order to assess the risk associated with the acute inhalation of contaminated air or ingestion of PAH-contaminated water or soils by humans living in areas surrounding hazardous waste sites. Additional inhalation and oral studies in animals involving a range of exposure concentrations and employing sensitive histological and biochemical measurements of injury to a comprehensive set of end points would be useful for establishing dose-response relationships and identifying thresholds for these effects. This information would be useful for determining levels of significant exposure to PAHs that are associated with adverse health effects. Both routes are considered significant for individuals living in the vicinity of hazardous waste sites because exposures to particulate PAHs in air and PAHs bound to soil particles, sediments in water, and contaminated food are possible in such areas. Furthermore, the pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. Additional studies should be conducted on the effects of PAHs after acute-duration dermal exposure, since dermal exposure may be important to populations around hazardous waste sites. It is known that acute-duration dermal exposure to PAHs results in adverse dermal effects. Further studies determining the relative importance of exposure by this route, with regard to subsequent toxicity, would be useful. Studies describing dermal and oral absorption of PAHs from complex mixtures, including soil and other mixtures that may actually be the vehicles of human exposure, would be useful in furthering understanding of the toxicity of these compounds. The studies should be conducted with benzo[a]pyrene, because this PAH has been found at the highest number of NPL sites and it is a representative altemant PAH; studies should also be conducted with a representative nonaltemant PAH such as fluoranthene, benzo[b]fluoranthene, or benzo[j]fluoranthene. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be cOnducted to determine the most appropriate animal species for extrapolation to humans.

Intermediate-Duration Exposure. Little is known regarding the adverse health effects associated with intermediate-duration inhalation exposure to any of the PAHs in either humans or animals. One inhalation study in rats failed to establish an effect level (Wolff et al. 1989c). Information is available

on the effects of intermediate-duration exposures to some of the PAHs in humans (dermal) and in animals (oral and dermal). Regressive verrucae and other epidermal changes were noted in the skin of human volunteers treated with topically applied benzo[a]pyrene (Cottini and Mazzone 1939). Intermediate-duration dermal exposure to benzo[a]pyrene in patients with preexisting dermal conditions of pemphigus vulgaris and xeroderma pigmentosum was associated with an exacerbation of the abnormal skin lesions (Cottini and Mazzone 1939). Target organs identified in animal studies with some of the PAHs were the skin, the liver, and the hemolymphatic system (Legraverend et al. 1983; Old et al. 1963; Robinson et al. 1975). The available information is insufficient to derive an intermediate inhalation MRL for PAHs because no intermediate-duration inhalation animal studies exist that adequately describe the effects of inhalation exposure to PAHs. Intermediate duration MRLs have been derived for acenaphthene, fluoranthene, fluorene, and anthracene, based on 90-day gavage studies in mice (EPA 1988e; 1989c; 1989d, 1989e). For acenaphthene, fluoranthene, and fluorene, liver effects, supported by effects in other organ systems were identified as the target toxicity. For anthracene, no effect was seen in the liver or any other organ system, even at the highest dose of 1,000 mg/kg/day. The PAHs in these studies were administered by gavage, a route that does not mimic the potential exposure of people living near hazardous waste sites. Identification of target organs from intermediate-duration animal studies following inhalation and oral (drinking water) exposures would be useful in order to assess the risk associated with the intermediate-duration inhalation of contaminated air or ingestion of PAH-contaminated water or soils by humans living in areas surrounding hazardous waste sites. Ninety-day studies in animals by the inhalation and oral (drinking water) routes would be helpful to establish dose-response relationships and to identify other possible target organs or systems in individuals living around hazardous waste sites who can be exposed to low levels of PAHs for an intermediate-duration period of time. Both routes are considered important for individuals living in the vicinity of hazardous waste sites because exposure to particulate PAHs in air and PAHs bound to soil particles, sediments in water, and contaminated food are significant routes of exposure for individuals living in the vicinity of hazardous waste sites. Furthermore, the pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. Additional studies should be conducted on the effects of PAHs after intermediate-duration dermal exposure, since dermal exposure may be important to populations around hazardous waste sites. It is known that acute-duration dermal exposure to PAHs results in adverse dermal effects. Further studies determining the relative importance of exposure by this route, with regard to subsequent toxicity, would be useful. Studies describing dermal and oral absorption of PAHs from complex mixtures, including soil and other

mixtures that may actually be the vehicles of human exposure, would be useful in furthering the understanding of the toxicity of these compounds. The studies should be conducted with benzo[a]pyrene, because it has been found at the hi.ghest number of NPL sites and it is a representative altemant PAH, and with a representative nonaltemant PAH such as fluoranthene, benzo[b]fluoranthene, or benzofilfluoranthene. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Chronic-Duration Exposure and Cancer. Few controlled epidemiological studies have been reported in humans on the effects of exposure to PAHs or PAH-containing mixtures; such studies would be difficult to conduct because of the presence of too many confounding factors. However, information is available on the effects of chronic-duration dermal exposures to PAH-containing mixtures in humans. Workers exposed to substances that contain PAHs (e.g., coal tar) experience chronic dermatitis and hyperkeratosis (EPA 1988a). Several chronic ingestion, intratracheal installation, and skin-painting studies have been conducted in animals using various PAHs, but none identified adverse effects other than cancer. Therefore, threshold levels for chronic-duration inhalation and oral exposure have not been thoroughly investigated, and no MRLs have been developed from this database. Although the existing animal studies are inadequate to establish threshold levels and dose-response relationships for toxic effects resulting from chronic exposure to PAHs, the data from 90-day studies recommended above should be evaluated before chronic studies are conducted. Inhalation and ingestion are probably the most significant routes of exposure for individuals living in the vicinity of hazardous waste sites contaminated with PAHs. Low dose chronic studies are needed to mimic these exposures.

Human data on the carcinogenicity of PAHs are available only for mixtures containing PAHs. Animal carcinogenicity data are available for only benzo[a]pyrene following inhalation exposure, for a limited number of PAHs following ingestion, and for almost all of the 17 PAHs following dermal exposure. A large database on carcinogenicity exists on complex mixtures that contain PAHs (such as crude oils, various high boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes). It is difficult to ascertain the carcinogenicity of the component PAHs in these mixtures because of the potential interactions that could occur and the presence of other carcinogenic substances in the mixtures. Furthermore, the levels of PAHs were not quantified in any

of these reports. However, most of the available information on the carcinogenicity of PAHs in humans must be inferred from studies that reported the effects of exposure to complex mixtures that contain PAHs. Epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Despite the limitations inherent in these studies, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs to cause cancer in humans, and more definitive studies in humans on individual PAHs are not recommended at this time.

Inhalation exposure to benzo[a]pyrene has been shown to induce respiratory tract tumors in hamsters (Thyssen et al. 1981). Certain PAHs are carcinogenic to animals by the oral route (e.g., benz[a]anthracene, benzo[a]pyrene, and dibenz[a,h]anthracene), and tumors have been noted in the liver, mammary gland, and respiratory and gastrointestinal tracts following oral administration of these compounds (Neal and Rigdon 1967; Rigdon and Neal 1969). However, only a few PAHs have been assayed by the oral route. The results of dermal studies indicate that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[l,2,3-c,d]pyrene are tumorigenic in rats and mice following dermal exposure. Although many of these studies would be considered inadequate by current standards, the results nevertheless indicate that these PAHs can induce skin tumors as well as act as tumor initiators and promoters (Habs et al. 1984; Warshawsky and Barkley 1987; Wynder and Hoffmann 1959b). Therefore, additional studies on the carcinogenicity of PAHs in animals are probably not necessary at this time.

Genotoxicity. The genotoxic potential of several of the PAHs (both altemant and nonaltemant) has been extensively investigated using both *in vivo* and *in vitro* assays. All but three of the PAHs (acenaphthene, acenaphthylene, and fluorene) were reported to be mutagenic in at least one *in vitro* assay with the bacteria *S. typhimurium.* No further genotoxicity data are considered necessary at this time.

Reproductive Toxicity. No data were located regarding reproductive effects of PAHs in humans, and the available information regarding reproductive effects of PAHs in animals is limited; data exist on only one of the PAHs (benzo[a]pyrene), and these data are conflicting. Adverse effects such as decreased fertility and total sterility in F1 progeny of CD-1 mice (Mackenzie and Angevine 1981) and

decreased incidence of pregnant female rats at parturition (Rigdon and Rennels 1964) were reported following oral exposure to benzo[a]pyrene. However, no adverse reproductive effects were observed in Swiss mice fed benzo[a]pyrene in their diet (Rigdon and Neal 1965). The metabolic differences and method of benzo[a]pyrene administration could account for the differential response to benzo[a]pyrene-induced toxicity in these studies. Parenteral studies in animals have also demonstrated adverse reproductive effects (Bui et al. 1986; Cervello et al. 1992; Mattison et al. 1992; Miller et al. 1992; Swartz and Mattison 1985). The limited animal data suggest that PAHs may be reproductive toxicants, but these data are not extensive enough to draw firm conclusions. Furthermore, the testes and ovaries contain rapidly proliferating cells and therefore should be considered susceptible to damage by PAHs. The 90-day studies identified above should be conducted with special emphasis on reproductive organ pathology. If reproductive effects are observed in these studies, multigeneration animal studies could then be conducted to evaluate properly the relevance of this end point. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans. Future epidemiological studies should give special emphasis to evaluation of reproductive toxicity.

Developmental Toxicity. No studies were located regarding developmental effects in humans exposed to PAHs by any route. However, results of *in vitro* studies suggest that human placental endocrine and hormonal function may be affected by exposure to benzo[a]pyrene (Avigdor et al. 1992; Bamea and Shurtz-Swirski 1992; Guyda 1991). Only limited data are available in animals on a few PAHs (mostly benzo[a]pyrene). These data indicate that ingested or parenterally administered PAHs have a potential to induce adverse developmental effects such as resorptions and malformations (Legraverend et al. 1984; Shum et al. 1979), sterility in F_1 progeny (Mackenzie and Angevine 1981), testicular changes including atrophy of seminiferous tubules with lack of spermatids and spermatozoa, interstitial cell tumors (Payne 1958), immunosuppression (Urso and Gengozian 1980), and tumor induction (Bulay and Wattenberg 1971; Soyka 1980). However, another study found no developmental effects when benzo[a]pyrene was administered orally to mice (Rigdon and Neal 1965). The available animal data suggest that PAHs may be developmental toxicants. However, most of the data are from parenteral routes of exposure, and there are no inhalation data. The oral data are limited because of conflicting results across studies, the use of inconsistent protocols (e.g., varying numbers of animals, administration of the test compound during different times of gestation), the use of only one

dose, lack of study details, and the fact that data are available only on benzo[a]pyrene. Furthermore, some studies have shown that the toxic manifestations of benzo[a]pyrene are dependent on the route of exposure. Therefore, a two-species developmental toxicity study would be helpful to assess fully the potential for PAHs to affect development in humans. The route of exposure should be determined following evaluation of the reproductive organs in the 90-day studies to see if any particular route of exposure has a greater effect. The pharmacokinetic data on PAHs are insufficient,to determine whether similar effects may be expected to occur across different routes of exposure. Developmental toxicity should also be assessed in future animal reproductive toxicology testing and human epidemiological studies. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Immunotoxicity.No studies were located regarding immunological effects in humans after exposure to PAHs by any route, or in animals following inhalation exposure. In the one oral exposure study in animals that was located, a single dose of fluorene failed to affect thymus or spleen weight (Danz and Brauer 1988). However, there is information available in animals on the immunotoxicity of several PAHs following dermal exposure (contact hypersensitivity) (Old et al. 1963) and intraperitoneal or subcutaneous administration (suppression of both humoral and cellular immunity) (Blanton et al. 1986, 1988; Lubet et al. 1984; Lyte and Bick 1985; White and Holsapple 1984). In general, the degree of immunosuppression correlates with the individual PAH’s carcinogenic potency. Because of the information in animals that suggests that PAHs may affect the immune system, Tier I testing to assess PAH-induced immunotoxicity, as recently defined by the NTP (Luster et al. 1988) is recommended. The parameters that should be measured include immunopathology, humoral-mediated immunity, cell-mediated immunity, and nonspecific immunity. Although relatively high doses of PAHs must be used to obtain immunotoxicity in animals, much information could be gained from these studies. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans. Future epidemiologic studies should also place emphasis on evaluation of this end point.

Neurotoxicity. The potential for short- or long-term neurotoxic effects following exposure to PAHs by any route has not been specifically studied in humans or animals. Although acute-, intermediate-, and chronic-duration studies conducted in animals do not indicate that any of the PAHs tested showed gross evidence of neurotoxicity, these tests were not designed to detect subtle neurological changes. It is recommended that neurobehavioral as well as neuropathological end points be included in future 90-day toxicity testing of PAHs. If these preliminary data indicate that any of the PAHs are neurotoxicants, then a more comprehensive neurotoxicity battery, using sensitive functional and neuropathological tests, could be conducted to characterize further the neurotoxic potential of these PAHs. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Epidemiological and Human Dosimetry Studies. There are no epidemiological studies available that have investigated the effects of single PAHs by any route of exposure. Most of the available information on the effects of PAHs in humans comes from reports of occupational exposures to PAH-containing mixtures. For example, epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Each of these mixtures contains benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and co-carcinogens such as nitrosamines, coal tar pitch, and creosote. Limitations inherent in these studies include unquantified exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. Despite their inadequacies, studies in humans suggest that PAH-containing mixtures are dermal irritants and carcinogens following inhalation and/or derrnal exposure. If either worker or general populations with appropriate exposure can be identified, epidemiologic studies should be undertaken with special emphasis placed upon evaluation of cancer (of the skin and other organs) and other adverse skin effects, reproductive/ developmental toxicity, and immunotoxicity. However, such studies would be difficult to conduct. With a group of chemicals that are as ubiquitous as PAHs, it would be extremely difficult to distinguish between exposed and nonexposed populations. The more these groups overlap, the higher the chance for misclassification bias. In addition, the statistical power of an epidemiological study

depends partially on the variance of the exposure measurements. If there is enormous variation in the exposure levels among the exposed and nonexposed groups, then the population size needed to obtain statistical significance in the study would be unmanageable and would most likely not be found in any one occupational setting or hazardous waste site. Furthermore, because of the size of the population needed, it would be very difficult to control for confounding factors such as smoking, geographical location, lifestyle.

Biomarkers of Exposure and Effect.

Exposure. Sensitive analytical methods are available to quantify PAH exposure in humans. Although PAHs can be detected in the body fluids and tissues, because of the ubiquitous nature of PAHs in the environment, these biomarkers are not specific for any particular source of PAH exposure. PAHs and their metabolites (e.g., 1-hydroxypyrene) can be measured in the urine of exposed individuals. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to PAHs and mixtures that contain PAHs. Studies attempting to identify suitable and reliable biomarkers from phenanthrene, chrysene, and fluoranthene have been conducted (e.g., Grimmer et al. 1988). However, no other biomarkers (specific or otherwise) that have practical utility have been identified following exposure to PAHs. Further work on developing biomarkers that enable exposure to be quantified would be useful to ascertain whether individuals have been exposed to potentially toxic levels of PAHs. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies addressing mixtures of PAHs should be conducted.

Effect. The available biomarkers of effect for PAHs are not specific for effects induced by PAHs. The available genotoxicity data indicate that several of the 17 PAHs considered here are genotoxic in both nonmammalian and mammalian systems and are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system). There were no tests reported for humans exposed to benzo[a]pyrene (the most widely tested PAH) *in vivo*, but several types of cultured human tissue cells demonstrated positive results for benzo[a]pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange) and binding of benzo[a]pyrene to DNA. Thus, although these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to PAHs have been negative, these genotoxic effects observed in human tissue cells may serve as a biomarker of effects for at least one of the PAHs, benzo[a]pyrene. The formation of benzo[a]pyrene-DNA adducts has been demonstrated, and

this may serve as a biomarker of PAH-induced carcinogenicity. Additional studies on the relative sensitivity of DNA adducts and sister chromatid exchanges to identify threshold levels of exposure that could be detected in human populations would be useful. In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies addressing mixtures of PAHs should be conducted.

Absorption, Distribution, Metabolism, and Excretion. The quantitative data on the toxicokinetics of PAHs are based, to a large extent, on short-term exposure to benzo[a]pyrene in animals. Occupational exposure to PAHs generally occurs as a mixture. Therefore, inhalation, oral, and dermal studies exploring how PAHs interact with each other to affect their disposition would be more representative of exposures in humans.

The presence of PAHs and their metabolites in human urine and blood following inhalation, oral, and dermal exposures indicates that PAH absorption occurs in humans (Becher and Bjorseth 1983; Buckley and Lioy 1992; Hecht et al. 1979). However, there was no quantitative information on the extent and rate of PAH absorption in humans. Most of the information regarding the pulmonary and oral absorption and distribution of PAHs in animals is based on acute-duration exposures (Chang 1943; Hecht et al. 1979; Weyand and Bevan 1986, 1987b, 1988; Withey et al. 1991; Wolff et al. 1989c). PAHs appear to be widely distributed in tissues of animals following oral and inhalation exposure; peak tissue concentrations occurred earlier with higher exposure levels. Studies on the absorption and distribution of PAHs following long-term exposures would indicate whether the kinetics are similar to acute-duration exposures. The dermal study conducted by Storer et al. (1984) revealed that several PAHs in a crude coal tar mixture were absorbed, but that benzo[a]pyrene was not. In contrast, animal studies indicate that benzo[a]pyrene was dermally absorbed (Ng et al. 1992; Wester et al. 1990; Yang et al. 1989); however, tissue distribution was not discussed.

PAH metabolism has been extensively reviewed in human and animal tissue homogenates, cultures, and perfused systems (Autrup et al. 1978; Cavalieri et al. 1987; Cohen et al. 1976; Kiefer et al. 1988; Leung et al. 1988). However, these studies are limited to the biotransformation of individual compounds. Since most metabolic pathways have been identified or can be predicted for the individual PAHs, it is now important to understand how these metabolic pathways are affected when the PAHs compete. The carcinogenic and toxic potential of PAHs is associated with their metabolites. Alterations in rates of metabolism and metabolite profiles may affect the toxic consequences of PAHs.

Available data on several of the nonaltemant tumorigenic PAHs discussed in this profile indicate that they exert their adverse effects by mechanisms that differ from those that have been more recently elucidated for altemant PAHs (Amin et al. 1982, 1985b; Rice et al. 1987b). The mechanisms by which benzo[b]fluoranthene and benzo[j]fluoranthene are metabolically activated to genotoxic agents have been elucidated (LaVoie et al. 1993b; Marshall et al. 1993; Weyand et al. 1993a, 1993b). Additional studies designed to assess the potential toxic effects of these reactive metabolites in various species and at various organ sites would be useful.

No studies were located that monitored the rate and extent of PAH excretion in humans. Most studies in animals concentrated on the extent of PAH excretion and the distribution of the compound and its metabolites in urine, feces, and bile following short-term exposures (Bevan and Weyand 1988; Grimmer et al. 1988; Petridou-Fischer et al. 1988; Weyand and Bevan 1986; Wolff et al. 1989c; Yamazaki and Kakiuchi 1989). Data regarding the excretion pattern and rate following long-term exposure to PAHs would be useful to determine if bioaccumulation occurs.

In addition, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Comparative Toxicokinetics. Occupational studies provide evidence that inhaled PAHs are absorbed. Animal studies also show that pulmonary absorption of benzo[a]pyrene occurs, but the extent of absorption is not known. Ingestion of benzo[a]pyrene is low in humans while oral absorption in animals varies among the PAH compounds depending on the lipophilicity. The absorption and distribution of PAHs in various species would be expected to be similar based on the lipophilicity of the compounds. In general, percutaneous absorption of PAHs in several animal species appears to be rapid and high (Ng et al. 1992; Sanders et al. 1986; Wester et al. 1990; Yang et al. 1989). This suggests that dermal absorption in humans may also occur rapidly; however, the extent of absorption may vary depending on the vehicle.

There was no information available on the distribution of PAHs in humans. In general, tissue distribution of benzo[a]pyrene following inhalation exposure is qualitatively similar for different species (Bevan and Weyand 1988; Weyand and Bevan 1986, 1987a, 1988; Wolff et al. 1989c). In

general, orally absorbed PAHs were rapidly and widely distributed in the rat (Bartosek et al. 1984; Withey et al. 1991; Yamazaki and Kakiuchi 1989). Qualitative similarities in distribution among species suggest that distribution in humans would also be similar. Placental transfer of PAHs in mice and rats appears to be limited (Neubert and Tapken 1988; Withey et al. 1992); therefore, human fetuses may be exposed to PAHs, but levels would not be as high as maternal levels.

Qualitatively, metabolism and excretion would be relatively similar in humans and animals, but variability in specific activities of enzymes will alter the metabolic profiles among the species. Knowledge of these differences in enzyme activity in various species would assist in predicting which pathways and metabolites would prevail. For instance, AHH activity is not induced by PAHs in some strains of mice. Therefore, it would be useful to examine the metabolism of those less-well-studied PAHs in several species (i.e., rodent and nonrodent) so that the carcinogenic potential of PAHs in various species could be predicted. The feces (via the bile) appears to be the major excretion route, but the extent of elimination of PAHs varies among species (Bevan and Weyand 1988; Grimmer et al. 1988; Ng et al. 1992; Petridou-Fischer et al. 1988; Sanders et al. 1986; Weyand and Bevan 1986; Wolff et al. 1989c). Further comparative studies on excretion would be useful because differences in human and animal excretion rates are not known. In addition, many of the toxicity tests have used mice, while a larger proportion of toxicokinetic studies have used rats. Thus, more kinetic studies should be conducted in mice to provide data to correspond to the toxicity data. Further, since PAHs rarely occur alone, but are found in the environment in combinations and mixtures, studies, particularly feeding studies, addressing mixtures of PAHs should be conducted. In all cases, research should be conducted to determine the most appropriate animal species for extrapolation to humans.

Methods for Reducing Toxic Effects. Efforts are currently underway to develop ways to mitigate the adverse effects of PAHs, especially with regard to natural products. Efforts to reduce or eliminate cigarette smoking in the general population also contribute toward reducing exposure to and toxic effects of PAHs. The target organs of PAHs have been identified (i.e., the skin and rapidly proliferating tissue such as the hematopoietic and lymphoid systems). Furthermore, several PAHs are considered to be carcinogenic. The mechanism of action for altemant PAH-induced carcinogenicity is fairly well understood. However, additional information would be useful to understand the mechanism of nonaltemant PAH-induced carcinogenicity, how PAHs exert their adverse effects on rapidly proliferating tissue, and how various interactions between PAHs can affect their toxicity and carcinogenicity.

2.9.3 Ongoing Studies

Ongoing research on the health effects and toxicokinetics of PAHs is summarized in Table 2-7.

TABLE 2-7. Ongoing Studies on Polycyclic Aromatic Hydrocarbons[a]

Investigator	Affiliation	Research description	Sponsor
E.J. La Voie	Rutgers State University, New Brunswick, NJ	Environmental polyclics—Metabolism and activation (mice, humans)	National Institute of Environmental Health Sciences
S.P. Mudzinski	Albany Medical College of Union University, Albany, NY	Immunotoxicologic screening of chemical carcinogens (mice)	National Institute of Environmental Health Sciences
W.F. Busby	Massachusetts Institute of Technology, Cambridge, MA	Core—Tumorigenicity testing (mice)	National Institute of Environmental Health Sciences
D.R. Bevan	Virginia Polytechnic Institute, Blacksburg, VA	Disposition of benzo(*a*)pyrene *in vivo*	U.S. Department of Agriculture
R.L. Hill	Florida State University, Tallahassee, FL	The impact of energy-related pollutants on chromosome structure	Not specified
N. Hahon	NIOSH DRDS, Morgantown, WV	Polycyclic aromatic hydrocarbons, particulates and defense mechanisms	National Institute of Occupational Safety and Health
M.K. Sanyal	Yale University, New Haven, CT	Abnormal fetal development during to toxic exposure (humans, rats, mice)	National Institute of Environmental Health Sciences
M. Koreeda	University of Michigan, Ann Arbor, MI	Synthesis and reactions of polycyclic aromatic hydrocarbon metabolites	National Institute of Environmental Health Sciences
L.M. Anderson	National Institutes of Health, Bethesda, MD	Metabolic and pharmacological determinants in perinatal carcinogenesis	National Institutes of Health
K. Frenkel	New York University Medical Center, New York, NY	Tumor promoters affecting base modification in DNA (mice)	National Institutes of Health
M.E. Knuckles	Meharry Medical College, Nashville, TN	Acute and subchronic inhalation and oral toxicity testing of benzo(a)pyrene and fluoranthene	Agency for Toxic Substances and Disease Registry

[a]Information obtained from Federal Research in Progress (October, November 1992) and CRISP (October 1992) databases

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of PAHs is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of PAHs is located in Table 3-2.

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a]

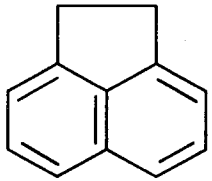
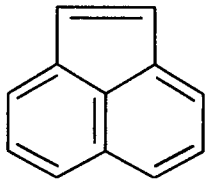
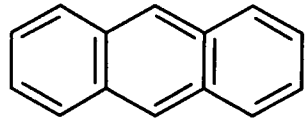
Characteristic	Acenapthene	Acenaphthylene	Anthracene
Synonym(s)	1,2-Dihydroacenaphthylene; 1,8-dihydroacenapthaline; 1,8-ethylenenapthalene; 1,2-dihydroacenapththylene	Cyclopenta[d,e]naphthalene	Anthracin; green oil; paranaphthalene[b]
Registered trade name(s)	No data	No data	Tetra olive NZG; Anthracene oil[d]
Chemical formula	$C_{12}H_{10}$	$C_{12}H_8$	$C_{14}H_{10}$[b]
Chemical structure			
CAS registry	83–29–9	208–96–8	120–12–7[b]
NIOSH RTECS	AB1000000	AB1254000	CA 9350000
EPA hazardous waste	No data	No data	No data
OHM/TADS	8200126	No data	82001222
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	2659	2661	702
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

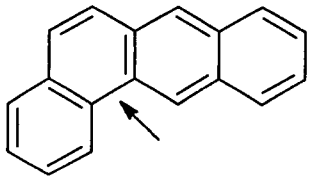
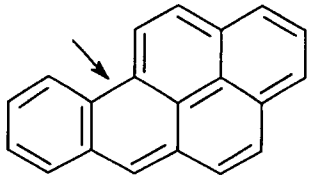
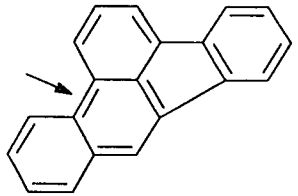
Characteristic	Benzo[a]anthracene	Benzo[a]pyrene	Benzo[b]fluoranthene
Synonym(s)	BA; benz[a]anthracene; 1,2-benzanthracene; benzo[b]-phenanthrene; 2,3-benzophenanthrene; tetraphene[c,d]	Benzo[d,e,f]chrysene; 3,4-benzopyrene, 3,4-benzpyrene; benz[a]pyrene; BP; B[a]P[b]	3,4-Benz[e]acephenanthrylene; 2,3-benzfluoranthene; 3,4-benzfluoranthene; 2,3-benzofluoranthene; 3,4-benzofluoranthene; benzo[e]fluoranthene;B[b]F[b]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{18}H_{12}$	$C_{20}H_{12}$[b]	$C_{20}H_{12}$[b]
Chemical structure			
Identification numbers:			
CAS Registry	56–55–3	50–32–8	205–99–2[b]
NIOSH RTECS	CV 9275000[e]	DJ3675000	CU 1400000[e]
EPA Hazardous Waste	U018	U022	No data
OHM/TADS	8200123	No data	8200124[e]
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4003	2554	4035
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

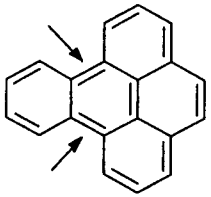
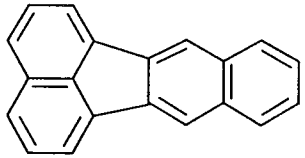
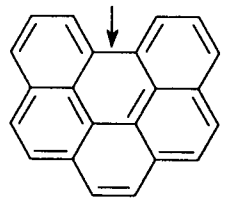
Characteristic	Benzo[e]pyrene	Benzo[k]fluoranthene	Benzo[g,h,i]perylene
Synonym(s)	1.2-Benzopyrene; 1.2-benzpyrene; 4.5 benzopyrene; 4.5-benzpyrene; B[e]P[e]	8.9-Benzfluoranthene; 8.9-benzofluoranthene; 11.12-benzofluoranthene; 2,3,1.8-binaphthylene; dibenzo[b,j,k]fluorene[b]	1,12-Benzoperylene[c]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{20}H_{12}$[e]	$C_{20}H_{12}$[b]	$C_{22}H_{12}$[c]
Chemical structure			
CAS registry	192–97–2[e]	207–08–9[b]	191–24–2[c]
NIOSH RTECS	D4500000[e]	DF 350000[e]	DI 6200500[e]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	8200125[e]	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4031[e]	6012[e]	6177[e]
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

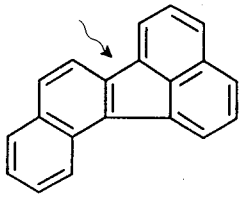
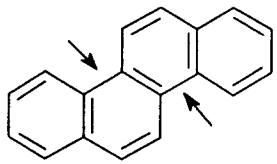
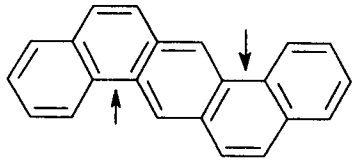
Characteristic	Benzo[j]fluoranthene	Chrysene	Dibenz[a,h]anthracene
Synonym(s)	10.11-Benzofluoranthene; benzo-12.13-fluoranthene; dibenzo[a,j,k]-fluorene; 7.8-benzofluoranthene; B[j]F[e]	1.2-Benzophenanthrene; benzo[a]-phenanthrene; 1,2-benzphenanthrene; benz[a]phenanthrene; 1,2,5,6-dibenzonaphthalene	Dibenz[a,h]anthracene; DB[a,h]A; DBA; 1,2:5,6-dibenz[a]anthracene[b,e]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{20}H_{12}$	$C_{18}H_{12}$[b]	$C_{22}H_{14}$[b]
Chemical structure			
CAS registry	205–82–3[e]	218–01–9[b]	53–70–3[b]
NIOSH RTECS	DF 6300000[e]	GC 0700000[e]	HN 2625000[e]
EPA hazardous waste	No data	U050[e]	U063
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4034[e]	2810	5097
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

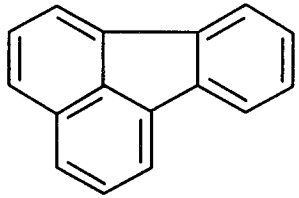
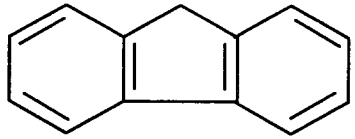
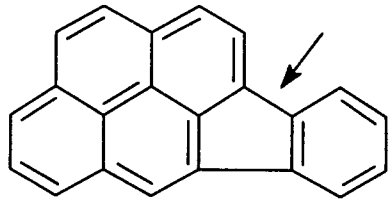
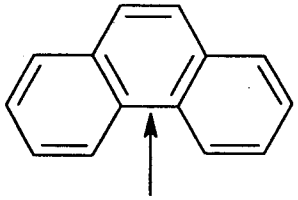
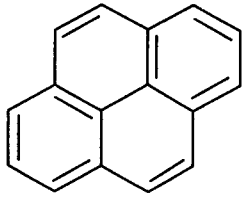
Characteristic	Fluoranthene	Fluorene	Indeno[1,2,3-c,d]pyrene
Synonym(s)	1.2-[1,8-Naphthylene]benzene; 1.2-benzacenaphthene; 1.2-[1.8-naphthalenediyl] benzene; benzo[j,k]fluorene	ortho-Biphenylene methane; diphenylenemethane; 2,2-methylene biphenyl; 2.3-benzidene[b,f]	Indenopyrene; IP; ortho-phenylene pyrene; 1,10-[ortho-phenylene]pyrene; 1,10-[1,2-phenylene]pyrene; 2,3-ortho-phenylene pyrene[b]
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{16}H_{10}$	$C_{13}H_{10}$[b]	$C_{22}H_{12}$[b]
Chemical structure			
Identification numbers:			
CAS registry	206–44–0	86–73–7[b]	193–39–5[b]
NIOSH RTECS	LL4025000	LL5670000	NK 9300000
EPA hazardous waste	U120	No data	U137
OHM/TADS	8200136	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	5486	2165	5101
NCI	No data	No data	No data

TABLE 3-1. Chemical Identity of Polycyclic Aromatic Hydrocarbons[a] (continued)

Characteristic	Phenanthrene	Pyrene
Synonym(s)	Phenanthrene; Phenantrin[b]	Benzo[d,e,f]phenanthrene; 8-pyrene[b]
Registered trade name(s)	No data	No data
Chemical formula	$C_{14}H_{10}$[b]	$C_{16}H_{10}$[b]
Chemical structure		
Identification numbers:		
CAS registry	85–01–8[b]	129–00–00[b]
NIOSH RTECS	SF7175000	UR 245000[e]
EPA hazardous waste	No data	No data
OHM/TADS	8200140	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	2166	4023
NCI	No data	No data

[a]All information obtained from HSDB 1994, except where noted.
[b]IARC 1983
[c]Eller 1984
[d]Sax and Lewis 1989
[e]HSDB 1992
[f]Weast et al. 1988

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 Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; PAHs = polycyclic aromatic hydrocarbons; RTECS = Registry of Toxic Effects of Chemical Substances; ⟶ = bay region; ⇝ = pseudo bay region

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a]

Property	Acenaphthene	Acenaphthylene	Anthracene
Molecular weight	154.21	152.20	178.2[b]
Color	White	No data	Colorless with violet fluorescence when pure; yellow with green fluorescence when impure
Physical state	Solid (needles)	Solid (prisms/plates)	Solid (tablet or prism)[b]
Melting point	95 °C	92–93 °C	218 °C[b]
Boiling point	96.2 °C	265–275 oC	342 °C[b], 340 °C[e]
Density at 20/4 °C	1.225 g/cm^3 at 0 °C	No data	No data
Specific gravity	1.0242 at 90 °C/4 °C[e]	0.8988 at 16 °C/2 °C	1.25 at 27 °C/4 °C; 1.283 at 25 °C/4 °C[e]
Odor	No data	No data	Weak aromatic odor
Odor threshold:			
Water	0.08 ppm	No data	No data
Air	0.08 ppm	No data	No data
Solubility:			
Water	1.93 mg/L[p]	3.93 mg/L water	0.076 mg/L[p]
Organic solvents	Soluble in alcohol, methanol, propanol, chloroform, benzene, toluene, glacial acetic acid	Alcohol, ether, benzene	Acetone; benzene, carbon disulphide, carbon tetrachloride, chloroform, ether, ethanol, methanol, toluene[e,b]
Partition coefficients:			
Log K_{ow}	3.98[k]	4.07[k]	4.45[k]
Log K_{oc}	3.66[k]	1.40[k]	4.15[k]
Vapor pressure	4.47x10^{-3} mm Hg[m]	0.029 mm Hg at 20 °C[k]	1 mm Hg at 145 °C[b]; 1.7x10^{-5} mm Hg at 25 °C[k]
Henry's law constant	7.91x10^{-5} atm-^{3}/mol[r]	1.45x10^{-3} atm-m^3/mol	1.77x10^{-5} atm-m^3/mol[r]
Autoignition temperature	No data	No data	540 °C[i]
Flashpoint	No data	No data	121 °C(closed cup)[d]
Flammability limits	Dust is moderately flammable[n]	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	Lower, 0.6% by volume[d]

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Benzo[a]anthracene	Benzo[a]pyrene	Benzo[b]fluoranthene
Molecular weight	228.29[c]	252.3[b]	252.3[b]
Color	Yellow-blue fluorescence[e]	Pale yellow	Colorless
Physical state	Solid (plates)	Solid (plates or needles)[f]	Solid (needles)[e] (recrystallized from benzene/ligroin)
Melting point	158–159 °C[c]; 162 °C[e]	179–179.3 °C[f]	168.3 °C[b]
Boiling point	400 °C[i]; 435 °C sublimes[f]	310–312 °C at 10 mm Hg[f]; 495 °C[j]	No data
Density	1.274 g/cm^3 at 20 °C	1.351 g/cm^{3,h}	No data
Specific gravity	No data	No data	No data
Odor	No data	Faint aromatic odor	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.010 mg/L[p]	2.3x10^{-3} mg/L[p]	0.0012 mg/L[q]
Organic solvents	Slightly soluble in acetic acid and hot ethanol; soluble in acetone and diethyl ether; very soluble in benzene[b]	Sparingly soluble in ethanol and methanol; soluble in benzene, toluene, xylene, and ether	Slightly soluble in benzene, acetone[b]
Partition coefficients:			
Log K_{ow}	5.61[k]	6.06[k]	6.04[k]
Log K_{oc}	5.30[k]	6.74[k]	5.74[k]
Vapor pressure	2.2x10^{-8} mm Hg at 20 °C	5.6x10^{-9} mm Hg[k]	5.0x10^{-7} mm Hg at 20–25 °C[r]
Henry's law constant	1x10^{-6} atm–m^3/mol	4.9x10^{-7} atm-m^3/mol[k]	1.22x10^{-5} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Benzo[e]pyrene	Benzo[k]fluoranthene	Benzo[g,h,i]perylene
Molecular weight	252.30[d]	252.3	276.34[c]
Color	Colorless[b]	Pale yellow	Pale yellow-green
Physical state	Prisms or plates (recrystallized from benzene)[g]	Solid (needles)	Solid (plate)
Melting point	178–179 °C[d]	215.7 °C	273 °C[c]
Boiling point	310–312 °C at 10 mm Hg[g]	480 °C	550 °C
Density	No data	No data	No data
Specific gravity	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	6.3×10^{-3} mg/L at 25 °C[d]	7.6×10^{-4} mg/L at 25 °C	2.6×10^{-4} mg/L at 25 °C
Organic solvents	Acetone[g]	Soluble in benzene, acetic acid, ethanol[b]	Soluable in benzene, dichloromethane, acetone[g]
Partition coefficients:			
Log K_{ow}	No data	6.06[k]	6.50[k]
Log K_{oc}	No data	5.74[k]	6.20[k]
Vapor pressure	5.7×10^{-9} mm Hg at 25 °C[d]	9.59×10^{-11} mm Hg	1.03×10^{-10} mm Hg at 25 °C[k]
Henry's law constant	No data	3.87×10^{-5} atm–m^3/mol[k]	1.44×10^{-7} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Benzo[j]fluoranthene	Chrysene	Dibenz[a,h]anthracene
Molecular weight	252.32[d]	228.3[b]	278.35[c]
Color	Yellow or orange[d]	Colorless with blue or red-blue fluorescence[b,e]	Colorless[b]
Physical state	Plates (recrystallized from ethanol) or needles (recrystallized from acetic acid)[d,h]	Solid (plates)[e]	Solid (plates or leaftlets)[e]
Melting point	166 °C[d]	255–256 °C[b]	262 °C[c]
Boiling point	No data	448 °C[b]	No data
Density	No data	No data	1.282 g/cm^3[,h]
Specific gravity	No data	1.274 at 20 °C/4 °C[i]	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	6.76x10^{-3} mg/L at 25 °C[d]	2.8x10^{-3} mg/L[p]	5x10^{-4} mg/L[b]
Organic solvent(s)	Slightly soluble in alcohol and acetic acid; soluble in hydrogen sulfide on heating[d]	Slightly soluble in acetone, carbon disulphide, diethyl ether, ethanol glacial acetic acid toluene hot xylene; soluble in benzene[b]	Slightly soluble in ethyl alcohol; soluble in acetone, acetic acid, benzene, toluene and xylene[e]
Partition coefficients:			
Log K_{ow}	6.12[d]	5.16[k]	6.84[k]
Log K_{oc}	4.7–4.8[d]	5.30[k]	6.52[k]
Vapor pressure	1.50x10^{-8} mm Hg at 25 °C[d]	6.3x10^{-7} mm Hg at 25 °C[k]	1x10^{-10} mm Hg at 20 °C[k]
Henry's law constant	1x10^{-6} atm–m^3/mol[d]	1.05x10^{-6} atm-m^3/mol[k]	7.3x10^{-8} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Fluoranthene	Fluorene	Indeno[1,2,3-c,d]pyrene
Molecular weight	202.26	166.2[g]	276.3[g]
Color	Pale yellow	White[g]	Yellow plates or needles showing a greenish-yellow fluorescence[g]
Physical state	Solid (needles or plates)	Solid (leaflets or flakes; crystalline plates)[g]	Solid (plates or needles)[g]
Melting point	11 °C	116–117 °C[g]	163.6 °C[g]
Boiling point	~375 °C	295 °C[g]	530 °C
Density	No data	No data	No data
Specific gravity	1.252 at 0 °C/4 °C	1.203 at 0 °C/4 °C	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.20–0.26 mg/L[g]	1.68–1.98 mg/L[g]	0.062 mg/L[g]
Organic solvents	Alcohol, ether, benzene, acetic acid	Acetic acid, acetone, benzene, carbon disulphide, carbon tetrachloride, diethyl ether, ethanol, pyrimidine, solution, toluene[g]	Soluble in organic solvents[g]
Partition coefficients:			
Log K_{ow}	4.90[k]	4.18[k]	6.58[k]
Log K_{oc}	4.58[k]	3.86[k]	6.20[k]
Vapor pressure	5.0×10^{-6} mm Hg at 25 °C[k]	3.2×10^{-4} mm Hg at 20 °C[d]	~10^{-11}–10^{-6} mm Hg at 20 °C[k]
Henry's law constant	6.5×10^{-6} atm–m^3/mol[k]	1.0×10^{-4} atm-m^3/mol[r]	6.95×10^{-8} atm-m^3/mol[k]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	0	0	0
Explosive limits	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of Polycyclic Aromatic Hydrocarbons[a] (continued)

Property	Phenanthrene	Pyrene
Molecular weight	178.2[b]	202.3[b]
Color	Colorless[b]	Colorless, pale yellow plates (recrystallized from toluene) or slight blue fluorescence (recrystallized from ethanol or sublimation)[b]
Physical state	Solid (plates, crystals, or leaflets)[b]	Solid (plates or tablets)[b]
Melting point	100 °C[b]	156 °C
Boiling point	340 °C	393 °C[e]; 404 °C[l]
Density	0.980 g/cm^3 at 4 °C	1.271 g/cm^3 at 23 °C
Specific gravity	No data	1.271 at 23 °C/4 °C
Odor	Faint aromatic odor	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 25 °C	1.20 mg/L[p]	0.077 mg/L[p]
Organic solvents	Soluble glacial acetic acid, benzene, carbon disulphide, carbon tetrachloride, anhydrous diethyl ether, ethanol, toluene[b]	Soluble in alcohol benzene, carbon disulphide, diethyl ether, ethanol, petroleum ether, toluene, race tone[b]
Partition coefficients:		
Log K_{ow}	4.45[k]	4.88[k]
Log K_{oc}	4.15[k]	4.58[k]
Vapor pressure	6.8x10^{-4} mm Hg at 25 °C[d]	2.5x10^{-6} mm Hg at 25 °C[k]
Henry's law constant	2.56x10^{-5} atm–m^3/mol[r]	1.14x10^{-5} atm-m^3/mol[r]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	0	0
Explosive limits	No data	No data

[a]All information obtained from HSDB except where noted
[b]IARC 1973
[c]Eller 1984
[d]HSDB 1994
[e]Weast et al. 1988
[f]Weast 1987
[g]IARC 1983
[h]Temperature not specified
[i]Sax and Lewis 1989
[j]Aldrich 1986
[k]Mabey et al. 1982
[l]Windholz 1983
[m]EPA 1987a
[n]ITII 1982
[p]Yalkowsky et al 1993
[q]Sims and Overcash 1983
[r]Nirmalakhandan and Speece 1988

The following equation can be used for the converstion of vapor phase PAHs at 25 °C:

$$\frac{\text{mg/m}^3 \times 24.45}{\text{Mol. wt.}}$$

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

4.1 PRODUCTION

The commercial production of PAHs is not a significant source of these compounds in the environment. The primary source of many PAHs in air is the incomplete combustion of wood and fuel (Perwak et al. 1982). PAHs are a ubiquitous product of combustion from common sources such as motor vehicles and other gas-burning engines, wood-burning stoves and furnaces, cigarette smoke, industrial smoke or soot, and charcoal-broiled foods (IARC 1983). Natural sources include volcanoes, forest fires, crude oil, and shale oil (HSDB 1994).

Of the 17 PAHs included in this profile, only three are produced commercially in the United States in quantities greater than research level: acenaphthene, acenaphthylene, and anthracene. Acenaphthene is manufactured by passing ethylene and benzene or naphthalene through a red hot tube or by heating tetrahydroacenaphthene with sulfur to 180 ºC. It can also be made from acenaphthenone or acenaphthenequinone by high-pressure hydrogenation in decalin with nickel at 180-240 ºC (Windholz 1983). Another manufacturing process involves the isolation and recovery of acenaphthene from a concentrated tar-distillation fraction (Grayson 1978). Technical grades of acenaphthene are typically 98% pure (HSDB 1994). Acenaphthylene is produced by catalytic degradation of acenaphthene (Grayson 1978). Toxic Release Chemical Inventory (TRI) production data for acenaphthylene and acenaphthene are not available (TRI92 1994) and no other data on the production volumes for these compounds in the United States could be found.

Anthracene is produced commercially by recovery from the coal tar distillation fraction known as “anthracene oil” or “green oil.” Purification techniques, including heating and vacuum distillation, are required to remove the major contaminant, potassium carbazole (IARC 1985). Zone melting of solid anthracene and crystallization from benzene followed by sublimation are also effective purification techniques (Hampel and Hawley 1973). Technical grades of anthracene are typically 90-98% pure (HSDB 1994). Table 4-l shows the number of facilities per state that manufacture or process anthracene, as well as a range of the maximum amounts of anthracene present at the facilities (TR192 1994). The following companies have been cited as current U.S. manufacturers of anthracene for sale/distribution: ABC Coke Division (Tarrant City, Alabama); Granite City Steel (Granite City, Illinois); Citizens Gas and Coke Utility (Indianapolis, Indiana); National Steel Corporation (Encore,

Table 4-1. Facilities that Manufacture or Process Anthracene

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds [b]	Activities and uses[c]
AL	7	1-1000	1, 4, 6, 8, 9
AR	1	1-10	3, 9
CA	1	10-100	1, 5
FL	2	1-100	8
IL	5	10-10000	1, 2, 4, 5, 6, 8, 10
IN	5	1-1000	1, 4, 5, 8
KY	2	1-100	1, 6, 11
LA	7	0-10000	1, 2, 5, 6, 9
MI	2	1-100	1, 4, 5, 6, 8
MN	1	1-10	1, 4
MO	1	1-10	13
MS	2	1-100	1, 6, 8
NJ	3	10-50000	1, 3, 4, 7, 8, 10
NY	2	1-1000	1, 5, 6, 8
OH	12	0-10000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
OK	1	10-100	2, 3, 9
PA	7	0-10000	1, 4, 5, 6, 7, 8, 10
SC	2	1-10	5, 8
TX	13	0-10000	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 13
UT	2	10-50000	1, 3, 4, 7, 10
VI	1	10000-50000	1, 4, 7
WA	2	10-1000	1, 2, 6, 12
WV	3	10-10000	1, 5, 6, 9, 12

Source: TRI92 1994

[a]Post office state abbreviations used
[b]Data in TRI are maximum amounts on site at each facility.
[c]Activities/Uses

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a byproduct
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

Missouri); Koch Refining Company (Pine Bend, Montana); Amerada Hess Corporation (Port Reading, New Jersey); Reilly Industries, Incorporated (Cleveland, Ohio, and Lone Star, Texas); New Boston Coke Corporation (New Boston, Ohio); Bethlehem Steel Structural (Bethlehem, Pennsylvania); Geneva Steel (Vineyard, Utah); and Hess Oil Virgin Islands Corporation (St. Croix, Virgin Islands). It should be noted that another source (SRI 1994) lists no anthracene processing or manufacturing facilities. In 1982, more than 2,270 kg of anthracene were produced in the United States; more recent production data are not available (HSDB 1994).

The following compounds are not produced commercially in the United States: benz[a]anthracene, benzo[b]fluoranthene, benzo[e]pyrene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indeno[l,2,3-c,d]pyrene, phenanthrene, and pyrene (HSDB 1994; IARC 1985).

4.2 IMPORT/EXPORT

The most recent data available on U.S. import and export volumes of individual PAHs are as follows: in 1986, 4,000 kg of acenaphthene were imported into the United States; in 1985, 5,730,000 kg of anthracene oil, 882,000 kg of anthracene (≥ 30% purity by weight), 1,040 kg of fluoranthene, and 57,400 kg of pyrene were imported into the United States; in 1984, 79,200 kg of chrysene, 9,440 kg of fluoranthene, 9.1 kg of fluorene, and 551 kg of phenanthrene were imported into the United States; in 1984, 502,000 kg of anthracene oil and pitch of tar coke were exported from the United States, increasing to 3,890,000 kg by 1987 (HSDB 1994; USDOC 1985). In 1985, the United States imported a total of almost 12 million gallons of creosote oil from the Netherlands, France, West Germany, and other countries and almost 185 million pounds of coal tar pitch, blast furnace tar, and oil-gas tar from Canada, Mexico, West Germany, Australia, and other countries (USDOC 1985). The only relevant information found on more recent import and export volumes is for the following group of compounds which contains two PAHs: acenaphthene, chrysene, cymene, and indene (NTDB 1994). Annual import volumes for this group of compounds were $2x10^6$, $3x10^6$, and $9x10^5$ kg for the years 1991, 1992, and 1993, respectively. While these numbers set an upper limit on the import volume for any one of the compounds in this group, they do not provide any further information on import volumes of acenaphthene and chrysene.

4.3 USE

There is no known use for acenaphthylene, benz[a]anthracene, benzo[b]fluoranthene, benzo[e]pyrene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, or pyrene except as research chemicals (Hawley 1987; HSDB 1994).

Anthracene is used as an intermediate in dye production, in the manufacture of synthetic fibers, and as a diluent for wood preservatives. It is also used in smoke screens, as scintillation counter crystals, and in organic semiconductor research (Hawley 1987). Anthracene is used to synthesize the chemotherapeutic agent, Amsacrine (Wadler et al. 1986). Acenaphthene is used as a dye intermediate, in the manufacture of pharmaceuticals and plastics, and as an insecticide and fungicide (HSDB 1994; Windholz 1983).

Fluorene is used as a chemical intermediate in many chemical processes, in the formation of polyradicals for resins, and in the manufacture of dyestuffs (Hawley 1993; HSDB 1994). Phenanthrene is used in the manufacture of dyestuffs and explosives and in biological research (Hawley 1987; HSDB 1994). Fluoranthene is used as a lining material to protect the interior of steel and ductile-iron drinking water pipes and storage tanks (NRC 1983).

4.4 DISPOSAL

PAHs serve as the basis for listing certain hazardous wastes under the Resource Conservation and Recovery Act (RCRA); they are listed as constituents for groundwater monitoring and are monitored in hazardous wastes as part of the RCRA land disposal restrictions (EPA 1989c). Specific regulations governing the generation, treatment, storage and disposal of hazardous wastes containing PAHs are listed in Chapter 7.

Approximately two-thirds of the PAHs in surface waters are particle-bound and can be removed by sedimentation, flocculation, and filtration processes. The remaining one-third of the dissolved PAHs usually require oxidation for partial removal/transformation (EPA 1980).

Acenaphthene, acenaphthylene, benz[a]anthracene; benzo[a]pyrene, benzo[b]fluoranthene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, and fluoranthene are all good candidates for rotary kiln incineration at temperatures ranging from 820 to 1,600 ºC and residence times of seconds for liquids and gases, and hours for solids (EPA 1981a; HSDB 1994). Benz[a]anthracene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, and fluoranthene all are good candidates for fluidized-bed incineration at a temperature of 450-980 ºC and residence times of seconds for liquids and gases and longer for solids (EPA 1981a; HSDB 1994). Benz[a]anthracene also is a good candidate for liquid injection incineration at a temperature range of 650-1,600 ºC and a residence time of 0.1 to 2 seconds (EPA 1981a; HSDB 1994). Liquids containing pyrene should be atomized in an incinerator. Combustion is improved by mixing with a more flammable solvent. Solids should be combined with paper or other flammable material prior to incineration (UN 1985). Benz[a]anthracene, chrysene, dibenz[a,h]anthracene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[b]fluoranthene, and benzo[a]pyrene laboratory wastes can be oxidized using agents such as concentrated sulfuric acid, potassium dichromate, or potassium permanganate (IARC 1985). Water contaminated with benzo[g,h,i]perylene can be decontaminated by carbon adsorption (EPA 1981c). Anthracene in waste chemical streams may be subjected to ultimate disposal by controlled incineration (HSDB 1994; EPA 1981a).

Bioremediation is emerging as a practical alternative to traditional disposal techniques (Cemiglia 1993; Thomas and Lester 1993; Wilson and Jones 1993). It has only recently been considered as a viable treatment method for contaminated soils but is now being used or is under consideration by the EPA for clean-up in over 135 Super-fund and underground storage tank sites (Carraway and Doyle 1991; Sims 1990; EPA 1989d). *In situ* treatment involves addition of nutrients, an oxygen source, and, sometimes, specifically adapted microorganisms that enhance degradation. Current *in situ* treatments have been used with some success for removal of two- and three-ring PAHs but generally are considered ineffective for removal of most PAHs from soil (Wilson and Jones 1993).

On-site methods such as landfarming also have been used successfully to degrade PAHs with three or fewer aromatic rings. The waste material is applied to the soil as a slurry and the area is fertilized, irrigated, limed, and tilled. The major disadvantage of landfarming is that contaminants can move from the treatment area. To enhance treatment and minimize movement of contaminants, prepared beds have been used. For this type of remediation, the contaminated soil is removed to a specially

prepared area lined with a low permeability material and the bed is managed to optimize degradation (Wilson and Jones 1993).

A third type of bioremediation involves the use of a bioreactor in a dedicated treatment area. The contaminated soil is excavated, slurried with water, and treated in the reactor. The horizontal drum and airlift-type reactors are usually operated in the batch mode but may also be operated in a continuous mode. Because there is considerable control over the operating conditions, treatment often is quick and effective. Contaminated groundwater and effluent also may be treated in either fixed-film' or stirred-tank bioreactors. However, bioreactors are still in the developmental stages and further research is required to optimize their efficiency and cost effectiveness (Wilson and Jones 1993).
A pilot-scale evaluation of the bioreactor method was carried out in a joint Superfund Innovative Technology Evaluation (SITE) project and a project to collect information for the Best Demonstrated Available Technologies (BDAT) database (Lewis 1993). Five 64-L bioslurry reactors were charged with a 30% (wt/vol) ratio of creosote-contaminated soil from a Superfund site, inoculated with PAH degraders, and inorganic nutrients were added. Total PAH -degradation averaged 93.4 ± 3.2% over all reactors during the 12-week study, with 97.4% degradation of the 2- and 3-ring PAHs and 90% degradation of the 4- to 6-ring PAHs.

Huesemann et al. (1993) carried out a 16-week laboratory study to assess the biotreatability of PAHs in refinery American Petroleum Institute (API) oil separator sludge. Two biotic treatments were evaluated: (1) a nutrient-amended, inoculated, aerated slurry reactor, and (2) an oxygen-sparged reactor. A sterile, nitrogen-sparged reactor was used as a control. Naphthalene, anthracene, phenanthrene, and benzo[a]pyrene were completely biodegraded in 4 weeks in both biotic reactors. Chrysene biodegraded in 4 weeks in the aerated reactor and in 16 weeks in the oxygen-sparged reactor. No significant changes in pyrene concentration were observed in the oxygen-sparged reactor and only a 30% degradation was observed in the aerated reactor. The authors concluded that aerobic biotreatment was successful in removing most BDAT PAHs from refinery API oil separator sludge.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

This chapter provides a discussion of the environmental fate and potential for human exposure to 17 PAHs. For the purposes of describing environmental fate, these PAHs have been grouped into low, medium, and high molecular weight classes (see Section 5.3.1, Transport and Partitioning). In general, chemicals within each class have similar environmental fates. When available, data are provided for the individual PAHs that are the subject of the profile. When data on each compound are not available, data on members of the weight class are provided. Data regarding total PAHs or generalizations about PAHs are also used to provide insight into the behavior of the compounds cbvered in this profile.

PAHs are released to the environment through natural and synthetic sources with emissions largely to the atmosphere. Natural sources include emissions from volcanoes and forest fires. Synthetic sources provide a much greater release volume than natural sources; the largest single source is the burning of wood in homes. Automobile and truck emissions are also major sources of PAHs. Environmental tobacco smoke, unvented radiant and convective kerosene space heaters, and gas cooking and heating appliances may be significant sources of PAHs in indoor air. Hazardous waste sites can be a concentrated sources of PAHs on a local scale. Examples of such sites are abandoned wood-treatment plants (sources of creosote) and former manufactured-gas sites (sources of coal tar). PAHs can enter surface water through atmospheric deposition and from discharges of industrial effluents (including wood-treatment plants), municipal waste water, and improper disposal of used motor oil. Several of the PAHs have been detected at hazardous waste sites at elevated levels. In air, PAHs are found sorbed to particulates and as gases. Particle-bound PAHs can be transported long distances and are removed from the atmosphere through precipitation and dry deposition. PAHs are transported from surface waters by volatilization and sorption to settling particles. The compounds are transformed in surface waters by photooxidation, chemical oxidation, and microbial metabolism. In soil and sediments, microbial metabolism is the major process for degradation of PAHs. Although PAHs are accumulated in terrestrial and aquatic plants, fish, and invertebrates, many animals are able to metabolize and eliminate these compounds. Bioconcentration factors (BCFs), which express the concentration in tissues compared to concentration in media, for fish and crustaceans are frequently in

the 10-10,000 range. Food chain uptake does not appear to be a major source of exposure to PAHs for aquatic animals.

The greatest sources of exposure to PAHs for most of the United States population are active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and ingestion of the compounds in foodstuffs. The general population may also be exposed to PAHs in drinking water and through skin contact with soot and tars. Higher than background levels of PAHs are found in foods that are grilled or smoked. Estimates of human exposures to PAHs vary. The average total daily intake of PAHs by a member of the general population has been estimated to be 0.207 µg from air, 0.027 µg from water, and 0.16-l .6 µg from food. The total potential exposure to carcinogenic PAHs for adult males in the United States was estimated to be 3 µg/day. Smokers of unfiltered cigarettes may experience exposures twice as high as these estimates. Persons living in the vicinity of hazardous waste sites where PAHs above background levels have been detected may also be exposed to higher levels.

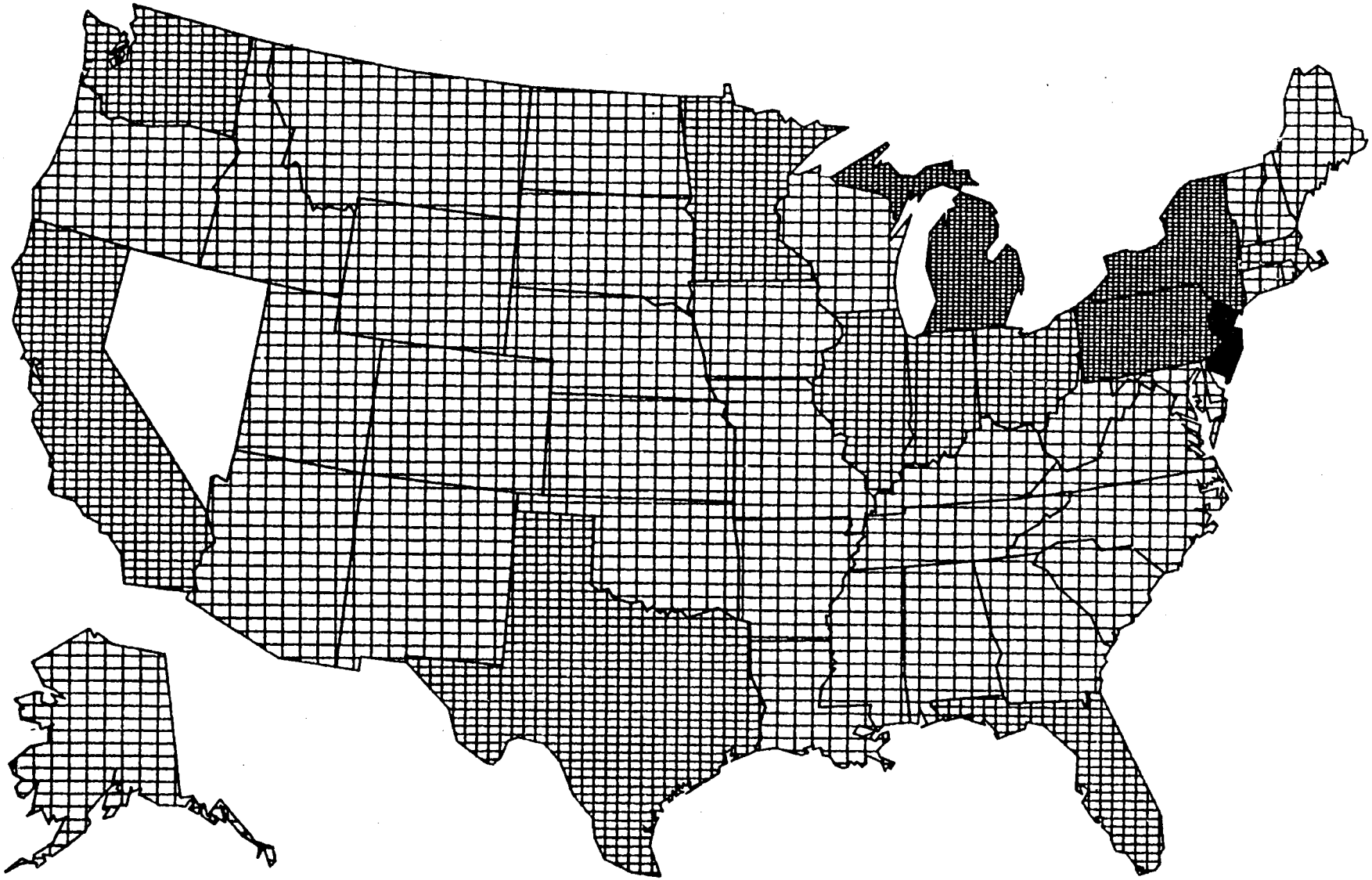
PAHs have been identified in at least 600 of the 1,408 hazardous waste sites that have been proposed for inclusion in the EPA National Priorities List (NPL) (HazDat 1994). However, the number of sites evaluated for PAHs is not known. The frequencies of these sites can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Most of the direct releases of PAHs to the environment are to the atmosphere from both natural and anthropogenic sources, with emissions from human activities predominating. PAHs in the atmosphere are mostly associated with particulate matter; however, the compounds are also found in the gaseous phase (NRC 1983; Yang et al. 1991). The primary natural sources of airborne PAHs are forest fires and volcanoes (Baek et al. 1991; NRC 1983). The residential burning of wood is the largest source of atmospheric PAHs (Peters et al. 1991; Ramdahl et al. 1982); releases are primarily the result of inefficient combustion and uncontrolled emissions (Freeman and Cattell 1990; NRC 1983; Tan et al. 1992). Other important stationary anthropogenic sources include industrial power generation, incineration (Shane et al. 1990; Wild et al. 1992); the production of coal tar, coke, and asphalt; and petroleum catalytic cracking (Baek et al. 1991; Guerin 1978; Perwak et al. 1982; Santodonato 1981).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH PAHs CONTAMINATION*



*Derived from HazDat 1994

Environmental tobacco smoke, unvented radiant and convective kerosene space heaters, and gas cooking and heating appliances may be important sources of PAHs in indoor air (Chuang et al. 1991; Hoffmann and Hoffmann 1993; Mumford et al. 1991; NRC 1986; Traynor et al. 1990). Stationary sources account for about 80% of total annual PAH emissions; the rest are from mobile sources. The most important mobile sources of PAHs are vehicular exhaust from gasoline and diesel-powered engines (Baek et al. 1991; Johnson 1988; Yang et al. 1991). Mobile sources are often the major contributors to PAH releases to the atmosphere in urban or suburban areas (Baek et al. 1991). The amount of anthracene released to the atmosphere in 1992 by U.S. industrial facilities sorted by state is given in Table 5-l (TRI92 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. TRI92 (1994) data were not available for other PAHs included in this profile.

The U.S. annual emissions (from early to mid 1970s) of polycyclic organic matter (a term generally used to describe PAHs, their nitrogen-containing analogs, and their quinone degradation products [Santodonato et al. 1981]) were estimated by NRC (1983) as follows: open buming 4,024 metric tons (39%), residential heating-3,956 metric tons (38%), automobiles and trucks-2,266 metric tons (22%), and industrial boilers-74 metric tons (1%). NRC (1983) estimated that the total amount of benzo[a]pyrene produced in the United States is between 300 and 1,300 metric tons annually. Peters et al. (1981) estimated that a total of 11,031 metric tons of PAHs were released to the atmosphere in the United States on an annual basis, with 36% of the total coming from residential heating, 6% from industrial processes, 1% from incineration, 36% from open burning, 1% from power generation, and 21% from mobile sources. This estimate can be compared to that of Ramdahl et al. (1982), who reported that a total of 8,598 tons of PAHs were emitted to the atmosphere annually from the following sources: (1) residential heating-16%; (2) industrial processes 41%; (3) incineration-l % (4) open burning-13%; (5) power generation-5%; and (6) mobile sources-25%.

The composition of PAH emissions varies with the combustion source. For example, emissions from residential wood combustion contain more acenaphthylene than other PAHs (Perwak et al. 1982), whereas auto emissions contain more benzo[g,h,i]perylene and pyrene (Rogge et al. 1993a; Santodonato et al. 1981). PAHs in diesel exhaust particulates are dominated by three- and four-ring compounds, primarily fluoranthene, phenanthrene, and pyrene (KelIy et al. 1993; Rogge et al. 1993a; Westerholm and Li 1994). Diesel exhaust vapor emissions are dominated by phenanthrene and anthracene (Westerholm and Li 1994). Acenaphthene, fluorene, and phenanthrene have been found to

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Anthracene

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground Injection	Total Environment[c]	POTW Transfer	Off-site Waste Transfer
AL	7	2-3500	0-5	0	0	2-3505	0	0-465000
AR	1	327-327	0	0	0	327-327	0	0
CA	1	1-1	0	0	0	1-1	0	0
FL	2	0-702	0	0	0	0-702	0	0-250
IL	5	126-1000	0	0	0	126-1000	0-250	0-10273
IN	5	0-11090	0	0	0	0-11090	0-88	0
KY	2	20-94	0-78	0	0	20-172	0	0-680
LA	7	0-125	0-9	0	0	0-125	0	0-7370
MI	2	85-4085	0	0	0	85-4085	0-5	0-1190
MN	1	160-160	0	0	0	160-160	0	0
MO	1	10-10	5-5	0	0	15-15	0	0
MS	2	0-250	108-250	0-250	0	108-750	0	0
NJ	3	0-272	0-5	0-7	0	0-272	0	2-250
NY	2	0-910	0	0	0	0-910	0	0
OH	12	0-3700	0-250	0-720	0	0-4425	0-5	0-14112
OK	1	0-0	0	1-1	0	1-1	0	5-5
PA	7	0-997	0-37	0-560	0	0-1594	0	0-7900
SC	2	0-255	0	0	0	0-255	0-250	0-145
TX	13	0-2780	0	0-1532	0	0-2780	0	0-493911
UT	2	2-4	0	0	0	2-4	0	0
VI	1	3879-3879	15-15	0	0	3894-3894	0	0
WA	2	34-5395	11-250	0	0	45-5645	0	0-6650
WV	3	10-1500	0	0	0	10-1500	0	0-250

Source: TRI92 1994

be predominant in total (particle- and vapor-phase) diesel emissions (Lowenthal et al. 1994). Phenanthrene was the most abundant and frequently detected PAH in samples of fly ash and bottom ash collected from municipal refuse incinerators in the United States (Shane et al. 1990), whereas benzo[g,h,i]perylene was the most abundant and frequently detected PAH in fly ash samples collected from municipal solid waste incinerators in the United Kingdom (Wild et al. 1992). Fluoranthene, benzo[a]fluoranthene, benzo[g,h,i]perylene, indeno[1,2,3-c,d]pyrene, phenanthrene, and chrysene were predominant in emission particle samples collected from a municipal waste incinerator, whereas benzo[g,h,i]perylene and benz[a]anthracene were predominant in emission particle samples collected from a municipal and medical/pathological waste incinerator (Williams et al. 1994). Emission particle samples from a pilot scale rotary kiln incinerator charged with polyethylene contained predominantly benz[a]anthracene and phenanthrene when an afterburner was used, whereas pyrene, fluoranthene, and phenanthrene were predominant without an afterburner; total PAH concentrations were reduced by a factor greater than 100 by the use of an afterburner (Williams et al. 1994). In coal tar pitch emissions, concentrations of phenanthrene and pyrene have been reported to be 20-80 times greater than the concentrations of benzo[a]pyrene and benzo[g,h,i]perylene (Sawicki 1962). Chrysene/triphenylene, pyrene, and fluoranthene were dominant among the PAHs found in fine particle emissions from natural gas home appliances (Rogge et al. 1993b). Cigarette mainstream smoke contains a wide variety of PAHs with reported concentrations of benzo[a]pyrene ranging from approximately 5-80 ng/cigarette; sidestream smoke concentrations are significantly higher with sidestream/mainstream concentration ratios for benzo[a]pyrene ranging from 2.5 to 20 (Hoffmann and Hoffmann 1993; IARC 1983).

5.2.2 Water

Important sources of PAHs in surface waters include deposition of airborne PAHs (Jensen 1984), municipal waste water discharge (Barrick 1982), urban storm water runoff (MacKenzie and Hunter 1979), runoff from coal storage areas (Stahl et al. 1984; Wachter and Blackwood 1979), effluents .from wood treatment plants and other industries (DeLeon et al. 1986; Snider and Manning 1982; USDA 1980), oil spills (Giger and Blumer 1974), and petroleum pressing (Guerin 1978). Brown and Weiss (1978) estimated that l-2 tons of benzo[a]pyrene were released from municipal sewage effluents and 0.1-0.4 tons of benzo[a]pyrene were released from petroleum refinery waste waters in the United States in 1977.

Most of the PAHs in surface waters are believed to result from atmospheric deposition (Santodonato et al. 1981). However, for any given body of water, the major source of PAHs could vary. Jensen (1984) studied benzo[a]pyrene loading in a marine coastal area and determined that atmospheric deposition was indeed the major source of benzo[a]pyrene, with lesser amounts contributed by refinery effluent, municipal waste water, urban runoff, and rivers. Prahl et al. (1984) found that combustion-derived PAHs adsorbed to suspended sediments in rivers accounted for the major portion of PAHs in the waters of a Washington coastal area, and other studies have identified industrial effluents, road runoff, and oil spills as the major contributors in specific bodies of water (DeLeon et al. 1986; Santodonato et al. 1981).

The amount of anthracene released to surface water and publicly owned treatment works (POTWs) in 1992 by U.S. industrial facilities sorted by state is shown in Table 5-l (TRI92 1994). The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. TRI92 (1994) data were not available for other PAHs included in this profile. Because most of the PAHs released to aquatic environments tend to remain near the sites of deposition, lakes, rivers, estuaries, and coastal marine environments near centers of human populations and industrial activity tend to be the major repositories of aquatic PAHs (Neff 1979).

5.2.3 Soil

Most of the PAHs in soil are believed to result from atmospheric deposition after local and long-range transport. The presence of PAHs in the soil of regions remote from any industrial activity supports this contention (Thomas 1986). Other potential sources of PAHs in soil include sludge disposal from public sewage treatment plants, automotive exhaust, irrigation with coke oven effluent, leachate from bituminous coal storage sites, and use of soil compost and fertilizers (Perwak et al. 1982; Santodonato et al. 1981; Stahl et al. 1984; White and Lee 1980). The principal sources of PAHs in soils along highways and roads are vehicular exhausts and emissions from wearing of tires and asphalt. PAHs may also be released to soils at concentrations above background and landfill sites (Black et al. 1989) and industrial sites, including creosote production (Ellis et al. 1991), wood-preserving (Mueller et al. 1991; Weissenfels et al. 1990), and coking plants (Weissenfels et al. 1990; Werner et al. 1988). Soils at the sites of former manufactured gas plants are also heavily contaminated with PAHs (Bewley et al. 1989; Tumey and Goerlitz 1990).

The amount of anthracene released to surface water and publicly owned treatment works (POTWs) in 1992 by U.S. industrial facilities sorted by state is shown in Table 5-l (TRI92 1994). Based on data in Table 5-1, only relatively small amounts of anthracene were discharged in hazardous waste sites from U.S. industrial facilities in 1992. However, some of the anthracene wastes transferred off-site (see Table 5-l) ultimately may be disposed of on land. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. TRI92 (1994) data were not available for other PAHs included in this profile.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The global movement of PAHs can be summarized as follows: PAHs released to the atmosphere are subject to short- and long-range transport and are removed by wet and dry deposition onto soil, water, and vegetation. In surface water, PAHs can volatilize, photolyze, oxidize, biodegrade, bind to suspended particles or sediments, or accumulate in aquatic organisms (with bioconcentration factors often in the 10-10,000 range). In sediments, PAHs can biodegrade or accumulate in aquatic organisms. PAHs in soil can volatilize, undergo abiotic degradation (photolysis and oxidation), biodegrade, or accumulate in plants. PAHs in soil can also enter groundwater and be transported within an aquifer.

Transport and partitioning of PAHs in the environment are determined to a large extent by physicochemical properties such as water solubility, vapor pressure, Henry's law constant, octanol-water partition coefficient (K_{ow}), and organic carbon partition coefficient (K_{oc}). In general, PAHs have low water solubilities. The Henry's law constant is the partition coefficient that expresses the ratio of the chemical's concentrations in air and water at equilibrium and is used as an indicator of a chemical's potential to volatilize. The K_{oc} indicates the chemical's potential to bind to organic carbon in soil and sediment. The K_{ow} is used to estimate the potential for an organic chemical to move from water into lipid and has been correlated with bioconcentration in aquatic organisms. Some of the transport and partitioning characteristics (e.g., Henry's law constant, K_{oc} values, and K_{ow}, values) of the 17 PAHs are roughly correlated to their molecular weights. These properties are discussed by grouping these PAHs as follows:

- Low molecular weight compounds (152-l 78 g/mol)-acenaphthene, acenaphthylene, anthracene, fluorene, and phenanthrene;
- Medium molecular weight compounds (202 g/mol)-fluoranthene and pyrene; and
- High molecular weight compounds (228-278 g/mol)-benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, benzo[e]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene.

As an example, Hattemer-Frey and Travis (1991) found that the low solubility, low vapor pressure and high K_{ow} of benzo[a]pyrene result in its partitioning mainly between soil (82%) and sediment (17%), with ≈1% partitioning into water and <1% into air, suspended sediment and biota.

PAHs are present in the atmosphere in the gaseous phase or sorbed to particulates. The phase distribution of PAHs in the atmosphere is important in determining their fate because of the difference in rates of chemical reactions and transport between the two phases. The phase distribution of any PAH depends on the vapor pressure of the PAH, the atmospheric temperature, the PAH concentration, the affinity of the PAH for the atmospheric suspended particles (K_{oc}), and the nature and concentrations of the particles (Baek et al. 1991). In general, PAHs having two to three rings (naphthalene, acenaphthene, acenaphthylene, anthracene, fluorene, phenanthrene) are present in air predominantly in the vapor phase. PAHs that have four rings (fluoranthene, pyrene, chrysene, benz[a]anthracene) exist both in the vapor and particulate phase, and PAHs having five or more rings (benzo[a]pyrene, benzo[g,h,i]perylene) are found predominantly in the particle phase (Baek et al. 1991; Jones et al. 1992). The ratio of particulate to gaseous PAHs in air samples collected in Antwerp, Belgium, was 0.03 for anthracene, 0.49 for pyrene, 3.15 for summed benz[a]anthracene and chrysene, and 11.5 for summed benzo[a]fluoranthene and benzo[b]fluoranthene (NRC 1983).

Using field data from Osaka, Japan, Pankow et al. (1993) examined the effects of relative humidity. (RH) on measured gas/particle partition coefficients over the range 42% ≥ 95%. They found that for seven PAHs or groups of PAHs (including phenanthrene + anthracene, fluoranthene, and pyrene) sorption decreased with increasing RH.

Atmospheric residence time and transport distance depend on the size of the particles to which PAHs are sorbed and on climatic conditions which will determine rates of wet and dry deposition. About 90-95% of particulate PAHs are associated with particle diameters <3.3 μm, and the peak distributions

are localized between 0.4 and 1.1 μm (Baek et al: 1991). Both coarse particles with aerodynamic diameters >3-5 μm and nucleic particles with diameters <0.1 μm have limited atmospheric residence times. The coarse particles are removed from the atmosphere by wet and dry deposition, while the nucleic particles are removed mainly by coagulation with other nucleic particles or with larger particles, followed by wet and dry deposition. Particles with a diameter range of 0.1-3.0 μm, with which airborne PAHs are principally associated, remain airborne for a few days or longer, due to slower dry deposition and less efficient wet deposition (Baek et al. 1991). Therefore, airborne particulate PAHs in this size range can transport long distances (Lunde and Bjorseth 1977). Larger particles emitted from urban sources tend to settle onto streets and become part of urban runoff. However, PAHs in urban air are primarily associated with submicrometer-diameter soot particles that have residence times of weeks and are subject to long-range transport (Butler and Crossley 1981). Long-range transport of PAHs was examined by Lunde and Bjorseth (1977), Bjorseth et al. (1978a), and Bjorseth and Olufsen (1983) who found that PAHs originating in Great Britain had been transported as far as Norway and Sweden.

The relative importance of wet and dry deposition in removing PAHs from the atmosphere varies with the individual PAH. For example, Perwak et al. (1982) estimated that a total of 23% of benzo[a]pyrene released to the atmosphere is deposited on soil and water surfaces. Dry deposition of benzo[a]pyrene adsorbed to atmospheric aerosols accounts for most of the removal; wet deposition is less significant by a factor of 3-5. In a mass balance study of the atmospheric deposition of PAHs to Siskiwit Lake, which is located on a wilderness island in northern Lake Superior, dry aerosol deposition of particulate phase PAHs was found to be the predominant form of input to surface waters by an average ratio of 9:l over wet deposition (McVeety and Hites 1988).

PAH compounds tend to be removed from the water column by volatilization to the atmosphere, by binding to suspended particles or sediments, or by being accumulated by or sorbed onto aquatic biota. The transport of PAHs from water to the atmosphere via volatilization will depend on the Henry's law constants (Hs) for these compounds. The low molecular weight PAHs have Henry's law constants in the range of 10^{-3}-10^{-5} atm-m^3/mol; medium molecular weight PAHs have constants in the 10^{-6} range; and high molecular weight PAHs have values in the range of 10^{-5}-10^{-8}. Compounds with values ranging from 10^{-3} to 10^{-5} are associated with significant volatilization, while compounds with values less than 10^{-5} volatilize from water only to a limited extent (Lyman et al. 1982). Half-lives for volatilization of benz[a]anthracene and benzo[a]pyrene (high molecular weight PAHs) from water have

been estimated to be greater than 100 hours (Southworth 1979). Southworth et al. (1978) stated that lower molecular weight PAHs could be substantially removed by volatilization if suitable conditions (high temperature, low depth, high wind) were present. Southworth (1979) estimated half-lives for volatilization of anthracene (a low molecular weight PAH) of 18 hours in a stream with moderate current and wind, versus about 300 hours in a body of water with a depth of 1 meter and no current. Even for PAHs susceptible to volatilization, other processes, such as adsorption, photolysis or biodegradation (see Section 5.3.2.2) may become more important than volatilization in slow-moving, deep waters.

Because of their low solubility and high affinity for organic carbon, PAHs in aquatic systems are primarily found sorbed to particles that either have settled to the bottom or are suspended in the water column. It has been estimated that two-thirds of PAHs in aquatic systems are associated with particles and only about one-third are present in dissolved form (Eisler 1987). In an estuary, volatilization and adsorption to suspended sediments with subsequent deposition are the primary removal processes for medium and high molecular weight PAHs, whereas volatilization and biodegradation (see Section 5.3.2.2) are the major removal processes for low molecular weight compounds (Readman et al. 1982). In an enclosed marine ecosystem study, less than 1% of the original amount of radiolabeled benz[a]anthracene added to the system remained in the water column after 30 days; losses were attributed to adsorption to settling particles and to a lesser extent to photodegradation (Hinga and Pilson 1987).

Baker et al. (1991) found that several PAHs were significantly recycled in the water column of Lake Superior. Fluorene and phenanthrene were rapidly removed from surface waters and settled through the water column to the sediment-water interface where a large fraction of the recently settled contaminants were released back into the water column. Higher molecular weight PAHs were found to have lower settling fluxes, but these compounds were efficiently buried in the surficial sediments with little recycling. Settling particles were found to be greatly enriched in hydrophobic organic chemicals.

The K_{oc} of a chemical is an indication of its potential to bind to organic carbon in soil and sediment. The low molecular weight PAHs have K_{oc} values in the range of 10^3-10^4, which indicates a moderate potential to be adsorbed to organic carbon in the soil and sediments. The medium molecular weight compounds have K_{oc} values in the lo4 range. High molecular weight PAHs have K_{oc} values in the

range of 10^5-10^6, which indicates stronger tendencies to adsorb to organic carbon (Southworth 1979). PAHs from lands cleared by slash and bum methods have been found to be deposited in charred litter and to move into soils by partitioning and leaching (Sullivan and Mix 1985). Phenanthrene and fluoranthene (low and medium molecular weight PAHs, respectively) from these areas were incorporated into soil to a greater extent (i.e., less strongly adsorbed to organic carbon in the charred litter) than high molecular weight PAHs such as benzo[g,h,i]pyrene and indeno[1,2,3-c,d]pyrene.

Because mobile colloids may enhance the mobility in porous medias of hydrophobic pollutants such as PAHs, Jenkins and Lion (1993) tested bacterial isolates from soil and subsurface environments for their ability to enhance transport of phenanthrene in aquifer sand. The most mobile isolates tested significantly enhanced the transport of phenanthrene, as a model PAH, in sand.

Sorption of PAHs to soil and sediments increases with increasing organic carbon content and with increasing surface area of the sorbent particles. Karickhoff et al. (1979) reported adsorption coefficients for sorption of pyrene to sediments as follows: sand-9.4-68; silt-1,500-3,600; and clay-l ,400-3,800. Gardner et al. (1979) found that from three to four times more anthracene and about two times more fluoranthene, benz[a]anthracene, and benzo[a]pyrene were retained by marsh sediment than by sand.

PAHs may also volatilize from soil. Volatilization of acenaphthene, acenaphthylene, anthracene, fluorene, and phenanthrene (low molecular weight PAHs) from soil may be substantial (Coover and Sims 1987; Southworth 1979; Wild and Jones 1993). However, of 14 PAHs studied in two soils, volatilization was found to account for about 20% of the loss of 1-methylnaphthalene and 30% of the loss of naphthalene; volatilization was not an important loss mechanism for anthracene, phenanthrene, fiuoranthene, pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, dibenz[a,h]anthracene, benzo[a]pyrene, and indeno[l,2,3-c,d]pyrene (Park et al. 1990).

Physicochemical properties of several phenanthrene and anthracene metabolites [1-hydroxy-2-napthoic acid (lH2NA); 2,3-dihydroxy naphthalene (23DHN); 2-carboxy benzaldehyde (2CBA); and 3,4-dihydroxy benzoic acid (34DHBA)] were experimentally measured and/or estimated and used with a Fugacity Level 1 model to estimate the distribution of the metabolites and their parent compounds in a contaminated soil (Ginn et al. 1994). The volumes of the air, water and soil phases were assumed to be 20%, 30%, and 48%, respectively. A volume of 2% was assumed for nonaqueous phase liquid

(NAPL) phase. The parent compounds, anthracene and phenanthrene, had the greatest tendency to be associated with the NAPL and soil phases. The polar metabolites of phenanthrene, lH2NA and 34DHBA, were associated more with the water phase of the subsurface. The metabolites 2CBA and 23DHN had a stronger affinity for the NAPL phase than for the water phase.

PAHs have been detected in groundwater either as a result of migration directly from contaminated surface waters or through the soil (Ehrlich et al. 1982; Wilson et al. 1986). Fluorene from an abandoned creosote pit was found to migrate through sand and clay into groundwater (Wilson et al. 1986). PAHs have also been shown to be transported laterally within contaminated aquifers (Ehrlich et al. 1982).

PAHs can be accumulated in aquatic organisms from water, sediments, and food. Bioconcentration factors (BCFs) for several species of aquatic organisms are listed in Table 5-2. In fish and crustaceans BCFs have generally been reported in the range of 10-10,000 (Eisler 1987). In general, bioconcentration was greater for the higher molecular weight compounds than for the lower molecular weight compounds. Bioconcentration experiments performed with radiolabeled compounds may overestimate the BCFs of some PAHs. For example, Spacie et al. (1983) estimated BCFs of 900 for anthracene and 4,900 for benzo[a]pyrene in bluegills (whole body) based on total radiolabeled carbon (^{14}C) activity. However, the estimated BCFs based only on the parent compounds were 675 and 490, respectively, indicating that biotransformation of the parent compounds occurred in addition to bioconcentration. Biotransformation by the mixed function oxidase (MFO) system in the fish liver can result in the formation of carcinogenic and mutagenic intermediates; exposure to PAHs has been linked to the development of tumors in fish (Eisler 1987). The ability of fish to metabolize PAHs may explain why benzo[a]pyrene frequently is not detected or found only at very low levels in fish from environments heavily contaminated with PAHs (Varanasi and Gmur 1980, 1981). The breakdown products (polyhydroxy compounds) are eliminated in feces (via bile) and urine. Although fish and most crustaceans evaluated to date have the MFO system required for biotransformation of PAHs, some molluscs and other aquatic invertebrates are unable to metabolize PAHs efficiently (Varanasi et al. 1985). Varanasi et al. (1985) ranked the extent of benzo[a]pyrene metabolism by aquatic organisms as follows: fish > shrimp > amphipod crustaceans > clams. Half-lives for elimination of PAHs in fish ranged from >2 days to 9 days (Niimi 1987).

TABLE 5-2. Polycyclic Aromatic Hydrocarbon (PAHs) Bioconcentration Factors (BCFs) for Selected Species of Aquatic Organisms[a]

PAH compound and organism	Exposure period[b]	BCF
ANTHRACENE		
Mayfly, *Hexagenia* sp.	28 h	3,500
Cladoceran, *Daphnia pulex*	24 h	760–1,200
Cladoceran, *Daphnia magna*	60 m	200
Fathead minnow, *Pimephales promelas*	2–3 d	485
Rainbow trout, *Salmo gairdneri*	72 h	4,400–9,200
BENZ(*a*)ANTHRACENE		
Cladoceran, *D. pulex*	24 h	10,109
BENZO(*a*)PYRENE		
Midge, *Chironomus riparius*, larvae	8 h	166
Mosquito, *Culex pipiens quinquefasciatus*	3 d	11,536
Alga, *Oedogonium cardiacum*	3 d	5,258
Periphyton, mostly diatoms	24 h	9,600
Cladoceran, *D. pulex*	3 d	134,248
Cladoceran, *D. magna*	6 h	2,837
Snail, *Physa* sp.	3 d	82,231
Clam, *Rangia cuneata*	24 h	9–236
Oyster, *Crassostrea virginica*	14 d	242
Northern pike *Esox lucius*	3.3 h–23 d	<55
Mosquitofish, *Gambusia affinis*	3 d	930
Bluegill, *Lepomis macrochirus*	4 h	12
Bluegill, *L. macrochirus*		
No dissolved humic material (DHM)	48 h	2,657
20 mg/L DHM	48 h	225
CHRYSENE		
Clam, *Rangia cuneata*	24 h	8
Pink shrimp, *Penaeus duorarum*		
Cephalothorax	28 d	248–361
Cephalothorax	28 d + 28 d postexposure	21–48
Abdomen	28 d	84–199
Abdomen	28 d + 28 d postexposure	22–91

TABLE 5-2. Polycyclic Aromatic Hydrocarbon (PAHs) Bioconcentration Factors (BCFs) for Selected Species of Aquatic Organisms[a] (continued)

PAH compound and organism	Exposure period[b]	BCF
FLUORENE		
Bluegill	30 d	200–1,800
PHENANTHRENE		
Cladoceran, *D. pulex*	24 h	325
Clam, *R. cuneata*	24 h	32
PYRENE		
Cladoceran, *D. pulex*	24 h	2,702

[a]Data summary from multiple studies; adapted from Eislen (1987)

[b]m = minutes; h = hours; d = days

Mollusks also eliminate accumulated PAHs. Neff (1982) reported that oysters (*Crassostrea gigas*) eliminated the following percentages of accumulated PAHs during a 7-day elimination period: benzo[a]pyrene-0%; benz[a]anthracene-32%; fluoranthene-66%; and anthracene-79%.

Fish and crustaceans readily assimilate PAHs from contaminated food, whereas mollusks and polychaete worms have limited assimilation (Eisler 1987). Biomagnification (a systematic increase in tissue concentrations moving up a food chain) has not been reported because of the tendency of many aquatic organisms to eliminate these compounds rapidly (Eisler 1987). In general, PAHs obtained from the diet contribute to total tissue concentrations only to a limited extent. For example, food chain uptake of anthracene by fathead minnows *(Pimephales promelas)* consuming water fleas *(Daphnia pulex)* was estimated to be about 15% of the amount accumulated from the water (Southworth 1979). In a simple aquatic food chain involving seston (i.e., organic and inorganic particulate matter >0.45 µm), blue mussels, and the common eider duck, significant changes were observed in the composition of 19 PAHs moving through the trophic levels. Decreasing PAH concentrations were found with increasing trophic level, probably as a result of the selective biotransformation capacity of the organisms for different PAHs. The high theoretical flux of PAHs through the food chain did not result in increasing concentrations with increasing trophic level (i.e., biomagnification was not observed), indicating rapid biotransformation of the compounds (Broman et al. 1990).

Sediment-associated PAHs can be accumulated by bottom-dwelling invertebrates and fish (Eisler 1987). For example, Great Lakes sediments containing elevated levels of PAHs were reported by Eadie et al. (1983) to be the source of the body burdens of the compounds in bottom-dwelling invertebrates. Varanasi et al. (1985) found that benzo[a]pyrene was accumulated in fish, amphipod crustaceans, shrimp, and clams when estuarine sediment was the source of the compound. Approximate tissue to sediment ratios were 0.6-1.2 for amphipods, 0.1 for clams, and 0.05 for fish and shrimp.

Some terrestrial plants can take up PAHs from soil via the roots or from air via the foliage; uptake rates are dependent on the concentration, solubility, and molecular weight of the PAH and on the plant species (Edwards 1983). Mosses and lichens have been used to monitor atmospheric deposition of PAHs (Thomas et al. 1984). About 30-70% of atmospheric PAHs (indeno[l,2,3-c,d]pyrene, fluoranthene, and benzo[a]pyrene) deposited on a forest were sorbed onto tree foliage (i.e., leaves and

needles) and then deposited as falling litter (Matzner 1984). Vaughan (1984) stated that atmospheric deposition on leaves often greatly exceeds uptake from soil by roots as a route of PAH accumulation.

The uptake of PAHs from soil to plants and the subsequent biomagnification is generally quite low (Sims and Overcash 1983). Ratios of PAH concentrations in vegetation to those in soil have been reported to range from 0.001 to 0.18 for total PAHs and from 0.002 to 0.33 for benzo[a]pyrene (Edwards 1983). ,In a study of PAH uptake from cropland soils conducted in the United Kingdom, elevated concentrations of PAHs in soils were not correlated with concentrations in plant tissues (Wild et al. 1992). The cropland soils had received repeated applications of PAHs in sewage sludge that was applied to the soils over a number of years. PAH content of the soils substantially increased as a result of the sludge amendments, and residues of some PAHs persisted in the soils for years. Tissues from plants grown in the treated soils were relatively enriched with low molecular weight PAHs (e.g., acenaphthene, fluorene, phenanthrene), but increased PAH concentrations (relative to tissues from plants grown in control plots that did not receive sludge amendments) were not consistently detected. The PAH concentrations in aboveground plant parts were not strongly related to soil PAH levels but were probably the result of atmospheric deposition. The presence of PAHs in root crop tissues was probably due to adsorption of the compounds to root surfaces. In a similar study, Wild and Jones (1993) used carrots. (Daucus carotu) as a test crop to investigate the potential for PAHs to move from sewage sludge amended soil into the human food chain. Due to the over-riding influence of atmospheric delivery of PAHs, there was no evidence that sludge application increased the PAH concentration of the foliage. Low molecular weight PAHs such as fluoranthene and pyrene were relatively enriched in the peel, probably because of their greater bioavailability. Transfer of PAHs from the root peel to the core appeared to be minimal. This again suggests that simple adsorption onto the peel maybe an important process.

Simonich and Hites (1994a) studied the partitioning of PAHs between vegetation and the atmosphere throughout the growing season and under natural conditions. They found the partitioning process to be dependent primarily upon the atmospheric gas-phase PAH concentration and the ambient temperature. During the spring and fall, when ambient temperatures are low, gas-phase PAHs partition into vegetation. In the summer, some PAHs volatilize and return to the atmosphere. They also developed a mass-balance model for PAHs in the northeastern United States and published values for PAH concentrations and fluxes in air, water, sediments, and soils (Simonich and Hites 1994b). Their model showed that 44 ± 18% of PAHs emitted into the atmosphere from sources in the region studied

were removed by vegetation. They further hypothesized that most of the PAHs absorbed by vegetation at the end of the growing season are incorporated into the soil and permanently removed from the atmosphere.

PAHs may accumulate in terrestrial animals through the food chain or by ingestion of soil. The environmental fate of creosote coal tar distillate (which contained 21% phenanthrene and 9% acenaphthene) was studied in a terrestrial microcosm containing soil, rye grass, insects, snails, mealworm larvae, and earthworms by Gile et al. (1982). Two gray-tailed voles (*Microtus canicaudus)* were added 54 days after the start of the experiment, which continued for 19-26 more days. Average surface soil concentrations (measured on an unspecified day) were 0.60 ppm (phenanthrene) and 1.19 ppm (acenaphthene). During the last 3 days of the experiment, the following phenanthrene concentrations were measured: snail-3.27 ppm; pill bugs-l .72 ppm; and earthworm-l 8.30 ppm. The acenaphthene concentrations measured were as follows: snail-11.2 ppm (day 37); pill bugs-0.99 ppm (day 75); and earthworm-71.9 ppm (days 72-75). The whole body concentration in the vole analyzed for phenanthrene was 7.20 ppm; in the vole analyzed for acenaphthene it was 37.00 ppm. The authors found that these compounds were not metabolized in this system. Whole body concentrations in the vole exceeded soil concentrations by a factor of 12 for phenanthrene and 31 for acenaphthene; however, most of the radiolabeled acenaphthene was found as bound residues in the gastrointestinal tract of the animal and, therefore, was not accumulated.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The processes that transform and degrade PAHs in the atmosphere include photolysis and reaction with NO_x, N_2O_5, OH, ozone, sulfur dioxide, and peroxyacetyl nitrate (Baek et al. 1991; NRC 1983). Possible atmospheric reaction products are oxy-, hydroxy-, nitro- and hydroxynitro-PAH derivatives (Baek et al. 1991). Photochemical oxidation of a number of PAHs has been reported with the formation of nitrated PAHs, quinones, phenols, and dihydrodiols (Holloway et al. 1987; Kamens et al. 1986). Some of these breakdown products are mutagenic (Gibson et al. 1978). Reaction with ozone or peroxyacetylnitrate yields diones; nitrogen oxide reactions yield intro and dinitro PAHs. Sulfonic acids have also been formed from reaction with sulfur dioxide.

The rates of homogeneous vapor phase chemical reactions are usually faster than heterogeneous chemical reactions of particulate PAHs with sunlight and oxidants in the atmosphere, particularly due to light shielding and stabilizing (toward both oxidation and photolysis) effects in the adsorbed state (Behymer and Hites 1988).

PAHs have a wide range of volatilities and therefore are distributed in the atmosphere between the gas and particle phases. The 24 ring PAHs exist, at least partially, in the gas phase. Atkinson et al. (1991) calculated atmospheric lifetimes (1.44 times the half-life) of several gas-phase PAHs due to reactions with measured or estimated ambient concentrations of OH radicals, NO_3 radicals, N_2O_5, and O_3. Their laboratory studies showed that, for PAHs not containing cyclopenta-fused rings, the major gas-phase process resulting in atmospheric loss will be reaction with the OH radical. Calculated atmospheric lifetimes for acenaphthene, acenaphthylene, phenanthrene, and anthracene were on the order of a few hours. Nighttime reaction with N_2O_5 was estimated to be a minor source of atmospheric loss. The reactions of PAHs, including fluoranthene and pyrene, with the OH radical (in the presence of NO_x) and with N_2O_5 led to the formation of nitroarenes that have been identified in the ambient air. As a class of compounds, the nitrated PAHs have been found to be much more mutagenic than their parent PAHs (Kamens et al. 1993).

Most PAHs in the atmosphere .are associated with particulates (Baek et al.. 1991). Vu-Due and Huynh (1991) describe two types of chemical reactions that appear to be the predominant mode of transformation of these PAHs: (1) reactions between PAHs adsorbed on the particle surfaces and oxidant gases like NO_2, O_3, and SO_3 that do not appear to be influenced by exposure to UV irradiation and (2) photooxidation of PAHs irradiated either under solar radiation or simulated sunlight which produces a variety of oxidized derivatives such as quinones, ketones, or acids. Kamens et al. (1990) estimate that, even in highly polluted air, photolysis is the most important factor in the decay of particle-sorbed PAHs in the atmosphere, followed by reaction with NO_2, N_2O_5, and HNO_3.

The National Research Council (NRC 1983) noted that compounds adsorbed to soot are more resistant to photochemical reactions than pure compounds. Butler and Crossley (1981) estimated half-lives for degradation of the following PAHs adsorbed to soot particles and exposed to sunlight in air containing 10 ppm nitrogen oxides: benzo[a]pyrene-7 days; benzo[g,h,i]perylene-8 days; benz[a]anthracene-11 days; pyrene-14 days; chrysene-26 days; fluoranthene-27 days; and phenanthrene-30 days. However, Thomas et al. (1968) reported that benzo[a]pyrene adsorbed on

soot was readily photooxidized, with 60% of the compound destroyed within the first 40 minutes of exposure to sunlight. The effect of substrate on PAH photolytic half-lives was investigated by Behymer and Hites (1988). Photolysis of 18 PAHs adsorbed to low-carbon fly ash produced a wjde range of half-lives that indicated a relationship between structure and photochemical reactivity. Photolysis of the same compounds adsorbed to fly ash samples containing >5% carbon produced similar half-lives, indicating that for these fly ash samples, photolysis is dependent on the physical and chemical structure of the adsorbent and independent of PAH structure. The investigators postulated that dark (i.e., high carbon content) substrates stabilize PAHs to photolytic breakdown since they absorb more light, making less light available for photolysis. McDow et al. (1993) hypothesized that PAHs in atmospheric particles may be either dissolved in a liquid organic phase or adsorbed at an organic phase-solid elementai carbon interface. Therefore, the reactivity of PAHs might depend, not only on the surface characteristics of the particle's solid core, but also on the chemical composition of the organic phase that surrounds the core. Experiments revealed that photodegradation of PAHs (including benz [a]anthracene, chrysene, benzo[a]pyrene, benzo[b]fluoranthene, and benzo[k]fluoranthene) in a mixture of methoxyphenols, based on relative amounts collected in actual samples from hardwood burning, was 10-30 times faster than in hexane. Their results demonstrated that variations in chemical composition of different types of particles such as diesel exhaust and wood smoke might strongly affect the reactivity of PAHs. Eisenberg and Cunningham (1985) found that the photochemical reaction products of PAHs (anthracene, phenanthrene, fluoranthene, benz[a]anthracene, chrysene, and benzo[a]pyrene) adsorbed on particulates include singlet oxygen, which may be implicated in the formation of mutagenic compounds.

Some PAHs are degraded by oxidation reactions that have been measured in the dark (to eliminate the possibility of photodegradation). Korfmacher et al. (1980) found that, while fhrorene was completely oxidized, fluoranthene and phenanthrene were not oxidized, and benzo[a]pyrene and anthracene underwent minimal oxidation. These compounds were tested adsorbed to coal fly ash; the authors stated that the form of the compound (adsorbed or pure) and the nature of the adsorbent greatly affected the rate and extent of oxidation.

Several studies have been carried out to investigate the reaction of PAHs with ozone at ambient concentrations (Baek et al. 1991). Alebic-Juretic et al. (1990) found degradation of PAHs on particle surfaces by ozone to be an important pathway for their removal from the atmosphere. Half-lives of PAHs obtained under laboratory conditions were used to predict lifetimes in an atmosphere containing

a constant ozone concentration of 0.05 ppm. The predicted lifetimes were 3 hours for benzo[a]pyrene, 12 hours for pyrene, and 6 days for fluoranthene. Lane and Katz (1977) investigated the kinetics of the dark reaction of several PAHs with ozone and found the reaction to be extremely fast under simulated atmospheric conditions, with a reported half-life of 0.62 hours for benzo[a]pyrene exposed to 190 ppb of ozone.

In an attempt to determine the atmospheric oxidation processes that would result in an arene oxide functional group in PAHs, Murray and Kong (1994) studied the reaction of particle-bound PAHs with oxidants derived from the reactions of ozone with alkenes. Phenanthrene and pyrene were converted to arene oxides under these simulated atmospheric conditions. Control experiments indicated that the oxidant responsible for the transformation was not ozone, but a product of the reaction of ozone with tetramethylethylene (TME), probably the carbonyl oxide or the dioxirane derived from TME.

5.3.2.2 Water

The most important processes contributing to the degradation of PAHs in water are photooxidation, chemical oxidation, and biodegradation by aquatic microorganisms (Neff 1979). Hydrolysis is not considered to be an important degradation process for PAHs (Radding et al. 1976). The contribution of the individual processes,to the overall fate of a PAH will depend largely on the temperature, depth, pollution status, flow rate, and oxygen content of the water. As a result, a process that is a major loss/degradation process for a particular PAH in a certain surface water may not be so in another surface water with different water quality.

The rate and extent of photodegradation vary widely among the PAHs (Neff 1979). Unfortunately, there is no easily defined trend in the rates of photolysis that could be correlated with the chemical structure of PAHs. For example, the rate of aquatic photolysis of naphthalene containing two benzene rings is much slower than anthracene which contains three benzene rings (Anderson et al. 1986). Based on half-life data, photolysis in water may be an important fate determining process for acenaphthene, acenaphthylene, anthracene, pyrene, benzo[a]pyrene, and benz[a]anthracene relative to the other PAHs discussed in this document (Behymer and Hites 1988; Anderson et al. 1986; Zepp and Schlotzhauer 1983). A study by Nagata and Kondo (1977) reported that anthracene, phenanthrene, and benz[a]anthracene were susceptible to photodegradation, and that benzo[a]pyrene, chrysene, fluorene, and pyrene were resistant to photodegradation. In the photooxidation of PAHs, the most common

reactions result in the formation of peroxides, quinones, and diones (NAS 1972). The major photoproducts of anthracene, phenanthrene, and benz[a]anthracene are anthraquinone, 9,10-phenanthrequinone, and 7,12-benz[a]anthraquinone, respectively (David and Boule 1993).

The rate of photolysis is accelerated by the presence of certain sensitizers (Zepp and Schlotzhauer 1983). Conversely, the rate of photolysis is decreased by the presence of certain quenchers in water (e.g., certain carbonyl compounds). The importance of photolysis will also decrease with the increase of depth in a body of water, particularly in turbid water, because of light attenuation and scattering (Zepp and Schlotzhauer 1979).

Generally, oxidation with singlet oxygen and peroxy radicals are the two important oxidative processes for environmental pollutants in water. The rate constants for reactions of PAHs with singlet oxygen and peroxy radicals (Mabey et al. 1981) and the typical concentrations of the two oxidants in environmental waters (Mill and Mabey 1985) suggest that these reactions may not be important in controlling the overall fate of PAHs in water.

PAHs in water can be chemically oxidized by chlorination and ozonation. A high efficiency of PAH degradation from chlorination has been reported by Harrison et al. (1976a, 1976b) for both laboratory and waste-water treatment plant conditions. Pyrene was the most rapidly degraded PAH. Benz[a]anthracene, benzo[a]pyrene, and perylene were also highly degraded. Indeno[1,2,3-c,d]pyrene and benzo[g,h,i]pyrene were intermediate with respect to relative degradation. Benzo[k]fluoranthene and fluoranthene were the most slowly degraded of the compounds tested.

The PAH-related by-products resulting from chlorination are not fully known (Neff 1979). Oyler et al. (1978) identified the following products resulting from the chlorination of PAHs: anthraquinone, a chlorohydrin of fluoranthene; and monochloro derivatives of fluorene, phenanthrene, l-methyl-phenanthrene, and 1-methylnaphthalene. Mori et al. (1993) found that treatment of aqueous benz[a]anthracene (B[a]A) solution with chlorine in both the presence and absence of bromide ion produced a variety of halogenated compounds. The main product was the oxygenated compound, B[a]A-7, l2-dione. A variety of mutagenic halogen substituted and halogen additive (polar) compounds also were produced. The oxidation reaction with chlorine of B[a]A in water was accelerated in the presence of bromide ion.

In water, ozonation is generally slower and less efficient than chlorination in degrading PAHs (Neff 1979). Reaction pathways for ozonation of some PAHs include benz[a]anthracene to 7,12-quinone; benzo[a]pyrene to 3,6-, 1,6-, and 4,5diones; and fluorene to fluorenone (NAS 1972).
In general, PAHs can be significantly metabolized by microbes under oxygenated conditions. However, under anoxic conditions, degradation will be extremely slow (Neff 1979). Concentrations of dissolved oxygen >0.7 mg/L is adequate for biotransformation and the presence of a minimal concentration of PAH is required for biodegradation to proceed (Borden et al. 1989). The minimum total PAH concentration below which biotransformation may be inhibited under ambient nutrient conditions may be 30-70 µg/L (Borden et al. 1989). Some other factors that increase the rates of PAH biodegradation are higher water temperature (summer versus winter) and the presence of adapted microorganisms (Aamand et al. 1989; Anderson et al. 1986; Lee and Ryan 1983). Some PAHs are partially or completely degraded by some species of aquatic bacteria and fungi. The bacterial degradation pathway includes an initial dioxygenase attack to form cis-dihydrodiols (via dioxetane intermediates) that are further oxidized to dihydroxy products. In fungi and mammalian systems (which, unlike bacteria, have cytochrome P-450 enzyme systems), truns-dihydrodiol is produced via an arene oxide intermediate (Anderson et al. 1986; Cemiglia and Heitkamp 1989; Neff 1979). This is significant since the arene oxides have been linked to the carcinogenicity of PAHs. Algae were found to transform benzo[a]pyrene to oxides, peroxides, and dihydrodiols (Kirso et al. 1983; Warshawsky et al. 1983).

Microorganisms in stored groundwater samples completely degraded acenaphthene and acenaphthylene within 3 days (Ogawa et al. 1982). When these reactions occurred under aerobic conditions, there was no evidence of anaerobic degradation of PAHs within the aquifer from which the samples were obtained.

Information on the biodegradation of PAHs by fungi is limited compared to the information that is available about bacteria. However, the fungus *Cunninghamella elegans* has been reported to be capable of metabolizing naphthalene (Cemiglia and Gibson 1979), anthracene, benzo[a]pyrene (Cemiglia and Heitkamp 1989), and fluorene (Pothuluri et al. 1993).

No correlation between biodegradability and molecular weight is evident in three- to four-ring PAHs. For example, phenanthrene with three benzene rings biodegraded in an estuarine water from Savannah,

Georgia, with a half-life of 19 days in August, but anthracene, containing the same number of benzene rings, did not biodegrade at all (Lee and Ryan 1983). Based on estimated reaction rates or half-lives, acenaphthylene, acenaphthylene, and fluorene, the three PAHs that have lower molecular weights than phenanthrene, may not readily biodegrade in water (Lee and Ryan 1983; Mabey et al. 1981). While both naphthalene and phenanthrene biodegraded in water, other PAHs, such as anthracene, benz[a]anthracene, chrysene, and fluorene, did not readily biodegrade in water, but degraded readily in sediment water slurries (Lee and Ryan 1983). On the other hand, PAHs with five or more benzene rings, such as benzo[a]pyrene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene, may not biodegrade readily even in sediment-water slurries (Lee and Ryan 1983; Mabey et al. 1981).

Based on theoretical modeling, photolysis would account for 5% and biodegradation 91% of the transformation/removal of anthracene from deep, slow moving, and somewhat turbid water. The corresponding values in a very shallow, fast-moving, clear water were 47 and 12%, respectively (Southworth 1979).

5.3.2.3 Sediment and Soil

Microbial metabolism is the major process for degradation of PAHs in soil environments. Photolysis, hydrolysis, and oxidation generally are not considered to be important processes for the degradation of PAHs in soils (Sims and Overcash 1983). However, in a study of PAH losses from four surface soils amended with PAHs in sewage sludge, losses due to volatilization and photolysis from sterilized soils were considered to be important for PAHs composed of less than four aromatic rings, whereas abiotic losses were insignificant for PAHs containing four or more aromatic rings (Wild and Jones 1993). Another study that assessed the fate of several PAHs, which included naphthalene, anthracene, phenanthrene, fluoranthene, pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, dibenz[a,h]anthracene, benzo[a]pyrene, dibenzo[a,i]pyrene and indeno[l,2,3-c,d]pyrene, in two soils concluded that abiotic degradation (photolysis and oxidation) accounted for mean losses of 13, 8.3, and 15.8% loss in case of naphthalene, anthracene, and phenanthrene, respectively. No significant abiotic loss was observed for the other PAHs (Park et al. 1990).

The rate and extent of biodegradation of PAHs in soil are affected by environmental factors; the organic content; structure and particle size of the soil; characteristics of the microbial population; the presence of contaminants such as metals and cyanides that are toxic to microorganisms; and the

physical and chemical properties of the PAHs (Wilson and Jones 1993). Based on experimental results, the estimated half-lives (days) of the PAHs in soil were: naphthalene, 2.1-2.2; anthracene, 50-l34; phenanthrene, 16-35; fluoranthene, 268-377; pyrene, 199-260; chrysene, 371-387; benz[a]anthracene, 162-261; benzo[b]fluoranthene, 211-294; benzo[a]pyrene, 229-309; dibenz[a,h]anthracene, 361-420; dibenzo(a,i)pyrene, 232-361; and indeno[l,2,3-c,d]pyrene, 288-289 (Park et al. 1990). Although there are differences in the biodegradation half-life values estimated by different investigators (Park et al. 1990; Wild and Jones 1993; Symons et al. 1988), their results suggest that the biodegradation half-lives of PAH with more than three rings will be considerably longer (>20 days to hundreds of days) than the PAHs with three or fewer rings. Environmental factors that may influence the rate of PAH degradation in soil include temperature, Ph, oxygen concentration, PAH concentrations and contamination history of soil, soil type, moisture, nutrients, and other substances that may act as substrate co-metabolites (Sims and Overcash 1983). The size and composition of microbial populations in turn can be affected by these factors. For example, in low-Ph soils, fungi are dominant over bacteria, and thereby control microbial degradation in these environments. Sorption of PAHs to organic matter and soil particulates also influences bioavailability, and hence, biotransformation potential. Sorption of PAHs by soil organic matter may limit biodegradation of compounds that would otherwise rapidly undergo metabolism (Manila1 and Alexander 1991; Weissenfels et al. 1992).

Although the pathways of microbial degradation are well known for anthracene, benzo[a]pyrene, and phenanthrene, degradation pathways for other PAHs are largely unknown (Sims and Overcash 1983). Metabolism of PAHs by bacteria includes the formation of cis-dihydrodiols through dioxetane intermediates, whereas in fungi (and mammalian systems) trans-dihydrodiols are produced through arene oxide intermediates (Sims and Overcash 1983). MacGillivray and Shiaris (1994) estimated the relative contribution of prokaryotic (bacteria) and eukaryotic (yeast, fungi) microorganisms to PAH biotransformation using phenanthrene as a model compound. They found that the relative contribution of eukaryotic microorganisms to phenanthrene transformation in inoculated sterile sediment was less than 3% of the total activity.

In laboratory studies, Sims et al. (1988) demonstrated extensive degradation of two-ring PAHs in sandy soils, with half-lives of approximately 2 days. The three-ring PAHs, anthracene, and phenanthrene had half-lives of 16 and 134 days, respectively. Four- to six-ring PAHs generally had half-lives >200 days. Anthracene and fluoranthene showed slightly higher biodegradation rates than

benz[a]anthracene or benzo[a]pyrene in a study with fine and medium sands and marsh sediments (Gardner et al. 1979). Degradation rates expressed as a percentage of the mass removed per week for the four compounds were anthracene-2.0-3.0%, fluoranthene-1.9-2.4%, benz[a]anthracene-1.4-l .8%, and benzo[a]pyrene-0.84-1.4%. The ranges of half-lives of phenanthrene and benzo[g,h,i]perylene in four soils amended with PAHs in sewage sludge were 83-193 days and 282-535 days, respectively. Mean half-lives were found to be positively correlated with log K_{ow} and inversely correlated with log water solubility. Previous exposure of the test soils to PAHs enhanced the rate of biodegradation of low molecular weight PAHs but had little effect on the loss of higher molecular weight compounds (Wild and Jones 1993).

Herbes and Schwall (1978) investigated the rates of microbial transformation of PAHs in freshwater sediments from both pristine and oil-contaminated streams. They found that turnover times (l/k) in the uncontaminated sediment were 10-400 times greater than in contaminated sediment. Absolute rates of PAH transformation (micrograms of PAH per gram of sediment per hour) were 3,000-125,000 times greater in the contaminated sediment. Turnover times in the oil-contaminated sediment increased 30-l00-fold per additional ring from naphthalene through benz[a]anthracene; naphthalene was broken down in hours while the turnover times for benz[a]anthracene and benz[a]pyrene were ~400 days and >3.3 years, respectively. Therefore, four- and five-ring PAHs, including the carcinogenic benz[a]anthracene and benz[a]pyrene, may persist even in sediments that have received chronic PAH inputs.

The rate of biodegradation may be altered by the degree of contamination. At hazardous waste sites, half-lives may be longer since other contaminants at the site may be toxic to degrading . microorganisms. Bossert and Bartha (1986) reported reduced biodegradation of PAHs in soil containing a chemical toxic to microorganisms.

Efroymson and Alexander (1994) investigated the effects of nonaqueous phase-liquids (NAPLs) on the biodegradation of hydrophobic compounds, including phenanthrene, in soil and subsoil. Mineralization of phenanthrene in the subsoil was reduced if the compound was dissolved in a NAPL. However, the suppression of the mineralization of phenanthrene in soil by NAPLs was short-lived, suggesting growth of organisms capable of using phenanthrene.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

There is a relatively large body of data characterizing PAH air levels at a variety of U.S. sites. Caution must be used in interpreting and comparing results of different studies, however, because of the different sampling methods used. PAHs occur in the atmosphere in both the particle phase and the vapor phase, as discussed in Section 5.2.1. Three-ring PAH compounds are found in the atmosphere primarily in the gaseous phase, whereas, five- and six-ring PAHs are found mainly in the particle phase; four-ring PAH compounds are found in both phases. To fully characterize atmospheric PAH levels, both particle- and vapor-phase samples must be collected. Many of the earlier monitoring studies used filter sampling methods, which provided information on particle-phase PAH concentrations only, and which did not account for losses of some of the lower molecular weight PAHs by volatilization. As a result, the early use of particulate samples may have resulted in an underestimation of total PAH concentrations. More recent monitoring studies often use sampling methods that collect both particle- and vapor-phase PAHs and that prevent or minimize volatilization losses, thus providing more reliable characterization of total atmospheric PAH concentrations (Baek et al. 1991).

Several monitoring studies indicate that there are higher concentrations of PAHs in urban air than in rural air. Pucknat (1981) summarized 1970 data from the U.S. National Air Surveillance Network and reported that benzo[a]pyrene concentrations in 120 U.S. cities were between 0.2 and 19.3 ng/m^3. Ambient benzo[a]pyrene concentrations in nonurban areas ranged between 0.1 and 1.2 ng/m^3. More recently, Greenberg et al. (1985) evaluated atmospheric concentrations of particulate phase PAHs at four New Jersey sites (three urban and one rural) over two summer and winter seasons during 198l-82. Urban PAH concentrations were approximately 3-5 times higher than those at the rural site; in addition, winter concentrations were approximately 5-10 times higher than summer concentrations. Geometric mean concentrations of ten PAHs (benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzofi]fluoranthene, benzo[k]fluoranthene, benz[a]anthracene, indeno[l,2,3-c,d]pyrene, benzo[g,h,i]perylene, pyrene, and chrysene) ranged from 0.03 to 0.62 ng/m^3 in urban areas and from 0.01 to 0.12 ng/m^3 in the rural area during the summer seasons. During the winter seasons, geometric mean concentrations of these PAHs ranged from 0.40 to 11.15 ng/m^3 in urban areas and from 0.08 to 1.32 ng/m^3 in the rural area. Geometric mean concentrations of benzo[a]pyrene ranged from 0.11 to

0.23 ng/m^3 (urban) and 0.04 to 0.06 ng/m^3 (rural) during the summer seasons, and from 0.69 to 1.63 ng/m^3 (urban) and 0.17 to 0.32 (rural) during the winter seasons. A more extensive study by Harkov and Greenberg (1985) of atmospheric benzo[a]pyrene concentrations at 27 New Jersey sites indicated similar differences in mean urban (0.6 ng/m^3) and rural (0.3 ng/m^3) concentrations. Significant seasonal trends were also observed, with mean benzo[a]pyrene concentrations during the winter more than an order of magnitude greater than during the summer.

Several other studies provide evidence that atmospheric concentrations of particle-phase PAHs are higher in winter than in summer. In a 1981-82 study conducted in the Los Angeles area; atmospheric concentrations of 10 PAHs (anthracene, fluoranthene, pyrene, chrysene, benz[a]anthracene, combined benzo[e]pyrene and perylene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, and combined benzo[g,h,i]perylene, and indeno[l,2,3-c,d]pyrene) ranged from 0.14 to 1.45 ng/m^3 (with an average of 0.43 ng/m^3) during the summer (August-September), and from 0.40 to 4.46 ng/m^3 (with an average of 1.28 ng/m^3) during the winter (February-March) (Grosjean 1983). A similar seasonal variation in particle-phase PAH concentrations in the Los Angeles atmosphere was seen in an earlier 1974-75 study (Gordon 1976). Quarterly geometric mean concentrations of 11 PAHs (pyrene, fluoranthene, benz[a]anthracene, chrysene, benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, and indeno[1,2,3-c,d]pyrene) ranged from 0.06 to 2.71 ng/m^3 (with an average of 0.45 ng/m^3) during the May-October period, and from 0.26 to 8.25 ng/m^3 (with an average of 1.46 ng/m^3) during the November-April period. The highest and lowest concentrations were observed during the fourth (November-January) and second (May-July) quarters, respectively. Ratios of fourth quarterly and second quarterly geometric mean concentrations ranged from 3.9 for indeno[l,2,3-c,d]pyrene to 7.5 for benzo[a]pyrene and 9.8 for benz[a]anthracene. Possible factors contributing to these seasonal variations in PAH levels include the following: changes in emission patterns; changes in meteorological conditions (i.e., daylight hours and temperature); and changes in space heating emissions, volatilization, and photochemical activity.

Certain monitoring data suggest that ambient levels of some PAHs may be decreasing. Faoro and Manning (1981) analyzed a limited sample of U.S. National Air Surveillance Network data updated through 1977, which indicated that benzo[a]pyrene concentrations have shown consistent, sizable declines during the period from 1967 to 1977 at 26 urban sites and 3 background sites studied (data not provided).

Over the past two decades, the ambient air levels of PAHs in a number of major cities have been characterized. Although data from studies in different areas cannot be used to indicate definitive temporal trends in PAH air levels, a comparison of the results of these studies yields no strong suggestion that the ambient air levels of PAHs may be decreasing, except in traffic tunnels.

In a 1981-82 study that characterized air levels of 13 PAHs in Los Angeles, Grosjean (1983) reported mean ambient particle-phase PAH concentrations ranging from 0.32 ng/m^3 for benzo[k]fluoranthene to 3.04 ng/m^3 for combined benzo[g,h,i]perylene and indeno[1,2,3-c,d]pyrene. Mean concentrations of anthracene, fluoranthene, pyrene, chrysene, benz[a]anthracene, combined perylene and benzo[e]pyrene, benzo[b]fluoranthene, and benzo[a]pyrene were 0.54; 0.94, 1.62, 0.97, 0.48, 0.43, 0.94, and 0.64 ng/m^3, respectively. Similar results were obtained in an earlier (1974-1975) study of atmospheric particle-phase PAHs in the Los Angeles area, where ambient annual geometric mean concentrations ranged from 0.17 ng/m^3 for benzo[j]fluoranthene to 3.27 ng/m^3 for benzo[g,h,i]perylene (Gordon 1976). The annual geometric mean concentration of benzo[a]pyrene was 0.46 ng/m^3; most individual PAHs had annual geometric mean concentrations of <0.6 ng/m^3. The relatively high levels of benzo[g,h,i]perylene found in these studies.have been attributed to high levels of automobile emissions, which are known to contain high levels of benzo[g,h,i]perylene relative to other PAHs (Santodonato et al. 1981). During the same time period, Fox and Staley (1976) reported somewhat higher ambient average concentrations of particle-phase PAHs in College Park, Maryland, ranging from 3.2 ng/m^3 for benzo[a]pyrene to 5.2 ng/m^3 for pyrene.

In a 1985-86 study, reported average ambient concentrations (combined particle- and vapor-phase) of eight PAHs in Denver ranged between 0.83 ng/m^3 for benzo[k]fluoranthene and 39 ng/m^3 for phenanthrene (Foreman and Bidleman 1990). In a study conducted in Hamilton, Ontario, between May 1990 and June 1991, the concentrations of PAHs in respirable air particulate samples were found to range from 0.6 ng/m^3 for phenanthrene to 4.3 ng/m^3 for benzo[g,h,i]perylene, and 5.1 ng/m^3 for combined benzo[b,j,k]fluoranthenes (Legzdins et al. 1994). In a recent limited study, mean concentrations of particle-phase PAHs in New York City air were reported to range from 0.11 ng/m^3 for anthracene to 4.05 ng/m^3 for benzo[g,h,i]perylene (Tan and Ku 1994).

Atmospheric PAH concentrations have been found to be significantly elevated in areas of enclosed traffic tunnels. In a 1985-86 study in the Baltimore Harbor Tunnel the average concentrations of particle-phase PAHs ranged from 2.9 ng/m^3 for anthracene to 27 ng/m^3 for pyrene (Benner and

Gordon, 1989). These values are up to an order of magnitude lower than those obtained in 1975 by Fox and Staley (1976), which ranged from 66 ng/m^3 for benzo[a]pyrene to 120 ng/m^3 for pyrene. Benner and Gordon (1989) postulated that the observed decrease in PAH concentrations over the 1975-85 decade resulted from the increasing use of catalytic converters in U.S. automobiles over that period, These authors also reported concentrations of PAHs in a typical vapor-phase sample from the Boston Harbor Tunnel for four PAHs included in this profile: anthracene (32.3 ng/m^3), fluoranthene (25.6 ng/m^3), phenanthrene (184 ng/m^3), and pyrene (28.3 ng/m^3). They emphasized that the vapor-phase samples included PAHs inherently present in the vapor phase as well as the more volatile 3- and 4-ring PAHs that may be desorbed from particles during sampling. These results underscore the need to evaluate both particle- and vapor-phase samples to obtain more reliable estimates of total atmospheric PAH concentrations.

5.4.2 Water

PAHs have been detected in surface waters of the United States. In an assessment of STORET data covering the period 1980-82, Staples et al. (1985) reported median concentrations in ambient water of <10 µg/L for 15 PAHs (acenaphthene, acenaphthylene, anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, fluoranthene, fluorene, indeno[1,2,3-c,d]pyrene, naphthalene, phenanthrene,. and pyrene). The number of samples ranged from 630 (naphthalene) to 926 (fluoranthene); the percentage of samples in which these PAHs were detected ranged from 1.0 (benzo[g,h,i]perylene) to 5.0 (phenanthrene) and 7.0 (naphthalene).

Basu and Saxena (1978a) reported concentrations of selected PAHs in surface waters used as drinking water sources in four U.S. cities (Huntington, West Virginia; Buffalo, New York; and Pittsburgh and Philadelphia, Pennsylvania). Total concentrations of PAHs ranged from 4.7 ng/L in Buffalo to 600 ng/L in Pittsburgh. Mean concentrations of benzo[a]pyrene in the Great Lakes have been detected at levels between 0.03 and 0.7 ppt (ng/L) (Environment Canada 1991).

DeLeon et al. (1986) analyzed surface water from 11 locations in the Mississippi River. Seventeen PAHs were identified in the samples at levels ranging from 1 ng/L for 6 compounds to a high of 34 ng/L for phenanthrene. The highest concentration of phenanthrene was detected in a sample

collected near New Orleans, Louisiana, near an industrial area, implicating industrial effluent or surface runoff from this area as a possible source.

During April and May 1990, Hall et al. (1993) analyzed 48-hour composite samples from three locations in the Potomac River and three locations in the upper Chesapeake Bay for eight PAHs: perylene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benz[a]anthracene, and chrysene. Pyrene was the.only PAH found (0.42 µg/L) in these samples; it was detected in only one of nine Chesapeake Bay samples and not detected in any of the Potomac River samples (detection limit, 0.04 µg/L).

In a more recent study by Pham et al. (1993), raw water samples from 5 areas in the St. Lawrence River and its tributaries were analyzed for 12 PAHs. The highest mean total PAH concentrations were observed in samples collected in the spring (27.3 ng/L) and autumn (21.03 ng/L), which was attributed to snow melt and increased runoff during these respective seasons. The lowest mean total PAH concentration was observed in summer (14.63 ng/L). High molecular weight PAHs were detected more frequently in the spring and autumn samples. Phenanthrene, benzo[b]fluoranthene, fluoranthene, and pyrene were predominant, comprising on average 33.8%, 17.4%, 17.1%, and 12.8% of the total PAHs, respectively: With the exception of anthracene and benzo[b]fluoranthene, a general decrease in concentration with increasing molecular weight was observed.

PAHs have been detected in urban runoff generally at concentrations much higher than those reported for surface water. Data collected as part of the Nationwide Urban Runoff Program indicate concentrations of individual PAHs in the range of, 300-10,000 ng/L, with the concentrations of most PAHs above 1,000 ng/L (Cole et al. 1984). In a recent study by Pitt et al. (1993) which involved the collection and analysis of approximately 140 urban runoff samples from a number of different source areas in Birmingham, Alabama, and under various rain conditions, fluoranthene was one of two organic compounds detected most frequently (23% of samples). The highest frequencies of detection occurred in roof runoff, urban creeks, and combined sewer overflow samples. The maximum reported concentration of fluoranthene in these samples was 130 µg/L.

Industrial effluents also have elevated PAH levels. Morselli and Zappoli (1988) reported elevated PAH levels in refinery waste waters, with concentrations for most PAHs in the range of 400 ng/L (benzo[b]fluoranthene) to 16,000 ng/L (phenanthrene). In an analysis of STORET data covering the

period 1980-88, Staples et al. (1985) reported median concentrations in industrial effluents of <10 µg/L (10,000 ng/L) for 15 PAHs. The number of samples ranged from 1,182 (benzo-[blfluoranthene) to 1,288 (phenanthrene); the percentage of samples in which PAHs were detected ranged from 1.5 (benzo[g,h,i]perylene) to 7.0 (fluoranthene).

Few data are available on the concentrations of PAHs in U.S. groundwater. Basu and Saxena (1978b) reported total PAH concentrations in groundwater from three sites in Illinois, Indiana, and Ohio to be in the range of 3-20 ng/L. Groundwater levels of PAHs near a coal and oil gasification plant and U.S. wood treatment facilities have been found to be elevated. Groundwater samples from the site of a Seattle coal and oil gasification plant which ceased operation in 1956 were found to contain acenaphthylene, acenaphthene, fluorene, phenanthrene, fluoranthene, pyrene, and chrysene at concentrations ranging from not detected (detection limit 0.005 mg/L) to 0.25, 0.18, 0.14, 0.13, 0.05, 0.08, and 0.01 mg/L, respectively (Tumey and Goerlitz 1990). Individual PAHs in the groundwater from 5 U.S. wood treatment facilities were reported at average concentrations of 57 ppb (0.057 mg/L) for benzo[a]pyrene to 1,825 ppb (1.8 mg/L) for phenanthrene (Rosenfeld and Plumb 1991).

An evaluation of the analytical data from 358 hazardous waste sites with over 5,000 wells indicated that anthracene, fluoranthene, and naphthalene were detected (practical quantitation limit, 10-200 µg/L) in groundwater from at least 0.1% of the sites in three of the ten EPA Regions into which the United States is divided (Garman et al. 1987). A review of groundwater monitoring data from 479 waste disposal sites (178 CERCLA or Super-fund sites, 173 RCRA sites, and 128 sanitary/municipal landfill sites) located throughout the United States indicated that 14 of the PAHs included in this profile were detected at frequencies ranging from 2 detections at one site in one EPA Region for indeno[l,2,3-c,d]pyrene, to 85 detections at 16 sites in 4 EPA Regions for fluorene (Plumb 1991). Benzo[a]pyrene was detected 13 times at 6 sites in 6 EPA Regions. Concentrations were not reported.

Data summarized by Sorrel et al. (1980) indicate low levels of PAHs in finished drinking waters of the United States. Reported maximum concentrations for total PAHs (based on measurement of 15 PAHs) in the drinking water of 10 cities ranged from 4 to 24 ng/L; concentrations in untreated water ranged from 6 to 125 ng/L. The low concentrations of PAHs in finished drinking water were attributed to efficient water treatment processes. Shiraishi et al. (1985) found PAHs in tap water at concentrations of 0.1-1.0 ng/L, primarily as chlorinated derivatives of naphthalene, phenanthrene, fluorene, and fluoranthene. The significance to human health of these compounds is not known (Eisler 1987).

5.4.3 Sediment and Soil

PAHs are ubiquitous in soil. Because anthropogenic combustion processes are a major source of PAHs in soils, soil concentrations have tended to increase over the last 100-150 years, especially in urban areas (Jones et al. 1989a, 1989b). Background concentrations for rural, agricultural, and urban soils (from the United States and other countries) are given in Table 5-3. In general, concentrations ranked as follows: urban > agricultural > rural. Evidence of the global distribution of PAHs was given by Thomas (1986) who detected benzo[g,h,i]perylene and fluoranthene at concentrations above 150 µg/kg in arctic soils. Soil samples collected from remote wooded areas of Wyoming contained total PAH concentrations of up to 210 µg/kg.

Recent data on PAH concentrations in soil at contaminated sites are summarized in Table 5-4. Because of the different sampling methods and locations at each site, this tabulation does not provide a reliable inter-site comparison. Additional studies indicate significantly elevated concentrations of PAHs at contaminated sites. Soil samples collected from the Fountain Avenue Landfill in New York City contained PAH concentrations ranging from 400 to 10,000 µg/kg (Black et al. 1989). In a 1988 study at a hazardous waste land treatment site for refinery process wastes, which had been operative since 1958, average PAH concentrations in surface soils (0-30 cm) ranged from not detected (detection limits 0.1-2.0 mg/kg dry weight) for acenaphthylene, acenaphthene, anthracene, benz[a]anthracene, and benzo[k]fluoranthene to 340 mg/kg dry weight for dibenz[a,h]anthracene (Loehr et al. 1993). In addition to dibenz[a,h]anthracene, the three most prevalent compounds at this depth were benzo[a]pyrene (204 mg/kg), benzo[b]fluoranthene (130 mg/kg), and chrysene (100 mg/kg). PAH concentrations decreased with increasing depth and the majority of PAHs were not detected at depths below 60 cm. At 90-135 cm, only phenanthrene (1.4 mg/kg), pyrene (4.0 mg/kg), chrysene (0.9 mg/kg), and dibenz[a,h]anthracene (0.8 mg/kg) were found.

Sediments are major sinks for PAHs, primarily because of the low solubility of these compounds and their strong affinity for organic carbon in particulate matter. PAH concentrations in sediment are generally much higher than those detected in surface water, i.e., in the range of µg/kg (ppb) rather than ng/kg (ppt) .

In an assessment of STORET data covering the period 1980-1982, Staples et al. (1985) reported median concentrations in sediment of ≤500 µg/kg dry weight for 15 PAHs (acenaphthene,

TABLE 5-3. Background Soil Concentrations of Polycyclic Aromatic Hydrocarbons (PAHs)

Compound	Concentrations (μg/kg)		
	Rural soil	Agricultural Soil	Urban Soil
Acenaphthene	1.7	6	
Acenaphthylene		5	
Anthracene		11–13	
Benzo(a)anthracene	5–20	56–110	169–59,000
Benzo(a)pyrene	2–1,300	4.6–900	165–220
Benzo(b)fluoranthene	20–30	58–220	15,000–62,000
Benzo(e)pyrene		53–130	60–14,000
Benzo(g,h,i)perylene	10–70	66	900–47,000
Benzo(k)fluoranthene	10–110	58–250	300–26,000
Chrysene	38.3	78–120	251–640
Fluoranthene	0.3–40	120–210	200–166,000
Fluorene		9.7	
Ideno(1,2,3-c,d)pyrene	10–15	63–100	8,000–61,000
Phenanthrene	30.0	48–140	
Pyrene	1–19.7	99–150	145–147,000

[a]Derived from:

IARC 1973
White and Vanderslice 1980
Windsor and Hites 1979
Edwards 1983
Butler et al. 1984
Vogt et al. 1987
Jones et al. 1987

TABLE 5-4. Soil Concentrations (mg/kg dry weight) Polycyclic Aromatic Hydrocarbons (PAHs) at Contaminated Sites[a]

Compound	Wood-preserving[b]		Creosote production[c]		Wood treatment[d]	Coking plant[d]	Coking plant[e]	Gas works[f]		Gas works[g]
	Surface-soil	Subsoil	mean	range				mean	range	range
Acenaphthene	7	1,368					29	2	0–11	nd–3.0
Acenaphthylene	5	49	33	6–77			187			nd–3.0
Anthracene	10	3,037	334	15–693	766	6	130	156	57–295	nd–3.1
Benz(*a*)anthracene	12	171			356	16	200	317	155–397	nd–8.6
Benzo(*a*)pyrene	28	82			94	14		92	45–159	nd–15
Benzo(*e*)pyrene										nd–12[i]
Benzo(*b*)fluoranthene	38	140						260	108–552	nd–19
Benzo(*k*)fluoranthene								238	152–446	
Benzo(*j*)fluoranthene										nd–1.2[i]
Benzo(*g,h,i*)perylene										nd–16
Chrysene	38	481	614	8–1,586	321	11	135	345	183–597	nd–12
Dibenz(*a,h*)anthracene					101	2		2,451	950–3,836	nd–2.0
Fluoranthene	35	1,629	682	21–1,464	1,350	34		2,174	614–3,664	nd–2.6
Fluorene	3	1,792	650	49–1,294	620	7	245	225	113–233	nd–6.5
Indeno(1,2,3-*c,d*)pyrene	10	23						207	121–316	nd–13
Naphthalene	1	3,925	1,313	<1–5,769	92	56	59			nd[h]–46
Phenanthrene	11	4,434	1,595	76–3,402	1,440	27	277	379	150–716	nd–26
Pyrene	49	1,016	642	19–1,303	983	28	285	491	170–833	nd–4.3

[a]Modified from Wilson and Jones 1993
[b]Mueller et al. 1991—composite samples
[c]Ellis et al. 1991—samples are 1·5 m or 3·5 m
[d]Weissenfels et al. 1990a—no range or sampling details provided
[e]Werner et al. 1988—no range or sampling details provided
[f]Bewley et al. 1989—samples taken from prototype treatment bed
[g]Turney and Goerlitz 1990—samples taken in 1986 from plant inoperative since 1956.
[h]nd = not detected (no detection limit given)
[i]estimated value

acenaphthylene, anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, chrysene, fluoranthene, fluorene, indenopyrene, naphthalene, phenanthrene, and pyrene). The number of samples ranged from 236 (anthracene) to 360 (benzo-[alpyrene, fluoranthene); the percentage of samples in which these PAHs were detected ranged from 6.0 (acenaphthene, benzo[b]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-c,d]pyrene) to 22.0 (fluoranthene, pyrene).

Eadie et al. (1982) analyzed surficial sediments in southwestern Lake Erie near a large coal-fired power plant. Sediment concentrations for total PAHs were generally in the range of 530-700 µg/kg, although concentrations in river and near-shore sediments reached nearly 4,000 µg/kg (4 ppm). Heit et al. (1981) reported total concentrations of PAHs (3-7 ring PAHs) from two lakes in the Adirondack acid lake region of 2,660 µg/kg and 770 µg/kg (calculated from data presented). Average concentrations of total PAHs in sediments from three coastal South Carolina marinas were reported to range from 35.6 to 352.3 µg/kg (Marcus et al. 1988). Benzo[a]pyrene levels in bottom sediments of the Great Lakes have been reported to range from 34 to 490 ppb (µg/kg) (Environment Canada 1991). Concentrations of PAHs in sediments from Cape Cod and Buzzards Bay in Massachusetts and the Gulf of Maine have been reported to be in the range of 540-1,300 µg/kg (Hites et al. 1980). Concentrations of low molecular weight PAHs (naphthalene, acenaphthylene, fluorene, phenanthrene, anthracene, and 2-methylnaphthalene) and high molecular weight PAHs (fluoranthene, pyrene, benz[a]anthracene, chrysene, benzofluoranthenes, benzo[a]pyrene, indeno[l,2,3-c,d]pyrene, dibenz[a,h]anthracene, and benzo[g,h,i]perylene) in sediment from the highly polluted Boston Harbor have been reported to range from approximately 100 to 11,000 µg/kg dry wt, and 800 to 23,000 µg/kg dry wt, respectively (Demuth et al. 1993).

Total PAH concentrations in bottom sediments from the main stem of the Chesapeake Bay were reported to range from 45 to 8,920 µg/kg for samples collected from 16 stations in 1986 (Huggett et al. 1988). At least 14 PAHs were found to be dominant among pollutants of surface sediments from the Elizabeth River, a subestuary of the James River in Virginia, with a maximum total PAH concentration of 170,000 µg/g (ppm) observed in one sample from a site of two large wood preservative spills (Bieri et al. 1986). In a more recent study, surface sediment samples from the highly contaminated Elizabeth River were found to contain total concentrations of 14 PAHs ranging from 1.5 to 4,230 µg/g (ppm) dry weight (Halbrook et al. 1992). Significantly lower concentrations,

ranging from 0.34 to 0.95 µg/g (340-950 µg/kg) dry weight, were found in sediment samples from the nearby Nansemond River which served as a clean reference site.

Two-thirds of 105 sediment samples collected throughout Florida during the summers of 1989 and 1990 from sites known or suspected to be contaminated with priority pollutants were found to contain at least one of 15 PAH target analytes (Jacobs et al. 1993). Pyrene was detected most frequently (61% of samples); dibenz[a,h]anthracene and naphthalene were detected least frequently (4% of samples). Total PAH concentrations ranged from below the detection limit to 1,090 mg/kg. Mean concentrations for individual PAHs ranged from 0.87 mg/kg (dibenz[a,h]anthracene and naphthalene) to 30.8 mg/kg (acenaphthene).

Drainage stream sediments from a wood-preserving facility near Pensacola, Florida, were found to be highly contaminated with creosote-derived PAHs, with maximum concentrations from two sampling sites ranging from 300 µg/kg for naphthalene to 12,000 µg/kg for phenanthrene and 140,000 µg/kg for anthracene (Elder and Dresler 1988). Fluoranthene, pyrene, benz[a]anthracene, chrysene, acenaphthene, and fluorene were other dominant PAHs. PAHs were not detected in water samples from the drainage stream. Furthermore, no significant PAH contamination was found in surface sediments from estuarine sites adjacent to the drainage stream; PAHs were detected in sediment samples from only one of seven estuarine sites at concentrations ranging from 75 µg/kg for benz[a]anthracene to 190 µg/kg for fluoranthene.

In 1991, Kennicutt et al. (1994) found that sediment samples from Casco Bay in Maine contained total PAH concentrations ranging from 16 to 20,800 µg/kg dry weight. PAHs were found at all 65 locations sampled. PAHs with four or more rings accounted for more than 60% of Casco Bay sedimentary PAHs. The predominance of PAHs with highly condensed ring structures with few alkylations indicated a pyrogenic or combustion source as the major contributor.

Mean total PAH concentrations of sediments collected in 1985-87 from Moss Landing Harbor, Elkhom Slough, and nearshore Monterey Bay, California, were found to range from 1,470 to 3,080, 157 to 375, and 24 to 114 µg/kg dry weight, respectively (Rice et al. 1993). The Moss Landing Harbor and nearshore Monterey Bay ecosystems are subject to PAH contamination from various local industries, harbor-related activities, power generation, municipal waste treatment, and agricultural runoff. The largest Pacific Coast fossil-fueled power plant is located at Moss Landing. Elkhom

Slough is a seasonal estuary which receives freshwater runoff. Combustion PAHs (i.e., benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, benzo[e]pyrene, chrysene, fluoranthene, and pyrene) were predominant, with mean total concentration at these 3 sites ranging from 1,250 to 2,710, to 335, and 11 to 59 ug/kg dry weight, respectively.

Median concentrations of PAHs in sediment coves collected in 1991 from three northern New Jersey waterways (Arthur Kill, Hackensack River, and Passaic River) highly contaminated with petroleum hydrocarbons ranged from 0.47 mg (470 ug/kg) (acenaphthylene) to 5.10 mg (5,100 µg/kg) (pyrene) (Huntley et al. 1993). In addition to pyrene, fluoranthene, chrysene, and benzo[a]pyrene were the most frequently detected PAHs, with median concentrations at the three sites ranging from 2.40 to 4.10, 1.35 to 2.85, and 0.86 to 2.30 mg/kg, respectively. Mean total PAH concentrations at the 29 sampling stations ranged from 0 to 161 mg/kg. A mean total PAH concentration of 139 mg/kg was found at a sampling station downstream from a chemical control Superftmd site. At most sampling stations, PAH concentrations increased with sample depth up to approximately 45-50 cm, indicating a decline in recent loadings relative to historic inputs.

5.4.4 Other Environmental Media

PAHs have been detected in many food products including cereal, potatoes, grain, flour, bread, vegetables, fruits, oils, and smoked or broiled meat and fish. The concentrations in uncooked foods largely depend on the source of the food. For example, vegetables and fruits obtained from a polluted environment may contain higher PAH concentrations than those obtained from nonpolluted environments. Benzo[a]pyrene, dibenz[a,h]anthracene, and chrysene have been detected in vegetables grown near a heavily traveled road (Wang and Meresz 1982). The method of cooking can also influence the PAH content of food; the time of cooking, the distance from the heat source, and the drainage of fat during cooking (e.g., cooking in a pan versus on a grill) all influence PAH content. For example, charcoal broiling increases the amounts of PAHs in meat. In a composite sample characterized to be typical of the U.S. diet, Howard (1979) found that PAH concentrations in all food groups were less than 2 ppb (µg/g). The following ranges of benzo[a]pyrene concentrations (wet or dry weight not specified) were summarized by Santodonato et al. (1981) from studies conducted in many countries:

- cooking oils: 0.5-S ppb (µg/g)
- margarine: 0.2-6.8 ppb

- smoked fish: trace-6.6 ppb
- smoked or broiled meats: trace-105 ppb
- grains and cereals: not detected-60 ppb
- fruits: not detected-29.7 ppb
- vegetables: not detected-24.3 ppb

These data include samples from areas identified as “polluted.”

Gomaa et al. (1993) recently reported the results of a study to screen smoked foods, including turkey, pork, chicken, beef, and fish products, for carcinogenic and noncarcinogenic PAHs. Eighteen commercially available liquid smoke seasonings and flavorings were also evaluated. All smoked meat products and liquid smoke seasonings were purchased from local supermarkets in Michigan. Total PAH concentrations in smoked red meat products ranged from 2.6 µg/kg in cooked ham to 29.8 µg/kg in.grilled pork chops, while those in smoked poultry products ranged from 2.8 µg/kg in smoked turkey breast to 22.4 µg/kg in barbecued chicken wings. Total PAH concentrations in smoked fish products ranged from 9.3 µg/kg in smoked shrimp to 86.6 µg/kg in smoked salmon. Total concentrations of carcinogenic PAHs (benz[a]anthracene, benzo[b]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, and indeno[l,2,3,-c,d]pyrene) ranged from not detected in several red meat products to 7.4 µg/kg in grilled pork chops; from not detected in several poultry products to 5.5 µg/kg in barbecued chicken wings; and from 0.2 µg/kg in smoked trout and shrimp to 14.9 and 16.1 µg/kg in smoked oysters and salmon, respectively. Total PAH concentrations in liquid smoke flavorings and seasonings ranged from 6.3 to 43.7 µg/kg, while total carcinogenic PAH concentrations ranged from 0.3 to 10.2 µg/kg. Smoked meat products processed with natural wood smoke had higher total PAH and total carcinogenic PAH concentrations than those processed with liquid smoke flavorings. Carcinogenic PAHs were not detected in 10% of the smoked food samples and 24% of the samples had concentrations of carcinogenic PAHs <I µg/kg. Benzo[a]pyrene was not detected in 31% of the samples; 45% of the samples had concentrations <l µg/kg. Benzo[a]pyrene was found at concentrations >l µg/kg in 24% of the samples, which included pork sausage (1.8-2.3 µg/kg), grilled pork chops (2.5 µg/kg), whole ham (1.1 µg/kg), beef sausage (1.1 µg/kg), salmon (3.9 µg/kg), and oysters (3.0 µg/kg). Benzo[a]pyrene was detected in 92% (12/13) of liquid smoke flavorings and seasoning samples, with concentrations ranging from 0.1 to 3.4 µg/kg.

Similar results have been obtained in recent investigations of benzo[a]pyrene concentrations in smoked foods in other countries. In Brazil, benzo[a]pyrene was detected in 52% (23/44) of smoked meat

samples; concentrations ranged from 0.1 to 5.9 µg/kg and were generally <1.0 µg/kg (Yabiku et al. 1993). In France, benzo[a]pyrene concentrations in smoked fish, poultry, and pork products were found to range from <0.2 to 1.9, 0.3 to 1.9, and <0.2 to 7.2 µg/kg, respectively; 36% (26/71) of the samples analyzed had benzo[a]pyrene concentrations >1 µg/kg (Moll et al. 1993). Because many imported food products are included in the U.S. food supply, these data may be relevant to estimating dietary PAH exposures of the general U.S. population.

In data summarized by Edwards (1983) the maximum total concentration of PAHs in vegetation near a source was 25,000 ppb (25 µg/g) (dry weight), while concentrations in nonsource areas ranged from 20 to 1,000 ppb (0.02-l .0 µg/g). In general, concentrations in leaves, stems, and fruits were higher than those in roots. Fluoranthene, pyrene, and chrysene/triphenylene were found in concentrations of 1.2, 2.0, and 2.9 µg/g, respectively, in composite samples of green leaves from 62 plant species in the Los Angeles area; corresponding values for dried leaf samples were 0.47, 1.l, and 1.9 µg/g (Rogge et al. 1993d). Edwards (1983) reported that washing removed a maximum of 25% of PAHs on the leaves of plants.

PAHs have been found in the tissues of aquatic organisms. In an assessment of STORET data covering the period 1980-1982, Staples et al. (1985) reported median concentrations in biota of <2.0 mg/kg (ppm) wet weight for 8 PAHs (acenaphthene, acenaphthylene, benz[a]anthracene, benzo[a]pyrene, chrysene, fluoranthene, fluorene, and pyrene) and <2.5 mg/kg wet weight for seven PAHs (anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, indenopyrene, naphthalene, and phenanthrene). The number of samples ranged from 83 (naphthalene) to 140 (acenaphthylene); only benzo[g,h,i]perylene (1 sample, 0.8%) and indenopyrene (1 sample, 0.8%) were found in detectable concentrations.

In summary of data on tissue contamination in mussels and oysters from the first 3 years (1986-1988) of the National Oceanic and Atmospheric Administration (NOAA) Mussel Watch Project, which involved the analysis of samples from 177 coastal and estuarine U.S. sites, overall mean concentrations of low molecular weight PAHs ranged from not detected (detection limits 3.3-67 ng/g dry weight) to 4,200 ng/g dry weight (NOAA 1989). Mean concentrations of low molecular weight PAHs for individual years 1986, 1987, and 1988 ranged up to 9,600, 3,200, and 4,300 ng/g dry weight, respectively. Overall mean concentrations of high molecular weight PAHs ranged from not detected (detection limits 3.9-47 ng/g dry weight) to 11,000 ng/g dry weight. Mean concentrations of high

molecular weight PAHs for 1986, 1987, and 1988 ranged up to 15,000, 10,000, and 11,000 ng/g dry weight, respectively. States with sites ranked among the highest five for concentrations of low molecular weight PAHs in 1986, 1987, 1988, and overall in 1986-1988, were California, Florida, Hawaii, Massachusetts, Mississippi, New York, Oregon, and Washington; for high molecular weight PAHs these states were California, Florida, Hawaii, Massachusetts, New York, and Washington. No consistent trends over the 1986-88 period were observed in the data; significant increases and decreases in concentrations of low and high molecular weight PAHs were observed with almost equal frequency. Low molecular weight PAH concentrations showed significant increasing trends at a single site each in New York, New Jersey, Florida, Texas, California, and Oregon; significant decreasing trends were observed at a single site each in Massachusetts, Maryland, and Mississippi, and at two sites in Texas. High molecular weight PAH concentrations showed significant increasing trends at a single site each in New York and Washington, and at two sites in Florida; significant decreasing trends were observed at a single site each in Connecticut, Maryland, and Florida.

Concentrations of phenanthrene and total PAHs ranged from 2 to 296 and 63 to 2,328 µg/kg (ng/g) wet weight, respectively, in caged mussels *(Elliptio complanata)* after 3 weeks' exposure at various locations in St. Mary's River, which is heavily contaminated from industrial and municipal discharges in the Sault Ste. Marie, Ontario, area (Kauss 1991). PAH concentrations ranging from approximately 50 ng/g wet weight for acenaphthylene to 4,660 nglg wet weight for fluoranthene were found in the digestive glands of the American lobster *(Homerus americancus)* collected in the proximity of a coal-coking plant that had been closed for a decade (King et al. 1993). Benzo[a]pyrene concentration was reported to be 720 nglg wet weight.

In a study to evaluate the concentrations of PAHs in various fish and shellfish species from Prince William Sound, Alaska, following the 1989 Exxon Valdez spill of more than 10 million gallons of crude oil, PAHs were not detected in 18% (72/402) of the samples; trace levels were found in 78% (312/402) of the samples; and individual PAH concentrations ranging from 5 to 12 µg/kg (wet or dry weight not specified) were found in 4% (18/402) of the samples. There was no apparent difference between PAH concentrations in salmon collected from impacted areas and those collected from control areas; however, there was a suggestion that contamination may be increasing with time. No PAHs were detected in 14% (31/221) of samples collected in 1989, trace levels were found in 85% of these samples, and only 1% (3 samples) had individual PAH concentration >5 µg/kg; whereas in the 1990

samples, PAHs were detected in all of the 41 samples, trace levels were found in 87% of the samples, and 13% (6 samples) had individual PAH concentrations >5 µg/kg.

PAHs are present at 1–2 weight percent in crude oils (Guerin 1978). Actual PAH concentrations in crude oil depend on the geological source of the oil (IARC 1989). For example, the NRC (1985) has reported concentrations of seven individual carcinogenic PAHs ranging from 1.2 µg/g for benzo[a]pyrene to 23 µg/g for chrysene in a South Louisiana crude oil and from 0.5 µg/g for benzo[e]pyrene to 6.9 µg/g for chrysene in a Kuwaiti crude oil. PAHs are also found in refined petroleum products including gasoline, kerosene, diesel fuel, some heating oils, and motor oil (Guerin 1978).

PAHs have also been detected in used motor oils. The following concentrations of benzo[a]pyrene and benz[a]anthracene measured in 1,071 samples of used motor oils were reported by Franklin Associates (1984):

Positive	Samples(%)	Mean (mg/kg)	Median (mg/kg)	Range (mg/kg)
Benzo[a]pyrene	58	24.5	10	<1–405
Benz[a]anthracene	74	71.3	12	<5–660

The levels, either in concentration or percent weight, in which several PAHs appear in various other substances are given below. A coal tar sample has been found to contain approximately 0.007 mg/kg benz[a]anthracene, 3 mg/kg benzo[b]fluoranthene, 4 g/kg chrysene, and 30 mg/kg benzo[a]pyrene (Perwak et al. 1982). High-temperature coal tar contains 1,000 mg/kg dibenz[a,h]anthracene (IARC 1985). A sample of coal tar pitch was found to contain <10 mg/kg benz[a]anthracene, <10 mg/kg chrysene, and approximately 10 mg/kg benzo[a]pyrene; creosote oil contains <3 mg/kg benz[a]anthracene, <1 mg/kg chrysene, and <10 mg/kg benzo[a]pyrene (Perwak et al. 1982). Creosote has been reported to contain 21% phenanthrene, 10% fluorene, 10% fluoranthene, 9% acenaphthene, 8.5% pyrene, 3% chrysene, 3% naphthalene, and 2% anthracene (Lorenz and Gjovik 1972).

PAHs have also been reported to occur in chewing tobacco, snuff, and in mainstream and sidestream tobacco smoke. Reported concentrations of some PAHs in various types of tobacco smoke are shown in Table 5-5 (IARC 1983). These data show concentrations of benzo[a]pyrene in cigarette mainstream smoke ranging between 5 and 78 ng/cigarette (IARC 1983). Other studies indicate that concentrations of carcinogenic PAHs in mainstream smoke from unfiltered cigarettes may range from 0.1 to 0.25 µg

per cigarette (Hoffmann and Hecht 1990). Concentrations of PAHs in sidestream smoke are significantly higher than in mainstream smoke with sidestreammainstream concentration ratios for benzo[a]pyrene ranging from 2.5 to 20 (Adams et al. 1987; Evans et al. 1993; Grimmer et al. 1987; Hoffmann and Hoffmann 1993; IARC 1983). Benzo[a]pyrene concentrations of 0.42-63 ppb (ng/g) have been reported in snuff (Brunnemann et al. 1986).

PAH concentrations in a variety of other media have been evaluated. PAH concentrations in fly ash and bottom ash samples from domestic municipal incinerators ranged from not detected to 7,400 µg/kg, with phenanthrene the most abundant and frequently detected compound (Shane et al. 1990). Machado et al. (1993) reported the total concentrations of 16 PAHs (all PAHs in this profile except benzo[e]pyrene) in asphalt and coal tar pitch to be 50, 122 and 294, 300 ppm µg/g), respectively; benzo[a]pyrene concentrations were <6 and 18,100 ppm, respectively. The concentrations of benzo[a]pyrene (250-480 ppm) and several other PAHs in coal tar fumes were higher than those in asphalt fumes by two to three orders of magnitude. The PAH content of asphalt and coal tar pitch fumes increased with increasing generation temperature.

Tire wear particles, brake lining particles, and paved road dust from a residential area had total PAH concentrations of 226.1, 16.2, and 58.7 µg/g, with maximum concentrations of individual PAHs of 54.1 µg/g (pyrene), 2.6 µg/g (benzo[g,h,i]perylene), and 9.4 µg/g (pyrene), respectively (Rogge et al. 1993c). Benzo[a]pyrene concentrations in these media were 3.9, 0.74, and 2.3 µg/g, respectively. Combined particle- and vapor-phase emissions from scrap tire fires have been reported to contain average total PAH concentrations of 3.2 mg/m^3, with average benzo[a]pyrene concentrations ranging from 0.07 to 0.08 mg/m^3 (Lemieux and Ryan 1993). Tire pyrolysis oil, which may be used as a fuel, contains high levels of PAHs, with average total PAH concentrations ranging from 14,540 ppm (µg/g) to over 100,000 ppm (10%); benzo[a]pyrene concentrations ranged from <10 to 600 ppm (Williams and Taylor 1993).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The greatest sources of exposure to PAHs for most of the U.S. population are active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and ingestion of these compounds in foodstuffs. Smoking one pack of cigarettes a day has been estimated to result in exposure to carcinogenic PAHs of up to 5 µg/day (Menzie et al. 1992) and in exposure to

TABLE 5-6. Average Indoor Concentrations (μg/m^3) of Polycyclic Aromatic Hydrocarbons (PAHs) in Different Categories of Sample Homes Occupied by Smokers and Non-smokers[a]

	E/E		Home-type G/E		G/G		
Compound	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Outdoor Air
Acenaphthylene	18	11	71	15	33	17	4.2
Anthracene	3.5	1.8	8.3	3.4	8.9	2.2	0.96
Benz[a]anthracene	0.32	0.25	1.7	0.34	1.1	0.55	0.42
Benzo[a]pyrene	0.37	0.30	1.7	0.27	0.96	0.58	0.23
Benzo[e]pyrene	1.4	0.67	5.5	0.52	2.4	1.0	0.46
Benzofluoranthenes	0.79	0.68	1.1	0.97	2.0	2.0	1.1
Benzo[g,h,i]perylene	0.53	0.44	1.4	0.59	1.2	0.75	0.50
Chrysene	0.91	0.76	3.6	0.81	2.3	1.6	1.1
Fluorothene	7.2	7.7	13	7.5	13	16	5.6
Indeno[1,2,3-c,d]pyrene	0.35	0.28	1.1	0.40	0.84	0.64	0.35
Phenanthrene	79	57	130	63	130	110	31
Pyrene	4.3	4.6	11	4.8	5.0	9.3	4.4

[a]Adapted from Chuang et al. (1991)
[b]E/E denotes electric heating and cooking systems; G/E denotes gas heating and electric cooking systems; G/G denotes gas heating and cooking systems

benzo[a]pyrene of 0.4 μg/day (Santodonato et al. 1981). Other potential routes of human exposure are ingestion of contaminated drinking water and food products, and skin contact with soot and tars. PAHs are ubiquitous in the environment, resulting from the incomplete combustion of organic materials, whether natural (forest fires or volcanoes) or synthetic (combustion of fuels for heating and transportation). The amount of PAHs found in food products depends as much on the method of preparation (especially grilling or smoking) as on the origin of the food. Disinfection of public water supplies with chlorine can result in the presence of chlorinated and oxygen substituted PAHs (Shiraishi et al. 1985). Coal tar preparations have been used in the clinical treatment of skin disorders. Contamination of the ambient air can be derived from industrial and construction sources. Eldridge et al. (1983) measured substantial levels of PAHs emitted from freshly laid petroleum road asphalt.

Estimates of general population exposure to total PAHs (μg/day) and carcinogenic PAHs in comparison to readily measured benzo[a]pyrene concentrations were presented by Santodonato et al. (1981), as follows:

Source	Benzo[a]pyrene	Select Carcinogenic PAHs[a]	Total PAHs
Air	0.0095–0.0435	0.038	0.207
Water	0.0011	0.0042	0.027
Food	0.16–1.6	–	1.6–16

[a]Total of benzo[a]pyrene, benzo[j]fluoranthene, and indeno[1,2,3-c,d]pyrene.

The most noteworthy of these estimates are the relatively high exposures from ingestion of contaminate food; however, it was noted that because of the lack of reliable monitoring data for PAHs in food, the uncertainty of the food estimates was greater than the uncertainty of the estimates for air or water. Nevertheless, the authors concluded that estimates from all three exposure sources were probably accurate within one order of magnitude, so that food was predominant among the sources of exposure.

More recent estimates of the potential exposures of American adult males to carcinogenic PAHs were provided by Menzie et al. (1992). The estimates provided by these investigators do not include potential exposures experienced in occupational settings or those resulting from use of consumer products (e.g., cosmetics or asphaltic materials added to roofs or driveways). From the average American diet, the intake of carcinogenic PAHs was estimated to be 1–5 μg/day, mostly from

ingestion of unprocessed grains and cooked meats. This dietary intake estimate was increased to 6-9 µg/day for individuals consuming diets with a large meat content as a result of the additional contribution from charcoal-cooked or smoked meats and fish. Exposure via inhalation of ambient air was estimated to be 0.16 µg/day (median), with a range of 0.02-3 µg/day, assuming an inhalation rate of 20 m^3/day. Smoking one pack of unfiltered cigarettes per day increases this estimate by an additional 2-5 µg/day; chain smokers consuming three packs per day increase their exposure by an estimated 6-15 µg/day. Exposure to carcinogenic PAHs for the typical adult male from ingestion of drinking water and incidental ingestion of soil is minor compared to other potential routes of exposure. Drinking water exposure was estimated to be 0.006 µg/day (median), with a range of 0.0002-0.12 µg/day, assuming a consumption rate of 2 L/day. Assuming incidental ingestion of 50 mg soil/day, which may be more typical for small children than for most adults, the estimated median soil intake of carcinogenic PAHs was 0.06 µg/day (range, 0.003-0.3 µg/day). Therefore, the total potential exposure of carcinogenic PAHs for adult males was estimated to be 3 µg/day (median), with a maximum value of 15 µg/day. Smokers of nonfiltered cigarettes may experience exposures twice as high as these estimates. Ingestion of food appears to be the main source of exposure to PAHs for nonsmokers, although inhalation of ambient air is also an important route.

In a Dutch market-basket survey conducted from 1984 to 1986, the mean daily dietary intake of PAHs by 18-year-old males in composites of 221 different foods from 23 commodity groups was estimated to range from 5 to 17 µg/day. The most frequently detected PAHs were benzo[b]fluoranthene (59% of samples), fluoranthene (48%), and benzo[k]fluoranthene (46%). The largest contribution of PAHs to the total diet came from the sugar and sweets, cereal products, and oils, fats, and nuts commodity groups (de Vos et al. 1990).

Consumption of Great Lakes fish is not expected to contribute significantly to dietary intake unless the fish are smoked (Environment Canada 1991). The estimated exposure from consuming 114 g fish containing 50 ppt (ng/g) benzo[a]pyrene once a week would be 5.7 ng/person/week, or 11.6 pg/kg of body weight per day for a 70-kg individual. However, in some areas of the United States, fish consumption advisories have been issued based on elevated concentrations of PAHs found in locally caught fish or shell fish (see Section 5.6) (RTI 1993).

The average intake of benzo[g,h,i]perylene by adults from drinking water sources has been estimated to be 2 ng/day (assuming a drinking water ingestion rate of 2 L/day), inhalation exposure to the

compound has been estimated to be 10 ng/day (assuming an air intake rate of 20 m^3/day) (EPA 1989a).

Indoor air can be an important source of human exposure to PAHs. Potential indoor combustion sources of PAHs include tobacco smoke, unvented space heaters, and food preparation (Lioy and Greenberg et al. 1990). PAHs are among the major carcinogenic agents in environmental tobacco smoke (ETS), which is comprised primarily of diluted sidestream smoke, with a much smaller contribution from exhaled mainstream smoke (Hoffmann and Hoffmann 1993). Exposure to ETS is of particular concern because it has recently been declared a human lung carcinogen by the U.S. EPA. Concentrations of some PAHs in cigarette smoke-polluted environments are listed in Table 5-5. Chuang et al. (1991) monitored the concentrations of PAHs in the indoor and outdoor air of eight homes in Columbus, Ohio, in the winter of 1986-87 and obtained the indoor air results shown in Table 5-6.

Environmental tobacco smoke was the most significant influence on indoor air PAH levels; homes occupied by smokers had higher average concentrations of most PAHs than homes occupied by nonsmokers. In homes occupied by nonsmokers, the.highest average concentrations of most PAHs were found in homes that had gas cooking and heating appliances, followed by homes with gas heating and electric cooking appliances. Homes equipped with electric cooking and heating had the lowest average concentrations of most PAHs.

The Total Human Environmental Exposure Study (THEES), a multimedia study of human exposure to benzo[a]pyrene, was conducted in a rural town, Phillipsburg, New Jersey, where the major industry was a grey-iron pipe manufacturing plant that contributed to high levels of benzo[a]pyrene in the ambient atmosphere (Butler et al. 1993; Lioy 1990; Lioy et al. 1988; Waldeman et al. 1991). Benzo[a]pyrene concentrations in respirable particulate personal samples from 10 homes in areas near the foundry were measured in the range of 0.1 to 8.1 ng/m^3, depending on personal habits (whether the windows were kept open, how frequently the doors were opened, cooking methods, hobbies, whether home improvements were being made) and sources of home heating. The mean outdoor air concentration of benzo[a]pyrene was 0.9 ng/m^3. In samples of food collected from family meals over a 2-week period, the concentration level of benzo[a]pyrene ranged from 0.004 to 1.2 ng/g (wet weight)., No detectable amounts of benzo[a]pyrene were observed in the drinking water supply (detection limit, 0.1 ng/L). In comparing the inhalation and ingestion pathways in each home, Lioy et

TABLE 5-5. Concentrations of Some Polycyclic Aromatic Hydrocarbons (PAHs) in Tobacco Smoke[a]

Compound	Cigarette main stream smoke (µg/100 cigarettes)	Cigarette side stream smoke (µg/100 cigarettes)	Cigarette smoke-polluted environments (µg/m^3)	Cigar smoke (µg/100 g)	Pipe smoke (µg/100 g)
Anthracene	2.3–23.5			11.9	110.0
Benz(*a*)anthracene	0.4–7.6	4–20	0.1–100	2.5–3.9	
Benzo(*b*)fluoranthene	0.4–2.2		0.1–35[b]		
Benzo(*j*)fluoranthene	0.6–2.1				
Benzo(*k*)fluoranthene	0.6–1.2				
Benzo(*g,h,i*)fluoranthene	0.1–0.4				
Benzo(*g,h,i*)perylene	0.3–3.9	9.8	0.4–17		
Benzo(*a*)pyrene	0.5–7.8	2.5–19.9	0.4–760	1.8–5.1	8.5
Benzo(*e*)pyrene	0.2–2.5	13.5	0.4–18		
Chrysene	0.6–9.6		2.6–16		
Dibenz(*a,h*)anthracene	0.4		<0.1–13		
Fluoranthene	1–27.2	126	0.2–99	20.1	
Fluorene	present				
Indeno(1,2,3-*c,d*)pyrene	0.4–2.0		0.6–1		
Phenanthrene	8.5–62.4		4–87	115	
Pyrene	5–27	39–101	0.8–66	17.6	75.5

[a]Adapted from a tabulation of data from several studies in IARC (1983) and Guerin et al. (1992)
[b]Benzofluoranthenes

al. (1988) found that potential intake could be similar in each medium. Of the 20 weeks of exposure (10 homes over a 2-week exposure period), 10 had higher food benzo[a]pyrene exposures and 10 had higher inhalation benzo[a]pyrene exposures. The range of estimated food exposures (l0-4,005 ng/week) was much greater than the range of estimated air exposures (78-385 ng/week). The dominance of one pathway or the other seemed to depend on indoor combustion sources (e.g., cigarette smoke or coal-burning stoves) and personal eating habits. For smokers, inhalation of tobacco smoke was the main source of benzo[a]pyrene exposure; intake from this source was much higher than inhalation of ambient and indoor air or ingestion of food. Smokers also had higher exposure through food intake than nonsmokers. For the average nonsmoker, ingestion of food was the most important route of exposure (Lioy 1990).

Occupational exposures to PAHs can result from processes such as petroleum refining, metalworking, the production of coke, the manufacture of anodes, and the production of aluminum. In reviewing the available data on occupational exposures, it is important to understand that it cannot be implied that the results of a study at one industrial site would be valid for another site or for the same site at another time.

Occupational exposures to PAHs are possible in all operations involved in extraction and processing of crude oil, including drilling, pumping and treating, transport, storage, and refinement (Suess et al. 1985). The main route of exposure is inhalation, although there is also potential for significant dermal exposure (IARC 1989). Workers in petroleum refineries are exposed to PAHs from a variety of sources, including atmospheric distillation, catalytic cracking, residual fuel oil, lubricant oil processing, bitumen processing and loading, coking, and waste-water treatment (IARC 1989). In a study of nine US refineries, total PAH concentrations of 10 $\mu g/m^3$ were reported in personal samples taken in the fluid catalytic cracking and delayed coker units (Futagaki 1983). Total PAH concentrations ranging from approximately 1 to 40 $\mu g/m^3$ were observed in area samples from bitumen processing units. Total PAH concentrations in personal samples from the de-asphalting unit in one refinery were found to range from 2.5 to 49.8 $\mu g/m^3$. At least 85% of the total PAH in these samples was comprised of two-ring compounds (i.e., naphthalene and its derivatives) and 94% of two- or three-ring compounds. PAHs with five or more rings were found to contribute from <0.1% at the catalytic cracker unit to 2.5% at the delayed coker unit. The highest combined concentration of benzo[a]pyrene and benzo[e]pyrene was 9.3 $\mu g/g^3$ in a personal sample from a coker cutter; however, these two PAHs were not detected in most samples (detection limit, 0.01 µg/m3). Exposures to four- to six-ring PAHs

of <0.1 μg/m^3 have been associated with loading road tankers with bitumen in refineries (Brandt and Molyneux 1985). In an evaluation of turn-around operations on reaction and fractionator towers, concentrations of anthracene, benzo[a]pyrene, chrysene, and pyrene in personal samples were either too low to be detected or ≤1 μg/m^3; naphthalene and its methyl derivatives accounted for >99% of the total PAH measured in personal samples (Dynamac Corp. 1985). Area samples taken at various sites during shut-down, leak testing and start-up operations after turn-arounds showed the same distribution pattern of individual PAHs with total PAH concentrations generally ≤100 μg/m^3 (maximum 400 μg/m^3).

Metalworkers may also be exposed to PAHs from refined mineral oils used in machining operations, with the level of exposure depending on the type of oil refinement procedure used (IARC 1984). Acid refined mineral oils have a significant PAH content and have been shown to cause skin cancer in workers exposed to them (Jarvholm and Easton, 1990). Solvent refining procedures almost completely remove PAHs from mineral oils and, therefore, should almost completely eliminate the risks of exposure to carcinogenic PAHs (Bingham et al. 1965; Doak et al. 1983; IARC 1984). There is evidence, however, that the concentration of carcinogenic PAHs in solvent-refined cutting oils may increase during use, particularly during operations such as quenching where the oil is severely heated (Agarwal et al. 1986; Apostoli et al. 1993; IARC 1984; La Fontaine 1978; Thony et al. 1976). Total PAH concentrations in air samples from work areas related to the use of cutting, hardening, and extruding oilshave been reported to be 66, 90, and 106 ng/m^3, respectively (Apostoli et al. 1993).

In a summary of data on industrial exposures in IARC (1984), concentrations of airborne benzo[a]pyrene in aluminum production facilities from 1959 to 1982 in several countries ranged from not detected to 975 μg/m^3; concentrations in a U.S. aluminum reduction plant ranged from 0.03 to 53.0 μg/m^3, depending on the work site. Concentrations of airborne benzo[a]pyrene in coke oven operations ranged from 0 to 383 μg/m^3 depending on the work area; average concentrations in a U.S. plant were reported to range from 0.15 to 6.72 μg/m^3. More recently, inhalation exposures to phenanthrene, pyrene, and benzo[a]pyrene of 485, 108, and 48 μg/8 hours, respectively, have been reported for workers in a German coke plant (Grimmer et al. 1994). However, Van Rooij et al. (1993b) has recently concluded that among coke oven workers dermal absorption is a major route of exposure to PAHs, accounting for an average of 75% and 51% of total absorbed pyrene and benzo[a]pyrene, respectively; the mean dermal and respiratory uptakes of pyrene in 12 workers were reported to range from 4 to 34 and 0.5 to 32 μg/day, respectively.

The use of coal tar, pitch, asphalt, creosote, soot, and anthracene oil is widespread in the manufacture of fuel, dyes, plastics, paints, insulating materials, impregnating materials, building materials, road-building materials, embedding material, rubber, inks, and brushes (Hueper 1949). Faulds et al. (1981) faund that PAHs in diesel engine exhaust attach to respirable dust particles and travel long distances in underground mines, resulting in exposure of mine workers far removed from engine sites. Mechanics may also be exposed to PAHs resulting from the pyrolytic decomposition of the organic fractions of abraded particles from clutch and brake linings (Knecht et al. 1987). Potential exposure to PAHs in road sealing work involving coal tar and bitumen was discussed by Darby et al. (1986). In a study to evaluate inhalation and dermal exposures of 10 roofers removing an old coal tar pitch roof and applying a new asphalt roof, the PAH content of forehead skin wipes taken at the end of the workshift (0.097 µg/cm^2; equivalent to an estimated daily skin exposure of 19.4 µg/day) was found to correlate with the PAH concentrations in personal air samples (10.2 µg/m^3) (Wolff et al. 1989c). Relative concentrations of PAHs in air and wipe samples were: fluoranthene > pyrene > benz[a]anthracene > benzo[a]pyrene > benzo[b]fluoranthene > benzo[g,h,i]perylene > benzo[k]fluoranthene. Anthracene was found in the air samples but was not detected in the wipe samples.

Data on PAH exposures in the United States for many other occupations are limited. Most of the recent studies have been conducted in other countries. PAH concentrations (combined particle- and vapor-phase) in two work areas in a silicon carbide plant ranged from not detected (detection limit, 0.01 mg/m^3) for benzo[a]pyrene and benzo[e]pyrene, to 0.99 mg/m^3 for fluoranthene and 3.46 mg/m^3 for naphthalene (Dufresne et al. 1987). Higher ambient concentrations were observed in the furnace area, ranging from 0.04 mg/m^3 for benzo[a]pyrene and benzo[e]pyrene to 3.85 mg/m^3 for fluoranthene and 58.0 mg/m^3 for naphthalene. Total PAH concentrations in areas near cooking fume sources in the food and catering industries in Finland have been reported to range from 0.2 to 31.8 µg/m^3 (Vainiotalo and Matveinen 1993). Benzo[a]pyrene concentrations of <l-44 ng/m^3 in the breathing zone of urban bus drivers in France have been reported (Limasset et al. 1993). The mean particulate total PAH exposure level in a Swedish electrode paste plant was found to vary from 4.3 to 84.6 µg/m^3 over various work operations, with an overall mean particulate PAH exposure level in the plant of 14.4 µg/m^3 (Ovrebo et al. 1994). The mean PAH exposure level in a Belgian graphite electrode plant was reported to be 19.7 µg/m^3 (Van Hummelen et al. 1993). Drivers of large diesel-powered trucks in Switzerland were not found to have exposures to total PAHs or benzo[a]pyrene that were significantly different from controls (Guilleman et al. 1992).

Preliminary data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace from 1981 to 1983 (NIOSH 1990). Data for the seven PAHs included in the survey are summarized below:

Chemical	Number of industry/ occupation categories	Number of workers potentially exposed
Anthracene	5	2,303
Benz[a]anthracene	4	2,310
Benzo[a]pyrene	1	896
Chrysene	2	9,358
Fluoranthene	36	21,339
Fluorene	6	2,912
Pyrene	3	9,368

The NOES database does not contain information on the frequency, level, or duration of exposure of workers to any of the chemicals listed. It provides only estimates of workers potentially exposed to the chemicals.

PAHs have generally not been detected in surveys of human tissue, presumably because the compounds are fairly rapidly metabolized. Phenanthrene was the only PAH detected in the 1982 National Human Adipose Tissue Survey; it was found in trace concentrations in 13% of the samples (EPA 1986). Acenaphthylene, acenaphthene, fluorene, and chrysene were not found at levels below the detection limit (0.010 µg/g; 10 ppt). However, autopsies performed on cancer-free corpses found PAH levels of 11–2,700 ppt (ng/g) in fat samples (Obana et al. 1981). Several PAHs were detected, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, with pyrene being detected in the highest concentrations. A similar study done on livers from autopsied cancer-free corpses found levels of 6–500 ppt (ng/g) of all of the same PAHs except benzo[e]pyrene, which was not detected (Obana et al. 1981). As in the fat sample studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat.

Human exposure to PAHs can be monitored through analytical determination of PAHs and metabolites (e.g., 1-hydroxypyrene) in the urine of exposed individuals (Jongeneelen et al. 1985, 1987; Tolos et al. 1991; Weston et al. 1994). For example, Clonfero et al. (1990) detected increased levels of PAH metabolites in the urine of individuals occupationally (i.e., aluminum plant workers) and

therapeutically (i.e., psoriatic patients) exposed to coal tar, as compared to unexposed subjects. Weston et al. (1994) reported similar results for coal-tar treated psoriasis patients. Tolos et al. (1991) and Van Rooij et al. (1994) reported significant increases in the average 1-hydroxypyrene concentrations in the urine of smokers over nonsmokers. Significant increases in urinary 1-hydroxypyrene levels have also been observed in children living in areas of high density automobile traffic over those of children in suburban areas (Kanoh et al. 1993). Several researchers have reported substantial increases in the urinary concentrations of 1-Hydroxypyrene and other PAH metabolites among workers exposed to PAHs in a variety of occupational settings, including coke plants (Grimmer et al. 1994; Jongeneelen et al. 1990; Van Hummelen et al. 1993), graphite electrode plants (Van Hummelen et al. 1993), foundries (Santella et al. 1993), and creosote wood treatment plants (Viau et al. 1993) and during clean-up of dump sites contaminated with coal tars (Viau et al. 1993), handling of petroleum coke (Jongeneelen et al. 1989), and road surfacing operations (Jongeneelen et al. 1988). Most of these increases were statistically significant over controls. There is conflicting evidence regarding an exposure-response relationship between PAH exposures levels and urinary PAH metabolite concentrations. For example, Grimmer et al. (1994) reported a good correlation between PAH inhalation exposures and levels of urinary metabolites of benzo[a]pyrene, phenanthrene, and pyrene, whereas Jongeneelen et al. (1990) did not find a strong relationship between air monitoring data and urinary levels of 1-hydroxypyrene. In a study of PAH inhalation exposures of aluminum plant workers, Becher and Bjorseth (1983) found that the high concentrations in the occupational setting did not correspond to the measured concentrations of urinary PAH metabolites. The authors suggested that PAHs adsorbed to airborne particulate matter may not be bioavailable and that the exposure-uptake relationship may not be linear over the entire PAH concentration range. When urinary 1-hydroxypyrene excretion is used in the assessment of PAH exposure, the contributions of alternative routes of exposure (i.e., inhalation and dermal) and the variability in the baseline excretion among individual PAH metabolites due to tobacco smoking and dietary PAH intake should be taken into account (Van Rooij et al. 1993b, 1994). Assays for other biomarkers of PAH exposure are currently being developed in animal models (Singh and Weyard 1994), but have not been evaluated in humans.

The detection of PAH-DNA adducts in urine, blood and other tissues by immunoassay and ^{32}P-postlabelling has also been used as an indicator of exposure (Harris et al. 1985; Herikstad et al. 1993; Ovrebo et al. 1994; Perera et al. 1993; Santella et al. 1993).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to PAHs is expected to be highest among certain occupational groups (e.g., individuals working with coal tar and its products, foundry workers, miners, chimney sweeps), smokers and nonsmokers living or working in close proximity to smokers, members of the general population who heat their homes with wood-burning stoves, individuals living in the vicinity of emission sources or using products containing PAHs, and people living in the vicinity of NPL sites where PAHs have been detected above background levels. People who consume grilled or smoked food may ingest high levels of these compounds. Anyone who works extensively with products such as roofing materials, asphalt, and other PAH-containing substances may be exposed through inhalation or skin contact.

Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated waterbodies may be exposed to higher levels of PAHs associated with dietary intake (EPA 1993b). PAH contamination has triggered the issuance of several human health advisories. As of September 30, 1993, PAHs were identified as the causative pollutants in five fish consumption advisories in three different states. This information is summarized in Table 5-7 (RTI 1993). EPA is considering including PAHs as target analytes and has recommended that these chemicals be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. EPA recommends that residue data obtained from these monitoring programs be used by states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories for the protection of the general public as well as recreational and subsistence fishers (EPA 1993b).

5.7 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 PAHs is available. Where adequate information is not available, ATSDR, in conjunction with the 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 PAHs.

Table 5-7. Fish Consumption Advisories

State	Waterbody	Extent
Massachusetts	Hocomoco Pond	Entire pond
Michigan	Hersey River	Downstream from Reed City
Ohio	Black River	6.2 miles from the 31st Street Bridge (Loraine) to the harbor (includes confined disposed facility)
Ohio	Little Scioto River	3.9 miles from Holland Road (Marion) south to St. Rt. 739
Ohio	Mahoning River	29.24 miles from Northwest Bridge Street (Warren) to Pennsylvania border

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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties (K_{ow}, K_{oc}, vapor pressure, Henry's law constant, etc.) have been sufficiently characterized for most of the 17 PAHs and allow prediction of their environmental fate.

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 chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, .became available in May of 1994. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

PAHs are produced primarily as a result of combustion processes both from anthropogenic and natural sources (HSDB 1994; IARC 1982). Of the 17 PAH compounds discussed in this profile, only acenaphthene, acenaphthylene, and anthracene are produced commercially. However, several other PAH compounds were imported into the United States in 1984 and 1985 (see Section 4.2).

There is no known commercial use for most of the 17 PAHs discussed in this profile. Anthracene, acenaphthene, fluorene, and phenanthrene are chemical intermediates used in the manufacture of dyes, plastics, pesticides, explosives, and chemotherapeutic agents (Hawley 1987; HSDB 1992; Windholz 1983). Fluoranthene is used as a lining material to protect the interior of steel and ductile iron drinking water pipes and storage tanks (NRC 1983).

PAHs are most likely to be released directly in the atmosphere. Other contaminated media of relevance to human exposure include foods and drinking water.

Rules governing the disposal of PAHs have been promulgated by EPA. Although information regarding recommended remedial techniques is available for most of the 17 PAHs discussed in this profile (EPA 1980, 1981a; HSDB 1992; IARC 1985), additional information about the amounts of these compounds disposed of by these remediation methods would be helpful in determining important routes of human exposure.

Environmental Fate. The environmental fate of PAHs is well characterized. No further studies are needed. PAHs are transported in and partitioned to the air, water, and soil. Transformation and degradation processes of PAHs in the air, water, and soil have been well studied. Atmospheric halflives of PAHs are generally less than 30 days. Photochemical oxidation of a number of PAHs has been reported (EPA 1988a). The National Research Council (NRC 1983) noted that compounds adsorbed to soot are more resistant to photochemical reactions than pure compounds. In surface water, PAHs can volatilize, photodegrade, oxidize, biodegrade, bind to particulates, or accumulate in aquatic organisms (with bioconcentration factors often in the 100-2,000 range). Half-lives for volatilization of benz[a]anthracene and benzo[a]pyrene (high molecular weight PAHs) from water have been estimated to be greater than 100 hours (Southworth 1979), and the half-life for volatilization of anthracene (a low molecular weight PAH) was estimated to be 18 hours (Southworth et al. 1978). Hydrolysis is not considered to be an important degradation process for PAHs (Radding et al. 1976). The rate and extent of photodegradation varies widely among the PAHs (Neff 1979). PAHs in soil can biodegrade or accumulate in plants. Microbial metabolism is the major process for degradation of PAHs in soil environments. Photolysis, hydrolysis, and chemical oxidation are not considered important processes for the degradation of PAHs in soils (Sims and Overcash 1983).

Bioavailability from Environmental Media. Limited information is available regarding the bioavailability of PAHs from plants grown in contaminated soils. PAHs can be absorbed following inhalation, oral, or dermal exposure. All of these routes are of concern to humans because PAHs have been shown to contaminate the air, drinking water, soil, and food. There is a need to conduct additional studies on the bioavailability of PAHs from plants grown in contaminated soils and from contaminated soils. However, bioavailability of PAHs from contaminated air, water, and food is of primary concern, and some information is available concerning bioavailability following exposure by these routes. Indirect evidence indicates that PAHs are absorbed by humans following inhalation exposure (Becher and Bjorseth 1983). Furthermore, indirect evidence suggests that benzo[a]pyrene may be absorbed following oral exposure in humans. The concentration of benzo[a]pyrene in human

feces was studied after eight volunteers ingested broiled meat that contained approximately 9 µg of benzo[a]pyrene (Hecht et al. 1979). Less than 0.1 µg/person of benzo[a]pyrene was measured in the feces of these individuals, suggesting absorption and perhaps metabolism of the compound. More direct data are needed on the extent of bioavailability of PAHs, particularly those that are particlebound, following the three major routes of exposure.

Food Chain Bioaccumulation. PAHs can bioaccumulate in plants, aquatic organisms, and animals from intake of contaminated water, soil, and food. Extensive metabolism of the compounds by high-trophic-level consumers, including humans, has been demonstrated; therefore, food chain biomagnification of the compounds does not appear to be significant (Edwards 1983; Eisler 1983; Gile et al. 1982; Wild et al. 1992). However, in some areas of the United States, fish consumption advisories have been issued based on elevated concentrations of PAHs found in locally caught fish or shellfish (see Section 5.6) (RTI 1993). Additional information is needed on levels of PAHs in aquatic organisms that are of concern for human health.

Exposure Levels in Environmental Media. PAHs have been produced and used in large volumes in the environment, home, and industry and. are widely distributed in the environment. They have been detected in air, water, sediment, soil, and food. Although some studies of background levels in different media have been conducted, additional site-specific concentration data in the vicinity of hazardous waste sites are needed. Studies should focus particularly on ambient air, in order to estimate exposure of the general population through inhalation of contaminated air as well as ingestion of or dermal contact with contaminated water or soil. Levels of PAHs tend to be higher in urban air than in rural air (Greenberg et al. 1985; Pucknat 1981). One study reported benzo[a]pyrene air levels of 0.2-19.3 ng/m^3 for urban air and 0.1-0.2 ng/m^3 in rural air (Pucknat 1981). Higher levels of other PAHs have been measured in urban areas. Basu and Saxena (1978a) reported concentrations of selected PAHs in surface waters used as drinking water sources in four U.S. cities (Huntington, West Virginia; Buffalo, New York; and Pittsburgh and Philadelphia, Pennsylvania) as ranging from 4.7 ng/L in Buffalo to 600 ng/L in Pittsburgh. Data collected as part of the Nationwide Urban Runoff Program indicate concentrations of individual PAHs in the range of 300-10,000 ng/L, with the concentrations of most PAHs above 1,000 ng/L (Cole et al. 1984). Few data are available on the concentrations of PAHs in U.S. groundwater. Basu and Saxena (1978b) reported total PAH concentrations in groundwater from three sites in Illinois, Indiana, and Ohio to be in the range of 3-20 ng/L. Data summarized by Sorrel et al. (1980) indicate low levels of PAHs in finished drinking waters of the

United States. Reported maximum concentrations for total PAHs (based on measurement of 1.5 PAHs) in the drinking water of 10 cities ranged from 4 to 24 ng/L. PAHs have been detected in unprocessed cereal, potatoes , grain, flour, bread, vegetables, fruits, and refined fats and oils. The concentrations in uncooked foods largely depend on the source of the food. The amount of PAHs found in food products depends as much on the method of preparation (especially grilling, smoking, or pickling) as on the origin of the food.

Reliable monitoring data for the levels of PAHs in contaminated media at hazardous waste sites and associated background sites are needed so that the information obtained on levels of PAHs in the environment can be used in combination with the known body burden of PAHs to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. No data are available regarding the levels of PAHs in body tissues or fluids for populations living near hazardous waste sites. PAHs and their metabolites can be measured in the urine of exposed individuals. In workers exposed to PAHs, the PAH metabolite 1-hydroxypyrene has been detected in the urine at concentrations of 0-40 µg/g creatinine (Jongeneelen et al. 1985). No correlation was found between occupational exposure levels and urine levels, so it is not known whether-urine metabolites could be detected following exposure to low levels of PAHs (as might be expected to occur in individuals living in the vicinity of hazardous waste sites).

PAHs have generally not been detected in surveys of human tissue, presumably because the compounds are fairly rapidly metabolized. Phenanthrene was the only PAH detected in the 1982 National Human Adipose Tissue Survey; it was found in trace concentrations in 13% of the samples (EPA 1986). Acenaphthylene, acenaphthene, fluorene, and chrysene were not found at levels below the detection limit (0.010 µg/g; 10 ppt). However, autopsies performed on cancer-free corpses found PAH levels of 11-2,700 ppt (ng/g) in fat samples (Obana et al. 1981). Several PAHs were detected, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, with pyrene being detected in the highest concentrations. A similar study done on livers from cancer-free patients found levels of 6-500 ppt of all of the same PAHs except benzo[e]pyrene, which was not detected (Obana et al. 1981). As in the fat sample studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat.

A few exposure estimates for the general population have been made from inhalation of ambient air and ingestion of contaminated drinking water and food, but sparse monitoring data limit the reliability of these estimates. Relatively recent estimates of the size of the workforce exposed to a few of the PAHs (such as benzo[a]pyrene) are available from NIOSH. However, monitoring data on workplace exposure levels are generally inadequate, partially because of the complexity of air emissions in terms of number of compounds detected. Information on exposure levels in humans is needed to better define exposure estimates in the general population and workforce, and to examine the relationship between levels of PAHs in the environment, human tissue levels, and the subsequent development of health effects. These data should be collected simultaneously with data on levels of PAHs air, water, and soil. For a sound database to serve as a foundation for higher level environmental or toxicological research, it should contain information on human exposure levels to PAHs, particularly for individuals living near hazardous waste sites.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for PAHs were located. These substances are not currently compounds for which a subregistry has been established in the National Exposure Registry. The substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

The National Institute of Environmental Health Sciences is funding research at Miami University, Oxford, Ohio, to evaluate the transfer of benzo[a]pyrene from sediments directly to a sediment-feeding fish. Specific objectives are to (1) to examine the effects of seasonal parameters (i.e., temperature, body lipids, gonadal development) on the rate and pattern of metabolism of benzo[a]pyrene in a range of size, age, and sexual maturity classes; and (2) evaluate the relative importance of sediment and water as vectors of uptake of benzo[a]pyrene.

The National Institute of Environmental Health Sciences is funding research at the State University of New York at Albany to determine the aquatic bioavailability of PAHs from sediments collected near

discharge points from two aluminum manufacturing plants in the Massena area of the St. Lawrence River. The results of this study should provide a better understanding of the relative contributions of individual industries to pollution of fish and wildlife consumed by area residents.

The National Institute of Environmental Health Sciences is funding research at the State University of New York at Albany to conduct an epidemiologic study of Mohawk women and infants to test the hypotheses that exposure to PAHs, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-pdioxins and dibenzofurans (PCDD/Fs) from a nearby Superfund hazardous waste site elevates body burdens and affects the cytochrome P-450-dependent mixed function monooxygenase system. Determination of 15 PAHs in breast milk will be among the analyses included in this study. The results of the study should enhance our understanding of how these important classes of chemicals arising from hazardous waste bioaccumulate in human adults and infants and whether P-450IA2 induction is a sensitive biomarker of their early biologic effect.

The National Institute of Environmental Health Sciences is funding research at Johns Hopkins University to investigate the molecular dosimetry of ingested PAHs from cooked meats in humans, and identify susceptibility factors that modulate the formation of DNA and protein adducts with these dietary carcinogens. Ultimately, molecular biomonitoring may allow quantitation of biological dose from ingested PAHs, thus accounting for variation in exposure, cooking processes, and metabolism.

The National Institute of Environmental Health Sciences is funding the Massachusetts Institute of Technology to continue studies with fluoranthene by using a modification of a ^{32}P-postlabelling assay to detect and quantify DNA adducts in mice and human lymphoblast cell lines from eventual application as a dosimeter to monitor DNA damage in tissues from occupationally or environmentally exposed human populations.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring PAHs, its metabolites, and other biomarkers of exposure and effect to PAHs. 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.

6.1 BIOLOGICAL SAMPLES

Several analytical techniques have been used to determine trace levels of PAHs in biological tissues and fluids including adipose tissue, lungs, liver, skin, hair, blood, urine, and feces (Table 6-l). These include gas chromatography coupled with flame ionization detection (GC/FID), gas chromatography coupled with a mass spectrometry (GC/MS), high-performance liquid chromatography (HPLC) coupled with an ultraviolet (UV) or fluorescence detector, and thin-layer chromatography (TLC) with fluorescence detection.

Recently, Liao et al. (1988) developed a relatively simple and rapid procedure for purifying human and bovine adipose tissue extracts so that trace levels of complex mixture of target analytes (including PAHs) could be detected and quantified by capillary GC/MS. By employing an activated Florisil column, Liao and co-workers showed that lipid contaminants bind effectively (more than 99.75%) with Florisil, thereby producing a relatively clean sample extract. A detection limit at a low ng/g level and an average sample recovery of 85% were achieved (Gay et al. 1980; Liao et al. 1988; Modica et al. 1982).

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biological tissues (adipose)	Homogenization in 8% benzene in hexane; clean-up on Florisil column	GC/MS	5–50 ng/g	52–95	Liao et al. 1988
	Extraction into pentane; clean-up on Florisil and silica column	GC/MS	0.05 ng/sample	27–100	Gay et al. 1980
	Extraction into cyclohexane; clean-up on alumina column; concentration	GC/FID	50 ng/sample	83–95	Modica et al. 1982
Lungs	Homogenization in hexane; extraction with 25% DMSO in water (discarding aqueous phase); washing with water; concentration	SF	No data	95	Mitchell 1979
	Extraction into cyclohexane; centrifugation; dry with Na_2SO_4; concentration; analysis in acetonitrile	HPLC/UV	20 ng/g	93.7 (fluoranthene); 65.3 (pyrene); 65 (benzo[a]-anthracene)	Brandys et al. 1989

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Lungs (cont.)	Tissue digestion; extraction and precipitation of DNA with spermine; hydrolysis of DNA in 0.1 M HCl	HPLC/radioisotope counting	13.3–32.7x10^{-15} mol BPDE bound/mg DNA	No data	Weyand and Bevan 1987a
	Tissue digestion; extraction of DNA; isolation of BPDE-DNA adducts (immunoaffinity chromatography); hydrolysis to tetrahydrotetrols	HPLC/fluorescence detector	6 pg B[a]P-tetrol/mL	26–66	Weston and Bowman 1991
Human lymphocytes	Isolation and hydrolysis of DNA to tetrahydrotetral; oxidization to dicarboxylic acid with potassium superoxide; derivatization and clean up on silica	GC/NIEC-MS (BaP adduct)	5 adduct/10^{7} nucleotide	47	Allan et al. 1993
Liver	Homogenization with DMSO; incubation with S-9 mixture at 37 °C; extraction with ethyl acetate; concentration; analysis for metabolites of indeno[1,2,3-c,d]pyrene	HPLC/UV-VIS	No data	No data	Rice et al. 1985b

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver (cont.)	Homogenization with DMSO; incubation with S-9 mixture at 37 °C; extraction with ethyl acetate; concentration and analysis for metabolites of indeno[1,2,3-c,d]pyrene and benzo[b]fluoranthene	HPLC/UV-VIS	No data	No data	Amin et al. 1982
	Homogenization; saponification; extraction into hexane; clean-up on silica or alumina column	HPLC/fluorescence detector	0.006–0.46 ng/g range	No data	Obana et al. 1981
Skin	Digestion and deproteinization of PAH-treated skin tissue; extraction and precipitation of DNA; hydrolysis with 1.2 M HCl	HPLC/fluorescence detector	10^{-15} mol BPDE/sample	No data	Shugart et al. 1983
	Modification of PAH-treated skin DNA *in vitro*; labelling of PAH-DNA adduct by ^{32}P-postlabeling technique	TLC/ autoradiography	90–1,210x10^{-15} mol PAH adduct/ mg DNA	No data	Phillips et al. 1987

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish bile	Hydrolysis of the conjugated PAH metabolite; extraction of the free metabolite into n-hexane; concentration and methylation with methyl iodide; extraction of methylated product	LESS (3-hydroxy-BaP)	0.005 ng/mL	No data	Ariese et al. 1993b
Blood	Hydrolysis of BPDE-DNA adduct with 0.1 M HCl; analysis of hydrolysis products (benzo[a]pyrene-tetrols and triols)	SLS	No data	No data	Haugen et al. 1986
	Extraction into cyclohexane; centrifugation; drying with Na_2SO_4; concentration; analysis in acetonitrile solution	HPLC/UV	20 ng/mL	107 (fluoranthene); 108.6 (pyrene); 101 (benzo[a]-anthracene)	Brandys et al. 1989

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (cont.)	Treatment with 2% horse serum; incubation with rabbit anti-BPDE-DNA antiserum; incubation with alkaline phosphatase-conjugated goat anti-rabbit IgG, PNPP, radiolabeled PNPP, and $MgCl_2$; separation of hydrolyzed radiolabeled PNPP; measurement of radioactivity	USERIA	$0.38–2.2x10^{-15}$ mol/μg DNA	No data	Haugen et al. 1986
	Incubation of equal volumes rabbit anti-serum and sample; wash; incubation with reconstituted biotinylated anti-rabbit IgG; wash; incubation with buffered europium-labeled streptovidin; shaking with enhancement solution at room temperature	Time-related fluorometry (PAH-DNA adduct)	<1 adduct/10^8 nucleotides	No data	Schoket et al. 1993
Blood	Incubation of BPDE-DNA adduct sample with goat antihuman IgG reagent, horseradish peroxidase and substrate solution	ELISA	$0.38–2.2x10^{-15}$ mol BPDE/μg DNA	No data	Haugen et al. 1986

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (cont.)	Separation and isolation of white blood cell DNA by standard RNase and phenol treatment	ELISA	$1x10^{-15}$ mol BPDE/0.001 mg DNA	No data	Perera et al. 1988
			$2–120x10^{-15}$ BPDE/50 µg DNA	No data	Shamsuddin et al. 1985
	Separation of hemoglobin (hb) by lysis and centrifugation; isolation of BPDE-hb adduct by acid hydrolysis; clean-up on Sep-Pak and cellulose column	HPLC/fluorescence detector	$5x10^{-12}$ g BPDE/sample	No data	Shugart 1986
	Isolation of PAH-DNA adduct from white blood cells; digestion of adduct with [gamma ^{32}P] ATP; resolution and quantitation of the ^{32}P-labelled adduct by TLC;	TLC and auto-radiography	$0.3x10^{-15}$ mols adduct/µg DNA	No data	Phillips et al. 1988
	Collection of lymphocyte cells; isolation of BPDE-DNA adduct by standard treatment; assay of BPDE-DNA adduct by immunoassay; analyses by SLS	ELISA/USERIA; SLS	$0.06–0.23x10^{-15}$ mol BPDE/µg DNA	No data	Harris et al. 1985

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Feces	Extraction with benzene:MeOH (4:1); add MeOH:H_2O (4:1); clean-up on silica gel column	HPLC/UV	0.05 µg/g	No data	Hecht et al. 1979
Urine	Acidify to pH 3 with HCl; clean-up on activated Sep-Pak C_{18} cartridge column; reduction with hydriodic acid	HPLC/fluorescence detector	<1 µg PAH/mmol creatinine	10–85	Becher and Bjorseth 1983
	Extraction into cyclohexane; concentration; reduction with hot acid	GC/FID	1.2–6.48 µg PAH/mmol creatinine	No data	Becher and Bjorseth 1985
	Hydrolysis; isolation of tetrol by Sep-Pak chromatography; clean up by immunoaffinity chromatography (anti BP-tetrol-modified guanosine column)	HPLC/SFS (7,8,9,10-BaP tetrol)	0.01 pmol/mL	>30	Weston et al. 1993a
	Isolation on a Sep-Pak column, washing with water followed by 10% MeOH; elution with 100% MeOH; concentration; addition of 0.1 M HCl with heating	SLS	25 pg metabolite/mL	No data	Uziel et al. 1987

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (cont.)	Collection of radiolabeled benzo[a]pyrene urine sample; addition of MeOH; isolation on C_{18} Sep-Pak column; elution with aqueous MeOH	HPLC/UV	$5x10^{-12}$ mol 7-BPDE-Gua/10 µg of labelled benzo[a]-pyrene	No data	Autrup and Seremet 1986
	Buffer to pH=5.5; enzymatic hydrolysis with β-glucuronidase/sulfatase (4 hours at 37.5 °C); clean-up using Sep-Pak C_{18} cartridge; isolation of 1-pyrenol	HPLC/fluorescence detector	0.45 nmol/L (1-pyrenol)	No data	Tolos et al. 1990
	Dilution; extraction into $CHCl_3$; precipitation of protein; wash extract with CH_3OH; evaporation and analysis of residue	HPLC/UV; FLNS	~1 fmol (BP tetrol)	No data	Rogan et al. 1990
Feces	Homogenization and drying; extraction with $CHCl_3$; evaporation and analysis of residue	HPLC/UV; FLNS	~1 fmol (BP tetrol)	No data	Rogan et al. 1990
Hair	Incubation of hair follicle with (-)-B[a]P-7,8-diol for 24 hours; addition of acetone; centrifugation; analysis of supernatant	HPLC/fluorescence detector	~0.3 fmol of tetrols	No data	Alexandrov et al. 1990

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Thymus and liver	Preparation of fluoranthene-modified DNA *in vitro*; digestion with enzyme; isolation of adducts using disposable C_{18} cartridge; nuclease P1 pretreatment to remove residual unmodified nucleotides; labelling of fluoranthene-DNA adduct by ^{32}P-postlabelling technique; nuclease P1 digestion	HPLC/radioisotope counting	0.1 fmol adduct (3 adducts/10^8 nucleotides in 1 µg DNA)	10–15	Gorelick and Wogan 1989
Thymus	Preparation of B[a]P-DNA adduct; digestion; labelling of adduct by ^{35}S-postlabelling technique	HPLC/radioisotope counting	1 adduct/10^8 nucleotides for 60 µg DNA	20	Lau and Baird 1991
Embryo and thymus	Preparation of PAH-DNA adduct; digestion; labelling of adduct by ^{35}P-postlabelling; separation of steroisomers by immobilized boronate chromatography	IP-RP-HPLC/radioisotope flow detects (+) and (–) enantiomers of anti- and syn- PAH-DE-DNA adduct	No data	No data	Baird et al. 1993

TABLE 6-1. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Placenta	Hydrolysis of DNA; addition of phosphate-buffered saline; neutralization with NaOH; incubation of sensor in sample	FIS	$14x10^{-18}$ mol BPT	No data	Vo-Dinh et al. 1991

ATP = adenosine triphosphate; B[a]P = benzo[a]pyrene; BPDE = 7_{β},8α-dihydroxy-[9α, 10α]-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene; BPT = benzo[a]pyrene tetrol; $CHCl_3$ = chloroform; CH_3OH = methanol; DMSO = dimethyl sulfoxide; DNA = deoxyribonucleic acid; ELISA = enzyme linked immunosorbent assay; FIS = fluoroimmunosensor; FLNS = fluorescence line narrowing spectrometry; fmol = femtomole; GC/FID = gas chromatography/flame ionization detector; GC/MS = gas chromatography/mass spectrometry; Gua = Guanosine; H_2O = water; HCl = hydrogen chloride; HPLC = high performance liquid chromatography; IgG = immunoglobin; IP-RP-FPLC = ion-paired reverse phase high pressure liquid chromatography; KOH = potassium hydroxide; LESS = laser-excited Stepol'skii spectroscopy; M = molar; MeOH = methanol; $MgCl_2$ = magnesium chloride; mmol = millimole; $NADP^+$ = oxidized nicotinamide adenosine dinucleotide; NaOH = sodium hydroxide; Na_2SO_4 = sodium sulfate; ng = nanogram; NIEC-MS = negative ionization electron capture mass spectrometry; nmol = nanomole; PAHs = polycyclic aromatic hydrocarbons; pg = picogram; pmol = picomole; PNPP = para nitrophenyl phosphate; SF = spectrofluorometry; SFS = synchronous fluorescence spectroscopy; SLS = synchronous luminescence spectroscopy; TLC = thin-layer chromatography; USERIA = ultra sensitive enzyme radioimmuno assay; UV = ultraviolet; UV-VIS = UV-visible detector.

Obana et al. (1981) reported the identification and quantification of six PAHs on EPA's priority pollutant list: anthracene, pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene using the HPLC/fluorescence detector technique. Levels measured in human. tissue ranged from 0.006 to 0.460 ng/g. Following extraction of the PAHs from the sample matrices by saponification with KOH, the extract was cleaned on alumina and silica gel columns, prior to quantitation. The known carcinogens, benz[a]anthracene and dibenz[a,h]anthracene, were not detected (detection limit <0.005 ng/g). The HPLC/UV detection technique has also been used to simultaneously determine fluoranthene, benz[a]anthracene, and pyrene in blood and lung tissues (Brandys et al. 1989). A detection limit of ppb (ng/g or ng/mL), satisfactory recoveries (65-109%), and adequate precision (119% relative standard deviation [RSD]) were achieved (Brandys et al. 1989).

In addition to direct measurement of PAHs in biological tissues, it is also possible to determine the concentration of metabolites in biological fluids. Pyrene is predominantly excreted as a 1-hydroxypyrene conjugate (glucoronate and sulfate), although 1,2-dihydroxy- 1,2-dihydropyrene conjugates are .also excreted in urine (Grimmer et al. 1993). Phenanthrene, on the other hand, is mainly excreted as dihydrodiol conjugates. The metabolites of phenanthrene that have been detected in human urine are 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene, 9-hydroxyphenanthrene, 1,2-dihydroxy-1,2-dihydrophenanthrene, 3,4-dihydroxy-3,4-dihydro-phenanthrene, and 9,10-dihydroxy-9,10-dihydrophenanthrene (Grimmer et al. 1993). There are apparently individual variations in the phenanthrol (hydroxyphenanthrene) and phenanthrene dihydrodiol conjugates excreted in the 24-hour urine sample (Grimmer et al. 1993). The major metabolite of benzo[a]pyrene in human tissue and body fluid is 7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene (Weston et al. 1993a, 1993b).

Becher and Bjorseth (1983, 1985) and Becher (1986) developed an HPLC method for biological monitoring of PAHs and PAH metabolites in the urine of humans following occupational exposure to PAHs. Using the HPLC/fluorescence detector technique, recoveries of the individual PAH compounds varied between 10 and 85% with the more volatile 3-ring PAHs having the lowest recoveries. A detection limit of less than 1 µg of PAHs per mmol of creatinine was obtained. HPLC equipped with a fluorescence detector has also been used to measure 1-pyrenol (1-hydroxypyrene, a pyrene metabolite) in urine of workers exposed to PAHs in coal tar pitch with a detection limit of

0.45 nmol/L (Tolos et al. 1990). Recovery and precision data were not reported. A strong correlation was observed between the concentrations of urinary 1-hydroxypyrene in workers and environmental PAHs, indicating that pyrene may be used as a biomarker of exposure for assessing worker exposure to coal tar pitch containing pyrene (Tolos et al. 1990). Since 1-Hydroxypyrene glucuronide is approximately 5 times more fluorescent than 1-hydroxypyrene, the former may be a more sensitive biomarker for PAH exposure (Strickland et al. 1994). A sensitive HPLC/synchronous fluorescence spectroscopic method is available for the determination of 1-hydroxypyrene glucuronide (Strickland et al. 1994). Hecht et al. (1979) employed an HPLC analytical technique for determining the concentrations of benzo[a]pyrene and its metabolites in the feces of humans and rats following consumption of charcoal-broiled beef. A detection limit of 0.05 µg of benzo[a]pyrene metabolites per gram of sample was noted with HPLC/UV detection.

There is considerable evidence that PAHs are enzymatically converted to highly reactive metabolites that bind covalently to macromolecules such as DNA, thereby causing mutagenesis and carcinogenesis in experimental animals. Thus, benzo[ajpyrene, a prototype of the carcinogenic PAHs and the most thoroughly studied PAH, is activated by microsomal enzymes to 7β, 8α-dihydroxy-(9α,10α)-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE) and binds covalently to DNA, resulting in formation of BPDE-DNA adducts (Harris et al. 1985; Haugen et al. 1986; Uziel et al. 1987). Sensitive methods are available to detect PAH-DNA adducts in the blood and tissues of humans and animals. These include immunoassays, i.e., enzyme-linked immunosorbent assays (ELISA), radioimmunoassay (RIA), dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA), and ultrasensitive enzyme radioimmunoassay (USERIA); ^{32}P- and ^{35}S-postlabelling with radioactivity counting; surface-enhanced Raman spectroscopy; and synchronous luminescence spectroscopy (SLS) (Gorelick and Wogan 1989; Gorelick and Reeder 1993; Harris et al. 1985; Haugen et al. 1986; Helmenstine et al. 1993; Herikstad et al. 1993; Lau and Baird 1991; Perera et al. 1988; Phillips et al. 1987; Schoket et al. 1993).

The ELISA technique is used for detection of antibodies in serum bound to BPDE-DNA adducts. The USERIA method involves measuring the immunological response of BPDE-DNA in the presence of rabbit anti-serum. Several researchers have employed the immunoassay techniques for detecting PAH-DNA adducts at 10^{-l5} mol levels in the blood and tissues of humans occupationally exposed to

PAHs (Harris et al. 1985; Haugen et al. 1986; Newman et al. i988; Perera et al. 1988; Shamsuddin et al. 1985; Weston et al. 1988).

^{32}P-postlabelling is a highly sensitive and specific method for detecting PAH-DNA adducts in the blood and tissues of humans and animals (Gorelick and Wogan 1989; Phillips et al. 1988, 1987; Willems et al. 1991). Detection limits ranging from $0.3x10^{-15}$ mol of PAH adduct per µg of DNA (<1 adduct in 10^7 nucleotides) to $<10^{-18}$ mol of adduct per ug of DNA have been achieved (Phillips et al. 1988, 1987; Willems et al. 1991). Further advantages of the ^{32}P-postlabelling technique are that adducts do not need to be fully characterized in order to be detected, and that the method is particularly suited to occupational exposure to a complex mixture of PAHs. Coupling ^{32}P-postlabelling methodology with HPLC analysis has improved the resolution of the labeled nucleotides and can be used to identify and quantify specific PAH-DNA adducts such as fluoranthene-DNA adducts (Gorelick and Wogan 1989). A detection limit of 0.1 femtomole (fmol) of adduct (3 adducts per 10^8 nucleotides in 1 µg DNA) has been achieved. The advantage of this method is that it is not limited with respect to the amount of DNA that can be analyzed; therefore, sensitivity can be enhanced by analyzing larger quantities of DNA. Average recovery was 10-15% at 3 adducts per 10^6 nucleotides. Recovery was greater (30-40%) from DNA containing higher levels of adducts (Gorelick and Wogan 1989). The ^{32}P-postlabelling assay and a combination of thin-layer and reverse-phase HPLC was also used to separate DNA adducts of 6 nitrated PAHs (King et al. 1994). PAH-DNA adducts have also been detected and identified using [^{35}S]phosphorothioate postlabelling combined with HPLC analysis (Lau and Baird 1991). The sensitivity of this assay is 1 adduct per 10^8 nucleotides for a 60-µg DNA sample with an overall adduct recovery of 20%. An advantage of ^{35}S-postlabelling over ^{32}P-postlabelling is that ^{35}S has a longer half-life (87 days) than ^{32}P (14 days). This allows longer storage times between labeling and adduct analysis with minimal loss in sensitivity. ^{35}S also has a lower radioactive decay energy than ^{32}P, which reduces the risk of human radiation exposure and eliminates the need for the radioisotope-shielding equipment that is required for studies with high specific radioactivity. On the other hand, ^{35}S is also less sensitive than the ^{32}P-postlabelling analysis because of the lower specific activity of [^{35}S]adenosine triphosphatase (ATP) compared to [^{32}P]ATP and because of the requirement for more radioactivity per adduct for accurate HPLC analysis. However, if large samples of DNA are available, the sensitivity of ^{35}S-postlabelling/HPLC can be increased substantially (Lau and Baird 1991).

HPLC/UV detection and HPLC/fluorescence detection have been used for determining concentrations of PAH-DNA adduct and hydrolyzed PAH-DNA adducts in biological tissues and fluids (Alexandrov et al. 1990; Autrup and Seremet 1986; Jongeneelen et al. 1986; Rice et al. 1985b; Rogan et al. 1990; Salhab et al. 1987; Shugart 1986; Shugart et al. 1983; Weston and Bowman 1991; Weston et al. 1988). A detection limit of l0-l5 mol of tetrols per sample was achieved (Haugen et al. 1986; Shugart et al. 1983; Weyand and Bevan 1987a). HPLC with a fluorescence detector has been used to measure the stereospecific formation of benzo[a]pyrene tetrols from cytochrome P-450-dependent metabolism of (-)-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene to BPDE in human hair (Alexandrov et al. 1990). This assay is simple, requiring only three human hair follicles and a low (0.5-2 µmol) substrate concentration. The limit of detection is ≈0.3 fmol of tetrols (Alexandrov et al. 1990). This is a rapid and noninvasive method that could be used to determine an individual's capacity to activate carcinogens to DNA-binding intermediates (Alexandrov et al. 1990). HPLC with fluorescence detection has also been used to detect BPDE-DNA adducts in human lung tissues (Weston and Bowman 1991). A detection limit of 6 pg benzo[a]pyrene-tetrol/mL (1 adduct in 10^8 nucleotides) was achieved (Weston and Bowman 1991). Recoveries ranged from 26 to 66% for the procedure. HPLC/UV has been used to identify and quantify a benzo[a]pyrene-DNA adduct, specifically 7-(benzo[a]pyrene-6-yl)guanine (BP-N7Gua) in urine and feces in the femtomole range (Rogan et al. 1990). The structure of the adduct was established by fluorescence line narrowing spectrometry (FLNS). Recovery and precision data were not reported (Rogan et al. 1990).

Using benzo[a]pyrene as a model carcinogen, Vahakangas et al. (1985), Haugen et al. (1986), and Harris et al. (1985) have developed an synchronous luminescence spectroscopy (SLS) technique for detecting trace levels of PAH-DNA adducts in the blood of humans occupationally exposed to high levels of PAHs. Vahakangas et al. (1985) detected less than 1 benzo[a]pyrene moiety per 10^7 DNA molecules by SLS technique following *in vitro* acid hydrolysis of BPDE-DNA adduct. Fiber-optic antibody-based fluoroimmunosensor (FIS) has been used to measure DNA adducts of benzo[a]pyrene in biological samples such as human placenta (Tromberg et al. 1988; Vo-Dinh et al. 1991). The FIS is used to detect the highly fluorescent benzo[a]pyrene 7,8,9,10-tetrol (BPT) after release from the weakly fluorescent BPDE-DNA by mild hydrolysis. The FIS is highly specific because of the antigen-antibody reaction. This assay is highly sensitive, achieving a detection limit of $14x10^{-18}$ mol

of BPT (Vo-Dinh et al. 1991). FIS precision is adequate (6.2-15% RSD) (Tromberg et al. 1988). Recovery data were not reported.

6.2 ENVIRONMENTAL SAMPLES

One of the difficulties associated with determination of PAHs in environmental samples is the complexity of PAH mixture in these samples. Even after extensive and rigorous clean-up, the PAH fraction may contain hundreds of compounds. Analytical methods that offer combinations of good chromatographic resolving power and detector selectivity are usually required to quantify selected compounds in such mixtures. There is essentially a three-step procedure for the analysis and determination of PAHs in environmental samples: (1) extraction and isolation of PAHs from the sample matrix; (2) clean-up of the PAH mixtures from impurities and fractionation of PAH into subgroups; and (3) identification and quantitative determination of the individual components in each of these subgroups.

The collection of PAHs from air for quantification requires special considerations. Some of the PAHs, especially those with lower molecular weights, exist primarily in the vapor phase while PAHs with higher molecular weights exist primarily in the particulate phase (Santodonato et al. 1981). Therefore, a combination of a particulate filter (usually glass-fiber filter) and an adsorbent cartridge (usually XAD-2 or polyurethane foam) is used for the collection of PAHs (Andersson et al. 1983; Harvath 1983; Hawthorne et al. 1993). Therefore, collection methods that use either a filtration system or an adsorbent alone may be incapable of collecting both particulate and vapor phase PAHs. In addition, a few PAHs are known to be susceptible to oxidation by ozone and other oxidants present in the air during the collection process (Santodonato et al. 1981).

The commonly used methods for the extraction of PAHs from sample matrices are Soxhlet extraction, sonication, or partitioning with a suitable solvent or a solvent mixture. Dichloromethane, cyclohexane, benzene, and methanol have been widely used as solvents (see Table 6-2). Supercritical fluid extraction (SFE) of heterogeneous environmental samples with carbon dioxide in the presence of a modifier, such as 5-10%. methanol or dichloromethane is preferable to the conventional extraction method because SFE is much less time consuming and has comparable or better PAH extraction

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on XAD and glass-fiber filters with 2-D labeled PAH internal standards; extraction with toluene; fractionation and clean-up on activated silica and alumina	HRGC/MS	0.001–0.03 ng/m^3	No data	Hippelein et al. 1993
	Collection on glass-fiber filter; extraction with methylene chloride; clean-up on silica gel column; analysis at 254 nm	GC/DAD	0.2–4.8 ng/sample	75–100	Desilets et al. 1984
	Collection of on glass-fiber filter; extraction with benzene:MeOH (4:1); concentration; fractionation into acid/neutral/base fractions; clean-up neutral fraction by column chromatography; concentration	GC/FID; HPLC/fluor-escence detector	0.05 ng/m^3	No data	Matsumoto and Kashimoto 1985
	Collection on a glass-fiber filter; thermal desorbtion of filter onto GC column	GC/LIMF	1–15 µg/sample	No data	Galle and Grennfelt 1983
	Collection on a glass-fiber filter; extraction with 35% methylene chloride in cyclohexane	HPLC/fluorometric detector	<0.01 ng/sample	No data	Golden and Sawicki 1978
	Collection on filter; extraction with organic solvent	TLC; GC/MS	<1 pg/sample	No data	Majer et al. 1970

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (cont.)	Collection on fiber-glass filter; extraction with cyclohexane; concentration	GC/GPFD	$1x10^{-6}$ ppm	100.5	Mulik et al. 1975
	Collection on filter; extraction with toluene; acid/base fractionation; drying and concentration	HPLC; GC/MS	0.11 ppm	>85	Naikwadi et al. 1987
	Collection on glass-fiber filter; ultrasonic extraction with benzene; concentration; fractionation by HPLC	HRGC/FID	low ng/m^3	8–100	Tomkins et al. 1982
	Collection on filter; extraction with cyclohexane; clean-up on silica column	GC/MS	0.001–0.002 ppm	No data	Oehme 1983
	Collection on glass-fiber filter (particulates) and XAD-2 resin (vapor); extraction with benzene or methylene chloride	HPLC; GC/MS	0.001–0.1 ppm	No data	Harvath 1983
	Collection on glass-fiber filter; extraction with benzene; concentration	HPLC/fluor-escence detector	0.000025 ppm	92–100	Fox and Staley 1976
	Collection through filter onto XAD-2 resin; extract with benzene, cyclohexane or methylene chloride (NIOSH Methods 5506 and 5515)	HPLC; GC/FID	<1 ppm	No data	NIOSH 1984

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (cont.)	Collection on a glass-fiber filter; extraction with cyclohexane; clean-up by partitioning to DMSO and pentane	GC/MS	0.00001 ppm	No data	Karlesky et al. 1987
	Collection of air particulates with high-volume sampler; ultrasonic extraction with acetonitrile	HPLC/fluor-escence detector	10–50 pg	No data	Miguel and DeAndrade 1989
Sea water	Extraction with hexane or carbon tetrachloride; acid-base fractionation; and clean-up on silica and alumina column	GC/FID	0.024–0.045 µg/L	44–85	Desiderie et al. 1984
Water	Collection on a column containing XAD-4:XAD-8 (1:1) resin; elution with acetone followed by chloroform	HPLC/UV; GC/MS	0.01–3 µg/L	No data	Thruston 1978
	Extraction with cyclohexane	HPLC with time-resolved fluorescence detection	180×10^{-15} g/sample	89–100	Furuta and Otsuki 1983
	Filtration into flotation vessel; adjustment to pH 3; addition of Triton X-100; bubbling nitrogen through mixture; collection of foam, and extraction with methylene chloride; evaporation and dissolution of residue in methanol	HPLC/fluor-escence detector	low ng/L	86–107	Xu and Fang 1988

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (cont.)	Extraction at neutral pH with methylene chloride (EPA Methods 8100, 8250,and 8310)	HPLC/fluor-escence detector GC/FID GC/MS	0.64–0.013 µg/L 2.0–45.1 µg/L 1.9–7.8 µg/L	No data	EPA 1986
	Collection through sampling cartridges containing XAD-2 resin; elution with acetone:hexane (15:85)	GC/MS	0.00005 µg/L	57–100	Beniot et al. 1979
Municipal and industrial waste water	Extraction with methylene chloride; reconstitution in cyclohexane; clean-up on silica gel column (EPA Method 610)	HPLC/UV fluorescence detector	0.013–2.3 µg/L	78–116	EPA 1982
	Adjustment to pH >11.0; extraction with methylene chloride; drying with sodium sulfate; concentration (EPA Method 625)	GC/MS	1.6–7.8 µg/L	41–83	EPA 1982
Sediments	Extraction with methylene chloride; clean-up on alumina column	TLC; GC/MS	0.2–2.7 µg/g	86–89	John and Nickless 1977
	Freeze drying, sieving and homogenization; extraction with methylene chloride; clean-up on silica gel followed by sephadex column	HPLC/DAD/MS	pg range	No data	Quilliam and Sim 1988

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediments (cont.)	Extraction of dry sample with methylene chloride; injection into supercritical fluid extracting system	GC/MS	2.8–7.3 µg/g	91–97	Hawthorne and Miller 1987a, 1987b
	Extraction of dried sample with benzene; clean-up on silica gel and alumina column	GC/FID; GC/MS	0.014–0.093 µg/g	76–110	Szepesy et al. 1981
Sediments	Direct sampling of sediment in sample insert of SSJ/LIF	SSJ/LIF	1.8 ppm (B[a]P); 0.4 ppm (pyrene)	No data	Lai et al. 1990
	Extraction by sonication; clean-up on silica mini-columns	Spectrofluoro-metry	0.008–4.5 ng/mL	80–95	Saber et al. 1991
Waste water and sediments	Freeze drying; extraction with chloroform:MeOH (2:1); concentration of crude extract; clean-up by TLC followed by HPLC	GC/FID	0.12–0.46 µg/g	51–100	Readman et al. 1986
Water and sediments	Extraction in organic solvent	GC/FT-IR	0.01–0.06 µg/g	No data	Gurka et al. 1987
Soil	Extraction in organic solvent; concentration	GC/FT-IR	0.025–0.25 µg/sample	0.998–0.85 correlation coefficient	Gurka and Pyle 1988
	Ultrasonic extraction of sieved sample with acetonitrile; filtration through teflon filter	HPLC/SF	0.017 µg/g	No data	Tanaka and Saito 1988

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediments/ suspended matter (river), airborne particulate, dust and soil	Extraction of dried sample with methylene chloride; clean-up on activated copper column followed by sephadex	GC/FID; GC/MS	0.03–0.09 µg/g	99–113	Giger and Shaffner 1978
Diesel exhaust particulate and dust	Collection on fiber filter; extraction with hexane; concentration; partitioning with DMSO; concentration of organic extract	HPTLC; FSD	1–50 pg/sample	No data	Butler et al. 1984a
Cigarette smoke	Collection in trap of smoking machine; dissolution in benzene:MeOH:H_2O (2:1:2); clean-up on silicic acid and gel filtration column	GC/FID	No data	92–95	Severson et al. 1976
	Collection on filter pad; extraction with cyclohexane	HPLC/fluore-scence detector	3 pg/sample	89–108	Risner 1988
Cooking oil fume	Collection on glass-fiber filter; extraction with acetone; concentration, then dissolution in cyclohexane; clean-up by partitioning in DMF and reconstitution in cyclohexane	TLC/FSD	0.11–0.41 ng	96–99	Shuguang et al. 1994
Coal-fly ash	Drying at 150 °C, cooling in desiccator; ultrasonic extraction with methylene chloride; concentration	GC/MS	No data	No data	Low et al. 1986

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Highly refined coal- and petroleum-derived fuels	Dissolution in methylene chloride	HPLC/HPLC/fluorescence detector	3.5–46 µg/L	56–100	Tomkins and Griest 1987
	Collection in brown Winchester bag; addition of 20% aqueous MeOH with shaking; clean-up on Sep-Pak C_{18} cartridge column	HPLC/UV and fluorescence detector	0.1–7.1 µg/L	45–95	Symons and Crick 1983
	Dissolution in hexane; clean-up on silica and alumina gel column	TLC; SPF	µg/L range	No data	Monarca and Fagioli 1981
Highly refined coal- and petroleum-derived fuels (con.)	Dissolution in methylene chloride	HPLC/UV-VIS; GC/MS	2000 µg/L	No data	Tomkins et al. 1986
Solvent refined coal	Crushing into fine particles; dissolution in benzene; filtration	N-SSL R-SSL	$7x10^{-7}$ M $7x10^{-5}$ M	No data	Lin et al. 1991
Shale and fuel oil	Dissolution in cyclohexane; fractionation into acid and base/neutral fractions; clean-up base/neutral fraction on alumina followed by alumina-silica column	XEOL	10 ng/sample	No data	Woo et al. 1980
	Dilution in ethanol	RTP SLS	No data No data	±15 RSD ±4 RSD	Vo-Dinh et al. 1984
Sun tan oil	Extraction with hexane; clean-up on silica gel column	TLC; SPF	Low µg/L	79–93	Monarca et al. 1982

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
White petroleum products	Collection on silica gel column; elution with pentane:ether (1.5:1); concentration; clean-up on basic and acidic alumina column	FPS	µg/L range	No data	Popl et al. 1975
Sewage sludge	Homogenization; extraction with cyclohexane; centrifugation; separation and concentration of organic phase	2-Dimensional TLC/fluorescence detector	<1 µg/g	80–100	McIntyre et al. 1981
Smoked foods (e.g., fish and meat)	Saponification; extraction with cyclohexane; clean-up on Florisil column	HPLC/fluorescence detector GC/FID GC/MS	2–27 pg/sample 10 pg/sample 1,000 pg/kg	28–142	Lawrence and Weber 1984
	Soxhlet extraction of homogenized sample with acetone; saponification with ethanolic KOH; extraction with cyclohexane; drying and concentration; clean-up on alumina column; concentration, then dilution in methanol	HPLC/fluorescence detector	0.1–µg/kg	75–90	Moll et al. 1993
Charcoal-broiled beef	Extraction of ground sample with benzene:MeOH (4:1); evaporation to dryness; dissolution of residue in MeOH:H_2O (4:1); clean-up on silica gel column	HPLC/fluorescence detector	20–50 ng/g	No data	Hecht et al. 1979

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Seafoods	Saponification of homogenized sample with ethanolic KOH; extraction with 1,1,2-trichlorotrifluoroethane; concentration; clean-up by silica, alumina and C_{18} cartridge (modified FDA method)	GC-MS	1–5 µg/kg	73–144	Nyman et al. 1993
	Saponification of homogenized sample with ethanolic KOH; extraction with 1,1,2-trichlorotrifluoroethane; concentration; clean-up by silica alumina and gel permeation HPLC (NMFS method)	GC/MS	1–5 µg/kg	63–106	Nyman et al. 1993
Cooked beef	Saponification of ground sample with methanolic KOH; extraction with cyclohexane, DMF, and n-hexane; concentration	LT-MLS SLS HPLC/ fluorescence detector	0.9 ppb 0.2 ppb 1.0 ppb	75–85 (extraction efficiency)	Jones et al. 1988
Food (meat/fish, dried dairy products, cereals, leafy vegetables, and oils)	Digestion with alcoholic KOH; partitioning into cyclohexane or isooctane; removal of lipids by solvent partitioning with dimethylformamide or dimethylsulfoxide/water; clean-up on silica gel, Florisil, or Sephadex	HPLC/fluor-escence detector; GC-MS/SIM	2–90 ng/kg	20.6–92.5 (ocean perch); 34.2–62.7 (bran cereal); 98 (powdered milk)	Lawrence and Das 1986

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cereal products	Saponification; extraction with cyclohexane; reextraction with 15% caffeine in formic acid; dilution in sodium chloride solution; reextraction with cyclohexane; clean-up on silica gel; concentration	GC/MS	20 pg/inj	40–100	Tuominen et al. 1988
Vegetable oil	Dilution with *n*-pentane	LC-GC/MS	1 pg/sample	No data	Vreuls et al. 1991
Fat products	Dissolution in light petroleum; extraction with caffeine in formic acid; dilution in sodium chloride solution; reextraction with light petroleum; clean-up on silica gel column	HPLC/fluor-escence detector	0.1–0.5 ppb	76–85	Van Heddeghem et al. 1980
Barley malt	Homogenization; ultrasonic extraction with cyclohexane; centrifugation; clean-up of supernatant on silica gel-alumina column	HPLC/UV and fluorescence detector	2.5–5 ng/g	78–97	Joe et al. 1982
Alcoholic beverage	Continuous extraction with cyclohexane for 20 hours	HPLC/UV; GC/FID	1 µg/L	60	Toussaint and Walker 1979
Tea	Saponification; extraction with hexane; addition of DMSO with shaking; clean-up on silica gel	TLC; FSD	2–12 ng/g	92–95	Poole et al. 1987

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish tissue	Homogenization with 1.15% KCl solution; isolation on extraction cartridges packed with a styrene-divinylbenzene copolymer resin; washing with water; extraction with acetone:MeOH (1:1); extraction with methylene chloride:2-propanol (75:25)	HPLC/fluorescence detector; GC/MS	50–1,100 ng/g	>90	Krahn and Malins 1982
	Homogenization with distilled water and KOH pellets; reflux, then extraction with methylene chloride; clean-up on basic alumina column	GC/MS	<0.2 ng/g	72	Vassilaros et al. 1982
	Homogenization in methylene chloride; centrifugation; clean-up on alumina column	HPLC/UV; GC/MS	No data	89–98	Krahn et al. 1988
B[a]P metabolite formulation	Dissolution in MeOH	HPLC/MS	low ng/sample	No data	Bieri and Greaves 1987
PAH formulation	Dissolution in methylene chloride	GC/MS with laser multiphoton ionization detection	200×10^{-15} g sample	No data	Rhodes et al. 1983
	Dissolution in acetonitrile	UV-RRS	<1 ppb	No data	Asher 1984
	Dissolution in ethanol	HPLC/fluorescence detector	500–16,000 ppb	No data	Su et al. 1982

TABLE 6-2. Analytical Methods for Determining Polycyclic Aromatic Hydrocarbons in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
PAH formulation (cont.)	Conversion to nitroaromatic compound (packing sample in glass tube between glass-wool plugs, passing reagent gas through tube for 3 to 5 seconds); analysis for nitroaromatic compound	TQMS	100–500 ppb	No data	Hunt et al. 1983

B[a]P = benzo[*a*]pyrene; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EPA = Environmental Protection Agency; EtOH = ethanol; FPS = fluorescence and phosphorescence spectrometry; FSD = fluorescence scanning densitometry; GC = gas chromatography; GC/FID = gas chromatography/flame ionization detector; GC/DAD = gas chromatography/diode array detector; GC/LIMF = gas chromatography/laser induced molecular fluorescence; GC/GPFD = gas chromatography/gas phase fluorescence detector; GC/MS = gas chromatography/mass spectrometry; GC/FT-IR = gas chromatography/fourier transform-infra-red spectrometry; HPLC = high performance liquid chromatography; HCl = hydrochloric acid; HPLC/HPLC = high performance liquid chromatography/high performance liquid chromatography; HPLC/UV = high performance liquid chromatography/ultraviolet; HPLC/DAD/MS = high performance liquid chromatography/diode array detector/mass spectrometry; HPLC/SF = high performance liquid chromatography/spectrofluoremetry; HPTLC = high performance thin-layer chromatography; HPTLC/UV = high performance thin-layer chromatography/ultraviolet; H_2O = water; H_2SO_4 = sulfuric acid; inj = injection; KOH = potassium hydroxide; LC = liquid chromatography; LT-MLS = low temperature-molecular luminescence spectrometry; LC-GC/MS = liquid chromatography-gas chromatography/mass spectrometry; M = molar; MeOH = methanol; ng = nanogram; NMFS = National Marine Fisheries Service; PAHs = polycyclic aromatic hydrocarbons; R/N-SSL = resonant/nonresonant-synchronous scan luminescence; RSD = relative standard deviation; RTP = room temperature phosphorescence; SF = spectrofluorometry; SLS = synchronous luminescence spectroscopy; SSJ/LIF = supersonic jet/laser induced fluorescence; SIM = selected ion monitoring; SJS/SFC = supersonic jet spectroscopy/supercritical fluid chromatography; SP = spectrophotometer; SPF = spectrophotofluorometer; TCTFE = 1,1,2-trichloro-1,2,2-trifluoroethane; TLC = thin-layer chromatography; TQMS = triple quadruple mass spectrometer; UV-RRS = ultraviolet-resonance raman spectrometer; UV-VIS = UV-visible detector; XEOL = x-ray excited optical luminescence

recovery than the conventional methods (Burford et al. 1993; Dankers et al. 1993; Hawthorne et al. 1993; Hill and Hill 1993).

Column chromatography on silica, alumina, Sephadex or Florisil has been used most often for the clean-up and fractionation of PAHs in the sample extract (Desiderie et al. 1984; Desilets et al. 1984; Oehme 1983; Quilliam and Sim 1988). HPLC can also be used for the clean-up and fractionation of PAHs in sample extract (Readman et al. 1986). A disposable Sep-Pak cartridge with an amino stationary phase was used for the clean-up of benzo[a]pyrene in cigarette smoke condensate (Dumont et al. 1993). Some soil and sediment samples containing high amounts of sulfur may require clean-up on an activated copper column (Giger and Schaffner 1978).

A variety of analytical methods has been used for determining trace concentrations of PAHs in environmental samples (Table 6-2). These include GC with various detectors, HPLC with various detectors, and TLC with fluorimetric detectors. Various detection devices used for GC quantification include FID, MS, Fourier transform infrared spectrometer (FT-IR), laser induced molecular fluorescence detector (LIMF), diode array detector (DAD), and gas phase fluorescence detector (GPFDA). GC/MS and HPLC with UV or spectrofluorimetric detectors are perhaps the most prevalent analytical methods for determining concentrations of PAHs in environmental samples.

Oehme (1983) and Low et al. (1986) employed capillary GC coupled with negative ion chemical ionization MS for detecting and differentiating isomeric PAHs (including PAHs on EPA’s priority pollutant list). This procedure was successfully used to differentiate the isomers benzolj]fluoranthene and benzo[b]fluoranthene at low ppb levels in complex matrices, such as air particulate matter and coal fly ash. An alternative method for the elucidation of PAH isomers is GC coupled with a charge-exchange and chemical ionization MS (Simonsick and Hites 1985). Simonsick and Hites (1985) demonstrated that the structural isomers pyrene, fluoranthene, aceanthrylene and acephenanthrylene can be identified on the basis of their first ionization potential and $(M+l)^+/M^+$ mass ion ratio.

HPLC has been one of the most widely used analytical methods for determining PAHs in complex environmental samples. The development of a chemically nonpolar stationary phase for HPLC has

provided a unique selectivity for separation of PAH isomers that are often difficult to separate by GC columns. For example, chrysene, benz[a]anthracene, and triphenylene are baseline resolved with a C-18 reverse phase column packing. A detection limit of subpicogram to picogram levels of PAHs per sample has been achieved by HPLC with fluorescence detector (Fox and Staley 1976; Furuta and Otsuki 1983; Futoma et al. 1981; Golden and Sawicki 1978; Lawrence and Weber 1984; Marcomini et al. 1987; Miguel and De Andrade 1989; Nielsen 1979; Risner 1988; Ton&ins et al. 1982). HPLC equipped with a fluorescence detector has selectively measured 10 PAHs (phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[g,h,i]perylene, and indeno[l,2,3-c,d]pyrene) in ambient air (Miguel and De Andrade 1989). Detection limits for the 10 PAHs were in the range of 10-50 pg and RSD was <10%. Recovery data were not reported. PAH levels in the ng/L range have also been successfully determined in water using flotation enrichment and HPLC/fluorescence detection (Xu and Fang 1988). Good recoveries (86-107%) were achieved, and RSD was 2.7-13.6% RSD. A quenchofluorometric detection system provides an inexpensive method to achieve selective detection for the fluoranthenic PAHs as a group (Konash et al. 1981). UV detectors have been used to measure PAHs in fats and oil samples; however, these detectors lacked the sensitivity and specificity of the fluorescence detectors for determining PAHs at low levels (ppb and lower) (Van Heddeghem et al. 1980).

A number of less commonly used analytical techniques are available for determining PAHs. These include synchronous luminescence spectroscopy (SLS), resonant (R)/nonresonant (NR)-synchronous scan luminescence (SSL) spectrometry, room temperature phosphorescence (RTP), ultravioletresonance Raman spectroscopy (UV-RRS), x-ray excited optical luminescence spectroscopy (XEOL), laser-induced molecular fluorescence (LIMF), supersonic jet/laser induced fluorescence (SSJ/LlF), low-temperature fluorescence spectroscopy (LTFS), high-resolution low-temperature spectrofluorometry, low-temperature molecular luminescence spectrometry (LT-MLS), and supersonic jet spectroscopy/capillary supercritical fluid chromatography (SJS/SFC) (Asher 1984; Garrigues and Ewald 1987; Goates et al. 1989; Jones et al. 1988; Lai et al. 1990; Lamotte et al. 1985; Lin et al. 1991; Popl et al. 1975; Richardson and Ando 1977; Saber et al. 1991; Vo-Dinh et al. 1984; Vo-Dinh and Abbott 1984; Vo-Dinh 1981; Woo et al. 1980). More recent methods for the determination of PAHs in environmental samples include GC-MS with stable isotope dilution calibration (Bushby et al. 1993), capillary electrophoresis with UV-laser excited fluorescence detection (Nie et al. 1993), and

laser desorption laser photoionization time-of-flight mass spectrometry of direct determination of PAH in solid waste matrices (Dale et al. 1993).

Among the less commonly used spectroscopic methods, SLS and room temperature phosphorescence (RTP) are used for determining trace levels of PAHs in environmental media. Vo-Dinh (1981), Vo-Dinh and Abbott (1984), and Vo-Dinh et al. (1984) reported a cost-effective and relatively simple SLS and RTP technique for determining trace amounts of PAHs (less than $1x10^{-9}$ g per sample) in air particulate extracts collected at a wood-burning area. Improved selectivity is the main advantage of SLS and RTP over conventional luminescence or fluorescence spectroscopy. Additionally, R/N-SSL spectrometry has been applied to determine trace amounts of anthracene and its derivatives in solvent-refined coal (Lin et al. 1991). The sensitivity of N-SSL ($7x10^{-7}$ M) is about two orders of magnitude better than that of R-SSL spectrometry (7x10-5 M). The detection limit for N-SSL is several times better than that of conventional fluorescence spectrometry ($3x10^{-6}$ M). The better sensitivity comes from a higher efficiency in fluorescence collection (Lin et al. 1991). The combination of R- and N-SSL spectrometries provides a sensitive and selective analytical method because of the spectral simplicity of R-SSL and the high sensitivity of N-SSL spectrometry (Lin et al. 1991). This spectrometric method is also applicable to other PAHs in the environment, such as benzo[a]pyrene in airborne particulates.

Low temperature-molecular luminescence spectrometry (LT-MLS), SLS, and HPLC/fluorescence detection have been used to measure pyrene in broiled hamburger (Jones et al. 1988). A comparison of the three methods showed that sensitivity for all three methods was in the low-ppb range and that all methods were comparably reproducible (6-9% RSD). Adequate recovery (75-85%) was obtained from the extraction procedure for all three methods. While HPLC is the least expensive and easiest to operate, it has the longest analysis time (30 minutes), and it provides the least resolution of components. LT-MLS is the fastest technique (5 minutes), and it gives mores spectral information than the other two methods. SLS, with an analysis time of 15 minutes, offers no real advantages over LT-MLS other than cost of equipment.

Methods 8100, 8250, and 8310 are the test methods recommended by EPA (1986) for determining PAHs in a variety of matrices at solid waste sites. EPA Methods 610 and 625, recommended for

municipal and industrial waste water have been used to measure PAHs in groundwater contaminated by petroleum hydrocarbons at detection limits in the low-ppb range (Thomas and Delfino 1991). Recovery and precision data were not reported. NIOSH (1985) has recommended methods 5506 and 5515 as the analytical methods for determining PAHs in air samples at concentrations below ppm level.

6.3 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 PAHs is available. Where adequate information is not available, ATSDR, in conjunction with the 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 PAHs.

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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Adequate methods are available to separate and quantify PAHs in biological materials such as adipose tissue (Gay et al. 1980; Liao et al. 1988; Modica et al. 1982), lungs (Brandys et al. 1989; Mitchell 1979; Tomingas et al. 1976; Weston and Bowman 1991; Weyand and Bevan 1987a), liver (Amin et al. 1982; Obana et al. 1981; Rice et al. 1985b), skin (Phillips et al. 1987; Shugart et al. 1983), hair (Alexandrov et al. 1990), blood (Brandys et al. 1989; Harris et al. 1985; Haugen et al. 1986; Perera et al. 1988; Phillips et al. 1988; Shamsuddin et al. 1985; Shugart 1986), urine (Au&up and Seremet 1986; Becher and Bjorseth 1985; Rogan et al. 1990; Tolos et al. 1990; Uziel et al. 1987), and feces (Hecht et al. 1979; Rogan et

al. 1990). These methods include GC/FID, GCMS, HPLC, TLC, and spectrofluorometry (SF). The difficulties involved in recovering bound benzo[a]pyrene from feces hinder studies on absorption and bioavailability in humans after exposure to benzo[a]pyrene. Therefore, there is a need to develop a satisfactory analytical method for the determination of benzo[a]pyrene in feces. Immunoassays (i.e., ELISA and USERIA, ^{32}P-arid ^{35}S-postlabelling, SLS, and FIS) are methods currently being developed to detect the presence of carcinogenic PAH adducts bound covalently to macromolecules (e.g., DNA). The parent compound is generally measured in biological tissues, but both the parent compound and its metabolites can be measured in biological fluids, particularly urine. However, improved methods for identifying and characterizing conjugated PAH metabolites from various biological fluids would be useful. PAH-DNA adducts can be measured in blood, serum, and other tissues. These methods are accurate, precise, and sensitive enough to measure background levels in the population and levels at which biological effects occur. Additional quantitative information regarding the relationships between body and environmental levels of PAHs for both short- and long-term exposures might allow investigators to predict environmental exposure levels from measured body levels.

The urinary level of 1-Hydroxypyrene has the potential to be used as a biomarker for exposure to PAHs, and analytical methods for the detection of the hydroxy metabolite in urine of exposed and non-exposed control persons are available (Ariese et al. 1993a; Jongeneelen et al. 1988; Kanoh et al. 1993; Mercado Calderon 1993; Van Hummelen et al. 1993). The correlation coefficient between total PAHs in air of a coke production plant and hydroxypyrene in urine of workers was 0.77 ($p<0.0001$) (Mercado Calderon 1993). A study attempted to use benzo[a]pyrene metabolite 3-hydroxy-benzo[a]pyrene in urine as a biomarker for occupational exposure to PAH (Ariese et al. 1993a). Since the level of 3-hydroxybenzo[a]pyrene is about 3 orders of magnitude lower than 1-hydroxypyrene, a sensitive method was developed to estimate levels of 3-hydroxybenzo[a]pyrene in occupational groups (Ariese et al. 1993a). However, no significant correlation between the metabolite and levels of airborne benzo[a]pyrene was found.

The available biomarkers of effect for PAHs are not specific for effects induced by PAHs other than cancer or genotoxicity. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to PAHs and mixtures that contain PAHs. The formation of benzo[a]pyrene-DNA adducts has been demonstrated, and this may serve as a biomarker of PAH-induced carcinogenicity.

HPLC and immunoassays, (i.e., ELISA and USERIA, ^{32}P-and ^{35}S-postlabelling, SLS, and FIS) are sensitive, selective, and reproducible methods being developed to detect the presence of carcinogenic PAH adducts bound covalently to macromolecules (e.g., DNA) (Gorelick and Wogan 1989; Haugen et al. 1986; Lau and Baird 1991; Phillips et al. 1988; Weston and Bowman 1991). Chromosomal aberration and sister chromatid exchange methods were used to show that several types of cultured human tissue cells demonstrated positive results for benzo[a]pyrene-induced genotoxicity (Abe et al. 1983a, 1983b; Huh et al. 1982; Lo Jacono et al. 1992; Van Hummelen et al. 1993; Weinstein et al. 1977; Wienke et al. 1990). However, statistically significant correlation between the cytogenetic markers and airborne occupational PAH levels was not found (Van Hummelen et al. 1993).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Standardized methods are available that are reliable, reproducible, and sensitive enough to separate and quantify PAHs in air (Andersson et al. 1983; Fox and Staley 1976; Golden and Sawicki 1978; Harvath 1983; Karlesky et al. 1987; Majer et al. 1970; Miguel and De Andrade 1989; Naikwadi et al. 1987; NIOSH 1984; Oehme 1983; Tomkins et al. 1982; Matsumoto and Kashimoto 1985), water (Beniot et al. 1979; Desiderie et al. 1984; EPA 1986; Furuta and Otsuki 1983; Thomas and.Delfino 1991; Thruston 1978; Xu and Fang 1988), soil and sediment (Hawthorne and Miller 1987a, 1987b; John and Nickless 1977; Saber et al. 1991; Szepesy et al. 1981; Tanaka and Saito 1988), and other media, such as food (Hecht et al. 1979; Joe et al. 1984; Jones et al. 1988; Krahn and Malins 1982; Krahn et al. 1988; Lawrence and Das 1986; Lawrence and Weber 1984; Poole et al. 1987; Toussaint and Walker 1979; Tuominen et al. 1988; Van Heddeghem et al. 1980; Vassilaros et al. 1982; Vreuls et al. 1991), cigarette smoke (Risner 1988; Severson et al. 1976), coal tar (Alben 1980; Goates et al. 1989; Low et al. 1986), and fuels (Lin et al. 1991; Monarca and Fagioli 1981; Symons and Crick 1983.; Ton&ins and Griest 1987; Vo-Dinh et al. 1984; Woo et al. 1980). These methods include GC, HPLC, TLC, and others. Various detection devices used for GC quantification include FID, MS, FT-IR, LIMF, DAD, or GPFDA. GC/MS and HPLC are perhaps the most prevalent analytical methods for determining concentrations of PAHs in environmental samples. These methods are adequate to measure environmental levels that may be associated with adverse human effects. All of the available analytical methods for PAHs in soil and food items are sensitive down to levels of <1 ppb.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control and Prevention, is developing methods for the analysis of PAHs and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry, which gives detection limits in the low parts per trillion (ppt) range.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding polycyclic aromatic hydrocarbons (PAHs) in air, water, and other media are summarized in Table 7-1.

An MRL of 0.6 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to acenaphthene, based on a minimal LOAEL of 175 mg/kg/day for liver weight in mice (EPA 1989c).

An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluoranthene, based on a minimal LOAEL of 125 mg/kg/day for increased liver weight in mice (EPA 1988e).

An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to fluorene, based on a minimal LOAEL of 125 mg/kg/day for relative liver weight in mice (EPA 1989e).

Reference doses have been developed by EPA for anthracene (0.3 mg/kg/day), acenaphthene (0.06 mg/kg/day), fluoranthene (0.04 mg/kg/day), fluorene (0.04 mg/kg/day), and pyrene (0.03 mg/kg/day). No reference concentrations exists for any of the PAHs.

PAHs are regulated under The Emergency Planning and Community Right-to-Know (EPCRA) standards of 40 CFR Subpart J. EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use these chemicals to report annually their release of those chemicals to any environmental media.

OSHA regulates the benzene soluble fraction of coal tar pitch volatiles and mineral oil mist, which contain several of the PAH compounds. Employers of workers who are occupationally exposed must institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 0.2 mg/m^3 for coal tar pitch volatiles and 5 mg/m^3 for mineral oil mist.

7. REGULATIONS AND ADVISORIES

PAHs are regulated by the Clean Water Effluent Guidelines in Title 40, Sections 400-475, of the Code of Federal Regulations. For each point source category, PAHs may be regulated as a group of chemicals controlled as Total Toxic Organics, may have a specific regulatory limitation, or may have a zero discharge limitation. The point source categories for which the PAHs are controlled as a Total Toxic Organic include electroplating, and metal molding and casting. The point source categories for which the PAHs have specific regulatory limitations include organic chemicals, plastics, and synthetic fibers; cokemaking; and nonferrous metals manufacturing.

Under the Resource Conservation and Recovery Act (RCRA), several PAHs are listed as hazardous wastes when they are discarded commercial chemical products, off-specification species, container residues, and spill residues (40 CFR 261.33).

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons

Agency	Description	Information	Reference
INTERNATIONAL			
IARC	Carcinogenic classification[a]		IARC 1987; IARC 1984; IARC 1984; IARC 1983; IARC 1973
	(B[a]A; B[a]P)	Group 2A[b]	
	(B[b]F; B[j]F; B[k]F; I[123cd]P)	Group 2B[c]	
	(Anthracene; B[ghi]P; B[e]P; Chrysene; Fluoranthene; Fluorene; Phenanthrene; Pyrene)	Group 3[d]	
	(Mineral oil mists)	Group 1	
			IARC 1984
	Occupational exposure limits		
	Oil mists, mineral		
	Australia, Belgium, German Democratic Republic, Italy, Netherlands, Switzerland	5 mg/m^3 (TWA	
	Japan, Finland, Sweden	3 mg/m^3 (TWA)	
	Coal-tar pitch volatiles	0.2 mg/m^3 (TWA)	
	Australia, Belgium, Italy, Netherlands, Switzerland, Yugoslavia		
WHO	European standard for drinking water[e]	0.2 µg/L	WHO 1971
NATIONAL			
Regulations:			
a. Air:		0.2 mg/m^3	
OSHA	PEL, TWA		29 CFR 1910.1000
	Coal tar pitch volatiles-benzene soluble fraction[f]		29 CFR 1910.1002 OSHA 1993 ACGIH 1991
	Oil mist, mineral	5 mg/m^3	29 CFR 1910.1000
EPA	Hazarouds Air Pollutants: Proposed Regulations Governing Constructed, Reconstructed or Modified Major Sources	Yes	59 FR 15504 April 1, 1994 (40 CFR 63.44)
b. Non-specific media:			
EPA	Solid Waste		40 CFR Subchapter I
	Criteria for municipal solid waste landfills		40 CFR 258
	List of hazardous inorganic and organic constituents (all PAHs)	Yes	40 CFR App. II
	Identification and Listing of Hazardous Waste	Yes	40 CFR 261
	Off-specification and discarded materials, and residues (B[a]A, B[a]P, Chrysene, DB[a,h]A, DB[a,i]P, Fluoranthene, I[1,2,3-cd]P)		40 CFR 261.33

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Basis for listing hazardous waste (Acenaphthylene; B[a]A; B[a]P; B[b]F; B[k]F; Chrysene; DB[a,h]A; Fluoranthene; I[1,2,3-cd]P)	Yes		40 CFR 261, App. VII
	Hazardous constituents of waste (B[a]A; B[b]F; B[j]F; B[k]F; B[a]P; Chrysene; DB[a,e]P; DB[a,h]P; DB[a,i]P; Fluoranthene, I[1,2,3-cd]P)	Yes		40 CFR 261, App. VIII
	Waste excluded from nonspecific sources	Yes		40 CFR 261, App. IX
	Carbamate production identification and listing of hazardous waste: oral and inhalation toxicity information for waste constituents (Notice of proposed rulemaking)	Yes		59 FR 9808 March 1, 1994 (40 CFR 261.32) EPA 1994
	Standards for Owners, and Operators of Hazardous Waste Treatment, Storage & Disposal Facilities	Yes		40 CFR 264
	Groundwater monitoring list (all PAHs)			40 CFR 264, App. IX
	Standards for the Management of Specific Hazardous Wastes and Specific Types of Hazardous Waste Management Facilities			40 CFR 266
	Limits for exclusion of waste-derived residues			40 CFR 266, App. VII
	(B[a]A)	$1x10^{-4}$ mg/kg		
	(DB[a,h]A)	$7x10^{-6}$ mg/kg		
	Land Disposal Restrictions			40 CFR 268
	Waste to be evaluated (B[a]A; B[a]P; Chrysene; DB[a,h]A; I[1,2,3-cd]P)	Yes		40 CFR 268.10
	List of wastes to be identified by May 8, 1990	Yes		40 CFR 268.12
	Land disposal treatment concentrations			40 CFR 268.43
	Waste No. F039	Wastewaters (mg/L)	Non-wastewaters (mg/kg)	
	Acenaphthalene	0.059	3.4	
	Acenaphthene/Anthracene/ Fluorene	0.059	4.0	
	B[a]A; Chrysene	0.059	8.2	
	B[b]F; B[k]F	0.055	3.4	
	B[g,h,i]P	0.055	1.5	
	B[a]P	0.061	8.2	
	DB[a,h]A	0.055	8.2	
	DB[a,e]P	0.061	NA	
	Fluoranthene	0.068	8.2	
	Phenanthrene	0.059	3.1	
	Pyrene	0.067	8.2	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Waste No. K035			
	Acenaphthrene; Anthracene, B[a]P; DB[a,h]A; Fluorene; I[1,2,3-cd]P	NA	3.4	
	B[a]A; Chrysene; Phenanthrene	0.059	3.4	
	Fluoranthene	0.068	3.4	
	Pyrene	0.067	8.2	
	Waste No. K048			
	B[a]P	0.047	12	
	Chrysene	0.043	15	
	Fluorene	0.011	14	
	Phenanthrene	0.033	42	
	Pyrene	0.047	36	
	Waste No. K087			
	Acenaphthalene; Chrysene; Fluoranthene; I[1,2,3-cd]P; Phenanthrene	0.028	3.4	
	Waste No. K049			
	Anthracene	0.039	28	
	B[a]P	0.047	12	
	Chrysene	0.043	15	
	Phenanthrene	0.033	42	
	Pyrene	0.047	3.6	
	Waste No. K051			
	Acenaphthene	0.05	NA	
	Anthracene	0.039	28	
	B[a]A	0.043	20	
	Phenanthrene	0.011	14	
	Pyrene	0.033	42	
	Waste No. U018, U050 (B[a]A; Chrysene)	0.059	8.2	
	U022 (B[a]P)	0.061	8.2	
	U063 (DB[a,h]A)	0.055	8.2	
	U120 (Fluoranthene)	0.068	8.2	
	U137 (I[1,2,3-cd]P)	0.0055	8.2	
	Requirements Authorization of State Hazardous Waste Programs			40 CFR 271

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Regulations implementing the HSWA of 1984	Yes	40 CFR 271.1
	Proposed rule: Universal treatment standards for organics	Yes	58 FR 48092 Sept. 14, 1993
	Maximum grab sample (non-wastewaters)		(40 CFR 148, 260, 261, 268, 271)
	Acenaphthalene; acenaphthene; anthracene; B[a]A; B[a]P; chrysene; fluoranthene; fluorene; I[1,2,3-cd]P	3.4 mg/kg	
	B[b]F; B[k]F	6.8 mg/kg	
	B[g,h,i]P	1.8 mg/kg	
	DB[a,h]A; pyrene	8.2 mg/kg	
	Phenanthrene	5.6 mg/kg	
	Maximum grab sample (wastewaters)		
	Acenaphthalene; acenaphthene; anthracene; B[a]A; chrysene; fluorene; phenanthrene	0.059 mg/L	
	B[a]P; DB[a,e]P	0.061.mg/L	
	B[b]F; B[k]F	0.11 mg/L	
	B[g.h,i]P; I[1,2,3-cd]P	0.0055 mg/L	
	DB[a,h]A	0.055 mg/L	
	Fluoranthene	0.068 mg/L	
	Pyrene	0.067 mg/L	
	Proposed rule: BDAT standard		
	Maximum grab sample (non-wastewaters)		
	B[a]A; B[a]P; chrysene; I[1,2,3-cd]P	3.4 mg/kg	
	B[b]F; B[k]F	6.8 mg/kg	
	DB[a,h]A	8.2 mg/kg	
	Maximum grab samples (wastewaters)		
	B[a]A; chrysene	0.059 mg/L	
	B[a]P	0.061 mg/L	
	B[b]F; B[k]F	0.11 mg/L	
	I[1,2,3-cd]P	0.0055 mg/L	
	DB[a,h]A	0.055 mg/L	
	Superfund, Emergency Planning, and Community Right-To-Know Programs		40 CFR Subchapter J

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Designation, Reportable Quantities and Notification		40 CFR 302
	Designation and Reportable Quantities of Hazardous Waste		40 CFR 302.4
	Acenaphthene; chrysene, fluoranthene, I[1,2,3-cd]P	100 pounds	
	Acenaphthylene; anthracene, B[k]F; B[g,h,i]P; fluorene; phenanthrene, pyrene	5,000 pounds	
	B[a]A	10 pounds	
	B[b]F; B[a]P; DB[a,h]A	1 pound	
	Emergency Planning and Notification		40 CFR 355
	List of extremely hazardous substances and threshold planning quanitties		40 CFR 355, App. A
	Pyrene	1,000/10,000 lbs.	
	Toxic Chemical Release Reporting: Community Right-to-Know		40 CFR 372
	Toxic chemical listing (anthracene)	Yes	40 CFR 272.65
	Proposed Rule: National oil and hazardous substance pollution contingency plan; QA/QC of chemical analysis of oil compositoin using GC/MS	Yes	58 FR 54702 October 22, 1993 40 CFR 300
	Proposed Rule: Addition of certain chemicals; toxic chemical release reporting; comunity right-to-know	Yes	59 FR 1788 January 12, 1994 40 CFR 372
	Toxic Substances Control Act		40 CFR Subchapter R
	Reporting and Recordkeeping Requirements		40 CFR 704
	Chemical substance matrix for CAIR reporting (Phenanthrene, pyrene)	Yes	40 CFR 704.225
	Health and Safety Data Reporting		40 CFR 716
	Listing of substances and mixtures (anthracene)	Yes	40 CFR 716.120
	Significant New Uses of Chemical Substances		40 CFR 721
	Fluorene substituted aromatic amines	Yes	40 CFR 721.3764
	Provisional Test Guidelines		40 CFR 795

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Protocol for determining anaerobic microbiological transformation rate data for chemicals in the subsurface environment	Yes		40 CFR 795.54
DOT	Hazardous materials transport	Yes		49 CFR 171 DOT 1991
c. Water				
EPA	Water Programs			40 CFR Subchapter D
	National Pollution Discharge Elimination System (NPDES)			40 CFR 122
	Testing requirements for NPDES permits			
	B[a]P; acenaphthene; aenaphthalene	Yes		40 CFR 122, App. D
	Guidelines Establishing Test Procedures for the Analysis of Pollutants			40 CFR 136
	Guidelines for testing pollutants under the CWA (all PAHs)			40 CFR 136.3
	Testing procedures for PAHs base/neutrals and acids, semivolatile organic compounds (all PAHs)	Yes		40 CFR 136, App. A Methods 610, 625, 1625 (Revision B)
	National Primary Drinking Water Regulations			40 CFR 141
	Effective dates (B[a]P)	Yes		40 CFR 141.6
	Sampling and Analytical Requirements for organic chemicals (B[a]P)	Yes		40 CFR 141.24
	Public notification under the SDWA (B[a]P)	0.002 ppm		40 CFR 141.32
	Special monitoring for organic and inorganic compounds (B[a]P)	Yes		40 CFR 141.40
	Maximum contaminant levels for organic contaminants (B[a]P)	0.0002 mg/L		40 CFR 141.61
	Final Rule: Water quality standards; numeric criteria for priority toxic pollutants; states' compliance	Yes		57 FR 60848 Dec. 22, 1992 (40 CFR 131)
	Human health (10^{-6} risk for carcinogens); for consumption of (µg/L):	Water and Organism	Organism Only	
	Anthracene	9,600	110,000	
	B[a]A; B[a]P; B[b]F; B[k]F; chrysene; DB[a,h]A; I[1,2,3-cd]P	0.0028	0.031	
	Fluoranthene	300	370	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Fluorene	1,300	14,000	
	Pyrene	960	11,000	
	Proposed Rule: National primary and secondary drinking water regulations; analytical methods for regulated drinking water contaminants (B[a]P)	Yes		58 FR 5622 Dec. 15, 1993 (40 CFR 141, 143)
	Effluent Guidelines and Standards			40 CFR Subchapter N
	General Provisions			40 CFR 401
	Toxic pollutants under Sec. 307(a) of the CWA (Acenaphthene, fluoranthene)	Yes		40 CFR 401.15
	General Pretreatment Regulations for Existing and New Sources of Pollution			40 CFR 403
	Pretreatment regulations for POTWs (acenaphthene, fluoranthene)	Yes		40 CFR 403, App. B
	Electroplating Point Source Category			40 CFR 413
	Definition of total toxic organic (TTO) (all PAHs, excluding acenaphthene)	Yes		40 CFR 413.02
	Organic Chemicals, Plastics, and Synthetic Fiber			40 CFR 414
	Toxic effluent standards for point sources that use end-of-pipe biological treatment	Daily maximum (µg/L)	Monthly Maximum (µg/L)	40 CFR 414.91 (58 FR 36872) July 9, 1993
	Acenaphthene; acenaphthylene; anthracene; B[a]A; B[k]F; Chrysene; fluorene; phenanthrene	59	22	
	Fluoranthene	68	25	
	B[a]P	61	23	
	Pyrene	67	25	
	Toxic pollutant standards for point sources that do not use end-of-pipe biological treatment			58 FR 36872 (40CFT 414.101
	Acenaphthene; acenaphthylene; anthracene; B[a]A; B[k]F; Chrysene; fluorene; phenanthrene	47	19	
	B[a]P; pyrene	48	20	
	Fluoranthene	54	22	
	Toxic pollutant standards for indirect discharge point sources			58 FR 36872 40 CFR 414.111
	Acenaphthene; anthracene; fluorene; phenanthrene	47	19	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Fluoranthene	54	22	
	Pyrene	48	20	
	Iron and Steel Manufacturing Point Source Category			40 CFR 420
	Definition (B[a]P)	Yes		40 CFR 420.02
	Effluent limitations attainable using BAT for cokemaking B[a]P--1 day maximum (kg/kkg of product)			40 CFR 420.13
	cokemaking--iron and steel	0.0000319		
	--iron and steel with physical chemical treatment	0.0000215		
	--merchant	0.0000355		
	--merchant with physical chemical treatment	0.0000250		
	New source performance standards (B[a]P)--1 day maximum (kg/kkg of product)	Yes		40 CFR 420.14
	cokemaking--iron and steel	0.0000319		
	--merchant	0.0000355		
	Nonferrous Metals Manufacturing Point Source Category			40 CFR 421
	Definition of B[a]P for primary aluminum smelting	Yes		40 CFR 421.21
	Effluent limitations attainable by application of BAT for primary aluminum smelting plants (mg/kg)	Max. 1-day limit	Max. monthly avg.	40 CFR 421.23
	Anode and cathode plastic plant wet air pollution control	0.005	0.002	
	Anode contact cooling and briquette quenching	0.007	0.003	
	Anode bake plant wet air pollution control (closed top)	0.146	0.067	
	Anode bake plant wet air pollution control (open top ring furnace with spray tower only	0.002	0.001	
	Anode bake plant wet air pollution control (open top ring furnace with wet ESP and spray tower)	0.025	0.011	
	Anode bake plant wet air pollution control (tunnel kiln)	0.038	0.018	
	Cathode reprocessing (with dry potline scrubbing and not commigled)	1.181	0.547	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Cathode reprocessing (with wet potline scrubbing)	0.000	na	
	Potline wet air pollution control (w/o cathode reprocessing)	0.028	0.013	
	Potline wet air pollution control (w/cathode reprocessing and not commingled)	0.028	0.013	
	Potline wet air pollution control (w/cathode reprocessing and commingled)	0.028	0.013	
	Pot room wet air pollution control	0.056	0.026	
	Potline SO_2 emissions wet air pollution control	0.045	0.021	
	Degreasing wet air pollution control	zero	zero	
	Pot repair and pot soaking	0.000	na	
	Direct chill casting contact cooling	zero	zero	
	Continuous rod casting contact cooling	zero	zero	
	Stationary casting or shot casting contact cooling	0.000	na	
	New Source Performance Standards for Primary Aluminum Smelting (B[a]P) (mg/kg)	Max. 1-day limit	Max. monthly avg.	40 CFR 421.24
	Anode and cathode paste plant wet air pollution control	0.000	na	
	Anode contact cooling and briquette quenching	0.007	0.003	
	Anode bake plant wet air pollution control	0.000	na	
	Cathode reprocessing (operating with dry potline scrubbing and commingled)	1.181	0.547	
	Potline wet air pollution control	0.000	na	
	Potroom wet air pollution control	0.000	na	
	Potline SO_2 emissions wet air pollution control	0.045	0.021	
	Degassing wet air pollution control	0.000	na	
	Pot repair and pot soaking	0.000	na	
	Direct chill casting contact cooling	zero	zero	
	Continuous rod casting contact cooling	zero	zero	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information		Reference
NATIONAL (cont.)	Stationary casting or shot casting contact cooling	0.000	na	
	Pretreatment standards for primary aluminum smelting sources (B[a]P) (mg/kg)	Max. 1-day limit	Max. monthly avg.	40 CFR 421.26
	Anode and cathode paste plant wet air pollution control	0.000	na	
	Anode contact cooling and briquette quenching	0.007	0.003	
	Anode bake plant wet air pollution control	0.000	na	
	Cathode reprocessing (operating with dry potline scrubbing and not commingled)	1.181	0.547	
	Cathode reprocessing (operating with dry potline scrubbing and commingled)	1.181	0.547	
	Potline wet air pollution control	0.000	na	
	Potroom wet air pollution control	0.000	na	
	Potline SO_2 emissions wet air pollution control	0.045	0.021	
	Degassing wet air pollution control	0.000	na	
	Pot repair and pot soaking	0.000	na	
	Direct chill casting contact cooling	zero	zero	
	Continuous rod casting contact cooling	zero	zero	
	Stationary casting or shot casting contact cooling	0.000	na	
	Steam Electric Power Generating Point Source Category			40 CFR 423
	Priority pollutants for steam power generators (all PAHs)	Yes		40 CFR 423, App. A
	Metal Finishing Point Source Category			40 CFR 433
	Definition of total toxic organics (TTO) for metal refinishing (all PAHs)	Yes		40 CFR 433.11
	Metal Molding and Casting Point Source Category			40 CFR 464
	Definition of TTO for aluminum casting (Acenphthene; anthracene; B[a]A; B[a]P; chrysene; fluorene; fluoranthene; phenanthrene; pyrene)	Yes		40 CFR 464.11

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Definition of TTO for copper casting (Acenphthene; acenaphthylene; anthracene; B[a]A; B[b]F; chrysene; phenanthrene; pyrene)	Yes	40 CFR 464.21
	Definition of TTO for ferrous casting (Acenaphthene; chrysene; acenaphthylene; anthracene; fluoranthene; fluorene; phenanthrene; pyrene)	Yes	40 CFR 464.31
	Definition of TTO for zinc casting (Acenaphthene; fluoranthene)	Yes	40 CFR 464.41
	Aluminum Forming Point Source Category		40 CFR 467
	Definition of TTO for aluminum casting (Acenaphthene; acenaphtylene; anthracene; B[k]F; B[a]P; B[g,h,i]P; chrysene; DB{a,h]A; fluoranthene; fluorene, I[1,2,3-cd]P; phenanthrene; pyrene)	Yes	40 CFR 467.02
	Copper Forming Point Source Category		40 CFR 468
	Definition of TTO for copper forming (Anthracene; phenanthrene)	Yes	40 CFR 468.02
Guidelines:			
a. Air:			
ACGIH	TLV TWA; Confirmed human carcinogens		ACGIH 1991
	Coal tar pitch volatiles-benzene soluble fraction	0.2 mg/m^3	
	Phenanthrene: cyclohexane extractable fraction	1030 mg/m^3	
	Oil mist, mineral		
	TWA	5 mg/m^3	ACGIH 1991
	STEL	10 mg/m^3	
NIOSH	REL TWA		NIOSH 1992
	Coal tar pitch volatiles; B[a]P; cyclohexane extractable fraction	Ca[g]; 0.1 mg/m^3	
	Chrysene	Ca[g]; lowest feasible concentration	
	Oil mist, mineral		
	TWA	5 mg/m^3	
	STEL	10 mg/m^3	
b. Water:			
EPA OWRS	Ambient water quality criteria for protection of human health		IRIS 1994
	Ingestion of water and organisms[h]		
	PAHs	0.0028 µg/L	
	Fluoranthene	42 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)	Ingestion of organisms only PAHs Fluoranthene	0.031 µg/L 54 µg/L	
	Organoleptic effects (acenaphthene)	0.02 mg/L	
EPA OW	Drinking water standards and health advisories		EPA 1994
	Maximum contaminant level goal (B[a]P) for organic chemicals	0 mg/L	40 CFR 141.50
	Maximum contaminant level (B[a]A) (B[a]P, B[b]F, B[k]F, chrysene) (DB[ah]A) (I[123cd]P)	 0.0001 mg/L 0.0002 mg/L 0.0003 mg/L 0.0004 mg/L	
EPA	Clean Water Act: Toxic pollutants subject to the effluent standards of the Clean Water Act section 301(a)(l)		EPA 1981b (40 CFR 401.15) EPA 1991b (40 CFR 129)
	Polynuclear aromatic hydrocarbons (include: acenaphthene; benzanthracene; benzopyrenes; benzofluoranthene; chrysenes; dibenzoanthracenes; indenopyrenes; fluoranthenes)	Yes	
c. Non-specific media: EPA	Carcinogenic classification[i]		IRIS 1994
	(Fluoranthene, anthracene, acenaphthylene)	Group D	
	(B[a]A, I[123cd]P, DB[ah]A, chrysene, B[k]F, B[b]F, B[a]P)	Group B	
EPA	RfD (Oral)		IRIS 1994
	Anthracene	0.3 mg/kg/day (u.f. 3000)	
	Acenaphthene	0.06 mg/kg/day (u.f. 3000)	
	Fluoranthene	0.04 mg/kg/day (u.f. 3000)	
	Fluorene	0.04 mg/kg/day (u.f. 3000)	
	Pyrene	0.03 mg/kg/day (u.f. 3000)	
	Acenaphthylene; B[a]P; B[e]P; B[a]A; B[b]F; B[ghi]P; B[k]F; B[j]F; chrysene; DB[ah]A; I[123cd]P; BP; phenanthrene	No data	
OSHA	NRC recommendations concerning chemical hygiene in laboratories (B[a]P)	Yes	29 CFR 1910.1450, App. A

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE			
Regulations and Guidelines:			
a. Air			
	Average acceptable ambient air concentrations		NATICH 1992
Arizona			
(B[a]P; B[a]A; DB[ah]A)	1-hour average	0.79 $\mu g/m^3$	
	24-hour average	0.21 $\mu g/m^3$	
	Annual	0.00057 $\mu g/m^3$	
Connecticut			
(B[a]P;)	8-hour average	0.1000 $\mu g/m^3$	
(Coal tar pitch volatiles)	8-hour average	2.0000 $\mu g/m^3$	
(Fluorene)	8-hour average	50.000 $\mu g/m^3$	
(Naphthalene)	8-hour average	10000.0000 $\mu g/m^3$	
Florida- Ft Ldle			
Coal tar pitch volatiles	8-hour average	2.00×10^{-3} $\mu g/m$	
Florida-Pinella			
(B[a]P)	Annual	0.0003 $\mu g/m^3$	
(B[a]A)	8- and 24-hour average	0.00 $\mu g/m^3$	
	Annual	0.00110 $\mu g/m^3$	
(DB[ah]A)	Annual	7.10×10^{-5} $\mu g/m^3$	
Coal tar pitch volatiles	8-hour average	2.00 $\mu g/m^3$	
	24-hour average	0.48 $\mu g/m^3$	
Indiana			
(B[a]P)	8-hour average	0.100 $\mu g/m^3$	
	Annual	0.0006 $\mu g/m^3$	
Kansas			
(B[a]P)	Annual	3.03×10^{-4} $\mu g/m^3$	
(Coal tar pitch volatiles)	Annual	0.00161 $\mu g/m^3$	
Kansas-KC		3.03×10^{-4} $\mu g/m^3$	
(B[a]P)	Annual		
Louisiana			
(Fluoranthene)	Annual	0.0600 $\mu g/m^3$	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
Maryland (B[a]P; B[a]A; DB[ah]A; Fluorene; Fluoranthene; Acenaphthene; Acenaphthylene; Anthracene; B[b]F; B[k]F; B[ghi]P; Chrysene; I[123cd]P; Phenanthrene; Pyrene; B[e]P)		0.00 $\mu g/m^3$	
Maine (B[a]P)	Annual	5.70×10^{-4} $\mu g/m^3$	
Michigan (B[a]P)	Annual	3.00×10^{-4} $\mu g/m^3$	
Nevada (Coal tar pitch volatiles)	8-hour average	0.0050 mg/m^3	
New York (B[a]P)		0.00 $\mu g/m^3$	NATICH 1992
North Carolina (B[a]P)	Annual	3.30×10^{-5} mg/m^3	
(Coal tar pitch volatiles)	Annual	3.30×10^{-5} mg/m^3	
North Dakota (B[a]P; B[a]A; DB[ah]A; B[b]F; Chrysene; I[123cd]P)		0.00 $\mu g/m^3$	
Pennsylvania-Phila (B[a]P)	1-year average Annual	7.00×10^{-4} $\mu g/m^3$ 7.00×10^{-4} $\mu g/m^3$	
(Coal tar pitch volatiles)	1-year average	0.4800 $\mu g/m^3$	
Texas (B[a]P)	30-minute average Annual	0.03 $\mu g/m^3$ 0.003 $\mu g/m^3$	
(Chrysene)	30-minute average Annual	0.500 $\mu g/m^3$ 0.05 $\mu g/m^3$	
Virginia (B[a]P; chrysene)	24-hour average	0.00 $\mu g/m^3$	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
(Coal tar pitch volatiles)	24-hour average	2.0000 $\mu g/m^3$	
Vermont			
(B[a]P)	Annual	3.00×10^{-14} $\mu g/m^3$	
(Phenanthrene)	Annual	1.30 $\mu g/m^3$	
(Pyrene)	Annual	3.40 $\mu g/m^3$	
Washington-SWest (B[a]P)	Annual	6.00×10^{-4} $\mu g/m^3$	
Kentucky	Significant emission levels of toxic air pollutants		401 KAR 63:022 NREPC 1991
	B[a]P; B[b]F; B[a]A; DB[ah]A; I[123cd]P	5.100×10^{-7} pounds/hour	
	Chrysene; coal tar pitch volatiles	5.103×10^{-5} pounds/hour	
b. Water:			
	Water quality standards		NYSDEC 1994
New York Acenaphthene		20 µg/L	
	Drinking water quality standards		
Arizona (B[a]P)		0.003 µg/L	FSTRAC 1990
Kansas (B[a]P)		0.03 µg/L	
(All other PAHs)		0.029 µg/L	
Maine (PAHs)		25 µg/L	
Minnesota (PAHs)		0.028 µg/L	
New Hampshire (B[a]P)		0.003 µg/L	
New Mexico (B[a]P)		10 µg/L	
(All other PAHs)		30 µg/L	
New Jersey (All PAHs)		1 µg/L	NJDEP 1989

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
State (cont.)			
	ACENAPHTHYLENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	** (no value recorded)	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria	0.003 µg/L	
	Domestic Water Supply (DWS)	0.002 µg/L	
	Fish Consumption (FC)	0.12 µg/L	
	Full Body Contact (FBC)	NNS (no numerical standard)	
	Partial Body Contact (PBC)		
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply (This concentration is allowed for each of a goup of PAHs)	0.003 µg/L	
	Groundwater	0.003 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	ACENAPHTHENE		
	Water Quality: Human Health		CELDS 1994
AL	Consumption of Water and Fish	20(0) µg/L	
	Fish Consumption Only	20(0) µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	420 µg/L	
	Fish Consumption (FC)	2600 µg/L	
	Full Body Contact (FBC)	8400 µg/L	
	Partial Body Contact (PBC)	8400 µg/L	
MO	Class II Human Health Protection-Fish Consumption	2700 µg/L	
	Class III Drinking Water Supply	20 µg/L	
WI	Threshold conc. for substances causing taste and odor in water (not toxic to humans)	20 µg/L	
OH	Water Supply Public Water Supply Outside mixing zone Human health 30 day-average	20 µg/L	
DC	Numerical Standards for Water Quality Criteria for Classes (Maximum)		
	Classes A, B, C	50.0 µg/L	
	Classes D, E	20.0 µg/L	
	Water Quality: Aquatic Life		CELDs 1994
AZ	Acute Criteria for Aquatic and Wildlife Uses		
	Cold Water Fishery (A&Wc)	850	
	Warm Water Fishery (A&Ws)	850	
	Effluent Dominated Water (A&Wedw)	850	
	Ephemeral (A&We)	NNS	
	Chronic Criteria for Aquatic and Wildlife Uses		
	Cold Water Fishery (A&Wc)	550 µg/L	
	Warm Water Fishery (A&Ws)	5,500 µg/L	
	Effluent Dominated Water (A&Wedw)	NNS	
	Ephemeral (A&We)		
CO	Aquatic life segments-organic compounds to the second power		
	Standard (acute)	1,700 µg/L	
	Standard (chronic)	520 µg/L	
HI	Numeric Standards for Toxic Pollutants Applied to All Waters	570 µg/L	
	Freshwater (acute)	320 µg/L	
	Saltwater (acute)	NS (no standard developed)	
	Fish Consumption		
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone (maximum)	67 µg/L	
	Outside mixing zone (30-day average)	67 µg/L	
	Inside mixing zone (maximum)	134 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone (maximum) Inside mixing zone (maximum)	 67 µg/L 134 µg/L	
NY	Water Classes-A, A-S, AA, AA-S Standards µg/L Type-health (water source) Basis code-chem.correlation	 20 µg/L	
	Groundwater Monitoring		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Groundwater Quality Standards		CELDs 1994
MO	Class VII-Groundwater	20 µg/L	
	ANTHRACENE		
	Water Quality: Human Health		CELDs 1994
AZ	Numeric Water Quality Criteria Domestic Water Source (DWS) Fish Consumption (FC) Full Body Contact (FBC) Partial Body Contact (PBC)	 2100 µg/L 6300 µg/L 420000µg/L NNS	
MO	Human Health Protection-Fish Consumption Drinking Water Supply Groundwater	0.03 µg/L 0.003 µg/L 0.003 µg/L	
OH	Water Supply Public Water Supply		

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Outside mixing zone Human Health 30-day average	0.028 0.003 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CA		Yes	
IL		Yes	
KY		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater Outside mixing zone Human Health 30-day average	0.31 µg/L*	
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone Human Health 30-day average	0.31 µg/L*	
	*This value applies to the sum of PAHs		
	BENZ(a)ANTHRACENE		
	Hazardous Constituents		CELDs 1994
AL		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	Water Quality: Human Health		CELDs 1994
AL	Human Health Criteria:		
	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
	-Classified as a carcinogen		
AZ	Numeric Water Quality Criteria:		
	Domestic Water Source (DWS)	0.03 µg/L	
	Fish Consumption (FC)	0.00008 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
	-known, probable, or possible human carcinogen		
MO	Human Health Protection-Fish		
	Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
	Water Supply		
	Public Water Supply		
OH	Outside mixing zone		
	Human health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria*		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	*Human cancer criteria for PAHs are applicable to any combination of 10 PAHs (specific)		

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Cancer Criteria*		
	Non-Public Water Supplies		
	Warmwater Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	*Human cancer criteria are applicable to any combination of 9 PAHs.		
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L*	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L*	
	* This value applied to the sum of 13 PAHs		
	BENZO(b)FLUORANTHENE		
	Water Quality: Human Health		CELDs 1994
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L*	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 µg/L	
	Cold Water Communities	0.023 µg/L	
	Great Lakes	0.023 µg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 mg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
LA		Yes	
KY		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	BENZO(k)FLUORANTHENE		
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	
MD		Yes	
MT		Yes	
NE		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WY		Yes	
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.00001 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
OH	Water Supply		
	Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	BENZO(g,h,i)PERYLENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.0001 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
OH	Water Supply		
	Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	BENZO(a)PYRENE		
	Water Quality: Human Health Criteria		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only -Carcinogen	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.002 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
MO	Human Health Protection-Fish Consumption	0.03 µg/L 0.003 µg/L	
	Drinking Water Supply*	0.003 µg/L	
	Groundwater*		
	*These conclusions are allowed for each of the PAHs		
NM	Groundwater Standards		
	Human Health Standards	0.0007 mg/L	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
OK	Maximum Allowable Levels for Organic Chemicals	0.4 mg/L	
TN	National Primary Drinking Water		
	Standard Organic Chemicals	0.002 mg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Special Monitoring, Reporting and Public Notification Requirements for Unregulated Organic and Inorganic Contaminants Nonregulated Organic Contaminants	Yes	
	Water Quality: Aquatic Life		CELDs 1994
NY	Water Classes-GA Standards (µg/L)-ND Type-H(WS) Basis code-F		
OH	Aquatic Life Habitat-Coldwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L*	
	Aquatic Life Habitat-Limited Resource Warm Water Outside Mixing Zone Human Health 30-day average	0.31 µg/L*	
	*This value applies to the sum of 13 PAHs		
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Groundwater Quality Standards		CELDs 1994
NY	Groundwater Effluent Standard	Not detectable	
WI	Public Health Groundwater Quality Standards		
	Enforcement Standard	0.003 µg/L	
	Preventive Action	0.0003 µg/L	
	CHRYSENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.03 µg/L	
	Fish Consumption (FC)	0.0001 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	DIBENZ(a,j)ACRIDINE		
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	
LA		Yes	
KY		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MD		Yes	
MN		Yes	
MT		Yes	
NE		Yes	
ND		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	DIBENZO(a,h)ANTHRACENE		
	Water Quality: Human Health		CELDs 1994
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
AL	Human Health Criteria		
	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.00003 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		©ELDs 1994

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OH	Aquatic Life Habitat-Coldwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside Mixing Zone Human Health 30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
C0		Yes	
IL		Yes	
KY		Yes	
LA		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CA		Yes	
CO		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	FLUORANTHENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	280 µg/L	
	Fish Consumption (FC)	130 µg/L	
	Full Body Contact (FBC)	5600 µg/L	
	Partial Body Contact (PBC)	5600 µg/L	
IN	Continuous Criterion Concentration (4-Day) Average for Human Health		
	Outside of Mixing Zone	54 (T)*	
	Point of Water	42	
	*(T) - T is derived from threshold toxicity		
KY	Water Quality Criteria for Protection of Human Health from the Consumption of Fish Tissue Substances Not Linked to Cancer	54 µg/L	
	Organics		
	Domestic Water Supply Source Criteria Substances Not Linked to Cancer		
	Maximum Contaminant Level (organics)	0.042 mg/L	
MO	Drinking Water Supply	40 µg/L	
	Human Health Protection-Fish Consumption	54 µg/L	
	Groundwater	40 µg/L	
OH	Water Supply-Public Water Supply Outside Mixing Zone Human Health		
	30-day average	42 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Threshold Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	28 µg/L	
	Cold Water Communities	9.1 µg/L	
	Great Lakes	9.3 µg/L	
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	32 µg/L	
	Cold Water Communities	9.5 µg/L	
	Warm Water and Limited Fish and Limited Aquatic	41,000 µg/L	
HI	(Water Quality Standards: Basic Water Quality Criteria for All Waters)		
	Numeric Standards for Toxic Pollutants Applicable to All Waters		
	Freshwater		
	Acute	1,300 µg/L	
	Chronic	NS	
	Saltwater		
	Acute	13 µg/L	
	Chronic	NS	
	Fish Consumption	18 µg/L	
	Water Quality: Aquatic Life		CELDs 1994
AZ	Acute Criteria for Aquatic and Wildlife Uses	2000 µg/L	
	A&Wc: Cold Water Fishery	2000 µg/L	
	A&Ws: Warm Water Fishery	2000 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		
	Chronic Criteria for Aquatic and Wildlife Uses	1600 µg/L	
	A&Wc: Cold Water Fishery	1600 µg/L	
	A&Ws: Warm Water Fishery	1600 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		
CO	Aquatic Life Segments (organic compounds to the second power)	3,980 µg/L	
	Standard (acute)		
FL	Maximum Concentration Levels for Mixing Zone Pollutants	540 µg/L	
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone		
	Maximum	200 µg/L	
	30-day average	8.9 µg/L	
	Human Health		
	30-day average	54 µg/L	
	Inside Mixing Zone		
	Maximum	400 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Outside Mixing Zone Maximum Human Health 30-day average	 200 µg/L 54 µg/L	
	Inside Mixing Zone Maximum	 400 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	FLUORENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	280 µg/L	
	Fish Consumption (FC)	580 µg/L	
	Full Body Contact (FBC)	5600 µg/L	
	Partial Body Contact (PBC)	5600 µg/L	
MO	Human Health Protection-Fish	0.03 µg/L	
	Consumption	0.003 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater		
OH	Water Supply		
	Public Water Supply		
	Outside mixing zone		
	Human Health 30-day average	0.028 µg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater		
	Outside mixing zone		
	Human Health		
	30-day average	0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	INDENO(1,2,3-CD)PYRENE		
	Water Quality: Human Health Criteria		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.000003 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS µg/L	
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
OH	Water Supply-Public Water Supply		
	Outside Mixing Zone		
	Human Health		
	30-day average	0.028 µg/L	
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Human Cancer Criteria		
	Non-Public Water Supplies		
	Warm Water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OH	Aquatic Life Habitat-Coldwater Outside mixing zone Human Health 30-day average	0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone Human Health 30-day average	0.31 µg/L*	
	Hazardous Constituents		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MA		Yes	
ME		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	PHENANTHRENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Supply (DWS)	0.003 µg/L	
	Fish Consumption (FC)	0.0005 µg/L	
	Full Body Contact (FBC)	0.12 µg/L	
	Partial Body Contact (PBC)	NNS	
MO	Human Health Protection-Fish	0.03 µg/L	
	Consumption	0.003 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater		
WI	Human Cancer Criteria		
	Public Water Supplies		
	Warm Water Sport Fish Communities	0.023 mg/L	
	Cold Water Communities	0.023 mg/L	
	Great Lakes	0.023 mg/L	
	Non-Public Water Supplies		
	Warm water Sport Fish Communities	0.1 mg/L	
	Cold Water Communities	0.1 mg/L	
	Warm Water and Limited Fish and Limited Aquatic	6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994s
AZ	Acute Criteria for Aquatic and Wildlife Uses	30 µg/L	
	A&Wc: Cold Water Fishery	30 µg/L	
	A&Ws: Warm Water Fishery	540 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	Chronic Criteria for Aquatic and Wildlife Uses	6.3 µg/L	
	A&Wc: Cold Water Fishery	6.3 µg/L	
	A&Ws: Warm Water Fishery	6.3 µg/L	
	A&Wedw: Effluent Dominated Water	NNS	
	A&We: Ephemeral		
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	PYRENE		
	Water Quality: Human Health		CELDs 1994
AL	Consumption of Water and Fish	**	
	Fish Consumption Only	**	
AZ	Numeric Water Quality Criteria		
	Domestic Water Source (DWS)	210 µg/L	
	Fish Consumption (FC)	1100 µg/L	
	Full Body Contact (FBC)	4200 µg/L	
	Partial Body Contact (PBC)	4200 µg/L	
MO	Human Health Protection-Fish Consumption	0.03 µg/L	
	Drinking Water Supply	0.003 µg/L	
	Groundwater	0.003 µg/L	
OH	Water Supply		
	Public Water Supply		
	Outside mixing zone		
	Human Health		
	30-day average	0.028 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WI	Human Cancer Criteria Public Water Supplies Warm Water Sport Fish Communities Cold Water Communities Great Lakes	 0.023 mg/L 0.023 mg/L 0.023 mg/L	
	Human Cancer Criteria Non-Public Water Supplies Warm Water Sport Fish Communities Cold Water Communities Warm Water and Limited Fish and Limited Aquatic	 0.1 mg/L 0.1 mg/L 6.1 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Aquatic Life Habitat-Coldwater Outside mixing zone Human Health 30-day average	 0.31 µg/L	
	Aquatic Life Habitat-Limited Resource Warmwater Outside mixing zone Human Health 30-day average	 0.31 µg/L	
	Groundwater Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
CA		Yes	
IL		Yes	
LA		Yes	
KY		Yes	
MN		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	

[a]Degree of evidence in animals revised on the basis of data that appeared after the most recent monograph and/or on the basis of present criteria. Overall evaluation based on evidence of carcinogenicity in monograph 32, 1983.

[b]Group 2A = Probable human carcinogen

[c]Group 2B = Possible human carcinogen

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons (continued)

[d]Group 3 = Not classifiable as to carcinogenicity

[e]The following PAHs were used as indicators in deriving this standard: B[a]P; B[b]F; B[a]F; B[k]F; fluoranthene; and I[123cd]P. Source: EPA 1986b.

[f]Includes anthracene, B[a]P, phenanthrene, acridine, chrysene, and pyrene

[g]Agent recommended by NIOSH to be treated as a potential occupational carcinogen.

[h]Because of their carcinogenic potential, the EPA-recommended concentration for PAHs in ambient water is zero. However, because attainment of this level may not be possible, the recommended criteria requires a E-G estimated incremental lifetime cancer risks.

[i]Group D = not classifiable as to human carcinogenicity, Group B2 = Probable Human Carcinogen

[j]When "all PAHs" are listed, it includes the following compounds, unless specified otherwise:
Anthracene, Acenaphthylene, Acenaphthene, B[a]A, B[a]P, B[b]F, B[h]F, B[g,h,i]P, Chrysene, DB[a,h]A, Fluoranthene, Flourene, I[1,2,3-cd]P, Phenanthrene, Pyrene

ACHIH = American Conference of Govemmental Industrial Hygienists; B[a]A = Benzo[a]Anthracene; B[a]P = Benzo[a]Pyrene; B[b]F = Benzo[b]Fluoranthene; B[e]P = Benzo[e]Pyrene; B[ghi]P = Benzo(ghi)perylene; B[j]F = Benzo[j]Fluoranthene; B[k]F = Benzo[k]Fluoranthene; B[ghi]P = Benzo[ghi]perylene; BP = Benzopyrene; DB[a,h]A = Dibenz[a,h]Anthracene; DB[a,e]P = Dibenzo[a,e]pyrene; DB[a,i] = Dibenzo[a,i]pyrene; DOT = Department of Transportation; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; I[123cd]P = Indeno[1,2,3-c,d]Pyrene; ng = nanogram; NIOSH = Natinonal Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OWRS = Office of Water Regulations and Standards; PAH = Polycyclic Aromatic Hydrocarbons; PEL = Permissible Exposure Limit; RCRA = Resource Conservation and Recovery Act; REL = Recommended Exposure Limit; RfD = Reference Dose; TLV = Threshold Limit Value; TWA = Time-Weighted Average; u.f. = Uncertainty Factor; WHO = World Health Organization

8. REFERENCES

Aardema MJ, Gibson DP, Kerckaert GA, et al. 1990. Aneuploidy and nonrandom structural chromosome changes associated with early and late stages of benzo[a]pyrene-induced neoplastic transformation of Syrian hamster embryo. Environ Mol Mutagen Suppl 15(17):3.

*Abe S, Nemoto N, Sasaki M. 1983a. Comparison of aryl hydrocarbon hydroxylase activity and inducibility of sister-chromatid exchanges by polycyclic aromatic hydrocarbons in mammalian cell lines. Mutat Res 122:47-51.

*Abe S, Nemoto N, Sasaki M. 1983b. Sister-chromatid exchange induction by indirect mutagens/carcinogens, aryl hydrocarbon hydroxylase activity and benzo[a]pyrene metabolism in cultured human hepatoma cells. Mutat Res 109:83-90.

Abe S, Sasaki M. 1977. Chromosome aberrations and sister chromatid exchanges in Chinese hamster cells exposed to various chemicals. J Nat1 Cancer Inst 58:1635-1641.

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH, 143.

ACGIH. 1991. Documentation of the threshold limit values and biological exposure indices. 6th ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 504-505.

*ACGIH. 1992. 1993 Threshold limit values for chemical substances and physical agents and biological exposure indicies. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1993. 1993-1994 Threshold limit values for chemical substances and physical agents and biological exposure indicies. American Conference of Governmental Industrial Hygienists. Cincinnati, OH. Pp. 36-37.

Achard S, Perderiset M, Jaurand M-C. 1987. Sister chromatid exchanges in rat pleural mesothelial cells treated with crocidolite, attapulgite, or benzo 3-4 pyrene. Br J Ind Med 44:281-283.

*Adams JD, O'Mara-Adams J, Hoffmann D. 1987. Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes. Carcinogenesis 8:729-731.

*Adler I-D, Ingwersen I. 1989. Evaluation of chromosomal aberrations in bone marrow of lC3Fl mice. Mut Res 224(3):343-345

*Adler ID, Kliesch U, Kiefer F. 1989. Clastogenic effects of benzo[a]pyrene in postimplantation embryos with different genetic background. Teratogenesis Carcinog Mutagen 9(6):383-92.

*Agarwal R, Gupta KP, Kumar S, et al. 1986. Assessment of some tumorigenic risks associated with fresh and used cutting oil. Indian J Exp Biol 24:508-510.

*Cited in text

8. REFERENCES

*Agarwal R, Medrano EE, Khan IU, et al. 1991. Metabolism of benzo(a)pyrene by human melanocytes in culture. Carcinogenesis 12(10): 1963-1966.

Agrelo C, Amos H. 1981. DNA repair in human fibroblasts. In: Evaluation of short-term tests for carcinogens: Report of the International Collaborative Program. Prog Mutat Res 1:528-532.

*Akin FJ, Snook ME, Severson RE, et al. 1976. Identification of polynuclear aromatic hydrocarbons in cigarette smoke and their importance as tumorigens. J Nat1 Cancer Inst 57:191-195.

Alarie JP, Vo-Dinh T. 1991. Fibre-optic cyclodextrin-based sensor. Talanta 38(5):529-534.

*Alben K. 1980. Gas chromatographic-mass spectrometric analysis of chlorination effects on commercial coal-tar leachate. Anal Chem 52: 1825-l 828.

*Albert RE, Miller ML, Cody T, et al. 1991a. Benzo(a)pyrene-induced skin damage and tumor promotion in the mouse. Carcinogenesis 12(7):1273-1280.

*Albert RE, Miller ML, Cody TE, et al. 1991b. Cell kinetics and benzo[a]pyrene-DNA adducts in mouse skin tumorigenesis. Prog Clin Biol Res 369:115-22.

*Aldrich. 1986. Catalog handbook of fine chemicals. Milwaukee, WI: Aldrich Chemical Company.

*Alexandrov K, Rojas-Moreno M. 1990. *In vivo* DNA adduct formation by benzo(a)pyrene in mouse and rat epidermal and dermal fibroblasts after topical application of an initiating dose of benzo(a)pyrene. Arch Geschwulstforsch 60(5):329-340.

*Alexandrov K, Rojas-Moreno M, Goldberg M, et al. 1990. A new sensitive fluorometric assay for the metabolism of (--)-7 8-dihydroxy-7 8-dihydrobenzo[a]pyrene by human hair follicles. Carcinogenesis 11(12):2157-2161.

Alfheim I, Randahl T. 1984. Contribution of wood combustion to indoor air pollution as measured by mutagenicity in salmonella and polycyclic aromatic hydrocarbon concentration. Environ Mutagen 6:121-130.

Allen-Hoffman BL, Rheinwald JG. 1984. Polycyclic aromatic hydrocarbon mutagenesis of human epidermal keratinocytes in culture. Proc Natl Acad Sci USA 81:7802-7806.

*Alzieu P, Cassand P, Colin C, et al. 1987. Effect of vitamins A, C and glutathione on the mutagenicity of benzo[a]pyrene mediated by S9 from vitamin A-deficient rats. Mutat Res 192:227-231.

Amacher DE, Paillet SC. 1982. Hamster hepatocyte-mediated activation of procarcinogens to mutagens in the L5178Y/TK mutation assay. Mutat Res 106:305-316.

Amacher DE, Paillet SC. 1983. The activation of procarcinogens to mutagens by cultured rat hepatocytes in the L5178Y/TK mutation assay. Mutat Res 113:77-88.

Amacher DE, Turner GN. 1980. Promutagen activation by rodent-liver postmitochondrial fractions in the L5178Y/TK cell mutation assay. Mutat Res 74:485-501.

8. REFERENCES

Amacher DE, Paillet SC, Turner GN, et al. 1980. Point mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells: II. Test validation and interpretation. Mutat Res 72:447-474.

*Amin S, LaVoie EJ, Hecht SS. 1982. Identification of metabolites of benzo(b)fluoranthene. Carcinogenesis 3:171-174.

*Amin S, Hussain N, Brielmann H, et al. 1984. Synthesis and mutagenicity of dihydrodiol metabolites of benzo(b)fluoranthene. J Org Chem 49:1091-1095.

*Amin S, Huie K, Hecht S. 1985a. Mutagenicity and tumor-initiating activity of methylated benzo(b)fluoranthenes. Carcinogenesis 6: 1023-1025.

*Amin S, Hussain N, Balanikas G, et al. 1985b. Mutagenicity and tumor initiating activity of methylated benzo[k]fluoranthenes. Cancer Lett 26:343-347.

*Ampy FR, Saxena S, Verma K. 1988. Mutagenicity of benzo-a-pyrene in uninduced tissues from Balb-c mice and Sprague-Dawley rats as an index of possible health risks using the Salmonella mutagenicity assay. Cytobios 56(225):81-88.

*Andersson K, Levin J-O, Nilsson C-A. 1983. Sampling and analysis of particulate and gaseous polycyclic aromatic hydrocarbons from coal tar sources in the working environment. Chemosphere 12:197-207.

*Andrews AW, Thibault LH, Lijinsky W. 1978. The relationship between carcinogenicity and mutagenicity of some polynuclear hydrocarbons. Mutat Res 51:31l-318.

*Andrews FJ, Halliday GM, Muller HK. 1991a. A role for prostaglandins in the suppression of cutaneous cellular immunity and tumour development in benzo(a)pyrene but not dimethylbenz(a)anthracene-treated mice. Clin Exp Immunol 85(1):9-13.

*Andrews FJ, Halliday GM, Narkowicz CK, et al. 1991b. Indomethacin inhibits the chemical carcinogen benzo(a)pyrene but not dimethylbenz(a)anthracene from altering Langerhans cell distribution and morphology. Br J Dermatol 124(1):29-36.

*Antignac E, Koch B, Grolier P, et al. 1990. Prochloraz as potent inhibitor of benzo[a]pyrene metabolism and mutagenic activity in rat liver fractions. Toxicol Lett 54(2-3):309-315.

*Apostoli P, Crippa M, Fracasso ME, et al. 1993. Increases in polycyclic hydrocarbon content and mutagenicity in a cutting fluid as a consequence of its use. Int Arch Occup Environ Health 64:473-477.

Arce GT, Allen JW, Doerr CL, et al. 1987. Relationships between benzo(a)pyrene-DNA adduct levels and genotoxic effects in mammalian cells. Cancer Res 47:3388-3395.

*Arcos JC, Argus MF. 1968. Molecular geometry and carcinogenic activity of aromatic compounds. Adv Cancer Res 11:305-471.

*Ariese F, Kok SJ, Verkaik M, et al. 1993. Monitoring benzo(a)pyrene exposure using laser-excited Shpol’skii spectroscopy of benzo(a)pyrene metabolites. In: T. Vo-Dinh and K. Cammann, eds.

International conference on monitoring of toxic chemicals and biomarkers. SPIE Proceedings Series, volume 1716, 212-222.

Armstrong DW, DeMond W. 1984. Cyclodextrin bonded phases for the liquid-chromatographic separation of optical geometrical and structural isomers. J Chromatogr Sci 22(9): 411-415.

*Asher SA. 1984. UV resonance Raman spectrometry for detection and speciation of trace polycyclic aromatic hydrocarbons. Anal Chem 56:720-724.

*Assennato G, Ferri GM, Foa V, et al. 1993. Correlation between PAH airborne concentration and PAH-DNA adduct levels in coke-oven workers. Int Arch Occup Environ Health 65:S143-S145.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

*ATSDR. 1990. Toxicological profile for creosote. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

*ATSDR. 1994. Materials submitted in support of comments on toxicological profile for PAHs, regulations and advisories. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR/CDC. 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.

*Autrup H, Seremet T. 1986. Excretion of benzo[a]pyrene-Gua adduct in the urine of benzo[a]pyrene- treated rats. Chem Biol Interact 60:217-226.

*Autrup H, Harris CC, Stoner GD, et al. 1978. Metabolism of [^{3}H]benzo[*a*]pyrene by cultured human bronchus and cultured human pulmonary alveolar macrophages. Lab Invest 38:217-224.

*Avigdor S, Zakheim D, Bamea ER. 1992. Quinone reductase activity in the first trimester placenta: Effect of cigarette smoking and polycyclic aromatic hydrocarbons. Reprod Toxicol 6(4):363-336.

*Awogi T, Sato T. 1989. Micronucleus test with benzo[*a*]pyrene using a single peroral administration and intraperitoneal injection in males of the MS/Ae and CD-l mouse strains. Mutat Res 223(4):353-356.

*Ayrton AD, McFarlane M, Walker R, et al. 1990. Induction of the P-450 I family of proteins by polycyclic aromatic hydrocarbons: Possible relationship to their carcinogenicity. Toxicology 60(1-2):173-186.

*Azuine MA, Kayal JJ, Bhide SV. 1992. Protective role of aqueous turmeric extract against mutagenicity of direct-acting carcinogens as well as benzo [*alpha*] pyrene-induced genotoxicity and carcinogenicity. J Cancer Res Clin Oncol 118(6):447-452.

*Babich H, Sardana MK, Borenfreund E. 1988. Acute cytotoxicities of polynuclear aromatic hydrocarbons determined *in vitro* with the human liver tumor cell line, HepG2. Cell Biol Toxicol 4(3):295-309.

8. REFERENCES

Babson JR, Russo-Rodriquez SE, Rastetter WH, et al. 1986. *In vitro* DNA-binding of microsomally-activated fluoranthene: Evidence that the major product is a fluoranthene N_2-deoxyguanosine adduct. Carcinogenesis 7:859-865.

*Badiali D, Marcheggiano A, Pallone F, et al. 1985. Melanosis of the rectum in patients with chronic constipation. Dis Colon Rectum 28:241-245.

*Back SO, Field RA, Goldstone ME, et al. 1991. A review of atmospheric polycyclic aromatic hydrocarbons: Sources fate and behavior. Water Air Soil Pollut 60(3-4):279-300.

*Baird WM, Salmon CP, Diamond L. 1984. Benzo(e)pyrene-induced alterations in the metabolic activation of benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene by hamster embryo cells. Cancer Res 44(4):1445-1452.

Baker JE, Eisenreich SJ. 1990. Concentrations and fluxes of polycyclic aromatic hydrocarbons and polychlorinated biphenyls across the air-water interface of Lake Superior (USA and Canada). Environ Sci Technol 24(3):342-352.

*Baker JE, Eisenreich SJ, Eadie BJ. 1991. Sediment trap fluxes and benthic recycling of organic carbon, polycyclic aromatic hydrocarbons, and polychlorinated congeners in Lake Superior. Environ Sci Technol 25:500-509.

Barbieri O, Ognio E, Rossi O, et al. 1986. Embryotoxicity of benzo[a]pyrene and some of its synthetic derivatives in Swiss mice. Cancer Res 46:94-98.

Barfknecht TR, Hites RA, Cavaliers EL, et al. 1982. Human cell mutagenicity of polycyclic aromatic hydrocarbon components of diesel emissions. Dev Toxicol Environ Sci 10:277-294.

*Barnes ER, Shurtz-Swirski R. 1992. Modification of pulsatile human chorionic gonadotrophin secretion in first trimester placental explants induced by polycyclic aromatic hydrocarbons. Hum Reprod 7(3):305-310.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barnes DG, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): Description and use in health risk assessments. Volume 1, Appendix A: Integrated risk information system supportive documentation. Cincinnati, OH: US Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/g-86/0322.

Bamsley E. 1975. The bacterial degradation of fluoranthene and benzo[a]pyrene. Can J Microbial 21:1004-1008.

Barratt RW, Tatum EL. 1958. Carcinogenic mutagens. Ann NY Acad Sci 71:1072-1084.

*Barrick RC. 1982. Flux of aliphatic and polycyclic aromatic hydrocarbons to central Puget Sound from Seattle (Westpoint) primary sewage effluent. Environ Sci Technol 16:682-692.

8. REFERENCES

*Bartosek I, Guaitani A, Modica R, et al. 1984. Comparative kinetics of oral benz(a)anthracene, chrysene and triphenylene in rats: Study with hydrocarbon mixtures. Toxicol Lett 23:333-339.

*Bassett DJP, Bowen-Kelly E, Seed JL. 1988. Rat lung benzo[a]pyrene metabolism following three days continuous exposure to 0.6 ppm ozone. Res Commun Chem Pathol Pharmacol 60:291-307.

*Basu DK, Saxena J. 1978a. Monitoring of polynuclear aromatic hydrocarbons in water: II. Extraction and recovery of six representative compounds with polyurethane foams. Environ Sci Technol 12:791-795.

*Basu DK, Saxena J. 1978b. Polynuclear aromatic hydrocarbons in selected U.S. drinking waters and their raw water sources. Environ Sci Technol 12:795-798.

*Bayer U. 1979. *In vivo* induction of sister chromatid exchanges by three polyaromatic hydrocarbons. Carcinogenesis 3:423-428.

*Becher G. 1986. Determination of exposure to PAH by analysis of urine samples. Banbury Report., 33-44.

*Becher G, Bjorseth A. 1983. Determination of exposure to polycyclic aromatic hydrocarbons by analysis of human urine. Cancer Lett 17:301-311.

*Becher G, Bjorseth A. 1985. A novel method for the determination of occupational exposure to polycyclic aromatic hydrocarbons by analysis of body fluids. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Mechanisms, methods and metabolism. Columbus, OH: Battelle Press, 145-155.

*Becher G, Haugen A, Bjorseth A. 1984. Multimethod determination of occupational exposure to polycyclic aromatic hydrocarbons in an aluminum plant. Carcinogenesis 5:647-651.

*Bechtold WE, Sun JD, Wolff RK, et al. 1991. Globin adducts of benzo[a]pyrene: Markers of inhalation exposure as measured in F344/N rats. J Appl Toxicol 11(2):115-118.

*Behymer TD, Hites RA. 1988. Photolysis of polycyclic aromatic hydrocarbons adsorbed on fly ash. Environ Sci Tech 22:1311-1319.

*Beniot FM, Lebel GL, Williams DT. 1979. The determination of polycyclic aromatic hydrocarbons at the ng/L level in Ottawa, Canada tap water. Int J Environ Anal Chem 6:277-288.

*Benjamin H, Storkson J, Tallas PG, et al. 1988. Reduction of benzo[a]pyrene-induced forestomach neoplasms in mice given nitrite and dietary soy sauce. Food Chem Toxicol 26(8):671-678.

*Benner BA Jr., Gordon GE. 1989. Mobile sources of atmospheric polycyclic aromatic hydrocarbons: a roadway tunnel study. Environ Sci Technol 23:1269-1278.

Benson JM, Royer RE, Galvin JB, et al. 1983. Metabolism of phenanthridone to phenanthridone by rat lung and liver microsomes after induction with benzo(a)pyrene and Aroclor. Toxicol Appl Pharmacol 68(1):36-42.

8. REFERENCES

*Berenblum I, Haran H. 1955. The influence of croton oil and of polyethylene glycol-400 on carcinogenesis in the forestomach of the mouse. Cancer Res 15:510.

Bevan DR, Sadler VM. 1992. Quinol diglucuronides are predominant conjugated metabolites found in bile of rats following intratracheal instillation of benzo[a]pyrene. Carcinogenesis 13(3):403-407.

*Bevan DR, Ulman MR. 1991. Examination of factors that may influence disposition of benzo(a)pyrene *in vivo*: Vehicles and asbestos. Cancer Lett 57(2):173-180.

*Bevan DR, Weyand EH. 1988. Compartmental analysis of the disposition of benzo[a]pyrene in rats. Carcinogenesis 9(11):2027-2032.

*Bewley R, Ellis B, Theile P, et al. 1989. Microbial clean-up of contaminated soil. Chem Indus 4:778-783.

Bhatia AL, Tausch H, Stehlik G. 1987. Mutagenicity of chlorinated polycyclic aromatic compounds. Ecotoxicol Environ Safety 14:48-55.

*Biancifiori C, Caschera F. 1962. The relation between pseudopregnancy and the chemical induction by four carcinogens of mammary and ovarian tumours in BALB/c mice. Br J Cancer 16:722-730.

Bieri RH, Greaves J. 1987. Characterization of benzo(a)pyrene metabolites by high performance liquid chromatography-mass spectrometry with a direct liquid introduction interface and using negative chemical ionization. Biomed Environ Mass Spectrum 14:555-561.

Bieri RH, Hein C, Huggett RJ, et al. 1986. Polycyclic aromatic hydrocarbons in surface sediments from the Elizabeth river subestuary. Int J Environ Anal Chem 26:97-113.

*Bingham E, Falk HL. 1969. Environmental carcinogens: The modifying effect of carcinogens on the threshold response. Arch Environ Health 19:779-783.

*Bingham E, Horton AW, Tye R. 1965. The carcinogenic potency of certain oils. Arch Environ Health 10:449-451.

*Bjorseth A, Olufsen BS. 1983. Long-range transfer of polycyclic aromatic hydrocarbons. In: Bjorseth A, ed. Handbook of PAH. New York, NY: M. Dekker, Inc., 507.

*Bjorseth A, Bjorseth 0, Fjedstad PE. 1978a. Polycyclic aromatic hydrocarbons in the work atmosphere: I. Determination. Stand J Work Environ Health 4:212-223.

Bjorseth A, Bjorseth 0, Fjedstad PE. 1978b. Polycyclic aromatic hydrocarbons in the work atmosphere: II. Determination in a coke plant. Stand J Work Environ Health 4:224-236.

Bjorseth A, Bjorseth 0, Fjedstad 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. Stand J Environ Health 7:223-232.

*Bjelogrlic NM, Makinen M, Stenback F, et al. 1994. Benzo(a)pyrene-7,8-diol- 9,10-epoxide-DNA adducts and increased ~53 protein in mouse skin. Carcinogenesis 15(4):77 l-774.

8. REFERENCES

Black JJ, Dymerski PP, Zapisek WF. 1979. Routine liquid chromatographic method for assessing poly nuclear aromatic hydrocarbon pollution in fresh water environments. Bull Environ Contam Toxicol 22:278-284.

*Black WV, Kosson DS, Ahlert RC. 1989. Characterization and evaluation of environmental hazards in a large metropolitan landfill. In: Bell JM, ed. Proceedings of the Industrial Waste Conference. Chelsea, MI: Lewis Publishers, Inc. 147-152.

*Blackbum GM, Taussig PE. 1975. The photocarcinogenicity of anthracene: Photochemical binding to deoxyribonucleic acid in tissue culture. Biochem J 149:289-291.

*Blanton RH, Myers MJ, Bick PH. 1988. Modulation of immunocompetent cell populations by benzo(a)pyrene. Toxicol Appl Pharmacol 93:267-274.

*Blanton RJ, Lyte M, Myers MJ, et al. 1986. Immunomodulation by polyaromatic hydrocarbons in mice and murine cells. Can Res 46:2735-2739.

Bock FG, King DW. 1959. A study of the sensitivity of the mouse forestomach toward certain polycyclic hydrocarbons. J Natl Cancer Inst 23:833.

*Bock FG, Mund R. 1958. A survey of compounds for activity in the suppression of mouse sebaceous glands. Cancer Res 18:887-892.

*Bornpart G. 1990. *In vivo* effect of molybdenum on benzo(a)pyrene metabolism in liver and lung rat microsomes. J Toxicol Clin Exp 10(2):95-104.

*Bornpart G, Claments S. 1990. *In vitro* and *in vivo* benzo(a)pyrene metabolism in rat liver and lung microsomes: effect of sodium selenite. J Toxicol Clin Exp 10(1):3-14.

*Bornpart G, Puig P, Pipy B, et al. 1989. *In vitro* influence of molybdenum on benzo[a]pyrene metabolism in hepatic and pulmonary rat microsomes. J Toxicol Environ Health 26(4):459-468.

*Bond JA, Harkema JR, Russell VI. 1988. Regional distribution of xenobiotic metabolizing enzymes in respiratory airways of dogs. Drug Metab Dispos 16:116-124.

*Borden RC, Lee MD, Thomas JM, et al. 1989. In situ measurement and numerical simulation of oxygen limited biotransformation. Groundwater Monit Rev (winter):83-91.

*Borlakoglu JT, Scott A, Wolf CR, et al. 1993. Treatment of lactating rats with PCBs induces CYPlAl and enhances the formation of BP 7,8-dihydrodiol, the proximate carcinogen of benzo(a)pyrene. Int J Biochem 25(8):1209-1214.

Bos RP, Prinsen WJ, Van Rooy JG, et al. 1987. Fluoranthene: A volatile mutagenic compound, present in creosote and coal tar. Mutat Res 187:119-125.

Bos RP, Theuws JL, Jongeneelen FJ, et al. 1988. Mutagenicity of bi-, tri-, and tetracylcic aromatic hydrocarbons in the “taped-plate assay” and in the conventional salmonella mutagenicity assay. Mutat Res 204:203-206.

8. REFERENCES

*Bossert ID, Bartha R. 1986. Structure-biodegradability relationships of polycyclic aromatic hydrocarbons in soil. Bull Environ Contam Toxicol 37:490-495.

Bottomly AC, Twort CC. 1934. The carcinogenicity of chrysene and oleic acid. Am J Cancer 21:781-786.

Boyland E. 1986. The metabolism of foreign compounds and the induction of cancer. Xenobiotica 16899-913.

Boyland E, Sims P. 1967. The carcinogenic activities in mice of compounds related to benz(a)anthracene. Int J Can 2:500-504.

Bozicevic Z, Cvitas T, Curie M, et al. 1987. Airborne polycyclic aromatic hydrocarbons in the city of Zagreb, Yugoslavia. Sci Total Environ 66:127-136.

*Brandt HCA, Molyneux MKB. 1985. Sampling and analysis of bitumen fumes. Part 2: Field exposure measurements. 47-58.

*Brandys J, Lipniak M, Piekoszewski W. 1989. Determination of polycyclic aromatic hydrocarbons in rat tissue by HPLC. Chem Anal 34(3-6): 449-452.

Brauze D, Mikstacka R, Baer-Dubowska W. 1991. Formation and persistence of benzo[a]pyrene-DNA adducts in different tissues of C57BL/l0 and DBA/2 mice. Carcinogenesis 12(9):1607-1611.

Breuer GM. 1984. Solvents and techniques for the extraction of polynuclear aromatic hydrocarbons from filter samples of diesel exhaust. Anal Lett 17:1293-1306.

*Broman D, Naf C, Lundbergh I, et al. 1990. An in situ study on the distribution biotransformation and flux of polycyclic aromatic hydrocarbons (PAHs) in an aquatic food chain (*seston Mytilus edulis L* and *Somateria mollissima* L) from the Baltic: An ecotoxicological perspective. Environ Toxicol Chem 9(4):429-442.

*Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. Washington, DC: The C.V. Mosby Company, 221-222.

*Brown RA, Weiss FT. 1978. Fate and effects of polynuclear aromatic hydrocarbons in the aquatic environment. Washington, D.C: American Petroleum Institute. Publication no. 4297.

Bruce WR, Heddle JA. 1979. The mutagenic activity of 61 agents as determined by the micronucleus, salmonella, and sperm abnormality assays. Can J Genet Cytol 21:319-334.

Bruchlos E, Dogra S, Pauly K, et al. 1989. Formation of micronuclei in mouse bone marrow by benzo(a)pyrene and benzo(a)pyrene metabolites, and the role of induction of xenobiotic-metabolizing enzymes. Mutagenesis 4:307.

*Brune H, Deutsch-Wenzel RP, Habs M, et al. 1981. Investigation of the tumorigenic response to benzo(a)pyrene in aqueous carreine solution applied orally to Sprague-Dawley rats. J Cancer Res Clin Oncol 102(2):153-157.

8. REFERENCES

*Brunnemann KD, Prokopczyk B, Hoffmann D, et al. 1986. Laboratory studies on oral cancer and smokeless tobacco. Banbury Report 23:197-213.

Bryant MF, Erexson GL, Kwanyuen P, et al. 1989. Sister chromatid exchange and micronucleus analysis in rat peripheral blood lymphocytes after *in vivo* exposure to benzo(a)pyrene. Environ Mol Mutagen 14(suppl 15):30.

Bryant MF, Kwanyuen P, Atwater AL, et al. 1991. Cytogenetic effects of benzo-b-fluoranthene in Sprague-Dawley rat peripheral blood lymphocytes after *in-vivo* exposure. Environ Mol Mutagen Suppl 19:13-17.

*Buckley TJ, Lioy PJ. 1992. An examination of the time course from human dietary exposure to polycyclic aromatic hydrocarbons to urinary elimination of 1-hydroxypyrene. Br J Ind Med (England) 49(2):113-124.

*Buening MK, Levin W, Karle JM, et al. 1979a. Tumorigenicity of bay region epoxides and other derivatives of chrysene and phenanthrene in newborn mice. Cancer Res 39:5063-5068.

Buening MK, Levin W, Wood A, et al. 1979b. Tumorigenicity of the dihydrodiols of dibenz(a,h)anthracene on mouse skin and in newborn mice. Cancer Res 39:1310-1314.

*Bui QQ, Tran MB, West WL. 1986. A comparative study of the reproductive effects of methadone and benzo[a]pyrene in the pregnant and pseudopregnant rat. Toxicol 42:195-204.

*Bulay QM, Wattenberg LW. 1971. Carcinogenic effects of polycyclic hydrocarbon carcinogen administration to mice during pregnancy on the progeny. J Nat1 Cancer Inst 46:397-402.

Buonicore AJ. 1979. Analyzing organics in air emissions. Environ Sci Technol 13:1340-1342.

*Burford MD, Hawthorne SB, Miller DJ. 1993. Extraction rates of spiked versus native PAHs from heterogeneous environmental samples using supercritical fluid extraction and sonication in methylene chloride. Anal Chem 65:1497-1505.

Burlinson B, Ashby J. 1988. Inactivity of benzo(a)pyrene in a weanling rat liver, unscheduled DNA synthesis assay. In: Evaluation of short-term tests for carcinogens: Report of the International Collaborative Program. Prog Mutat Res 1:389-390.

*Busbee DL, Norman JO, Ziprin RL. 1990. Comparative uptake, vascular transport and cellular internalization of aflatoxin B 1 and benzo(a)pyrene. Arch Toxicol 64(4):285-290.

Busby WF, Goldman ME, Newbeme PM, et al. 1984. Tumorigenicity of fluoranthene in a newborn mouse lung adenoma bioassay. Carcinogenesis 5:1311-1316.

Busby WF Jr, Stevens EK, Martin CN, et al. 1989. Comparative lung tumorigenicity of parent and mononitro-polynuclear aromatic hydrocarbons in the BLU:Ha newborn mouse assay. Toxicol Appl Pharmacol 99(3):555-563.

*Bushby B, Femandes A, Wallace D, et al. 1993. Determination of trace organic micropollutants in atmospheric deposition. Sci Tot Environ 135:81-94.

8. REFERENCES

*Butler JD, Crossley P. 1981. Reactivity of polycyclic aromatic hydrocarbons adsorbed on soot particles. Atmos Environ 15:91-94.

Butler HT, Coddens ME, Poole CF. 1984a. Qualitative identification of polycyclic aromatic hydrocarbons by high performance thin-layer chromatography and fluorescence scanning densitometry. J Chromatogr 290:113-126.

Butler JD, Butterworth V, Kellow C, et al. 1984b. Some observations on the polycyclic aromatic hydrocarbon (PAH) content of surface soils in urban areas. Sci Total Environ 38:75-85.

*Butler JP, Post GB, Lioy PJ, et al. 1993. Assessment of carcinogenic risk from personal exposure to benzo(a)pyrene in the total human environmental exposure study (THEES). J Air Waste Manag Assoc 43:970-977.

Byczkowski JZ, Gessner T. 1989. Effects of inhibition of NADPH:cytochrome P-450 reductase on benzo(a)pyrene metabolism in mouse liver microsomes. Grace Cancer Drug Center, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, NY. Int J Biochem 21(5):525-529.

*Calabrese E. 1978. Pollutants and high risk groups: The biological basis of increased human susceptibility to environmental and occupational pollutants. New York, NY: John Wiley and Sons.

*Callahan MA, Slimak MW, Gabel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants volume II. Washington, DC: U.S. Environmental Protection Agency. EPA-440/4-79-029B.

*Carraway JW, Doyle JR. 1991. Innovative remedial action at a wood-treating Superfund site. Tappi J 74:113-118.

Carver JH, Machado ML, MacGregor JA. 1986. Application of modified salmonella/microsome prescreen to petroleum-derived complex mixtures and polynuclear aromatic hydrocarbons (PAHs). Mutat Res 174:247-253.

Casto BC. 1973. Enhancement of adenovirus transformation by treatment of hamsters with ultraviolet irradiation, DNA base analogs, and dibenz(a,h)anthracene. Cancer Res 33:402-407.

Casto BC, Pieczynski WJ, Dipaolo JA. 1973. Enhancement of adenovirus transformation be pretreatment of hamster cells with carcinogenic polycyclic hydrocarbons. Cancer Res 33:819-824.

Casto BC, Janosko N, DiPaolo JA. 1977. Development of a focus assay model for transformation of hamster cells *in vitro* by chemical carcinogens. Cancer Res 37:3508-3515.

*Cavalieri EL, Mailander P, Pelfrene A. 1977. Carcinogenic activity of anthanthrene on mouse skin. Z Krebsforsch Klin 89:113-118.

*Cavalieri EL, Devanesan PD, Cremonesi P, et al. 1987. Radical cations of polycyclic aromatic hydrocarbons (PAHs) in the binding. Proceedings of the American Association for Cancer Research Annual Meeting 28:129.

8. REFERENCES

Cavalieri EL, Devanesan PD, Rogan EG. 1988a. Radical cations in the horseradish peroxidase and prostaglandin H synthase mediated metabolism and binding of benzo[a]pyrene to deoxyribonucleic acid. Biochem Pharmacol 37:2183-2187.

*Cavalieri EL, Rogan E, Cremonesi P, et al. 1988b. Tumorigenicity of 6-halogenated derivatives of benzo[a]pyrene in mouse skin and rat mammary gland. J Cancer Res Clin Oncol 114:10-15.

Cavalieri EL, Rogan E, Sinha D. 1988c. Carcinogenicity of aromatic hydrocarbons directly applied to rat mammary gland. J Cancer Res Clin Oncol 114:3-9.

*CavaIieri EL, Higginbotham S, Ramakrishna N VS, et al. 1991. Comparative dose-response tumorigenicity studies of dibenzo(a)pyrene versus 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene and two dibenzo(a)pyrene dihydrodiols in mouse skin and rat mammary gland. Carcinogenesis 12(10):1939-1944.

*CELDS. 1994. Computer-aided Environmental Legislative Data Systems. United States Army Corps of Engineers Environmental Technical Information systems, University of Illinois, Urbana, IL. September 1992.

*Cerniglia CE. 1993. Biodegradation of polycyclic aromatic hydrocarbons. Curr Opinion Biotechnol 4:331-338.

*Cemiglia CE, Gibson DT. 1979. Oxidation of benzo[a]pyrene by the filamentous fungus *Cunninghamella elegans.* J Biol Chem 254:12174-12180.

*Cemiglia CE, Heitkamp MA. 1989. Microbial degradation of polycyclic aromatic hydrocarbons in the aquatic environment. In: Varanasi U, ed. Metabolism of polycyclic aromatic hydrocarbons in the aquatic environment. Boca Raton, FL: CRC Press, 41-68.

*Cervello I, Lafuente A, Giralt M, et al. 1992. Enhanced glutathione S-transferase (GST) activity in pregnant rats treated with benzo(a)pyrene. Placenta (England) 13(3):273-280.

*Chae YH, Ho DK, Cassady JM, et al. 1992. Effects of synthetic and naturally occurring flavonoids on metabolic activation of benzo[a]pyrene in hamster embryo cell cultures. Chem Biol Interact (Ireland) 82(2):181-193.

*Chakradeo PP, Kayal JJ, Bhide SV. 1993. Effect of benzo(a)pyrene and methyl(acetoxymethyl)nitrosamine on thymidine uptake and induction of aryl hydrocarbon hydroxylase activity in human fetal oesophageal cells in culture. Cell Biol Int 17(7):671-676.

*Chaloupka K, Harper N, Krishnan V, et al. 1993. Synergistic activity of polynuclear aromatic hydrocarbon mixtures as aryl hydrocarbon (Ah) receptor agonists. Chem-Bio Interact 89:141-158.

*Chang LH. 1943. The fecal excretion of polycyclic hydrocarbons following their administration to the rat. J Biol Chem 151:93-99.

*Chang RL, Levin W, Wood AW, et al 1981. Tumorigenicity of the diastereomeric bay-region benzo(e)pyrene 9,10-diol-11,12-epoxides in newborn mice. Cancer Res 41:915-918.

8. REFERENCES

*Cheung Y-L, Gray TJB, Ioannides C. 1993. Mutagenicity of chrysene, its methyl and benzo derivatives, and their interactions with cytochromes P-450 and the Ah-receptor; relevance to their carcinogenic potency. Toxicology 81:69-86.

*Chipman JK, Bhave NA, Hirom PC, et al. 1982. Metabolism and excretion of benzo(a)pyrene in the rabbit. Xenobiotica 12:397-404.

*Chou MW, Kong J, Chung K-T, et al. 1993. Effect of caloric restriction on the metabolic activation of xenobiotics. Mutat Res 295:223-235.

*Christou M, Moore CJ, Gould MN, et al. 1987. Induction of mammary cytochromes P-450: An essential first step in the metabolism of 7,12-dimethylbenz[a]anthracene by rat mammary epithelial cells. Carcinogenesis 8:73-80.

*Chu EW, Malmgren RA. 1965. An inhibitory effect of vitamin A on the induction of tumors in the forestomach and cervix in the Syrian hamster by carcinogenic polycyclic hydrocarbons. Cancer Res 25:884-895.

*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 Part B Urban Atmos 25(3):369-380.

Clive D, Johnson KO, Spector JFS, et al. 1979. Validation and characterization of the L5178Y/TK+/l- mouse lymphoma mutagen assay system. Mutat Res 59:61-108.

*Clonfero E, Jongeneelen F, Zordan M, et al. 1989. Biogical monitoring of human exposure to coal tar urinary mutagenicity assays and analytical determination of polycyclic aromatic hydrocarbon: Metabolites in urine. In: Vainio H, Sorsa M, McMichael J, eds. Complex mixtures, No. 104. Lyon, France: International Agency for Research on Cancer, 215-222.

*Clonfero E, Jongeneelen FJ, Zordan M, et al. 1990. Biological monitoring of human exposure to coal tar. Urinary mutagenicity assays and analytical determination of polycyclic aromatic hydrocarbon metabolites in urine. In: Vainio H, Sorsa M, McMichael AJ, eds. Complex mixtures and cancer risk. International Agency for Research on Cancer. Lyon, France: IARC Sci. Publ. No. 104, 215-222.

*CLPSD. 1988. Contract Laboratory Program Statistical Database. US Environmental Protection Agency, Contract Laboratory Program.

Coccioli F, Ronchetti M, et al. 1986. Determination of polycyclic aromatic hydrocarbons in natural waters by thin-layer chromatography and high-performance liquid chromatography. J Chromatogr 370:157-163.

Cohen GM. 1990. Pulmonary metabolism of foreign compounds its role in metabolic activation. Environ Health Perspect 85:31-42.

*Cohen GM, Haws SM, Moore BP, et al. 1976. Benzo(a)pyren-3-yl hydrogen sulfate, a major ethyl acetate-extractable metabolite of B(a)P in human, hamster and rat lung cultures. Biochem Pharmacol 25:2561-2570.

8. REFERENCES

*Cole RH, Frederick RE, Nealy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program journal. J Water Pollut Control Fed 56:898-908.

Collins JF, Brown JP, Dawson SV, et al. 1991. Risk assessment for benzo(a)pyrene. Regul Toxicol Pharmacol 13(2):170-184.

Coombs MM, Dixon C, Kissonerghis A-M. 1976. Evaluation of the mutagenicity of compounds of known carcinogenicity, belonging to the benz(a)anthracene, chrysene, and cyclopenta(a)phenanthrene series, using Ames' tests. Cancer Res 36:4525-2529.

*Coover MP, Sims RC. 1987. The effects of temperature on polycyclic aromatic hydrocarbon persistence. Haz Waste Haz Mat 4:69-82.

Cosma GN, Jamasbi R, Marchok AC. 1988. Growth inhibition and DNA damage induced by benzo[a]pyrene and formaldehyde in primary cultures of rat tracheal epithelial cells. Mutat Res Sep 201(1):161-168.

Cosma GN, Marchok AC. 1988. Benzo[a]pyrene- and formaldehyde-induced DNA damage and repair in rat tracheal epithelial cells. Toxicology 51(2-3):309-320.

*Cottini GB, Mazzone GB. 1939. The effects of 3,4-benzpyrene on human skin. Am J Cancer 37:186-195.

*Creasia DA, Poggenburg JK, Nettesheim P. 1976. Elution of benzo(a)pyrene from carbon particles in the respiratory tract of mice. J Toxicol Environ Health 1:967-975

Crespi CL, Liber HL, Behymer TD, et al. 1985. A human cell line sensitive to mutation by particle-borne chemicals. Mutat Res 157:71-75.

*Csaba C, Inczefi-Gonda A. 1992. Benzpyrene exposure at 15 days of prenatal life reduces the binding capacity of thymic glucocorticoid receptors in adulthood. Gen Pharmacol 23(1):123-124.

*Csaba G, Inczefi-Gonda A, Szeberenyi S. 1991. Lasting impact of a single benzpyrene treatment in pre-natal and growing age on the thymic glucocorticoid receptors of rats. Gen Pharmacol 22(5):815-818.

*Gulp SJ, Beland FA. 1994. Comparison of DNA adduct formation in mice fed coal tar or benzo(a)pyrene. Carcinogenesis 15(2):247-252.

*Dahl AR, Coslett DC, Bond JA, et al. 1985. Metabolism of benzo(a)pyrene on the nasal mucosa of Syrian hamsters: Comparison to by other extrahepatic tissues and possible role of nasally produced metabolites in carcinogenesis. J Nat1 Cancer Inst 75:135-139.

*Dale MJ, Jones AC, Pollard JT, et al. 1993. Application of two-step laser mass spectrometry to the analysis of polynuclear aromatic hydrocarbons in contaminated soils. Environ Sci Technol 27:1693-1695.

8. REFERENCES

*Danheiser SL, Liber HL, Thilly WG. 1989. Long-term low-dose benzo-alpha-pyrene-induced mutation in human lymphoblasts competent in xenobiotic metabolism. Mutat Res 210(1):143-148.

*Daniel PM, Pratt OE, Prichard MML. 1967. Metabolism of labelled carcinogenic hydrocarbons in rats. Nature 215:1142-1146.

*Dankers J, Groenenboom M, Scholtis LHA, et al. 1993. High-speed supercritical fluid extraction method for routine measurement of polycyclic aromatic hydrocarbons in environmental soils with dichloromethane as a static modifier. J Chromatogr 641:357-362.

*Dankovic DA, Wright CW, Zangar RC, et al. 1989. Complex mixture effects on the dermal absorption of benzo[a]pyrene and other polycyclic aromatic hydrocarbons from mouse skin. J Appl Toxicol 9(4):239-244.

*Danz M, Brauer R. 1988. Carcinogenic and non-carcinogenic fluorene derivatives: Induction of thymocyte stimulating serum factors by 2-acetylaminofluorene (AAF) and their synergy with lymphocyte mitogens. Exp Pathol 34(4):217-221.

*Danz M, Hartmann A, Otto M, et al. 1991. Hitherto unknown additive growth effects of fluorene and 2-acetylaminofluorene on bile duct epithelium and hepatocytes in rats. Arch Toxicol Suppl 14:71-74.

*Darby FW, Willis AF, Winchester RV. 1986. Occupational health hazards from road construction and sealing work. Ann Occup Hyg 30(4):445-454.

*Dasgupta PS, Lahiri T. 1992. Alteration of brain catecholamines during growth of benzo(a)pyrene induced murine fibrosarcoma. Neoplasma 39(3): 163-165.

*Davidson GE, Dawson GWP. 1976. Chemically induced presumed somatic mutations in the mouse. Mutat Res 38:151-154.

*Davidson GE, Dawson GWP. 1977. Induction of somatic mutations in mouse embryos by benzo[a]pyrene. Arch Toxicol 38:99-103.

Davis BR, Whitehead JK, Gill ME, et al. 1975. Response of rat lung to 3,4-benzpyrene administered by intratracheal instillation in infusine with or without carbon black. Br J Cancer 31:443-452.

*Day BW, Skipper PL, Wishnok JS, et al. 1990. Identification of an *in vivo* chrysene diol epoxide adduct in human hemoglobin. Chem Res Toxicol 3(4):340-343.

*De Bruin A. 1976. Metabolism of chemical carcinogens and their interactions with macromolecules. In: Biochemical toxicology of environmental agents. Amsterdam, Netherlands: Elsevier/North-Holland Biomedical Press, 230-231.

*De Flora S, D'Agostini F, Izzotti A, et al. 1991. Prevention by N-acetylcysteine of benzo[a]pyrene clastogenicity and DNA adducts in rats. Mutat Res 250(1-2):87-93.

*de Vos RH, Van Dokkum W, Schouten A. 1990. Polycyclic aromatic hydrocarbons in Dutch total diet samples (1984-1986). Food Chem Toxicol 28(4):263-268.

8. REFERENCES

Dean BJ. 1981. Activity of 27 coded compounds in the RLl chromosome assay. In: Evaluation of short-term tests for carcinogens: Report of the International Collaborative Program. Prog Mutat Res 1570-579.

*Dean RG, Bynum G, Jacobson-Kram D, et al. 1983. Activation of polycyclic hydrocarbons in Reuber H4-II-E hepatoma cells. Mutat Res 111:419-427.

Delclos KB, Heflich RH. 1992. Mutation induction and DNA adduct formation in Chinese hamster ovary cells treated with 6-nitrochrysene, 6-aminochrysene and their metabolites. Mutat Res 279(3):153-164.

*DeLeon IR, Byrne CJ, Peuler EL, et al. 1986. Trace organic and heavy metal pollutants in the Mississippi River. Chemosphere 15:795-805.

*Demuth S, Casillas E, Wolfe DA, et al. 1993. Toxicity of saline and organic solvent extracts of sediments from Boston Harbor, Massachusetts and the Hudson River-Raritan Bay Estuary, New York using the Microtox bioassay. Arch Environ Contam Toxicol 25:377-386.

Den Hollander H, Van de Meent D, Van Noort P, et al. 1986. Wet deposition of polycyclic aromatic hydrocarbons in the Netherlands. Sci Total Environ 52:211-219.

*Desiderie PG, Lepri L, Heimler D, et al. 1984. Concentration, separation and determination of hydrocarbons in sea water. J Chromatogr 284:167-178.

Desilets DJ, Kissinger PT, Lytle FE, et al. 1984. Determination of polycyclic aromatic hydrocarbons in biomass gasifier effluents with liquid chromatography-diode array spectroscopy. Environ Sci Technol 18:386-391.

Deutsch-Wenzel RP, Bmne H, Grimmer G, et al. 1983. Experimental studies in rat lungs on the carcinogenicity and dose-response relationships of eight frequently occurring environmental polycyclic aromatic hydrocarbons. J Nat1 Cancer Inst 71:539-544.

*Diamond L, Kruszewski F, Knowles BB, et al. 1980. Metabolic activation of B[a]P by a human hepatoma cell line. Carcinogenesis 1:871-875.

*DiGiovanni J, Rymer J, Slaga TJ, et al. 1982. Anticarcinogenic and cocarcinogenic effects of benzo[e]pyrene and dibenz[u,c]anthracene on skin tumor initiation by polycyclic hydrocarbons. Carcinogenesis 3(4):371-375.

DiPaolo JA, Casto BC. 1976. *In vitro* transformation--Interaction of chemical carcinogens with viruses and physical agents. Int Agency Res. Cancer Scientific Publications 12:415-432.

DiPaolo JA, Donovan JP, Nelson RL. 1969. Quantitative studies of *in vitro* transformation by chemical carcinogens. J Nat1 Cancer Inst 42:867-876.

DiPaolo JA, Donovan JP, Nelson RL. 1971. Transformation of hamster cells *in vitro* by polycyclic hydrocarbons without cytotoxicity. Proc Nat1 Acad Sci (USA) 68:2958-2961.

8. REFERENCES

Dipple A, Bigger CAH. 1991. Mechanism of action of food-associated polycyclic aromatic hydrocarbon. Carcinogens. Mutat Res 259(3-4):263-276.

*Doak SMA, Brown VKH, Hunt PF, et al. 1983. The carcinogenic potential of twelve refined mineral oils following long-term topical application. Br J Cancer 48:429-436.

Dock L, Scheu G, Jemstrom B, et al. 1988. Benzo[a]pyrene metabolism and induction of enzyme-altered foci in regenerating rat liver. Chem Biol Interact 67(3-4):243-253.

Dorman BH, Genta VM, Mass MJ, et al. 1981. Benzo(a)pyrene binding to DNA in organ cultures of human endometrium. Cancer Res 41:2718-2722.

*DOT. 1990. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101.

*DOT. 1991. Hazardous materials transport. Department of Transportation. Code of Federal Regulations. 49 CFR 171.2.

*Dufresne A, Lesage J, Perrault G. 1987. Evaluation of occupational exposure to mixed dusts and polycyclic aromatic hydrocarbons in silicon carbide plants. Am Ind Hyg Assoc J 48(2):160-166.

*Dumont J, Larocque-Lazure F, Iorio C. 1993. An alternative isolation procedure for the subsequent determination of benzo(a)pyrene in total particulate matter of cigarette smoke. J Chromatogr Sci 31:371-374.

Duncan ME, Brookes P. 1972. Metabolism and macromolecular binding of dibenz(a,c)anthracene and dibenz(a,h)anthracene by mouse embryo cells in culture. Int J Cancer 9(2):349-352.

Dunkel VC, Pienta R-J, Sivak A, et al. 1981. Comparative neoplastic transformation responses of Balb 3T3 cells, Syrian hamster embryo cells, and Rauscher mm-me leukemia virus-infected Fischer 344 rat embryo cells to chemical carcinogens. J Nat1 Cancer Inst 67:1303-1315.

Dunkel VC, Zeiger E, Brusick D, et al. 1984. Reproducibility of microbial mutagenicity assays: 1. Tests with *Salmonella typhimurium* and *Escherichia coli* using a standardized protocol. Environ Mutagen 6: l-251.

*Dynamac Corp. 1985. Industrial hygeine assessment of petroleum refinery turnaround activities. Washington, DC: American Petroleum Institute.

*Eadie BJ, Faust W, Gardner WS, et al. 1982. Polycyclic aromatic hydrocarbons in sediments and associated benthos in Lake Erie, USA. Chemosphere 11:185-102.

*Eadie BJ, Faust WR, Landrum PF, et al. 1983. Bioconcentrations of PAH by some benthic organisms of the Great Lakes. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Formation, metabolism and measurement. Columbus, OH: Battelle Press, 437-449.

*Edwards NT. 1983. Polycyclic aromatic hydrocarbons (PAHs) in the terrestrial environment - a review. J Environ Qua1 12:427-441.

8. REFERENCES

Edwards NT. 1989. Fate and effects of PAHs in the terrestrial environment: An overview. GRA&I Issue 21. Washington, DC: Department of Energy. Contract Number CONF-890692-5, Contract AC05-840R21400.

*Ehrlich GG, Goerlitz DF, Godsy EM, et al. 1982. Degradation of phenolic contaminants in ground water by anaerobic bacteria: St. Louis Park, MN. Ground Water 20:703-710.

Eiceman GA, Clement R, Karosek F. 1979. Analysis of fly ash from municipal incinerators for trace organic compounds. Anal Chem 51:2343.

*Eisenberg WC, Cunningham DLB. 1985. Analysis of polycyclic aromatic hydrocarbons in diesel emissions using high performance liquid chromatography: A methods development study. In: Cook M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Mechanisms, methods and metabolism. Columbus, OH: Battelle Press, 379-393.

*Eisler R. 1983. Polycyclic aromatic hydrocarbon hazards to fish, wildlife, and invertebretes: a synoptic review. U.S. Fish and Wildlife Service, U.S. Department of the Interior. Biological report 85(1.11).

*Eisler R. 1987. Polycyclic aromatic hydrocarbon hazards to fish, wildlife, and invertebrates: A synoptic review. Laurel, MD: US Fish and Wildlife Service, Patuxent Wildlife Research Center.

*Elder JF, Dresler PV. 1988. Bioconcentration of polycyclic aromatic hydrocarbons in a nearshore estuarine environment near a Pensacola, Florida creosote contamination site. Environ Pollut 49(2):117-132.

*Eldridge 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. Columbus, OH: Battelle Press, 471-482.

*Elgjo K. 1968. Growth kinetics of the mouse epidermis after a single application of 3,4-benzpyrene, croton oil, or 1,2-benzpyrene. Acta Pathol Microbial Stand 73:183-190.

*Eller PM. 1984. NIOSH manual of analytical methods. Vol. 2. Cincinnati, OH: US Department of Health and Human Services, National Institute for Occupational Safety and Health, 5506/7-5506/9, 5515/6-5515/7.

*Ellis B, Harold P, Kronberg H. 1991. Bioremediation of a creosote contaminated site. Environ Technol 12:447-459.

Emura M, Mohr U, Riebe M, et al. 1987. Predispostion of cloned fetal hamster lung epithelial cells to transformation by a precarcinogen, benzo(a)pyrene, using growth hormone supplementation and collagengel substratum. Cancer Res 47:1155-1160.

*Emura M, Richter-Reichhelm HB, Schneider P, et al. 1980. Sensitivity of Syrian golden hamster fetal lung cells to benzo(a)pyrene and other polycyclic hydrocarbons *in vitro*. Toxicology 17:149-155.

8. REFERENCES

*Environment Canada. 1991a. Toxic chemicals in the Great Lakes and associated effects: Vol. I. Contaminant levels and trends. Environment Canada, Department of Fisheries and Oceans, Health and Welfare Canada.

*Environment Canada. 1991b. Toxic chemicals in the Great Lakes and associated effects: Volume II. Effects. Environment Canada, Department of Fisheries and Oceans, Health and Welfare Canada.

*EPA. 1975. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.24.

*EPA. 1979a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.6.

*EPA. 1979b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

*EPA. 1980a. Ambient water quality criteria document for polynuclear aromatic hydrocarbons. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA 440/5-8-069.

*EPA. 1980b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33.

*EPA. 1981a. Engineering handbook for hazardous waste incineration. Washington DC: U.S. Environmental Protection Agency, Office of Solid Waste. EPA/SW-889.

*EPA. 1981b. Toxic pollutants/effluent standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

*EPA. 1981c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 App. VII.

*EPA. 1981d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.02.

*EPA. 1982a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 420.02.

*EPA. 1982b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 420.13.

*EPA. 1982c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 420.14.

*EPA. 1982d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 465.02.

*EPA. 1982e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 423.

8. REFERENCES

*EPA. 1982f. Test methods. Methods for organic chemical analysis of municipal and industrial wastewater. U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory, Cincinnati, OH.

*EPA. 1983a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 271.l.

*EPA. 1983b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122.

*EPA. 1983c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433.11.

*EPA. 1983d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 467.02.

*EPA. 1983e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 468.02.

*EPA. 1984a. Health effects assessment for polynuclear aromatic hydrocarbons (PAH). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. First Draft. ECAO-CIN-H013.

*EPA. 1984b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 App. IX.

*EPA. 1984c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136.

*EPA. 1984d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.21.

*EPA. 1984e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.23.

*EPA. 1984f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.24.

*EPA. 19848. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.26.

*EPA. 1985a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 464.11.

*EPA. 1985b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 464.21.

*EPA. 198%. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 464.3 1.

*EPA. 1985d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 464.41.

8. REFERENCES

*EPA. 1985e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50.

*EPA. 1986a. Test methods for evaluating solid waste. Volume 1B: Laboratory manual, physical/chemical methods. Washington, D.C.: US Environmental Protection Agency, Office of Solid Waste and Emergency Response. SW-846.

*EPA. 1986b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.10.

*EPA. 1986c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.12.

*EPA. 1986d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 403.

*EPA. 1987a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 246, Appendix XI.

EPA. 1987b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.

*EPA. 1987c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264 App. IX.

*EPA. 1987d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355.

*EPA. 1987e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.32.

*EPA. 1987f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.40

*EPA. 19878. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 414.91.

*EPA. 1988a. Drinking water criteria document for polycyclic aromatic hydrocarbons (PAHs). Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. ECAO-CIN-D010

EPA. 1988b. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, EPA/600/6-87/008.

*EPA. 1988c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 App. VIII.

*EPA. 1988d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.43.

*EPA. 1988e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

8. REFERENCES

*EPA. 1988f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 704.225.

*EPA. 1988g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 716.120.

*EPA. 1988h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 795.54.

*EPA. 1989a. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency. EPA/600/8-90/066F.

EPA. 1989b. Health and environmental effects profile for benzo(g,h,i)perylene. Cincinnati, OH: Environmental Protection Agency, Environmental Criteria and Assessment Office. Contract Number EPA-600-X-87-395.

*EPA. 1989c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1989d. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of federal regulations. 40 CFR 302.4

EPA. 1990. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency. EPA/600/8-90/066A.

EPA. 1991a. Ambient water quality criteria document: Addendum for acenaphthene. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. Contract Number ECAO-CIN-6 13.

*EPA. 1991b. EPA toxic pollutant effluent standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 129.

*EPA. 1991c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 258.

*EPA. 1991d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 265 App. VII.

*EPA. 1991e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61.

*EPA. 1992a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 721.3764.

*EPA. 1992b. U.S. Environmental Protection Agency. Federal Register. 57 FR 60848.

*EPA. 1993a. Provisional guidance for quantitative risk assessment of polycyclic aromatic hydrocarbons. Environmental Criteria and Assessment Office. Cincinnati, OH. Final Draft. ECAO-CIN-842. March 1993.

*EPA. 1993b. U.S. Environmental Protection Agency. Federal Register. 58 FR 48092.

8. REFERENCES

*EPA. 1993c. U.S. Environmental Protection Agency. Federal Register. 58 FR 54702.

*EPA. 1993d. U.S. Environmental Protection Agency. Federal Register. 58 FR 65622.

*EPA. 1993e. U.S. Environmental Protection Agency. Federal Register. 58 FR 36872.

*EPA. 1994a. U.S. Environmental Protection Agency. Federal Register. 59 FR 15504

*EPA. 1994b. U.S. Environmental Protection Agency. Federal Register. 59 FR 9808.

*EPA. 1994c. U.S. Environmental Protection Agency. Federal Register. 59 FR 1788.
Epstein S. 1968. Chemical mutagens in the human environment. Nature 219:365.

*Estensen RD, Wattenberg LW. 1993. Studies of chemopreventative effects of myo-inositol on benzo[a]pyrene-induced neoplasia of the lung and forestomach of female A/J mice. Carcinogenesis 14(9):1975-1977.

*Evans WH, Thomas NC, Boardman MC, et al. 1993. Relationships of polycyclic aromatic hydrocarbon yields with particulate matter (water and nicotine free) yields in mainstream and sidestream cigerette smoke. Sci Tot Environ 136:101-109.

Fahmy M, Fahmy OG. 1980. Altered control of gene activity in the soma by carcinogens. Mutat Res 72:165-172.

*Faiderbe S, Chagnaud JL, Geffard M. 1992. Identification and characterization of a specific autoantiphosphatidylinositol immune response during the time course of benzo(a)pyrene-induced malignant tumors in female Sprague-Dawley rats. Cancer Res 52(10):2862-2865.

*Falk HL, Kotin PTS. 1964. Inhibition of carcinogenesis: The effects of polycyclic hydrocarbons and related compounds. Arch Environ Health 9:169-179.

Falkson G, Klein B, Falkson H. 1985. Hematological toxicity: Experience with anthracyclines and anthracenes. Exp Hematol 13:64-71.

*Faoro RB, Manning JA. 1981. Trends in benzo[a]pyrene, 1966-77. J Air Pollut Control Assoc 31:62-64.

*Faulds AJ, Waszczylo Z, Westaway KC. 1981. Polynuclear aromatic hydrocarbons in the underground mine environment. CIM Bull 74:84-90.

Feron VJ. 1972. Respiratory tract tumors in hamsters after intratracheal instillations of benzo[a]pyrene alone and with furfural. Cancer Res 32:28-36.

Feron VJ. 1973. Dose-response correlation for the induction of respiratory-tract tumors in Syrian golden hamsters by intratracheal instillations of benzo[a]pyrene. Eur J Cancer 9:387.

Feron VJ, Kruysse A. 1978. Effects of exposure to furfural vapor in hamsters simultaneously treated with benzo[a]pyrene and diethylnitrosamine. Toxicology 11:127-144.

8. REFERENCES

Ferrario JB, DeLeon H, Tracy R. 1985. Evidence for toxic anthropogenic chemicals in human thrombogenic coronary plaques body burdens. Arch Environ Contam Toxicol 14:529-534.

Fielden PR, Packham AJ. 1989. Selective determination of benzo(a)pyrene in petroleum-based products using multi-column liquid chromatography. J Chromatogr 479(1): 117-124.

Finch MA. 1990. What is FT Raman spectroscopy and where can I use it? Spectroscopy (Eugene Oreg) 5(6):12, 14-16.

*Fiume M, Guaitani A, Modica R, et al. 1983. Effect of fasting, induction, sex and age on clearance of benz(a)anthracene and chrysene by isolated perfused rat liver. Toxicol Lett 19:73-79.

*Forbes PD, Davies RE, Urbach F. 1976. Phototoxicity and photocarcinogenesis: Comparative effects of anthracene and 8-methoxypsoralen in the skin of mice. Food Cosmet Toxicol 14:303-306.

*Foreman WT, Bidleman TF. 1990. Semivolatile organic compounds in the ambient air of Denver Colorado. Atmos Environ 24(9):2405-2416.

*Foth H, Kahl R, Kahl GF. 1988a. Pharmacokinetics of low doses of benzo[a]pyrene in the rat. Food Chem Toxicol 26(1):45-51.

*Foth H, Rude11 U, Ritter G, et al. 1988b. Inhibitory effect of nicotine on benzo(a)pyrene elimination and marked pulmonary metabolism of nicotine in isolated perfused rat lung. Klin Wochenschr 66(Suppl 11):98-104.

*Foumier J, Pezerat H. 1986. Studies on surface properties of asbestos: III. Interactions between asbestos and polynuclear aromatic hydrocarbons. Environ Res 41:276-295.

*Fox MA, Staley SW. 1976. Determination of polycyclic aromatic hydrocarons in atmospheric particulate matter by high pressure liquid chromatography coupled with flourescene techniques. Anal Chem 48:992-998.

*Franklin Associates. 1984. Composition and management of used oil generated in the United States. Washington, D.C.: US Environmental Protection Agency. NTIS PB 85-180-297.

*Fraumeni JR, ed. 1975. Persons at high risk of cancer: An approach to cancer etiology and control. New York, NY: Academic Press, Inc., 172, 187-189.

*Freeman DJ, Cattell CR. 1990. Woodburning as a source of atmospheric polycyclic aromatic hydrocarbons. Environ Sci Technol 24(10):1581-1585.

FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee, Washington, D.C. March, 1988.

FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee, Washington, D.C. February 1990.

8. REFERENCES

*Fuchs J, Mlcoch J, Platt K-L, et al. 1993a. Characterization of highly polar bis-dihydrodiol epoxide-DNA adducts formed after metabolic activation of dibenz[a,h]anthracene. Carcinogenesis 14(5):863-867.

*Fuchs J, Mlcoch J, Oesch F, et al. 1993b. Characterization of highly polar DNA adducts derived from dibenz[a,h]anthracene (DBA), 3,4-dihydroxy-3,4-dihydro-DBA, and 3,4,10,11-tetrahydroxy-3,4,10,11-tetrahydro-DBA. Toxicol Ind Health 9(3):503-509.

*Furman GM, Silverman DM, Schatz RA. 1991. The effect of toluene on rat lung benzo[a]pyrene metabolism and microsomal membrane lipids. Toxicology 68(1):75-87.

*Furuta N, Otsuki A. 1983. Time-resolved fluorometry in detection of ultratrace polycyclic aromatic hydrocarbons in lake waters by liquid chromatography. Anal Chem 55:2407-2413.

*Futagaki SK. 1983. Petroleum refinery workers exposure to PAHs at fluid catalytic cracker, coker, and asphalt processing units. Cincinnati, OH: National Institute for Occupational Safety and Health, NIOSH publ. no. 83-111.

*Futoma DJ, Smith SR, Tanaka J, et al. 1981. Chromatographic methods for the analysis of polycyclic aromatic hydrocarbons in water systems. Crit Rev Anal Chem 12:69-153.

*Gallagher J, George M, Kohan M, et al. 1993. Detection and comparison of DNA adducts after in vitro and *in vivo* diesel emission exposures. Environ1 Health Perspect 99:225-228.

Galle B, Grennfelt P. 1983. Instrument for polycyclic aromatic hydrocarbon analysis of airborne particules by capillary gas chromatography with laser induced fluorescence detection. J Chromatogr 279:643-648.

*Gao N, Aidoo A, Heflich RH. 1991. Analysis of rat lymphocyte activation of benzo[a]pyrene, 2-acetylaminofluorene, and several of their metabolites to mutagenic and DNA-damaging species *in vitro.* Teratogen Carcinog Mutagen 11(2):65-76.

*Gardner WS, Lee RF, Tenore KR, et al. 1979. Degradation of selected polycyclic aromatic hydrocarbons in coastal sediments: Importance of microbes and polychaete worms. Water Air Soil Pollut 11:339-348.

*Garg A, Beach AC, Gupta RC. 1993. Interception of Reactive, DNA aduct-forming metabolites present in rodent serum following carcinogen exposure: Implications for use of body fluids in biomonitoring. Teratogen Carcinog Mutagen 13:151-166.

*Garman JR, Freund T, Lawiess EW. 1987. Testing for groundwater contamination at hazardous waste sites. J Chromatogr Sci 25:328-337.

*Gamer RC, Dvorackova I, Tursi F. 1988. Immunoassay procedures to detect exposure to aflatoxin B-l and benzo-a-pyrene in animals and man at the DNA level. Int Arch Occup Environ Health 60(3):145-150.

8. REFERENCES

*Garrigues P, Ewald M. 1987. High resolution emission spectroscopy (Shpol'skii effect): A new analytical technique for the analysis of polycyclic aromatic hydrocarbons (PAH) in environmental samples. Chemosphere 16:485-494.

*Gay ML Belisle AA, Patton JF. 1980. Quantification of petroleum-type hydrocarbons in avian tissue. J Chromatogr 187:153-160.

Generoso WM, Cain KT, Hellwig CS, et al. 1982. Lack of association between induction of dominant-lethal mutations and induction of heritable translocations with benzo[a]pyrene in postmeiotic germ cells of male mice. Mutat Res 94: 155-163.

*Gensler HL. 1988. Enhancement of chemical carcinogenesis in mice by systemic effects of ultraviolet irradiation. Cancer Res 48:620-623.

Georgellis A, Parvinen M, Rydstrom J. 1989. Inhibition of stage-specific DNA synthesis in rat spermatogenic cells by polycyclic aromatic hydrocarbons. Chem Biol Interact 72(1-2):79-92.

Georgellis A, Toppari J, Veromaa T, et al. 1990. Inhibition of meiotic divisions of rat spermatocytes *in vitro* by polycyclic aromatic hydrocarbons. Mutat Res 23 l(2): 125-136.

*Gerde P, Medinsky MA, Bond JA. 1991. The retention of polycyclic aromatic hydrocarbons in the bronchial airways and in the alveolar region: A theoretical comparison. Toxicol Appl Pharmacol 107(2):239-252.

*Gerde P, Muggenburg BA, Hoover MD, et al. 1993a. Disposition of polycyclic aromatic hydrocardons in the respiratory tract of the beagle dog. I. The aveolar region. Toxicol Appl Pharmacol. 121:313-318.

*Gerde P, Muggenburg BA, Sabourin PJ, et al. 1993b. Disposition of polycyclic aromatic hydrocarbons in the respiratory tract of the beagle dog. II. The conducting airways. Toxicol Appl Pharmacol. 121:319-327.

*Gerde P, Scholander P. 1989. An experimental study of the penetration of polycyclic aromatic hydrocarbons through a model of the bronchial lining layer. Environ Res 48(2):287-295.

*Gershbein LL. 1975. Liver regeneration as influenced by the structure of aromatic and heterocyclic compounds. Res Commun Chem Pathol Pharrnacol 11:445-466.

*Ghaisas SD, Bhide SV. 1994. *In vitro* studies on chemoprotective effects of pumark against benzo(a)pyrene-induced chromosomal damage in human lymphocytes. Cell Biol Int 18:(1)21-23.

*Gibson TL, Smart VB, Smith LL. 1978. Non-enzymatic activation of polycyclic aromatic hydrocarbons as mutagens. Mutat Res 49:153-161.

*Giger W, Blumer M. 1974. Polycyclic aromatic hydrocarbons in the environment: Isolation and characterization by chromatography visible, ultraviolet, and mass spectrometry. Anal Chem 46:1163.

*Giger W, Schaffner C. 1978. Determination of polycyclic aromatic hydrocarbons in the environment by glass,capillary gas chromatography. Anal Chem 50:243-249.

8. REFERENCES

*Gile JD, Collins JC, Gillet JW. 1982. Fate and impact of wood preservatives in a terrestrial microcosm. J Agric Food Chem 30:295-301.

*Ginsberg GL, Atherholt TB. 1989. Transport of DNA-adducting metabolites in mouse serum following benzo[a]pyrene administration. Carcinogenesis 10(4):673-679.

*Ginsberg GL, Atherholt TB, Butler GH. 1989. Benzo[a]pyrene-induced immunotoxicity: Comparison to DNA adduct formation *in vivo*, in cultured splenocytes, and in microsomal systems. J Toxicol Environ Health 28(2):205-220.

Glatt H, Bucker M, Platt KL, et al. 1985. Host-mediated mutagenicity experiments with benzo[a]pyrene and two of its metabolites. Mutat Res 156:163-169.

Glatt H, Seidel A, Ribeiro O, et al. 1987. Metabolic activation to a mutagen of 3-hydroxy-tram-7,8-dihydroxy-7,8- dihydrobenzo(a)pyrene, a secondary metabolite of benzo(a)pyrene. Carcinogenesis 8:1621-1627.

*Glatt H, Wameling C, Elsberg S, et al. 1993. Genotoxicity characteristics of reverse diol-epoxides of chrysene. Carcinogenesis 14(1):11-19.

*Goates SR, Sin CH, Simons JK, et al. 1989. Supercritical-fluid chromatography - supersonic-jet spectroscopy: Part II. Capillary-column SFC with a sheath-flow nozzle. Microcolumn Sep 1(4):207-211.

*Golden C, Sawicki E. 1978. Determination of benzo(a)pyrene and other polynuclear aromatic hydrocarbons in airborne paritculates material by ultrasonic extraction and reverse phase pressure liquid chromatography. Anal Lett 11: 105l-1062.

*Goldstein LS, Safe S, Weyand EH. 1994. Carcinogenicity of coal tars: A multidisciplinary approach. Polycyclic Aromatic Compounds 7:161-174.

*Gomaa EA, Gray IJ, Rabie S, et al. 1993. Polycyclic aromatic hydrocarbons in smoked food products and commerical liquid smoke flavourings. Food Addit Contam 10(5):503-521.

*Games M, Santella RM. 1990. Immunologic methods for the detection of benzo[a]pyrene metabolites in urine. Chem Res Toxicol 3(4):307-310.

Gonzalez BL, Rejthar L. 1986. Quantitative determination of trace concentration of organics in water by solvent extraction and fused silica capillary gas chromatography: aliphatic and polynuclear hydrocarbons. Int J Environ Anal Chem 24:305-318.

*Gordon RJ. 1976. Distribution of airborne polycyclic aromatic hydrocarbons throughout Los Angeles. Env Sci Tech 10:370-373.

*Gorelick NJ, Reeder NL. 1993. Detection of multiple polycyclic aromatic hydrocarbon-DNA adducts by a high-performance liquid chromatography-^{32}P-postlabeling method. Environ Health Perspect 99:207-211.

8. REFERENCES

*Gorelick NJ, Wogan GN. 1989. Fluoranthene - DNA adducts: identification and quantification by an HPLC - phosphorus-32 post-labelling method. Carcinogenesis 10(9):1567-1577.

Govindwar SP, Kachole MS, Pawar SS. 1988. Effect of caffeine on the hepatic microsomal mixed function oxidase system during phenobarbital and benzo[a]pyrene treatment in rats. Toxicol Lett 42(2):109-115.

*Granella M, Clonfero E. 1993. Urinary excretion of 1-pyrenol in automotive repair workers. Int Arch Occup Environ Health 65: 241-245.

Grant GA, Roe FJC. 1963. The effect of phenanthrene on tumor induction by 3,4-benzpyrene administered to newly born mice. Br J Cancer 17:261-265.

*Grayson M, ed. 1978. Kirk-Othmer encyclopedia of chemical technology. Vol. 21. New York, NY: John Wiley and Sons.

*Greb W, Strobe1 R, Roehrborn G. 1980. Transformation of BHK 21/CL 13 cells by various polycyclic aromatic hydrocarbons using the method of styles. Toxicol Lett (Amst) 7:143-148.

*Greenberg A, Darack F, Harkov R, et al. 1985. Polycyclic aromatic hydrocarbons in New Jersey (USA): A comparison of winter and summer concentrations over a two-year period. Atmos Environ 19:1325-1340.

*Greife AL, Warshawsky D. 1993. Influence of the dose levels of cocarcinogen ferric oxide onthe metabolism of benzo(a)pyrene by pulmonary alveolar macrophages in suspension culture. J Toxicol Environ Health 38:399-417.

*Grimmer G, Brune H, Dettbarn G, et al. 1988. Urinary and faecal excretion of chrysene and chrysene metabolites by rats after oral, intraperitoneal, intratracheal or intrapulmonary application. Arch Toxicol 62(6):401-405.

Grimmer G, Jacob J, Schmoldt A, et al. 1985. Metabolism of benz(a)anthracene in hamster lung cells in culture in comparison to rat liver microsomes. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Mechanisms, methods and metabolism. Columbus, OH: Battelle Press, 521-532.

*Grimmer G, Naujack KW, Dettbam G. 1987. Gas chromatographic determination of polycyclic aromatic hydrocarbons azarenes aromatic amines in the particle and vapor phase of mainstream and sidestream smoke of cigarettes. Toxicol Lett (AMST) 35(l): 117-124.

*Grimmer G, Dettbarn G, Jacob J. 1993. Biomonitoring of polycyclic aromatic hydrocarbons in highly exposed coke plant workers by measurement of urinary phenanthrene and pyrene metabolites (phenols and dihydrodiols). Int Arch Occup Environ Health 65(3):189-199.

*Grimmer G, Dettbam, G, Naujack KW, et al. 1994. Relationship between inhaled PAH and urinary excretion of phenanthrene, pyrene and benzo(a)pyrene metabolites in coke plant workers. Polycyclic Aromatic Compounds 5:269-277.

8. REFERENCES

Grolier P, Cassand P, Antignac E, et al. 1989. Effects of prototypic PCBs on benzo-alpha-pyrene mutagenic activity related to vitamin A intake. Mutat Res 211(1)139-146.

*Grosjean D. 1983. Polycyclic aromatic hydrocarbons in Los Angeles air from samples collected teflon glass and quatz filters. Atmos Environ 17(12):2565-2573.

Grover PL, Sims P, Huberman E, et al. 1971. *In vitro* transformation of rodent cells by K-region derivatives of polycyclic hydrocarbons. Proc Nat Acad Sci USA 68:1098-1101.

*Grover PL, Sims P, Mitchley BCU, et al. 1975. The carcinogenicity of polycyclic hydrocarbon epoxides in newborn mice. Br J Cancer 31:182-188.

*Guerin MR. 1978. Energy sources of polycyclic aromatic hydrocarbons. In: Gelboin HV, Ts'o POP, eds. Polycyclic hydrocarbons and cancer. Vol. 1. New York, NY: Academic Press, 3-55.

*Guillemin MP, Herrera H, Huynh CK, et al. 1992. Occupational exposure of truck drivers to dust and polynuclear aromatic hydrocarbons: a pilot study in geneva, Switzerland. Int Arch Occup Environ Health. 63: 439-447.

*Gunnison AF, Sellakumar A, Snyder EA, et al. 1988. The effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene. Environ Res 46(1):59-73.

Gupta RS, Goldstein S. 1981. Mutagen testing in the human fibroblast diphtheria toxin resistance (HF Dipr) system. Prog Mutat Res 1:614-625.

Gupta RS, Singh B. 1982. Mutagenic responses of five independent genetic loci in CHO cells to a variety of mutagens: Development and characteristics of a mutagen screening system based on selection for multiple drug-resistant markers. Mutat Res 94:449-466.

*Gupta MP, Khanduja KL, Sharma RR. 1987. Effect of cigarette smoke inhalation on (^{3}H)benzo(a)pyrene binding to lung DNA of vitamine A-deficient rats. Med Sci Res 15:1323-1324.

Gupta PH, Mehta S, Mehta SK. 1989. Effects of dietary benzo(a)pyrene on intestinal phase I and phase II dmg metabolizing systems in normal and vitamin A-deficient rats. Biochem Int 19(4):709-722.

*Gupta MP, Khanduja KL, Koul IB, et al. 1990. Effect of cigarette smoke inhalation on benzo[a]pyrene-induced lung carcinogenesis in vitamin A deficiency in the rat. Cancer Lett 55(2):83-88.

*Gupta P, Banerjee DK, Bhargava SK, et al. 1993. Prevalence of impared lung function in rubber manufacturing factory workers exposed to benzo(a)pyrene and respirable particulate matter. Indoor Environ 2:26-31.

Gurka DF, Pyle SM. 1988. Qualitative and quantitative environmental anaylysis by capillary column gas chromatography/lightpipe Fourier-transforms infrared spectrometry. Environ Sci Technol 22:963-967.

8. REFERENCES

Gurka DF, Titus R, Giffiths PR, et al. 1987. Evaluation of an improved single-beam gas chromatography/Fourier transform infrared interface for environmental analysis. Anal Chem 59:2362-2369.

*Guyda HJ. 1991. Metabolic effects of growth factors and polycyclic aromatic hydrocarbons on cultured human placental cells of early and late gestation. J Clin Endocrinol Metab 72(3):718-723.

*Guyda HJ, Mathieu L, Lai W, et al. 1990. Benzo(a)pyrene inhibits epidermal growth factor binding and receptor autophosphorylation in human placental cell cultures. Mol Pharmacol 37(2):137-143.

Ha M, Grover PL. 1988. Stereoselective aspects of the metabolic activation of benzo[a]pyrene by human skin *in vitro.* Chem Biol Interact 64(3):281-296.

Haas JWI, Buchanan MV, Wise MB. 1988. Differentiation of polycyclic aromatic hydrocarbons using a multimode ionization gas chromatographic detector. J Chromatogr Sci 26:49-54.

*Habs M, Jahn SA, Schmahi D. 1984. Carcinogenic activity of condensate from coloquint seeds *(Citrullus colocynthis)* after chronic epicutaneous administration to mice. J Cancer Res Clin Oncol 108:154-156.

*Habs M, Schmahl D, Misfeld J. 1980. Local carcinogenicity of some environmentally relevant polycyclic aromatic hydrocarbons after lifelong topical application to mouse skin. Arch Geschwulstforsch 50:266-274.

*Hahon N, Booth JA. 1986. Coinhibition of viral interferon induction by benzo[a]pyrene and chrysotile asbestos. Environ Res 40(l): 103-109.

*Hahon N, Booth JA. 1988. Benzo[a]pyrene: Kinetics of *in vitro* bioactivation in relation to inhibition of viral interferon induction. J Interferon Res 8(2):151-167.

*Halbrook RS, Kirkpatrick RL, Bevan DR. 1992. DNA adducts detected in muskrats by ^{32}P-postlabeling analysis. Envion Toxicol Chem 11:1605-1613.

*Hall M, Grover PL. 1987. Differential stereoselectivity in the metabolism of benzo(a)pyrene and anthracene by rabbit epidermal and hepatic microsomes. Cancer Lett 38:57-64.

*Hall LWJr., Ziegenfuss MC, Fischer SA. 1993. The influence of contaminant and water quality conditions on larval striped bass in the Potomac river and Upper Chesapeake Bay in 1990. Arch Environ Contam Toxicol 24(1):1-10.

Hall M, Parker DK, Grover PL, et al. 1990. Effects of 1-ethynylpyrene and related inhibitors of P450 isozymes upon benzo[a]pyrene metabolism by liver microsomes. Chem Biol Interact 76(2):181-192.

*Hammond ED, Selikoff IJ, Lawther PO, et al. 1976. Inhalation of B[a]P and cancer in man. Ann NY Acad Sci 271:116-124.

*Hampel CA, Hawley GG, eds. 1973. The encyclopedia of chemistry. Third edition. New York, NY: Van Nostrand Reinhold Company.

8. REFERENCES

*Hansen AM, Poulsen OM, Menne T. 1993. Longitudinal study of excretion of Metabolies of Polycyclic Aromatic Hydrocarbons in Urine from two Psoriatic Patients.Acta Derm Venereol (stockh) 73:188-190.

*Harper BL, Ramanujam VMS, Legator MS. 1989. Micronucleus formation by benzene, cyclophosphamide, benzo(a)pyrene, and benzidine in male, female, pregnant female, and fetal mice. Teratogen Carcinogen Mutagen 9(4):239-252.

Harris CC, Autrup H, eds. 1983. Human carcinogenesis. New York, NY: Academic Press.

*Harris CC, Spom MB, Kaufman DG, et al. 1971. Acute ultrastmctural effects of benzo(a)pyrene and ferric oxide on the hamster tracheobronchial epithelium. Cancer Res 31: 1977-1981.

*Harris CC, Autrup H, Stoner GD, et al. 1979. Metabolism of B[a]P, N-nitrosodimethylamine, and N-nitrosopyrrolidine and identification of the major carcinogen-DNA adducts formed in cultured human esophagus. Cancer Res 39:4401-4406.

Harris CC, Grafstom RC, Shamsuddin AM, et al. 1984. Carcinogen metabolism and carcinogenic DNA adducts in human tissues and cells. In: Marquardt H, Oesch F, eds. Biochemical basis of chemical carcinogenesis. New York, NY: Raven Press, 123-135.

*Harris J, Perwak J, Coons S. 1985. Exposure and risk assessment for benzo(a)pyrene and other polycyclic aromatic hydrocarbons. Volume 1. Summary:123-135.

*Harrison RM, Perry R, Wellings RA. 1976a. Chemical kinetics of chlorination of some polynuclear aromatic hydrocarbons under conditions of water treatment processes. Environ Sci Technol 10:1156-1160.

*Harrison RM, Perry R, Wellings RA. 1976b. Effect of water chlorination upon levels of some polynuclear aromatic hydrocarbons in water. Environ Sci Technol 10:1151-1156.

Hartwell JL, ed. 1951. Survey of compounds which have been tested for carcinogenic activity. Public Health Series Publication No 149.

*Harvath PV. 1983. Quantitative analysis of multiple polycyclic aromatic hydrocarbons in the coal conversion atmosphere. Am Ind Hyg Assoc J 44:739-745.

Hass BS, Brooks EE, Schumann KE, et al. 1981. Synergistic, additive, and antagonistic mutagenic responses to binary mixtures of benzo(a)pyrene and benzo(e)pyrene as detected by strains TA98 and TA10 in the Salmonella/microsome assay. Environ Mutagen 3(2):159-166.

Haugen DA, Zegar IS. 1990. Formation of hemoglobin-benzo[a]pyrene adducts in human erythrocytes incubated with benzo[a]pyrene and hamster embryo cells. Toxicology 65(1-2):109-122.

*Haugen A, Becher G, Benestad C, et al. 1986. Determination of polycyclic aromatic hydrocarbons in the urine, benzo(a)pyrene diol epoxide-DNA adducts in lymphocyte DNA, and antibodies to the adducts in sera from coke oven workers exposed to measured amount of polycyclic aromatic hydrocarbons in the work atmosphere. Cancer Res 46:4178-4183.

8. REFERENCES

*Hawley GG. 1987. The condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company.

*Hawley GG. 1993. The condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company.

*Hawthorne SB, Miller DJ. 1987a. Directly coupled supercritical fluid extraction-gas chromatographic analysis of polycyclic aromatic hydrocarbons and polychlorinated biphenyls environmental from solids. J Chromatogr 403:63-76.

*Hawthorne SB, Miller DJ. 1987b. Extraction and recovery of polycyclic aromatic hydrocarbons from environmental solids using supercritical fluids. Anal Chem 59: 1705-1708.

*Hawthorne SB, Miller DJ, Burford MD. et al. 1993. Factors controlling quantitative supercritical fluid extraction of environmental samples. J Chromatogr 642:301-317.

*HazDat. 1993. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HazDat. 1994. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*He SL, Baker R. 1991. Micronuclei in mouse skin cells following *in vivo* exposure to benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, chrysene, pyrene and urethane. Environ Mol Mutagen 17(3):163-168.

Hecht SS, Bondinell WE, Hoffman D. 1974. Chrysene and methylchrysenes: Presence on tobacco smoke and carcinogenicity. J Nat1 Cancer Inst 53:1121-1133.

*Hecht SS, Grabowski W, Groth K. 1979. Analysis of faeces for B[a]P after consumption of charcoal-broiled beef by rats and humans. Food Cosmet Toxicol 17:223-227.

*Hecht SS, La Voie E, Amin S, et al. 1980. On the metabolic activation of the benzofluoranthenes. In: Polynuclear aromatic hydrocarbons: Chemistry and biological effects. 4th National Symposium 1980. 417-433.

Heinrich U, Pott F, Mohr U, et al. 1986. Lung tumors in rats and mice after inhalation of PAH-rich emissions. Exp Pathol 29:29-34.

*Heit M, Tan Y, Klusek C, et al. 1981. Anthropogenic trace elements and polycyclic aromatic hydrocarbon levels in sediment cores from two lakes in the Adirondack acid lake region. Water Air Soil Pollut 15:441-464.

*Helmenstine A, Uziel M, Vo-Dinh T. 1993. Measurement of DNA adducts using surface-enhanced Raman spectroscopy. J Toxicol Environ Health 40(2):195-202.

Henry MC, Port CD, Kaufman DG. 1975. Importance of physical properties of benzo[a]pyrene - ferric oxide mixtures. Cancer Res 35:207-217.

8. REFERENCES

Henry MC, Port DC, Bates RR, et al. 1973. Respiratory tract tumors in hamsters induced by benzo[a]pyrene. Cancer Res 33:1585-1592.

*Herberg R, Marcus M, Wolff MS, et al. 1990. A pilot study of detection of DNA adducts in white blood cells of roofers by 32P-postlabelling. IARC Sci Pub1 (104):205-214.

*Herikstad BV, Ovrebo S, Haugen A, et al. 1993. Determination of polycyclic aromatic hydrocarbons in urine from coke-oven workers with a radioimmunoassay.

*Hermann M. 1981. Synergistic effects of individual polycyclic aromatic hydrocarbons on the mutagenicity of their mixtures. Mutat Res 90:399-409.

Hess GG, McKenzie DE, Hughes BM. 1986. Selective preconcentration of polycyclic aromatic hydrocarbons and polychlorinated biphenyls by in situ metal hydroxide precipitation. J Chromatogr 366:197-203.

Heston WE, Schneiderman MA. 1953. Analysis of dose-response in relation to mechanisms of pulmonary induction. Science 117: 109.

*Higginbotham S, RamaKirshana NVS, Lohansson SL, et al. 1993. Tumor-initiating activity and carcinogenicity of dibenzo(a,Z)pyrene versus 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene at low doses in mouse skin. Carcinogenesis 14(5): 875-878.

*Hilali A, Crutzen-Fayt MC, Gerber GB. 1993. Effect of age on the ability of rat liver tissue to transform chemical promutagens to mutagens. Gerontology 39: 125-127.

*Hills JW, Hill HH. 1993. Carbon dioxide supercritical fluid extraction with a reaction solvent modifier for the determination of polycylic aromatic hydrocarbons. J Chromatogr Sci 3l(1):6-12.

*Hinga KR, Pilson MEQ. 1987. Persistence of benz(a)anthracene degradation products in an enclosed marine ecosystem. Env Sci Technol 21:648-653.

*Hinoshita F, Hardin JA, Sherr DH. 1992. Fluoranthene induces programmed cell death and alters growth of immature B cell populations in bone marrow cultures. Toxicology 73(2):203-218.

Hirakawa T, Ishikawa T, Nimoto N, et al. 1979. Induction of enzyme-altered islands in rat liver by a single treatment with B[a]P after partial hepatectomy. Gann 373-394.

*Hites RA, Laflamme RE, Windson JJ. 1980. Polycyclic aromatic hydrocarbons in an anoxic sediment core from the Pettaquamscutt River (Rhode Island, U.S.A.). Geochimica et Cosmochimica Acta 44:873-878.

Hluchan E, Jenik M, Maly E. Determination of airborne polycyclic hydrocarbons by paper chromatography. J Chromatogr 91:531-538.

Hoch-Ligeti C. 1941. Studies on the changes in the lymphoid tissue of mice treated with carcinogenic and non-carcinogenic hydrocarbons. Cancer Res 1:484-488.

8. REFERENCES

*Hoffmann D, Hecht SS. 1991. Mutagenicity and tumor-initiating activity of methylated benzo(b)fluoranthenes. In: Cooper CS, Grover PL, eds. Chemical carcinogenesis and mutagenesis I. New York, NY: Springer Verlag, 63-102.

*Hoffmann D, Hoffmann I. 1993. Tobacco smoke as a respiratory carcinogen. In: Hirsch A, Goldberg M, Martin J-P, et al., eds. Prevention of respiratory diseases. New York, NY: Marcel Dekker, Inc., 497-532.

*Hoffmann D, Rathkamp G, Nesnow S, et al. 1972. Fluoranthenes: Quantitative determination in cigarette smoke, formation by pyrolysis and tumor initiating activity. J Nat1 Cancer Inst 49:1165-1175.

*Hoffmann D, Wynder EL. 1966. On the carcinogenic activity of dibenzopyrenes. Zeitschrift fur Krebsforschung 68:137-149. (German)

Hogue C Jr, Brewster MA. 1991. The potential of exposure biomarkers in epidemiologic studies of reproductive health. Environ Health Perspect 90:261-270.

*Holloway.MP, Biaglow MC, McCoy EC, et al. 1987. Photochemical instability of 1-nitropyrene, 3-nitrofluoranthene, 1,8-dinitropyrene and their parent polycyclic aromatic hydrocarbons. Mutat Res 187:199-207.

Horikawa K, Sera N, Otofuji T, et al. 1991. Pulmonary carcinogenicity of 3,9-dinitrofluoranthene 3,7-dinitrofluoranthene, 3-nitrofluoranthene and benzo(alpha)pyrene in F344 rats. Carcinogenesis 12(6):1003-1008.

*Horton AW, Christian GM. 1974. Cocarcinogenic versus incomplete carcinogenic activity among aromatic hydrocarbons: Contrast between chrysenes and benzo[b]triphenylene. J Natl Cancer Inst 53:1017-1020.

*Horton JK, Rosenior JC, Bend, et al. 1985. Quantitation of B[a]P metabolite: DNA adducts in selected hepatic and pulmonary cell types isolated from [^{3}H]benzo[a]pyrene-treated rabbits. Cancer Res 45:3477-3481.

*Hoshino K, Hyashi Y, Takehira Y, et al. 1981. Influences of genetic factors on the teratogenicity of environmental pollutants: Teratogenic susceptibility to benzo[a]pyrene and Ah locus in mice. Congenital Anomalies 97-103.

*Hough JL, Baired MB, Sfeir GT, et al. 1993. Benzo(a)pyrene enhances atherosclerosis in White Carneau and Show Racer pigeons. Arterioscler Thromb 13:1721-1727.

Howard AG, Mills GA. 1983. Identification of polynuclear aromatic hydrocarbons in diesel particulate emissions. Int J Environ Anal Chem 14:43-54.

*Howard J. 1979. Analysis of B[a]P and other polycyclic aromatic hydrocarbons in food. In: Egan H, ed. Environmental carcinogens: Selected methods of analysis: Vol. 3. Analysis of polyaromatic hydrocarbons in environmental samples. Lyon, France: International Agency for Research on Cancer, 175-191.

8. REFERENCES

*HSDB. 1988. Hazardous Substance Data Bank. National Library of Medicine, National Toxicology Program, Bethesda, MD. December 1988.

*HSDB. 1992. Hazardous substances data bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. April 27, 1992.

*HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD.

Huberman E. 1975. Mammalian cell transformation and cell-mediated mutagenesis by carcinogenic polycyclic hydrocarbons. Mutat Res 29:285-291.

*Hueper WC. 1949. Occupational cancer hazards found in industry. Industrial Hygiene Newsletter 9:7-9.

*Huesemann MH, Moore KO, Johnson RN. 1993. The fate of BDAT polynuclear aromatic compounds during biotreatment of refinery API oil separator sludge. Environ Progress 12(1):30-38.

*Huggett RJ, Defur PO, Bieri RH. 1988. Organic compounds in Chesapeake Bay sediments. Mar Pollut Bull 19(9):454-458.

Huggins C, Yang NC. 1962. Induction and extinction of mammary cancer. Science 137:257-262.

*Hughes NC, Phillips DH. 1990. Covalent binding of dibenzpyrenes and benzo(a)pyrene to DNA: Evidence for synergistic and inhibitory interactions when applied in combination to mouse skin. Carcinogenesis (Eynsham) 11(9):161l-1620.

*Hughes NC, Pfau W, Hewer A et al. 1993. Covalent binding of polycyclic aromatic hydrocarbon components of coal tar to DNA in mouse skin. Carcinogenesis 14(1):135-144.

*Huh N, Nemoto N, Utakoji T. 1982. Metabolic activation of benzo[a]pyrene, aflatoxin Bl, and dimethylnitrosamine by a human hepatoma cell line. Mutat Res 94:339-348.

Hunt DF, Shabanowitz F, Harvey TM, et al. 1983. Analysis of organics in the environment by functional group using a triple quadrupole mass spectrometer. J Chromatogr 271:93-105.

*Huntley SL, Bonnevie NL, Wenning RJ, et al. 1993. Distribution of polycyclic aromatic hydrocarbons(PAHS) in three northern New Jersey waterways. Bull Environ Contam Toxicol 51(6):865-872.

Husgafvel-Pursiainen K, Sorsa M, Miller M, et al. 1986. Genotoxicity and polycyclic aromatic hydrocarbon analysis of environmental tobacco smoke samples from restaurants. Mutagenesis 1:287-292.

*IARC. 1973. Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. Monographs on the evaluation of carcinogenic risk of the chemical to man. Vol. 3. Lyon, France: World Health Organization, International Agency for Research on Cancer.

8. REFERENCES

*IARC. 1983. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 32: Polynuclear aromatic compounds: Part 1. Chemical, environmental and experimental data. Lyons, France: World Health Organization, International Agency for Research on Cancer, 155-161, 225-231.

*IARC. 1984. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: Polynuclear aromatic hydrocarbons, part 2, carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. Volume 33. Lyon, France: World Health Organization, International Agency for Research on Cancer.

*IARC. 1985. Monographs on the evaluation of the carcinogenic risk of chemicals to man. Vol. 35. Polynuclear aromatic compounds: Part 4, bitumens, coal-tars and derived products, shale oils and soots. Lyon, France: World Health Organization, International Agency for Research on Cancer, 104-140.

*IARC. 1987a. Monographs on the evaluation of carcinogenic risks to humans: An updating of IARC monographs. Volumes 1 to 42. Supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 56-71.

*IARC. 1987b. Monographs on the evaluation of the carcinogenic risk of chemicals to humans: an updating of IARC monographs. Volumes 1 to 42. Supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 252-254.

*IARC. 1989. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: occupational exposures in petroleum refining: crude oil and major petroleum fuels. Volume 45. Lyon, France: World Health Organization, International Agency for Research on Cancer.

Imaizumi N, Hayakawa K, Suzuki Y, et al. 1990. Determination of nitrated pyrenes and their derivatives by high performance liquid chromatography with chemiluminescence detection after online electrochemical reduction . J Biomed Chromatogr 4(3):108-112.

Ingram AJ, King DJ, Grasso P, et al. 1993. The early changes in mouse skin following topical application of a range of middle distillate oil products. J Appl Toxicol 13(4):247-257.

*IRIS. 1994. Integrated Risk Information System. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, OH.

Ishidate M, Odashima S. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro: A screening for chemical carcinogens. Mutat Res 48:337-354.

*ITII. 1982. International Technical Information Institute. Toxic and hazardous industrial chemicals safety manual. Tokyo, Japan: International Technical Information Institute.

Iwagawa M, Maeda T, Izumi K, et al. 1989. Comparative dose-response study on the pulmonary carcinogenicity of 1,6-dinitropyrene and benzo(a)pyrene in F344 rats. Carcinogenesis 10(7):1285-1290.

*Iwata K, Inui N, Takeuchi T. 1981. Induction of active melanocytes in mouse skin by carcinogens: A new method for detection of skin carcinogens. Carcinogenesis (London) 2:589-594.

8. REFERENCES

Izzotti A, Bagnasco M, Scatolini L, et al. 1993. Post-mortem stability of benzo(a)pyrene diolepoxide-DNA adducts in rat organs. Carcinogenesis 14(10):2185-2187.

*Jacob J, Schmoldt A, Grimmer G. 1983a. Benzo[e]pyrene metabolism in rat liver microsomes: Dependence of the metabolite profile on the pretreatment of rats with various monooxygenase inducers. Carcinogenesis 4(7):905-910.

*Jacob J, Schmoldt A, Raab G, et al. 1983b. Induction of specific monooxygenases by isosteric heterocyclic compounds of benz(a)anthracene, benzo(c)phenanthrene and chrysene. Cancer Lett 20:341-348.

*Jacob J, Schmoldt A, Raab G, et al. 1985. Monooxygenase induction by various xenobiotics and its influence on the rat liver microsomal metabolite profile of benz[a]anthracene. Cancer Lett 27: 105-113.

*Jacob J, Schmoldt A, Hamann M, et al. 1987. Monooxygenase induction by various xenobiotics and its influence on rat liver microsomal metabolism of chrysene in comparison to benz(a)anthracene. Cancer Lett 34:91-102.

*Jacobs MW, Coates JA, Delfino JJ, et al. 1993. Comparison of sediment extract Microtox toxicity with semi-volatile organic priority pollutant concentrations. Arch Environ Contam Toxicol 24(4):461-468.

*Jarvholm B, Easton D. 1990. Models for skin tumour risks in workers exposed to mineral oils. Br J Cancer 62:1039-1041.

*Jensen K. 1984. Benzo(a)pyrene input and occurrence in a marine area affected by refinery effluent. Water Air Soil Pollut 22:57-65.

*Jerina DM, Lehr RE, Yagi H, et al. 1976. Mutagenicity of B[a]P derivatives and the description of a quantum mechanical model which predicts the ease of carbonium ion formation from diol epoxides. In: de Serres FJ, Fouts JR, Bend JR, et al., eds. *In vitro* metabolic activation in mutagenesis testing. Amsterdam, The Netherlands: Elsevier/North Holland, 159-178.

*Jerina DM, Sayer JM, Thakker DR, et al. 1980. Carcinogenicity of polycyclic aromatic hydrocarbons: The bay-region theory. In: Pullman B, Ts'O POP, Gelboin H, eds. Carcinogenesis: Fundamental mechanisms and environmental effects. Hingham, MA: D. Reidel Publishing Co, 1-12.

*Jin CJ, Miners JO, Burchell B, et al. 1993. The glucuronidation of hydroxylated metabolites of benzo(a)pyrene and 2-acetylaminofluorene by cDNA-expressed human UDP-glucuronosyltransferases. Arch Environ Toxicol 27(3):47-52.

Joe FLJ, Salemme J, Fazio T. 1982. High performance liquid chromatography with fluorescence and UV detection of polynuclear aromatic hydrocarbons in barley malt. J Assoc Off Anal Chem 65:1395-1402.

*Joe FLJ, Salemme J, Fazio T. 1984. Liquid chromatographic determination of trace residues of polynuclear aromatic hydrocarbons in smoked foods. J Assoc Off Anal Chem 67:1076-1082.

8. REFERENCES

*John ED, Nickless G. 1977. Gas chromatographic method for the analysis of major polynuclear aromatics in particulate matter. J Chromatogr 138:399-412.

*Johnson JH. 1988. Automotive emissions. In: Watson AY, Bates RR, Kennedy D, eds. Air pollution: The automobile and public health. Washington, DC: National Academy Press, 39-76.

Jones KC, Stratford JA, Waterhouse K, et al. 1987. Polynuclear aromatic hydrocarbons in U.K. soils: Long-term termporal trends and current levels. Trace Subst Environ Health 2:140-148.

*Jones BT, Glick MR, Mignardi MA, et al. 1988. Determination of polycyclic aromatic hydrocarbons in cooked beef by low-temperature molecular luminescence spectrometry using a moving sample cooling belt. Appl Spectrosc 42(5):850-853.

*Jones KC, Grimmer G, Jacob J, et al. 1989a. Changes in the polynuclear aromatic hydrocarbon content of wheat grain and pasture grassland over the last century from one site in the UK. Sci Total Environ 78:117-130.

*Jones KC, Stratford JA, Waterhouse KS, et al. 1989b. Increase in the polynuclear aromatic hydrocarbon content of an agricultural soil over the last century. Environ Sci Technol 23:95-101.

*Jongeneelen FJ, Leijdekkers C-M, Bos RP, et al. 1985. Excretion of 3-hydroxy-benzo(o)pyrene and mutagenicity in rat urine after exposure to benzo(a)pyrene. J Appl Toxicol 5:277-282.

*Jongeneelen FJ, Bos RP, Anzion R, et al. 1986. Biological monitoring of polycyclic aromatic hydrocarbons - metabolites in urine. Stand J Work Environ Health 12:137-143.

*Jongeneelen FJ, Anzion RBM, Henderson PTH, et al. 1987. Determination of hydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. J Chromatogr 413:227-232.

*Jongeneelen FJ, Anzion BM, Scheepers PTJ, et al. 1988. 1-Hydroxypyrene in urine as a biological indicator of exposure to polycyclic aromatic hydrocarbons in several work environments. Am Ind Hyg 32:35-43.

*Jongeneelen FJ, Anzion RBM, Theuws JLG, et al. 1989. Urinary 1-Hydroxypyrene levels in workers handling petroleum coke. J Toxicol Environ Health 26:133-136.

*Jongeneelen FJ, van Leeuwen FE, Oosterink S, et al. 1990. Ambient and biological monitoring of cokeoven workers: determinants of the internal dose of polycyclic aromatic hydrocarbons. British J Indust Med 47:454-461.

Kagan J, Tuveson RW, Gong HH. 1989. The light-dependent cytotoxicity of benzo[a]pyrene: Effect on human erythrocytes, *Escherichia coli* cells, and *Huemophilus influenzae* transforming DNA. Mutat Res 216(5):231-242.

*Kamens RM, Fulcher JN, Zhishi G. 1986. Effects of temperature on wood soot: PAH decay in atmospheres with sunlight and low NOx. Atmos Environ 20:1579-1587.

*Kanoh T, Fukuda M, Hayami E, et al. 1990. Nitro reaction in mice injected with pyrene during exposure to nitrogen dioxide. Mutat Res 245(1):1-4.

8. REFERENCES

*Kanoh T, Fukuda M, Onozuka H, et al. 1993. Urinary 1-hydroxypyrene as a marker of exposure to polycyclic aromatic hydrocarbons in environment. Environ Res 62:230-241.

*Kao JK, Patterson FK, Hall J. 1985. Skin penetration and metabolism of topically applied chemicals in six mammalian species, including man: An *in vitro* study with benzo[a]pyrene and testosterone. Toxicol Appl Pharmacol 81:502-516.

*Kapitulnik J, Levin W, Lu AYH, et al. 1977. Hydration of arene and alkene oxides by epoxide hydrase in human liver microsomes. Clin Pharmacol Ther 21:158-165.

Karasek FW, Denney DW, Chan KW, et al. 1978. Analysis of complex organic mixtures on airborne particulate matter. Anal Chem 50:82-87.

*Karickhoff SW, Brown DS, Scott TA. 1979. Sorption of hydrophobic pollutants on natural sediments. Water Res 13:241-248.

*Karlesky DL, Ramelow G, Ueno Y, et al. 1987. Survey of polynuclear aromatic compounds in oil refining areas. Environ Poll 43:195-207.

*Katiyar SK, Agarwal R, Mukhtar H. 1993a. Protective effects of green tea polyphenols administered by oral intubation against chemical carcinogen-induced forestomach and pulmonary neoplasia in A/J mice. Cancer Lett 167-172.

*Katiyar SK, Agarwal R, Tarif Zaim M, et al. 1993b. Protection against N-nitrosodiethylamine and benzo[a]pyrene-induced forestomach and lung tumorigenesis in A/J mice by green tea. Carcinogenesis 14(5):849-855.

Katz M, Pierce RC. 1976. Quantitative distribution of polynuclear aromatic hydrocarbons in relation. In: Freudenthal RI, Jones PW, eds. Carcinogenesis: Polynuclear aromatic hydrocarbons: Chemistry, metabolism, and carcinogenesis.

*Kauss PB. 1991. Biota of the St. Marys River: habitat evaluation and environmental assessment. Hydrobiologia 219:1-35.

*Kawamoto T, Yoshikawa M, Matsuno K, et al. 1993. Effect of side-stream cigarette smoke on the hepatic cytochrome P450. Arch Environ Contam Toxicol 25:255-259.

*Kawamura Y, Kamata E, Ogawa Y, et al. 1988. The effect of various foods on the intestinal absorption of benzo-a-pyrene in rats. J Food Hyg Sot Jpn 29(1):21-25.

*Keller GM, Christou M, Pottenger LH, et al. 1987. Product inhibition of benzo(a)pyrene metabolism in uninduced rat liver microsomes: Effect of diol epoxide formation. Chem Biol Interact 61:159-175.

*Kelly GW, Bartle KD, Clifford AA, et al. 1993. Identification and quantitation of polycyclic aromatic compounds in air particulate and diesel exhaust particulate extracts by LC-GC. J Chromatogr Sci 31(3):73-76.

*Kemena A, Norpoth KH, Jacob J. 1988. Differential induction of the monooxygenase isoenzymes in mouse liver microsomes by polycyclic aromatic hydrocarbons. In: Cooke M, Dennis AJ, eds.

8. REFERENCES

Polynuclear aromatic hydrocarbons: A decade of progress. Proceedings of the Tenth International Symposium. Columbus, OH: Battelle Press, 449-460.

*Kenneway EL. 1924. On cancer-producing tars and tar-fractions. J Ind Hyg 5:462-490.

*Kennicutt MC II, 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):1-15.

Kertesz-Saringer M, Morlin Z. 1975. On the occurrence of polycyclic aromatic hydrocarbons in the urban area of Budapest. Atmos Environ 9:831-834.

Ketkar M, Resnick G, Schneider P, et al. 1978. Investigations on the carcinogenic burden by air pollution in man: Intratracheal instillation studies with benzo[a]pyrene in bovine serum albumin. Cancer Lett 4:235-239.

Ketkar M, Green V, Schnieder P, et al. 1979. Investigations on the carcinogenic burden by air pollution in man: Intratracheal instillation studies with benzo[a]pyrene in a mixture of Tris buffer and saline in Syrian golden hamsters. Cancer Lett 6:279-284.

*Khan MA, Matin MA, Beg MU. 1993. Effect of intratracheally administered lindane on aldrin and benzo[a]pyrene contents in lungs of rats. Toxicol Lett 69:63-67.

*Khanduja KL, Majid S. 1993. Ellagic acid inhibits DNA binding of benzo[a]pyrene activated by different modes. J Clin Biochem Nutr 15: l-9.

*Kiefer F, Cumpelik O, Wiebel FJ. 1988. Metabolism and cytotoxicity of benzo(a)pyrene in the human lung tumour cell line NCI-H322. Xenobiotica 18:747-755.

*King TL, Uthe JF, Musial CJ. 1993. Polycyclic aromatic hydrocarbons in the digestive glands of the american lobster, *Honarus americanus,* captured in the proximity of a coal-coking plant. Bull Environ Contam Toxicol 50:907-914.

*King LC, George M, Gallagher JE, et al. 1994. Separation of ^{32}P-postlabeled DNA adducts of polycyclic aromatic hydrocarbons and nitrated polycyclic aromatic hydrocarbons by HPLC. Chem Res Toxicol 7:503-510.

*Kirso U, Belykh L, Stom D, et al. 1983. Oxidation of benzo[a]pyrene by plant enzymes. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Formation, metabolism and measurement. Columbus, OH: Battelle Press, 679-687.

Klein M. 1952. Effect of croton oil on induction of tumors by 1,2-benzanthracene, deoxychloric or low doses of 20-methylcholanthrene in mice. J Nat1 Cancer Inst 13:333-341.

Klein M. 1960. A comparison of the initiating and promoting actions of 9,10-dimethyl-1,2-benzanthracene and 1,2,5,6-dibenzanthracene in skin tumorigenesis. Cancer Res 20: 1179.

*Klein M. 1963. Susceptibility of strain B6AFIJ hybrid infant mice to tumorigenesis with 1,2-benzanthracene, deoxycholic acid and 3-methylcholanthrene. Cancer Res 23:1701-1707.

8. REFERENCES

*Klemme JC, Mukhtar H, Elmets CA. 1987. Induction of contact hypersensitivity to dimethylbenz(a)anthracene and benzo(a)pyrene in C3H/HeN mice. Cancer Res 47:6074-6078.

*Knecht U, Elliehausen HJ, Jusas W, et al. 1987. Polycyclic aromatic hydrocarbons (PAH) in abraded particles of brake and clutch linings. Int J Environ Occup Sot Med 28:227-236.

Knobloch K, Szendzikowski S, Slusarczyk-Zalobna A. 1969. On the acute and sub-acute toxic effects of acenapthene and acenapthylene. Occup Med 20:210-220.

*KNREPC. 1991. Threshold ambient limits and significant emission levels of toxic pollutants. Frankfurt, KY: Kentucky Natural Resources and Environmental Protection Cabinet. 401 KAR 63:022.

Kolarovic L, Traitler H. 1982. Determination of polycyclic aromatic hydrocarbons in vegetable oils by caffeine complexation and glass capillary gas chromatography. J Chromatogr 237:263-272.

*Konash PL, Wise SA, May WE. 1981. Selective quenchofluorimetric detection of fluoranthenic polycyclic aromatic hydrocarbons in high-performance liquid chromatography. J Liq Chromatogr 4(8):1339-1349.

*Koratkar R, Das UN, Sangeetha Sagar P, et al. 1993. Prostacyclin is a potent anti-mutagen. Prostaglandins Leukotrienes and Essential Fatty Acids 48:175-184.

*Korfmacher WA, Wehry EL, Mamantov G, et al. 1980. Resistance to photochemical decomposition of polycyclic aromatic hydrocarbons vapor-adsorbed on coal fly ash. Environ Sci Technol 14:1094-1099.

*Kouri RE, Rude TH, Joglekar R, et al. 1978. 2,3,7,8-Tetrachloro-dibenzo-p-dioxin as cocarcinogen causing 3- methylcholanthrene initiated subcutaneous tumors in mice genetically ‘nonresponsive’ at Ah locus. Cancer Res 38:2777-2783.

*Krahn M, Malins DC. 1982. Gas chromatographic-mass spectrometric determination of aromatic hydrocarbon metabolites from livers of fish exposed to fuel oil. J Chromatogr 248:99-107.

*Krahn MM, Moore LK, Bogar RG, et al. 1988. High-performance liquid chromatographic method for isolating organic contaminants from tissue and sediment extracts. J Chromatogr 437:161-175.

Kraybill HF. 1983. Assessment of human exposure and health risk to environmental contaminants in the atmosphere and water with special reference to cancer. J Environ Sci Health [c] Carcinog Rev 1(2):175-232.

Kunstler K. 1983. Failure to induce tumors by intratracheal instillation of automobile exhaust condensate and fractions thereof in Syrian golden hamsters. Cancer Let 18:105-108.

Kushwaha SC, Clarkson SG, Mehkeri KA. 1985. Polycyclic aromatic hydrocarbons in barbecue briquets. J Food Saf 7:177-201.

*Ladies GS, Kawabata TT, White KL Jr. 1991. Suppression of the *in vitro* humoral immune response of mouse splenocytes by 7,12-dimethylbenz(a)anthracene metabolites and inhibition of immunosuppression by alpha-naphthoflavone. Toxicol Appl Pharmacol 110(1):31-44.

8. REFERENCES

*La Fontaine M. 1978. Huiles minerales et cancers cutaines. Paris, France: Institut National de Recheche et de Securite. (French)

Laher JM, Barrowman JA. 1987. Role of the lymphatic system in the transport of absorbed 7,12-dimethylbenzanthracene in the rat. Lipids 22:152-155.

*Lai LK, Filseth SV, Sadowski CM, et al. 1990. Direct determination of benzo(a)pyrene and pyrene in solid environmental samples by jet-cooled spectroscopy. Int J Environ Anal Chem 40(1-4):99-109.

*Lamotte M, Rima J, Garrigues P, et al. 1985. Quantitative analysis of PAH (polynuclear aromatic hydrocarbons) in environmental samples by fluorometry in Shpol'skii matrices at low temperature. Polynuclear Aromatic Hydrocarbons:785-798.

Laskin S, Kuscher M, Drew RT. 1970. Studies in pulmonary carcinogenesis. In: Hanna MG, Nettesheim P, Gilbert J, eds. Inhalation carcinogenesis. AEC Symposium Series No. 18. Oak Ridge, TN: Oak Ridge Division of Technical Information, U.S. Atomic Energy Commission, 321-351.

Lasnitzki A, Woodhouse DL. 1944. The effect of 1,2,5,6-dibenzanthracene on the lymph nodes of the rat. J Anat 78:121.

*Lau HH, Baird WM. 1991. Detection and identification of benzo[a]pyrene-DNA adducts by [^{35}S]phosphorothioate labeling and HPLC. Carcinogenesis 12(5):885-893.

*Lau HH, Baird WM. 1992. The co-carcinogen benzo[e]pyrene increases the binding of a low dose of the carcinogen benzo[a]pyrene to DNA in Sencar mouse epidermis. Cancer Lett (Ireland) 63(3):229-236.

*LaVoie E, Bedenko V, Hirota N, et al. 1979. A comparison of the mutagenicity, tumor initiating activity and complete carcinogenicity of polynuclear aromatic hydrocarbons. In: Jones PW, Leber P, eds. Polynuclear aromatic hydrocarbons. Ann Arbor, MI: Science Publishers, Inc.

LaVoie EJ, Hecht SS, Amin S, et al. 1980a. Identification of mutagenic dihydrodiols as metabolites of benzo(j)fluoranthene and benzo(k)fluoranthene. Cancer Res 40:4528-4532.

LaVoie EJ, Tulley L, Bedenko V, et al. 1980b. Mutagenicity, tumor-initiating activity, and metabolism of tricyclic polynuclear aromatic hydrocarbons. In: Bjorseth A, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Chemistry and biological effects. Columbus, OH: Batelle Press.

LaVoie EJ, Tulley L, Bedenko V, et al. 1981a. Mutagenicity of methylated fluorenes and benzofluorenes. Mutat Res 91 (3):167-176.

*LaVoie EJ, Tulley L, Bedenko V, et al. 1981b. Mutagenicity, tumor-initiating activity and metabolism of methylphenanthrenes. Cancer Res 41:3441-3447.

*LaVoie EJ, Amin S, Hecht SS, et al. 1982. Tumor initiating activity of dihydrodiols of benzo(b)fluoranthene, benzo(j)fluoranthene and benzo(k)fluoranthene. Carcinogenesis 3:49-52.

8. REFERENCES

*LaVoie EJ, Coleman DT, Tonne RL, et al. 1983a. Mutagenicity, tumor initiating activity and metabolism of methylated anthracenes. In: Cooke M, Dennis AJ, eds. Proceedings of the Seventh International Symposium. Columbus, OH: Battelle Press, 785-798.

LaVoie EJ, Tulley L, Bedenko V, et al. 1983b. Mutagenicity of substituted phenanthrenes in *Salmonella typhimurium.* Mutat Res 116:91-102.

LaVoie EJ, Coleman DT, Rice JE, et al. 1985. Tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes. Carcinogenesis (London) 6:1483-1488.

LaVoie EJ, Braley J, Rice JE, et al. 1987. Tumorigenic activity of non-altemant polynuclear aromatic hydrocarbons in newborn mice. Cancer Let 34:15-20.

*LaVoie EJ, Cai Z-W, Meegalla RL, et al. 1993a. Evaluation of the tumor-initiating activity of 4-, 5-, 6-, and 7-fluorobenzo[b]fluoranthene in mouse skin. Chem Bio Interact 89:129-139.

*LaVoie EJ, He Z-M, Meegalla RL, et al. 1993b. Exceptional tumor-initiating activity of 4-fluorobenzoljlfluoroanthene on mouse skin: comparison with benzo[j]fluoranthene, l0-fluoro-benzoIj]fluoranthene, benzo[a]pyrene, dibenzo[a,l]pyrene and 7,12-dimethylbenz[a]anthracene. Cancer Lett 70:7-14.

*Lawrence JF, Das BS. 1986. Determination of nanogram/kilogram levels of polycyclic aromatic hydrocarbons in foods by HPLC with fluorescence detection. Int J Environ Anal Chem 24(2):113-131.

*Lawrence JF, Weber DF. 1984. Determination of polycyclic aromatic hydrocarbons in some Canadian commercial fish, shellfish and meat products by liquid chromatography with confirmation by capillary gas chromatography-mass spectrometry. J Agric Food Chem 32:789-794.

Leadon SA, Stampfer MR, Bartley J. 1988. Production of oxidative DNA damage during the metabolic activation of benzo(a)pyrene in human mammary epithelial cells correlates with cell killing. Proc Nat1 Acad Sci 85:4365-4368.

*Lecoq S, Chalvet O, Strapelias H, et al. 1991a. Microsomal metabolism of dibenz(a,c)anthracene, dibenz(a,h)anthracene and dibenz(a,j)anthracene to bisdihydrodiols and polyhydroxylated products. Chem-Biol Interact 80(3):261-280.

*Lecoq S, Ni She M, Grover PL, et al. 1991b. The *in vitro* metabolic activation of dibenz[a, hlanthracene, catalyzed by rat liver microsomes and examined by ^{32}P-postlabelling. Cancer Lett 57(3):261-269.

*Lecoq S, Perin F, Plessis MJ, et al. 1989. Comparison of the *in vitro* metabolisms and mutagenicities of dibenzo[a,c]anthracene, dibenzo[a,h]anthracene and dibenzo[a,j]anthracene: Influence of norharman. Carcinogenesis 10(3):461-469. 0143-3334.

Lee BM, Santella RM. 1988. Quantitation of protein adducts as a marker of genotoxic exposure: Immunologic detection of benzo[a]pyrene-globin adducts in mice. Carcinogenesis 9(10):1773-1777.

8. REFERENCES

*Lee H, Lin JY. 1988. Antimutagenic activity of extracts from anticancer drugs in Chinese medicine. Mutat Res 204:229-234.

*Lee BM, Strickland PT. 1993. Antibodies to carcinogen-DNA adducts in mice chronically exposed to polycyclic aromatic hydrocarbons. Immunol Lett 36:117-124.

*Lee CK, Brown BG, Reed EA, et al. 1993. Ninety-day inhalation study in rats, using aged and diluted sidestream smoke from a reference cigarette: DNA adducts and alveolar macrophage cytogenetics. Fundam Appl Toxicol 20:393-401.

*Legraverend C, Guenther TM, Nebert DW. 1984. Importance of the route of administration for genetic differences in benzo[a]pyrene-induced in utero toxicity and teratogenicity. Teratology 29:35-47.

*Legraverend C, Harrison DE, Ruscetti W, et al. 1983. Bone marrow toxicity induced by oral benzo(a)pyrene: Protection resides at the level of the intestine and liver. Toxicol Appl Pharmacol 70:390-401.

*Legzdins AE, McCarry BE, Bryant DW. 1994. Polycyclic aromatic compounds in Hamilton air: Their mutagenicity, ambient concentrations and relationships with atmospheric pollutants. Polycyclic Aromatic Compounds 5(1-4):157-165.

*Lemieux PM, Ryan JV. 1993. Characterization of air pollutants emitted from a simulated scrap tire fire. Air Waste 43: 1106-l 115.

Lesage J, Perrault G, Durand P. 1987. Evaluation of worker exposure to polycyclic aromatic hydrocarbons. Am Ind Hyg Assoc J 48:753-759.

*Leung HW, Henderson RF, Bond JA, et al. 1988. Studies on the ability of rat lung and liver microsomes to facilitate transfer and metabolism of benzo(a)pyrene from diesel particles. Toxicology 51:1-9.

Levin W, Wood AW, Yagi H, et al. 1976. Carcinogenicity of benzo[a]pyrene 4,5-, 7,8-, 9 and 10-oxides on mouse skin. Proc Nat1 Acad Sci USA 73:243-247.

Levin W, Wood AW, Chang RL, et al. 1978. Evidence for bay region activation of chrysene 1,2 dihydrodiol to an ultimate carcinogen. Cancer Res 38:1831.

*Levin W, Wood A, Chang R, et al. 1982. Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate carcinogens. Drug Metab Rev 13:555-580.

*Levin W, Chang RL, Wood AW, et al. 1984. High stereoselectivity among the optical isomers of the diastereomeric bay-region diol-epoxides of benz(a)anthracene in the expression of tumorigenic activity in murine tumor models. Cancer Res 44:929-933.

*Lewis RF. 1993. Site demonstration of slurry-phase biodegradation of PAH contaminated soil. Air Waste 43:503-508.

8. REFERENCES

*Lewtas J, Mumford J, Everson RB, et al. 1993. Comparison of DNA adducts from exposure to complex mixtures in various human tissues and experimental systems. Environ Health Perspect 99:89-97.

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

Lijinsky WH, Garcia B, Terracini B. 1965. Tumorigenic activity of hydrogenated derivatives of dibenz(a,h)anthracene. J Natl Cancer Inst 34:1.

Likhachev AJ, Beniashvili DSh, Bykov VJ, et al. 1992. Relevance of quantitation of benzo(a)pyrene metabolites in animal excretes to evaluate individual human cancer risk. Prog Clin Biol Res 374:435-452.

*Likhachev AJ, Beniashvili DS, BYkov VJ, et al. 1993. Biomarkers of individual suseceptability to carcinogens: Application for biological monitoring. Int Arch Occup Environ Health 65:S155-S158.

*Limasset J-C, Diebold F, Hubert G. 1993. Assessment of bus drivers' exposure to the pollutants of urban traffic. Sci Tot Environ 134:39-49. (French)

*Lin CH, Fukii H, Imasaka T, et al. 1991. Synchronous scan luminescence techniques monitoring resonance and non-resonance fluorescence in supersonic jet spectrometry applied to anthracene derivatives. Anal Chem 63(14):1433-1440.

*Lindemann RA, Park N-H. 1989. The effects of benzo-a-pyrene nicotine and tobacco-specific nitrosamines on the generation of human lymphokine-activated killer cells. Arch Oral Biol 34(4):283-288.

Liotti FS, Bodo M, Mariucci G, et al. 1989. The role of antioxidant enzymes in benzo(a)pyrene-induced carcinogenesis. Bull Cancer 76(1):43-50.

Liotti FS, Pelliccia C, Pezzetti F. 1988. Different response of chicken embryo fibroblasts and hepatocytes to the interference of certain antioxidants on the binding of [G-^{3}H] benzo[a]pyrene to DNA. Cancer Lett 41:235-242.

*Lioy PJ. 1989. Exposure analysis and assessment for low-risk cancer agents. Int J Epidemiol 19(3 Suppl 1):53-61.

*Lioy PJ, Greenberg A. 1990. Factors associated with human exposures to polycyclic aromatic hydrocarbons. Toxicol Ind Health 6(2):209-224.

*Lioy PL, Waldman JM, Greenberg A, et al. 1988. The total human environmental exposure study (THEES) to benzo(a)pyrene: Comparison of the inhalation and food pathways. Arch Environ Health 43:304-312.

*Lipniak M, Brandys J. 1993. Toxicokinetics of fluoranthene, pyrene and benz(a)anthracene in the rat. Polycyclic Aromatic Hydrocarbons 3:111-119.

8. REFERENCES

Little JB, Vetroys H. 1988. Studies of ionizing radiation as a promoter of neoplastic transformation *in vitro.* Int J Radiat Biol 53:661-666.

*Lloyd JW. 1971. Long-term mortality study of steelworkers: V. Respiratory cancer in coke plant workers. J Occup Med 13:53-68.

*Lo Jacono F, Stecca C, Duverger M. 1992. Mutagenic activation of benzo[a]pyrene by human red blood cells. Mutat Res 268(1):21-26.

*Loehr RC, Erickson DC, Kelmar LA. 1993. Characteristics of residues at hazardous waste land treatment units. Water Res 27(7):1127-1138.

Lorenz E, Stewart HL. 1948. Tumors of alimentary tract in mice fed carcinogenic hydrocarbons in mineral oil emulsions. J Nat1 Cancer Inst 9:173.

*Lorenz LF, Gjovik LR. 1972. Analyzing creosote by gas chromatography: Relationship to creosote specifications. Proceedings of the American Wood-Preservers' Association 68:32-42.

*Low GK-C, Batley GE, Lidgard RO, et al. 1986. Determination of polycyclic aromatic hydrocarbons in coal fly ash using gas chromatography/negative ion chemical ionization mass spectrometry. Biomed Environ Mass Spectrom 13:95-104.

*Lowenthal DH, Zielinska B, Chow JC, et al. 1994. Characterization of heavy-duty diesel vehicle emissions. Atmos Environ 28(4):731-743.

*Lu L-J W, Anderson LM, Jones AB, et al. 1993. Persistence, gestation stage-dependent formation and interrelationship of benzo[a]pyrene-induced DNA adducts in mothers, placentae and fetuses of *Erythrocebus patas* monkeys. Carcinogenesis 14(9):1805-1813.

*Lubet RA, Brunda MJ, Lemaire B, et al. 1984. Polycyclic hydrocarbon: Induced immunotoxicity in mice: Role of the Ah locus. In: Cooke M, Dennis AJ, eds. Mechanisms, methods and metabolism: Polynuclear aromatic hydrocarbons. 8th International Symposium. Columbus, OH: Battelle Press, 843-855.

Lubet RA, Connelly GM, Nebert DW, et al. 1983a. Dibenz[a,h]anthracene-induced subcutaneous tumors in mice. Strain sensitivity and the role of carcinogen metabolism. Carcinogenesis 4:513-517.

Lubet RA, Kiss E, Gallagher MM, et al. 1983b. Induction of neoplastic transformation and DNA single-strand breaks in C3WlOT1/2 clone 8 cells by polycyclic hydrocarbons and alkylating agents. J Natl Cancer Inst 71:991-998.

*Lunde G, Bjorseth A. 1977. Polycyclic aromatic hydrocarbons in long-range transported aerosols. Nature 268:518.

*Luster MI, Rosenthal GJ. 1993. Chemical agents and the immune response. Environ Health Perspect 100:219-226.

*Lyman W, Reehl WF, Rosenblatt DH. 1982. Handbook of chemical property estimation methods. New York, NY: McGraw Hill, Inc., 15/10-15/21.

8. REFERENCES

*Lyte M, Bick PH. 198.5. Differential immunotoxic effects of the environmental chemical benzo[a]pyrene in young and aged mice. Mech Aging Dev 30:333-341.

Lyte M, Blanton RH, Myers MJ, et al. 1987. Effect of *in vivo* administration of the carcinogen benzo(a)pyrene on interleukin-2 and interleukin-3 production. Int J Immunopharmacol 9:307-3 12.

*Mabey WR, Smith JH, Podoll RT, et al. 1981. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency. EPA-440/4-81-014.

*Mabey WR, Smith JH, Podoll RT, et al. 1982. Aquatic fate process data for organic priority pollutants. Washington, D.C: US Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440/4-81-014.

*Machado ML, Beatty PW, Fetzer JC, et al. 1993. Evaluation of the relationship between PAH content and mutagenic activity of fumes from roofing and paving asphalts and coal tar pitch. Fundam Appl Toxicol 21:492-499.

*Mackenzie KM, Angevine DM. 1981. Infertility in mice exposed in utero to benzo[a]pyrene. Biol Reprod 24:183-191.

*MacKenzie MJ, Hunter JV. 1979. Sources and fates of aromatic compounds in urban stormwater runoff. Environ Sci Technol 13:179-183.

*Mackenzie PI, Rodboum L, Iyanagi T. 1993. Glucuronidation of carcinogen metabolites by complementary DNA-expressed uridine 5’-diphosphate glucuronosyltransferases. Cancer Res 53:1529-1533.

*MacLeod MC, Evans FE, Lay J, et al. 1994. Identification of a novel, N7-deoxyguanosine adduct as a major DNA adduct formed by a non-bay-region diol epoxide of benzo[a]pyrene with low mutagenic potential. Biochemistry 33:2977-2987.

*Maclure KM, MacMahon B. 1980. An epidemiologic perspective of environmental carcinogenesis. Epidemiol Rev 2:19-48.

MacNicoll AD, Grover PL, Sims P. 1980. The metabolism of a series of polycyclic hydrocarbons by mouse skin maintained in short-term organ culture. Chem Biol Interact 29(2): 169-188.

Mager R, Huberman E, Yang SK, et al. 1977. Transformation of normal hamster cells by benzo(a)pyrene diol-epoxide. Int J Cancer 19:814-817.

*Majer JR, Perry R, Reade MJ. 1970. The use of thin-layer chromatography and mass spectrometry for the rapid estimation of trace quantities of air pollutants. J Chromatogr 48:328-333.

*Malmgren RA. 1952. Reduced antibody titers in mice treated with carcinogenic and cancer chemotherapeutic agents. Proc Sot Biol Med 79:484.

Mamber SW, Bryson V, Katz SE. 1983. The *Esherichia coli* WP2/WP100 ret assay for detection of potential chemical carcinogens. Mutat Res 119:135-144.

8. REFERENCES

*Matsuoka A, Sofuni T, Miyata N, et al. 1991. Clastogenicity of I-nitropyrene, dinitropyrenes, fluorene and mononitrofluorenes in cultured Chinese hamster cells. Mutat Res 259(1):103-110.

*Matthews EJ. 1993. Transformation of BALB/c-3T3 cells: II. Investigation of experimental parameters that influence detection of benzo[a]pyrene-induced transformation. Environ Health Perspect 101(Supp 2):293-310.

*Mattison DR, Singh H, Takizawa K, et al. 1989. Ovarian toxicity of benzo(a)pyrene and metabolites in mice. Reprod Toxicol 3(2):115-126.

*Matzner E. 1984. Annual rates of deposition of polycyclic aromatic hydrocarbons in different forest ecosystems. Water Air Soil Polut 21:425-434.

May WE, Chesler SN, Hertz HS, et al. 1982. Analytical standards and methods for the determination of polynuclear aromatic hydrocarbons in environmental samples. Int J Environ Anal Chem 12:259-275.

*Mazumdar S, Redmond CK, Sollecito W, et al. 1975. An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. J Air Pollut Control Assoc 25:382-389.

McCabe DP, Flynn EJ. 1990. Deposition of low dose benzo(a)pyrene into fetal tissue: Influence of protein binding. Teratology 41(1):85-95.

*McCarthy DJ, Lindamood CI, Hill DL. 1987. Effects of retinoids on metabolizing enzymes and on binding on benzo(a)pyrene to rat tissue DNA. Cancer Res 47:5014-5020.

*McCormick DL, Burns FJ, Alberg RE. 1981. Inhibition of benzo[a]pyrene-induced mammary carcinogenesis by retinyl acetate. J Nat1 Cancer Inst 66:559-564.

McIntyre AE, Perry R, Lester JN. 1981. Analysis of polynuclear aromatic hydrocarbons in sewage sludges. Anal Lett 14:291-309.

*McVeety BD, Hites RD. 1988. Atmospheric deposition of polycyclic aromatic hydrocarbons to water surfaces a mass balance approach. Atmos Environ 22(3):511-536.

*Melikian AA, Bagheri K, Hecht SS. 1987. Contrasting disposition and metabolism of topically applied benzo(a)pyrene, trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene, and 7 beta, 8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene in mouse epidermis in viva. Cancer Res 47:5354-5360.

Melikian AA, Bagheri K, Hecht SS, et al. 1989. Metabolism of benzo[a]pyrene and 7 beta, 8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a pyrene in lung and liver of newborn mice. Chem Biol Interact 69(2-3):245-257.

*Menzie CA, Potocki BB, Santodonato J. 1992. Ambient concentrations and exposure to carcinogenic pahs in the environment. Environ Sci Technol 26(7):1278-1284.

Mercado Calderon F. 1993. Evaluation of 1-hydroxypyrene as a biological marker of industrial exposure to polycyclic aromatic hydrocarbons. Proc SPIE(Int Sot Opt Eng) 1716:256-267.

8. REFERENCES

*Mane SS, Pumell DM, Hsu IC. 1990. Genotoxic effects of five polycyclic aromatic hydrocarbons in human and rat mammary epithelial cells. Environ Mol Mutagen 15(2):78-82.

*Manila1 VB, Alexander M. 1991. Factors affecting the microbial degradation of phenanthrene in soil. Appl Microbial Biotechnol 35(3):401-405.

*Marcomini A, Sfriso A, Pavoni B. 1987. Variable wavelength absorption in detecting environmentally relevant PAHs by high-performance liquid chromatography. Mar Chem 21:15-24.

*Marcus JM, Swearingen GR, Williams AD, et al. 1988. Polynuclear aromatic hydrocarbon and heavy metal concentrations in sediments at coastal South Carolina marinas. Arch Environ Contam Toxicol 17(1):103-114.

Marino DJ. 1987. Evaluation of pluronic polyol F127 as a vehicle for petroleum hydrocarbons. Environ Mutagen 9:307-316.

*Marks HS, Anderson JA, Stoewsand GS. 1993. Effect of S-methyl cysteine sulphoxide and its metabolite methyl methane thiosulphinate, both occuring naturally in brassica vegetables, on mouse genotoxicity. Food Chem Toxic 31(7):491-495.

Marquardt H, Kuroki T, Huberman E, et al. 1972. Malignant transformation of cells derived from mouse prostate by epoxides and other derivatives of polycyclic hydrocarbons. Cancer Res 32:716-720.

*Marshall MV, He Z-M, Weyand EH, et al. 1993. Mutagenic activity of the 4,5- and 9, 10-dihydrodiols of benzo~]fluoranthene and their syn- and anti-dihydrodiol epoxides in *Salmonella typhimurium.* Environ Mol Mutagen 22:34-45.

Martin CN, McDermid AC, Gamer RC. 1978. Testing of known carcinogens and noncarcinogens for their ability to induce unscheduled DNA synthesis in HeLa cells. Cancer Res 38:2621-2627.

Masclet P, Pistikopoulos P, Beyne S, et al. 1988. Long range transport and gas/particle distribution of polycyclic aromatic hydrocarbons at a remote site in the Mediterranean sea. Atmos Environ 22:639-650.

Masento MS, Hewer A, Grover PL, et al. 1989. Enzyme-mediated phosphorylation of polycyclic hydrocarbon metabolites: Detection of non-adduct compounds in the phosphorus-32 post-labelling assay. Carcinogenesis 10(8):1557-1559.

*Mass MJ, Jeffers AJ, Ross JA, et al. Ki-ras oncogene mutations in tumors and DNA adducts formed by benz[j]aceanthrylene and benzo[a]pyrene in the lungs of strain A/J mice. Mol Carcinogen 8:186-192.

*Matsumoto H, Kashimoto T. 1985. Average daily respiratory intake of polycyclic aromatic hydrocarbons in ambient air determined by capillary gas chromatography. Bull Environ Contam Toxicol 34:17-23.

Matsuoka A, Hayashi M, Ishidate MJ. 1979. Chromasomal aberration tests on 29 chemicals combined with S9 mix *in vitro.* Mut Res 66:277-290.

8. REFERENCES

*Merk HF, Mukhtar H, Kaufmann I, et al. 1987. Human hair follicle benzo(a)pyrene and benzo(a)pyrene 7,8-diol metabolism: Effect of exposure to a coal tar-containing shampoo. J Invest Dermatol 88:71-76.

*Mersch-Sundermann V, Mochayedi S, Kevekordes S. 1992a. Genotoxicity of polycyclic aromatic hydrocarbons in Escherichia *coli.* Mutat Res 278(1):1-9.

*Mersch-Sundermann V, Rosenkranz HS, Klopman G. 1992b. Structural basis of the genotoxicity of polycyclic aromatic hydrocarbons. Mutagenesis 7(3):211-218.

*Metivier H, Wahrendorf J, Masse R. 1984. Multiplicative effect of inhaled plutonium oxide and benzo[a]pyrene on lung carcinogenesis in rats. Br J Cancer .50:215-221.

*Miguel AH, De Andrade JB. 1989. Rapid quantitation of ten polycyclic aromatic hydrocarbons in atmospheric aerosols by direct HPLC separation after ultrasonic acetonitrile extraction. Int J Environ Anal Chem 35(1):35-41.

*Mill T, Mabey W. 1985. Photochemical transformations. In: Neely W, Glau GE, eds. Environmental exposure from chemicals, Vol. I. Boca Raton, FL: CRC Press, Inc., 207.

*Miller MM, Plowchalk DR, Weitzman GA, et al. 1992. The effect of benzo(a)pyrene on murine ovarian and corpora lutea volumes. Am J Obstet Gynecol 166(5):1535-1541.

*Mile GE, Blakeslee J, Yohn DS, et al. 1978. Biochemical activation of aryl hydrocarbon hydroxylase activity, cellular distribution of polynuclear hydrocarbon metabolites, and DNA damage by polynuclear hydrocarbon products in human cells *in vitro*. Cancer Res 38:1638-1644.

Miralis JC, Tyson CK, Butterworth BE. 1982. Detection of genotoxic carcinogens in the *in vivo*-in vitro hepatocyte DNA repair assay. Environ Mutagen 4:553-562.

*Misfeld J. 1980. The tumor-producing effects of automobile exhaust condensate and of diesel exhaust condensate: Health effects of diesel engine emissions. Proceedings of an International Symposium. Cincinnati, OH: US Environmental Protection Agency. EPA 600/9-80-057b., 1012-1025.

Mishra NK, Wilson CM, Pant KJ, et al. 1978. Simultaneous determination of cellular mutagenesis and transformation by chemical carcinogens in Fischer rat embryo cells. J Toxicol Environ Health 4:79-91.

*Mitchell CE. 1979. A method for the determination of polycyclic aromatic hydrocarbons in animal tissue. Bull Environ Contam Toxicol 23:669-676.

Mitchell CE, Fischer JP, Dahl AR. 1987. Differential induction of cytochrome P-450 catalyzed activities by polychlorinated biphenyls and benzo[a]pyrene in $B6C3F_1$ mouse liver and lung. Toxicology 43:315-323.

*Modica R, Fiume M, Bartosek Z. 1982. Gas-liquid chromatographic assay of polycyclic aromatic hydrocarbon mixtures: Specifically modified method for rat tissues. J Chromatogr 24:352-355.

8. REFERENCES

*Mall N, Chevrier S, Moll M. 1993. Determination and occurence of 3,4-benzo(a)pyrene in smoked fish and meat products. Dev Food Sci 32:233-245.

*Molliere M, Foth H, Kahl R, et al. 1987. Metabolism of benzo(a)pyrene in the combined rat liver-lung perfusion system. Toxicology 45:143-154.

*Monarca S, Fagioli F. 1981. Evaluation of the potential carcinogenicity of paraffins for medicinal and cosmetic uses - determination of polycyclic aromatic hydrocarbons. Sci Total Environ 17:83-93.

Monarca S, Sforzolini GS, Fagioli F. 1982. Presence of benzo(a)pyrene and other polycyclic aromatic hydrocarbons in suntan oils. Food Chem Toxicol 20: 183-187.

*Monteith DK, Novotny A, Michalopoulos G, et al. 1987. Metabolism of benzo(a)pyrene in primary cultures of human hepatocytes: Dose-response over a four-log range. Carcinogenesis 8:983-988.

*Moore BP, Hicks RM, Knowles MA, et al. 1982. Metabolism and binding of benzo[a]pyrene and 2 acetylamino fluorene by short-term organ cultures of human and rat bladder. Cancer Res 42:642-648.

Moore CJ, Pruess-Schwartz D, Mauthe RJ, et al. 1987. Interspecies differences in the major DNA adducts formed from benzo(a)pyrene but not 7,12-dimethylbenz(a)anthracene in rat and human mammary cell cultures. Cancer Res 47:4402-4406.

*Moore M, Wang X, Lu Y-F, et al. 1994. Benzo[a]pyrene-resistant MCF-7 human breast cancer cells. J Biol Chem 269(16):11751-11759.

Morel G, Samhan 0, Literathy P, et al. 1991. Evaluation of chromatographic and spectroscopic methods for the analysis of petroleum-derived compounds in the environment. Fresenius' J Anal Chem 339(10):699-715.

*Mori Y, Goto S, Onodera S, et al. 1993. Changes in mutagenic properties and chemical fate of benz(a)anthracene in chlorine-treated water with and without bromide ion. Chemosphere 27(11):2155-2162.

Morris JJ, Seifter E. 1992. The role of aromatic hydrocarbons in the genesis of breast cancer. Med Hypotheses 38(3):177-184.

*Morris DL, Ward JB. 1992. Coumarin inhibits micronuclei formation induced by benzo(a)pyrene in male but not female ICR mice. Environ Mol Mutagen 19(2):132-138.

Morris HP, Velat CA, Wagner BP, et al. 1960. Studies of carcinogenicity in the rat of derivatives of aromatic amines related to 0-2-fluorenylacetamide. J Nat1 Cancer Inst 24:149-180.

Morse MA, Baird WM, Carlson GP. 1987. Distribution, covalent binding, and DNA adduct formation of 7,12- dimethylbenz(a)anthracene in Sencar and Balb/c mice following topical and oral administration. Cancer Res 47:4571-4575.

*Morse MA, Carlson GP. 1985. Distribution and macromolecular binding of benzo[a]pyrene in sencar and balblc mice following topical and oral administration. J Toxicol Environ Health 16:263-276.

8. REFERENCES

*Morselli L, Zappoli S. 1988. PAH determination in samples of environmental interest. Sci Total Environ 73:257-266.

Mossanda K, Poncelet F, Fouassin A, et al. 1979. Detection of mutagenic polycyclic aromatic hydrocarbons in African smoked fish. Food Cosmet Toxicol 17:141-143.

Moyer SR, Jurs PC. 1990. An SRA study of the mutagenicity of PAH compounds in *Salmonella typhimurium.* In: Mendelsohn ML, Albertini J, eds. Progress in clinical and biological research: Vol. 340. Mutation and the environment: Part B. Metabolism, testing methods, and chromosomes. New York, NY: Wiley-Liss, l-10.

*Mueller JG, Lantz SE, Blattmann BO, et al. 1991. Bench-scale evaluation of alternative biological treatment processes for the remediation of pentachlorophenol- and cresote-contaminated materials: solid-phase bioremediation. Environ Sci Technol 25(6):1045-1055.

*Mukhtar H, Asokan P, Das M, et al. 1986. Benzo(a)pyrene diol epoxide-I-DNA adduct formation in the epidermis and lung of sencar mice following topical application of crude coal tar. Cancer Letters 33:287-394.

*Mukhtar H, Das M, Khan WA, et al. 1988. Exceptional activity in tannic acid among naturally occurring plant phenols in protecteing against 7,12-dimethylbenz(a)anthracene-, benzo[a]pyrene-, 3-methylcholanthrene-, and N-methyl-N-nitrosourea-induced skin tumorigeneis in mice. Cancer Res 48:2361-2365.

Mulik CM, Guyer MF, Semeniuk GM, et al. 1975. A gas liquid chromatographic fluorescent procedure for the analysis of benzo(a)pyrene in 24 hour atmospheric particulate samples. Anal Lett 8:511-524.

*Mullaart E, Buytenhek M, Brouwer A, et al. 1989. Genotoxic effects of intragastrically administered benzo[a]pyrene in rat liver and intestinal cells. Carcinogenesis 10(2):393-395.

Muller J, Rohbock E. 1980. Method for measurement of polycyclic aromatic hydrocarbons in particulate matter in ambient air. Talanta 27:673-675.

*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.

*Mumford JL, Lee X, Lewtas J, et al. 1993. DNA adducts as biomarkers for assessing exposure to polycyclic aromatic hydrocarbons in tissues from Xuan Wei women with high exposure to coal combustion emissions and high lung cancer mortality. Environ Health Perspect 99:83-87.

*Murray RW, Kong W. 1994. Activation of PAH by ozone derived oxidants: results at ambient conditions. Polycyclic Aromatic Hydrocarbons 5:139-147.

Myers SR, Flesher JW. 1991a. Characterization of hemoglobin (hb) adducts with polynuclear aromatic hydrocarbons. Proceedings of the Annual Meeting of the American Association for Cancer Research 32:A532.

8. REFERENCES

Myers SR, Flesher JW. 1991b. Metabolism of chrysene, 5methylchrysene, 6-methylchrysene and .5,6-dimethylchrysene in rat liver cytosol, *in vitro*, and in rat subcutaneous tissue, *in vivo.* Chem Biol Interact 77(2):203-221.

Myers MJ, Schook LB, Bick PH. 1987. Mechanisms of benzo[a]pyrene-induced modulation of antigen presentation. J Pharmacol Exp Ther 242:399-404.

*Myers MJ, Blanton RH, Bick PH. 1988. Inhibition of IL-2 responsiveness following exposure to benzo(a)pyrene is due to alterations in accessory cell function. Int J Immunopharmacol 10:177-186.

Nagabhushan M, Ng YK, Elias R, et al. 1990. Acute inhibition of DNA synthesis in hamster buccal pouch epithelium exposed to indirect acting carcinogens. Cancer Lett 53(2-3):163-173

*Nagata S, Kondo G. 1977. Photo-oxidation of crude oils. Proceedings of the 1977 Oil Spill Conference (prevention, behavior, cleanup, control):617-620.

*Naikwadi KP, Charbonneau GM, Karasek FW, et al. 1987. Separation and identification of organic compounds in air particulate extracts by high-performance liquid chromatography and gas chromatography-mass spectrometry. J Chromatogr 398:227-238.

*NAS. 1972. Particulate polycyclic organic matter. Washington, D.C: National Academy of Sciences, Division of Medical Science, National Research Council, 28-81.

NAS. 1986. Drinking-water and health. Vol. 6. Washington, D.C: National Academy Press, 139-145.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

Naslund I, Rubio CA, Auer GU. 1987. Nuclear DNA changes during pathogenesis of squamous carcinoma of the cervix in 3,4-benzopyrene-treated mice. Anal Quant Cytol Histol 9:411-418.

NATICH. 1988. National Air Toxics Information Clearinghouse. Report on state, local, and EPA air toxics activities. US Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC. July 1988.

*NATICH. 1992. National Air Toxics Information Clearinghouse. Report on state, local, and EPA air toxics activities. US Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC. December 1992.

*Neal J, Rigdon RH. 1967. Gastric tumors in mice fed benzo[a]pyrene: A quantitative study. Tex Rep Biol Med 25:553-557.

*Neff JM. 1979. Polycyclic aromatic hydrocarbons in the aquatic environment - sources, fates and biological effects. London, England: Applied Science Publishers, Ltd.

*Neff JM. 1982. Accumulation and release of polycyclic aromatic hydrocarbons from water, food, and sediment by marine animals. Symposium: Carcinogenic polynuclear aromatic hydrocarbons in the

marine environment. Washington, D.C: US Environmental Protection Agency. Report no. 600/9-82-013.

Nettesheim P, Griesemer RA, Martin DH, et al. 1977. Induction of preneoplastic and neoplastic lesions in grafted rat tracheas continuously exposed to benzo(a)pyrene. Cancer Res 37:1272-1278.

*Neubert D, Tapken S. 1988. Transfer of benzo(a)pyrene into mouse embryos and fetuses. Arch Toxicol 62(2-3):236-239.

*Newman MJ, Light BA, Weston A, et al. 1988. Detection and characterization of human serum antibodies to polycyclic aromatic hydrocarbon diol-epoxide DNA adducts. J Clin Invest (United States) 82:145-153.

*Newman MJ, Weston A, Carver DC, et al. 1990. Serological characterization of polycyclic aromatic hydrocarbon diolepoxide-DNA adducts using monoclonal antibodies. Carcinogenesis 11(11):1903-1907.

*Ng KM, Chu I, Bronaugh RL, et al. 1991. Percutaneous absorption/metabolism of phenanthrene in the hairless guinea pig: Comparison of *in vitro* and *in vivo* results. Fundam Appl Toxicol 16(3):517-524.

*Ng KM, Chu I, Bronaugh RL, et al. 1992. Percutaneous absorption and metabolism of pyrene, benzo[a]pyrene, and di(2-ethylhexyl) phthalate: comparison of *in vitro* and *in vivo* results in the hairless guinea pig. Toxicol Appl Pharmacol 115(2):216-223.

*Nie S, Dadoo R, Zare RN. 1993. Ultrasensitive fluorescence detection of polycyclic aromatic hydrocarbons in capillary electrophoresis. Anal Chem 65:3571-3575.

*Nielsen PA, Grove A, Olsen H. 1993. The influence of fuel type on the emission of PAH and mutagenic activity from small wood stoves. In: The Thirteenth Polycyclic Aromatic Hydrocarbons Conference Proceedings. 993-1000.

*Nielsen T. 1979. Determination of polycyclic aromatic hydrocarbons in automobile exhaust by means of high-performance liquid chromatography with fluorescence detection. J Chromatogr 170:147-156.

*Niimi AJ. 1987. Biological half-lives of chemicals in fishes. Rev Environ Contam Toxicol. Vol. 99. New York, NY: Springer-Verlag, l-46.

*Nikonova TV. 1977. The transplacental effect of benzo(a)pyrene and pyrene. Byull Eksp Biol Med 84:1025-1027.

*NIOSH. 1976. National occupational hazard survey (1970). US Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH.

NIOSH. 1977. Criteria for a recommended standard: Occupational exposure to coal tar products. US Department of Health and Human Services, Department of Health and National Institute for Occupational Safety and Health, Cincinnati, OH.

8. REFERENCES

*NIOSH. 1984. National occupational hazard survey (1980-1983). US Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH.

*NIOSH. 1985. Pocket guide to chemical hazards. Washington, D.C.: US Department of Health and Human Services, National Institute for Occupational Safety and Health, 84.

*NIOSH. 1990. National Occupational Exposure Survey 1981-83. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, Ohio.

*NIOSH. 1992. NIOSH recommendations for occupational safety and health: Compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, 64.

*Nirmalakhandan NN, Speece RE. 1988. QSAR model for predicting Henry's constant. Environ Sci Technol 22:1349-1357.

*Nisbet ICT, LaGoy PK. 1992. Toxic equivalency factors (TEFs) for polycyclic aromatic hydrocarbons (PAHs). Reg Toxicol Pharmacol 16:290-300.

*NJDEP. 1991. State primary drinking water regulations. Trenton, NJ: New Jersey Department of Environmental Protection. Chapter 10, Subchapter 5,7:10-5.1.

*NOAA. 1989. A summary of data on tissue contamination from the first three years (1986-1988) of the Mussel Watch Program. NOAA Technical Memorandum NOS OMA 49, Rockville, MD: National Oceanic and Atmospheric Administration.

Norpoth K, Kemena A, Jacob J, et al. 1984. The influence of 18 environmentally relevant polycyclic aromatic hydrocarbons and Clophen A50, as liver monooxygenase inducers, on the mutagenic activity of benz(a)anthracene in the Ames test. Carcinogenesis 5:747-752.

*Nousiainen U, Torronen R, Hanninen 0. 1984. Differential induction of various carboxylesterases by certain polycyclic aromatic hydrocarbons in the rat. Toxicology 32:243-251.

*Nowak D, Meyer A, Schmidt-Preuss U, et al. 1992. Formation of benzo[a]pyrene-DNA adducts in blood monocytes from lung cancer patients with a familial history of lung cancer. J Cancer Res Clin Oncol 118(1):67-71.

*NRC. 1983. Polycyclic aromatic hydrocarbons: Evaluation of sources and effects. Washington, D.C.: National Research Council, National Academy Press, ES/l-ES/7.

*NRC. 1989a. Biologic markers in reproductive toxicology. National Research Council. Washington, DC: National Academy Press.

*NRC. 1989b. Biologic markers in pulmonary toxicology. National Research Council. Washington, DC: National Academy Press.

*NRC. 1992a. Biological markers in pulmonary immunotoxicology. National Research Council. Washington, DC: National Academy Press.

8. REFERENCES

*NRC. 1992b. Biological markers in pulmonary neurotoxicology. National Research Council. Washington, DC: National Academy Press.

NRC. 1995. Biologic markers in urinary toxicology. National Research Council. Washington, DC: National Academy Press.

NREPC. 1991. Acceptable ambient limits and significant emission levels of toxic air pollutants. Frankfurt, KY: Kentucky Natural Resources and Environmental Protection Cabinet. 401 KAR 63:022.

*NTDB. 1994. The National Trade Data Bank. Washington, DC: U.S. Department of Commerce, Economics and Statistics Administration (CD-ROM).

*NYSDEC. 1994. Water quality standards: surface waters and groundwaters. Albany, NY: New York State Department of Environmental Conservation. Chapter X, Section 703.5.

O'Donovan MR. 1990. Mutation assays of ethyl methanesulphonate, benzidine and benzo[a]pyrene using Chinese hamster V79 cells. Mutagenesis 5:9-13.

O'Gara RW, Kelly MG, Brown J, et al. 1965. Induction of tumors in mice given a minute single dose of dibenz[a,h]anthracene or 3-methylcholanthrene as newborns: A dose-response study. J Natl Cancer Inst 35(6):1027-1042.

O'Neill IK, Bingham S, Povey AC, et al. 1990a. Modulating effects in human diets of dietary fibre and beef, and of time and dose on the reactive microcapsule trapping of benzo[a]pyrene metabolites in the rat gastrointestinal tract. Carcinogenesis 11(4):599-607.

O'Neill IK, Povey AC, Bingham S, et al. 1990b. Systematic modulation by human diet levels of dietary fibre and beef on metabolism and disposition of benzo[a]pyrene in the gastrointestinal tract of Fischer F344 rats. Carcinogenesis 11(4):609-616.

*O'Neill IK, Goldberg MT, El Ghissassi F, et al. 1991. Dietary fiber, fat and beef modulation of colonic nuclear aberrations and microcapsule-trapped gastrointestinal metabolites of benzo(a)pyrene-treated C57/B6 mice consuming human diets. Carcinogenesis 12(2):175-180.

*O'Neill HJ, Pollock TL, Brun GL, et al. 1992. Toxic chemical survey of municipal drinking water sources in Atlantic Canada 1985-1988. Water Poll Res J Canada 27(4):715-732.

*Obana H, Hori S, Kashimoto T, et al. 1981. Polycyclic aromatic hydrocarbons in human fat and liver. Bull Environ Contam Toxicol 27:23-27.

*Oehme M. 1983. Determination of isomeric polycyclic aromatic hydrocarbons in air particulate matter by high-resolution gas chromatography negative ion chemical ionization mass spectrometry. Anal Chem 55:2290-2295.

Oesch F, Golan M. 1980. Specificity of mouse liver cytosolic epoxide hydrolase for K-region epoxides derived from polycyclic aromatic hydrocarbons. Cancer Lett 9:169-175.

Oesch F, Bucker M, Glatt HR. 1981. Activation of phenanthrene to mutagenic metabolites and evidence for at least two different activation pathways. Mut Res 81:1-10.

8. REFERENCES

Ogan K, Katz E, Slavin W. 1979. Determination of polycyclic aromatic hydrocarbons in aqueous samples by reversed-phase liquid chromatography. Anal Chem 51: 315-320.

*Ogawa I, Junk GA, Svec HJ. 1982. Degradation of aromatic compounds in groundwater, and methods of sample preparation. Talanta 28:725-730.

*Old LJ, Benacerraf B, Carswell E. 1963. Contact reactivity to carcinogenic polycyclic hydrocarbons. Nature 198:1215-1216.

*OSHA. 1974. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 1983. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1002.

*OSHA. 1985. Coal tar pitch volatiles; interpretation of term. US Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1002.

*OSHA. 1990. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1450.

Ostman CE, Colmsjo AL, Zebuehr Y. 1986. Polycyclic aromatic compounds in lubricating oil: A study of gasoline, gasoline/methanol, gas and diesel fueled engines. In: Cooke M, Dennis AJ, eds. Polycyclic aromatic hydrocarbons: Chemistry, characterization, and carcinogenesis. Proceedings of the Ninth International Symposium. Columbus, OH: Battelle Press, 729-744.

*OTA. 1990. Neurotoxicology: Identifying and controlling poisons of the nervous system. Office of Technology Assessment, Washington, DC. OTA-BA-438.

*Oueslati R, Alexandrov K, Chouikha M, et al. 1992. Formation and persistence of DNA adducts in epidermal and dermal mouse skin exposed to benzo(a)pyrene *in vivo*. *In vivo* 6(2):231-235.

*Ovrebo S, Haugen A, Fjeldstad PE, et al. 1994. Biological monitoring of exposure to polycyclic aromatic hydrocarbon in an electrode paste plant. J Occup Med 36(3):303-310.

*Oyler AR, Bodenner DL, Welch KJ, et al. 1978. Determination of aqueous chlorination reaction products of polynuclear aromatic hydrocarbons by reversed phase high performance liquid chromatography-gaschromatography. Anal Chem 50:837-842.

Pahlman R, Pelkonen O. 1987. Mutagenicity studies of different polycyclic aromatic hydrocarbons: The significance of enzymatic factors and molecular structure. Carcinogenesis 8:773-778.

*Palitti F, Cozzi R, Fiore M, et al. 1986. An *in vitro* and *in vivo* study on mutagenic activity of fluoranthene: Comparison between cytogenetic studies and HPLC analysis. Mutat Res 174: 125-130.

Pallardy M, Mishal Z, Lebrec H, et al. 1992. Immune modification due to chemical interference with transmembrane signalling: Application to polycyclic aromatic hydrocarbons. Int J Immunopharmacol 14(3):377-382.

8. REFERENCES

*Pankow JF, Storey JME, Yamasaki H. 1993. Effects of relative humidity on gas/particle partitioning of semivolatile organic compounds to urban particulate matter. Environ Sci Technol 27(10):2220-2226.

*Panthanickal A, Marnett LJ. 1981. Arachidonic acid-dependent metabolism of (+/-)-7,8-dihydroxy-7,8- dihydrobenzo[a]pyrene to polyguanylic acid-binding derivatives. Chem Biol Interact 33:239-252.

Park JK, Park SD. 1988. Effects of benzo(a)pyrene on dna strand breaks and replication in the presence of metabolic activation system in mammalian cells. Korean J Genetics 10(4):279-287.

*Park KS, Sims RC, DuPont RR, et al. 1990. The fate of PAH compounds in two soil types influence of volatilization abiotic loss and biological activity. Environ Toxicol Chem 9(2):187-196.

*Pavanello S, Levis AG. 1992. Coal tar therapy does not influence *in vitro* benzo[a]pyrene metabolism and DNA adduct formation in peripheral blood lymphocytes of psoriatic patients. Carcinogenesis 13:1569-1573.

*Payne. 1958. The pathological effects of the intraperitoneal injection of 3:4-benzopyrene into rats and mice. Br J Cancer 12:65-74.

*Penn A, Snyder C. 1988. Arteriosclerotic plaque development is ‘promoted’ by polynuclear aromatic hydrocarbons. Carcinogenesis 9(12):2185-2189.

*Perera FP, Hemminki K, Young TL, et al. 1988. Detection of polycyclic aromatic hydrocarbon-DNA adducts in white blood cells of foundry workers. Cancer Res 48:2288-2291.

*Perera FP, Tang DL, O’Neill JP, et al. 1988. HPRT and glycophorin A mutations in foundry workers: relationship to PAH exposure and to PAH-DNA adducts. Carcinogenesis 14(5):969-973.

*Pershagen GG, Nordberg G, Bjorklund NE. 1984. Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo[a]pyrene by the pulmonary route. Environ Res 34:227-241.

*Perwak J, Byrne M, Coons S, et al. 1982. An exposure and risk assessment for benzo[u]pyrene and other polycyclic aromatic hydrocarbons. Volume IV. Benzo[u]pyrene, acenaphthylene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluroanthene, benzo[g,h,i]perylene, chrysene, dibenz[u,h]anthracene, and indeno[l,2,3-c,apyrene. Washington, D.C.: US Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440/4-85-020-V4.

Peterson AR, Landolph JR, Peterson H, et al. 1981. Oncogenic transformation and mutation of C3W10T1/2 clone 8 mouse embryofibroblasts by alkylating agents. Cancer Res 41:3095-3099.

*Petridou-Fischer J, Whaley SL, Dahl AR. 1988. *In vivo* metabolism of nasally instilled benzo(a)pyrene in dogs and monkeys. Toxicology 48(1):31-40.

*Pfeiffer EH. 1977. Oncogenic interaction of carcinogenic and non-carcinogenic polycyclic aromatic hydrocarbons in mice: IARC Scientific Publication No. 16. Air pollution and cancer in man. Lyon, France: International Agency for Research on Cancer, 69-77.

8. REFERENCES

*Pham T, Lum K, Lemieux C. 1993. Sources of PAHs in the St. Lawrence River (Canada) and their relative importance. Chemosphere 27(7):1137-1149.

*Phillips DH, Hewer A, Grover PE. 1987. Formation of DNA adducts in mouse skin treated with metabolites of chrysene. Cancer Res 35:207-214.

*Phillips DH, Hemminki K, Alhonen A, et al. 1988. Monitoring occupational exposure to carcinogens: Detection by 32P-postlabelling of aromatic DNA adducts in white blood cells from iron foundry workers. Mutat Res 204:531-541.

Phillips DH, Hewer A, Seidel A, et al. 1991. Relationship between mutagenicity and DNA adduct formation in mammalian cells for fjord- and bay-region diol-epoxides of polycyclic aromatic hydrocarbons. Chem Biol Interact 1991 80(2):177-186.

*Phillipson CE, Ioannides C. 1989. Metabolic activation of polycyclic aromatic hydrocarbons to mutagens in the Ames test by various animal species including man. Mutat Res Mar 211(1):147-151.

*Pitt R, Lalor M, Field R, et al. 1993. The investigation of source area controls for the treatment of urban stormwater toxicants. Water Sci Technol 28(3-5):271-282.

*Platt ISL, Pfeiffer E, Petrovic P, et al. 1990. Comparative tumorigenicity of picene and dibenz[a,h]anthracene in the mouse. Carcinogenesis 11(10):1721-1726.

*Plumb RH, Jr. 1991. The occurence of appendix IX organic constituents in disposal site ground water. Ground Water Monitoring Revue 11:157-164.

Pollia JA. 1941. Investigation on the possible carcinogenic effect of anthracene and chrysene and some of their compounds: II. The effect of subcutaneous injection in rats. J Ind Hyg Toxicol 223:449-451.

*Poole SK, Dean TA, Poole CF. 1987. Preparation of environmental samples for the determination of polycyclic aromatic hydrocarbons by thin-layer chromatography. J Chromatogr 400:323-341.

Popescu NC, Tumbull D, DiPaolo JA. 1977. Sister chromatid exchange and chromosome aberration analysis with the use of several carcinogens and noncarcinogens. J Nat1 Cancer Inst 59:289-293.

*Popl M, Stejskal M, Mostecky J. 1975. Determination of polycyclic aromatic hydrocarbons in white petroleum products. Anal Chem 47:1947-1950.

*Pothuluri JV, Freeman JP, Evans FE, et al. 1993. Biotransformation of fluorene by the fungus *Cunninghamella elegans.* Appl Environ Microbial 59(6):1977-1980.

Pott P. 1775. Surgical observations relative to the cancer of the scrotum. London. Reprinted in Natl Cancer Institute Monographs 10:7-13. 1973.

*Pott F, Tomingas R, Misfeld J. 1977. Tumors in mice after subcutaneous injection of automobile exhaust condensates. In: Mohr U, Schmaehl D, Tomatis L, eds. IARC Scientific Publication No. 16: Air pollution and cancer in man. Hanover, West Germany: Scientific Publications, 79-87.

8. REFERENCES

*Prahl FG, Crecellus E, Carpenter R. 1984. Polycyclic aromatic hydrocarbons in Washington (USA) coastal sediments: An evaluation of atmospheric and riverine routes of introduction. Environ Sci Technol 18:687-693.

*Prasanna P, Jacobs MM, Yang SK. 1987. Selenium inhibition of benzo(a)pyrene, 3-methylcholanthrene, and 3-methylcholanthrylene mutagenicity in *Salmonella typhimurium* strains TA98 and Tal00. Mutat Res 190:101-105.

Propper R. 1988. Polycyclic aromatic hydrocarbons (PAH): A candidate toxic air contaminant. Stationary Source Div, California State Air Resources Board, Sacramento, CA.

*Pucknat AW, ed. 1981. Characteristics of PNA in the environment: Health impacts of polynuclear aromatic hydrocarbons. Park Ridge, NJ: Noyes Data Corporation, 78-122.

*Purde M, Etlin S. 1980. Cancer cases among workers in the Estonia oil shale processing industry: Health implications of new energy technologies. Ann Arbor, MI: Ann Arbor Science, 527-528.

Quarles JM, Sega MW, Schenley CK, et al. 1979. Transformation of hamster fetal cells by nitrosated pesticides in a transplacental assay. Cancer Res 39:4525-4533.

*Quilliam MA, Sim PG. 1988. Determination of polycyclic aromatic compounds by high-performance liquid chromatography with simultaneous mass spectrometry and ultraviolet diode array detection. J Chromatogr Sci 26:160-167.

*Radding SB, Mill T, Gould CW, et al. 1976. The environmental fate of selected polynuclear aromatic hydrocarbons. Washington, D.C: US Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-75-009.

*Rahimtula AD. 1977. The effects of antioxidants of the metabolism and mutagenicity of benzo[a]pyrene *in vitro.* Biochem J 164:473-475.

*Rahman A, Barrowman JA, Rahimtula A. 1986. The influence of bile on the bioavailability of polynuclear aromatic hydrocarbons from the rat intestine. Can J Physiol Pharmacol 64:1214-1218.

*Ramdahl T, Alfheim I, Bjorseth A. 1982. Nitrated polycyclic aromatic-hydrocarbons in urban air particles. Environ Sci Technol 16:861-865.

Ranadine KJ, Karande KA. 1963. Studies on 1,2,5,6-dibenzanthracene-induced mammary carcinogenesis in mice. Br J Cancer 17:272.

*Rao KP, Nandan BD. 1990. Modification of benzo(a)pyrene induced chromosomal damage in mouse bone marrow by vitamin A. Bull Environ Contam Toxicol 45(6):829-832.

*Rao KP, Ramadevi G, Das UN. 1986. Vitamin A can prevent genetic damage induced by benzo(a)pyrene to the bone marrow cells of mice. Int J Tissue React 8:219-223.

Rastetter WH, Nachbar RBJ, Russo-Rodriguez S, et al. 1982. Fluoranthene: Synthesis and mutagenicity of 4 diol epoxides. J Org Chem 47:4873-4878.

8. REFERENCES

*Readman JW, Mantourar RFC, Rhead MM, et al. 1982. Aquatic distribution and heterotrophic degradation and polycyclic aromatic hydrocarbons in the Tamar Estuary, England, UK. Estuarine Coastal Shelf Sci 14:369-389.

*Redmond E, Strobino B, Cypress R. 1976. Cancer experience among coke by-product workers. Ann NY Acad Sci 2-7:102-115.

Rees ED, Mandelstan P, Lowry JQ, et al. 1971. A study of the mechanism of intestinal absorption of benzo[a]pyrene. Biochim Biophys Acta 225:96-107.

Reynders JBJ, Immel HR, Scherrenberg PM, et al. 1985. Respiratory tract tumors in hamsters after severe focal injury to the trachea and intratracheal instillation of benzo(a)pyrene. Cancer Lett 29:93-99.

Rhodes G, Opsal RB, Meek JT, et al. 1983. Analysis of polycyclic aromatic hydrocarbon mixtures with laser ionization gas chromatography/mass spectrometry. Anal Chem 55:280-286.

*Rice JE, Hosted TJJ, Lavoie EJ. 1984. Fluoranthene and pyrene enhance benzo(a)pyrene-DNA adduct formation *in vivo* in mouse skin. Cancer Lett 24:327-333.

*Rice JE, Coleman DT, Hosted TJJ, et al. 1985a. Identification of mutagenic metabolites of indeno[l,2,3-cd] pyrene formed *in vitro* with rat liver enzymes. Cancer Res 45:5421-5425.

*Rice JE, Coleman DT, Hosted TJJ, et al. 1985b. On the metabolism, mutagenicity, and tumor-initiating activity of indeno(1,2,3-cd)pyrene. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Metabolisms, methods and metabolism. Proceedings of the Eighth International Symposium. Columbus, OH: Battelle Press, 1097-1109.

*Rice JE, Hosted TJ, DeFloria MC, et al. 1986. Tumor-initiating activity of major in-vivo metabolites of indeno-1 2 3 -cd-pyrene on mouse skin. Carcinogenesis 7(10):1761-1764.

*Rice JE, Geddie NG, Lavoie EJ. 1987a. Identification of metabolites of benzo[j]fluoranthene formed *in vitro* in rat liver homogenate. Chem Biol Interact 1987 63(3):227-237.

*Rice JE, Weyand EH, Geddie NG, et al. 1987b. Identification of tumorigenic metabolites of benzo[j]fluoranthene formed *in vivo* in mouse skin. Cancer Res 47(23):6166-6170.

*Rice JE, Defloria MC, Sensenhauser C, et al. 1988. The influence of fluoranthene on the metabolism and DNA binding of benzo[a]pyrene *in vivo* in mouse skin. Chem Biol Interact 1988 68(1-2):127-136.

Rice JW, Weyand EH, Burrill C, et al. 1990. Fluorine probes for investigating the mechanism of activation of indeno(1,2,3-cd)pyrene to a tumorigenic agent. Carcinogenesis 11(11):1971-1974.

*Rice DW, Seltenrich CP, Spies RB, et al. 1993. Seasonal and annual distribution of organic contaminants in marine sediments from Elkhom Slough, Moss Landing Harbor and Nearshore Monteray Bay, California. Environ Poll 82:79-94.

8. REFERENCES

*Richardson JH, Ando ME. 1977. Sub-part-per-trillion detection of polycyclic aromatic hydrocarbons by laser induced molecular fluorescence. Anal Chem 49:955-959.

Richter-Reichhelm HB, Emura M, Althoff J. 1985. Scanning electron microscopical investigations on the respiratory epithelium of the Syrian golden hamster: VI. *In vitro* effects of different polycyclic aromatic hydrocarbons. Zentralbl Bakteriol Mikrobiol Hyg [B] 181(3-5):272-280.

Riegel B, Watman WB, Hill WT. 1951. Delay of methylcholanthrene skin carcinogenesis in mice by 1,2,5,6- dibenzofluorene. Cancer Res 11:301-306.

*Rigdon RH, Giannukos NJ. 1964. Effect of carcinogenic hydrocarbons on growth of mice. Arch Pathol 77: 198-204.

*Rigdon RH, Neal J. 1965. Effects of feeding benzo[a]pyrene on fertility, embryos, and young mice. J Nat1 Cancer Inst 34:297-305.

*Rigdon RH, Neal J. 1966. Gastric carcinomas and pulmonary adenomas in mice fed benzo[a]pyrene. Tex Rep Biol Med 24:195-207.

*Rigdon RH, Neal J. 1969. Relationship of leukemia to lung and stomach tumors in mice fed benzo[a]pyrene. Proc Sot Exp Biol Med 130:146-148.

*Rigdon RH, Rennels EG. 1964. Effect of feeding benzpyrene on reproduction in the rat. Experimentia 20:224-226.

*Risner CH. 1988. The determination of benzo(a)pyrene in the total particulate matter of cigarette smoke. J Chromatogr Sci 26: 113-125.

Robinson DE, Mitchell AD. 1981. Unscheduled DNA synthesis response of human fibroblasts, WI-38 cells, to 20 coded chemicals: Evaluation of short-term tests for carcinogenesis: Report of the International Collaborative Program. Prog Mutat Res 1:5 17-527.

*Robinson JR, Felton JS, Levitt RC, et al. 1975. Relationship between “aromatic hydrocarbon responsiveness” and the survival times in mice treated with various drugs and environmental compounds. Mol Pharmacol 11:850-865.

Rocchi P, Ferreri AM, Borgia R, et al. 1980. Polycyclic hydrocarbons induction of diptheria toxin-resistant mutants in human cells. Carcinogenesis 1:765-767.

Roe FJC. 1962. Effect of phenanthrene on tumour-initiation by 3,4-benzpyrene. Br J Cancer 16:503-506.

*Rogan EG, RamaKrishna NVS, Higginbotham S, et al. 1990. Identification and quantitation of 7-(benzo(a)pyren-6-yl)guanine in the urine and feces of rats treated with benzo(a)pyrene. Chem Res Toxicol 3(5):441-444.

*Rogge WF, Hildemann LM, Mazurek MA, et al. 1993a. Sources of fine organic aerosol. 2. Noncatalyst and catalyst-equipped automobiles and heavy-duty diesel trucks. Environ Sci Technol 27:636-651.

8. REFERENCES

*Rogge WF, Hildemann LM, Mazurek MA, et al. 1993b. Sources of fine organic aerosol. 5. Natural gas home appliances. Environ Sci Technol 27:2736-2744.

*Rogge WF, Hildemann LM, Mazurek MA, et al. 1993c. Sources of fine organic aerosol. 3. Road dust, tire debris, and organometallic brake lining dust: roads as sources and sinks. Environ Sci Technol 27: 1892-l 904.

*Rogge WF, Hildemann LM, Mazurek MA, et al. 1993d. Sources of fine organic aerosol. 4. Particulate abrasion products from leaf surfaces of urban plants. Environ Sci Technol 27:2700-2710.

*Roggeband R, Wolterbeek APM, Melis OWM, et al. 1994. DNA adduct formation and repair in hamster and rat tracheas exposed to benzo[a]pyrene in organ culture. Carcinogenesis 15(4):661-665.

*Rosenfeld JK, Plumb RH. 1991. Ground water contamination at wood treatment facilities. Ground Water Monit Rev 11(1):133-140.

Rosenkranz HS, Poirier LA. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J Natl Cancer Inst 62:873-892.

*Ross J, Nelson G, Erexson G, et al. 1991. DNA adducts in rat lung, liver and peripheral blood lymphocytes produced by i.p. administration of benzo[a]pyrene metabolites and derivatives. Carcinogenesis 12(10):1953-1955.

*Ross J, Nelson G, Kligerman A, et al. 1990. Formation and persistence of novel benzo(a)pyrene adducts in rat lung, liver, and peripheral blood lymphocyte DNA. Cancer Res 50(16):5088-5094.

*Ross JA, Nelson GB, Holden KL, et al. 1992. DNA adducts and induction of sister chromatid exchanges in the rat following benzo[b]fluoranthene administration. Carcinogenesis 13: 1731-1734.

*Rossi L, Barbieri O, Sanguineti M, et al. 1983. Carcinogenic activity of benzo(a)pyrene and some of its synthetic derivatives by direct injection into the mouse fetus. Carcinogenesis 4:153-156.

*Roszinsky-Kocher G, Basler A, Rohrbom G. 1979. Mutagenicity of polycyclic hydrocarbons: V. Induction of sister-chromatid exchanges *in vivo*. Mutat Res 66(1):65-67.

*Ruby JC, Halliday GM, Muller HK. 1989. Differential effects of benzo[a]pyrene and dimethylbenz[a]-anthracene on Langerhans cell distribution and contact sensitization in murine epidermis. J Invest Dermatol 92(2):150-155.

Rudo KM, Dauterman WC, Langenbach R. 1989. Human and rat kidney cell metabolism of 2-acetylaminofluorene and benzo(a)pyrene. Cancer Res 49(5): 1187- 1192.

Rugen PJ, Stem CD, Lamm SH. 1989. Comparative carcinogenicity of the pahs as a basis for acceptable exposure levels aels in drinking water. Regul Toxicol Pharmacol 9(3):273-283.

Russell LB. 1977. Validation of the *in vivo* somatic mutation method in the mouse as a prescreen for germinal point mutations. Arch Toxicol 38:75-85.

8. REFERENCES

*Saber A, Morel G, Paturel L, et al. 1991. Application of the high-resolution low temperature spectrofluorometry to analysis of PAHs in lake sediments marine intertidal sediments and organisms. Fresenius' J Anal Chem 339(10):716-721.

*Saboori AM, Newcombe DS. 1992. Environmental chemicals with immunotoxic properties. In: Newcombe DS, Rose NR, Bloom JC, eds. Clinical immunotoxicology. New York, NY: Raven Press, 36.5400.

*Sadhana AS, Rao AR, Kucheria K, et al. 1988. Inhibitory action of garlic oil on the initiation of benzo(a)pyrene-induced skin carcinogenesis in mice. Cancer Lett 40:193-197.

*Saffiotti U, Montesane R, Sellakumar AR, et al. 1972. Respiratory tract carcinogenesis induced in hamsters by different dose levels of benzo[a]pyrene and ferric oxide. J Natl Cancer Inst 49:1199-1204.

Sajewicz M, Rzepa J, Sliwiok J. 1988. Determination of benzo(a)pyrene in coke tars. J Chromatogr 456(1):227-231.

Sakai M, Yoshida D, Mizusaki S. 1985. Mutagenicity of polycyclic aromatic hydrocarbons and quinones on *Salmonella typhimurium* TA97. Mutat Res 156:61-67.

*Salaman MH, Roe FJC. 1956. Further tests for tumour-initiating activity: N,N-di(2-chloroethyl)-paminophenylbutic acid (CB1348) as an initiator of skin tumour formation in the mouse. Br J Cancer 10:363-378 (Retrieval in progress).

*Salamone MF 1981. Toxicity of 41 carcinogens and noncarcinogenic analogs. Prog Mutat Res. 1:682-685.

*Salamone MF, Chiu S, Logan DM. 1988. Abnormal sperm test results for benzo(a)pyrene, pyrene, 2-acetylaminofluorene, and 4-acetylaminofluorene using both hybrid and outbred mice: Part 2. Gavage treatment: Evaluation of short-term tests for carcinogenicity. Report of the International Program for Chemical Safety's Collaborative Study 2:243-250.

*Salhab AS, James MO, Wang SL, et al. 1987. Formation of benzo(a)pyrene-DNA adducts by microsomal enzymes: Comparison of maternal and fetal liver, fetal hematopoietic cells and placenta. Chem Biol Interact (Ireland) 61:203-214.

*Sanders CL, Skinner C, Gelman RA. 1986. Percutaneous absorption of 7,l0 ^{14}C-benzo[a]pyrene and 7,12 ^{14}C- dimethylbenz[a]anthracene in mice. J Environ Pathol Toxicol Oncol 7:25-34.

*Santella RM, Hemminki K, Tang D-L, et al. 1993. Polycyclic aromatic hydrocarbon-DNA adducts in white blood cells and urinary 1-hydroxypyrene in foundry workers. Cancer Epidemiology, Biomarkers & Prevention 2:59-62.

*Santodonato J. 1981. Polycyclic organic matter. J Environ Pathol Toxicol 5:1-364.

*Sanyal MK, Li Y-L, Biggers WJ, et al. 1993. Augmentation of polynuclear aromatic hydrocarbon metabolism of human placental tissues of first-trimester pregnancy by cigarette smoke exposure. Am J Obstet Gynecol 168(5):1587-1597.

8. REFERENCES

*Sawicki E. 1962. Analysis for airborne particulate hydrocarbons: Their relative proportions as affected by different types of pollution. Bethesda, MD: National Cancer Institute Monograph No. 9, 201-220.

*Sax NI, Lewis RS. 1989. Dangerous properties of industrial materials. 7th ed. New York, NY: Van Nostrand Reinhold.

Schimberg RW. 1981. Polycyclic aromatic hydrocarbons (PAH) in the work environment. Kern - Kemi 8537-541.

*Schmahl D, Schmidt KG, Habs M. 1977. Syncarcinogenic action of polycyclic aromatic hydrocarbons in automobile exhaust gas condensates. In: Mohr U, Schmahl D, Tomatis L, eds. Air pollution and cancer in man. IARC publication 16. Lyon, France: World Health Organization.

*Schnizlein CT, Munson AE, Rhoades RA. 1987. Immunomodulation of local and systemic immunity after subchronic pulmonary exposure of mice to benzo(a)pyrene. Int J Immunopharmacol 9:99-106.

*Schoket B, Doty WA, Vincze I, et al. 1993. Increased sensitivity for determination of polycyclic aromatic hydrocarbon-DNA adducts in human DNA samples by dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA). Cancer Epidemiology, Biomarkers & Prevention 2:349-353.

*Schulte A, Ernst H, Peters L, et al. 1993. Induction of squamous cell carcinomas in the mouse lung after long-term inhalation of polycyclic aromatic hydrocarbon-rich exhausts. Exp Toxicol Pathol 45:415-421.

Sega GA. 1979. Unscheduled DNA synthesis (DNA repair) in the germ cells of male mice - its role in the study of mammalian mutagenesis. Genetics 92:49-58.

Selkirk JK, Huberman E, Heidelberger C. 1971. An epoxide is an intermediate in the microsomal metabolism of the chemical carcinogen, dibenz(a,h)anthracene. Biochem Biophys Res Commun 43(5):1010-1016.

Sellakumar A, Shubik P. 1974. Carcinogenicity of different polycyclic hydrocarbons in the respiratory tract of hamsters. J Nat1 Cancer Inst 53:1713-1719.

Sellakumar A, Stenback F, Rowland J. 1976. Effects of different dusts on respiratory carcinogenesis in hamsters induced by benzo[a]pyrene and diethylnitrosamine. Europ J Cancer 12:313-319.

*Seto H, Ohkubo T, Kanoh T, et al. 1993. Determination of polycyclic aromatic hydrocarbons in the lung. Arch Environ Contam Toxicol 24:498-503.

*Severson RF, Snook ME, Arrendale RF, et al. 1976. Gas chromatographic quantitation of polynuclear aromatic hydrocarbons in tobacco smoke: Analytic laboratory methods. Anal Chem 48:1866-1872.

Shah GM, Bhattacharya RK. 1989. Alteration in hepatic nuclear RNA polymerase activity following benzo[a]pyrene administration in rat. *In vivo* 3(2):125-127.

8. REFERENCES

*Shamsuddin AK, Gan R. 1988. Immunocytochemical localization of benzo(a)pyrene-DNA adducts in human tissue. Human Pathology 19(3):309-315.

*Shamsuddin AKM, Sinopoli NT, Hemminki K, et al. 1985. Detection of benzo(a)pyrene DNA adducts in human white blood cells. Cancer Res 45:66-68.

*Shane BS, Henry CB, Hotchkiss JH, et al. 1990. Organic toxicants and mutagens in ashes from eighteen municipal refuse incinerators. Arch Environ Contam Toxicol 19(5):665-673.

Shear MJ, Luter J. 1941. Studies in carcinogenesis: XVI. Production of subcutaneous tumors in mice by miscellaneous polycyclic compounds. J Nat1 Cancer Inst 2:241-258.

*Shendrikova IA, Aleksandrov VA. 1974. Comparative penetration of polycyclic hydrocarbons through the rat placenta into the fetus. Bull Exp Biol Med 77: 169-171.

*Sherson D, Sabro P, Sigsgaard T, et al. 1990. Biological monitoring of foundry workers exposed to polycyclic aromatic hydrocarbons. Br J Ind Med 47(7):448-453.

Shiba M, Marchok AC, Klein-Szanto AJ, et al. 1987. Pathological changes induced by formaldehyde in open-ended rat tracheal implants preexposed to benzo(a)pyrene. Toxicol Pathol 15:401-408.

*Shimada H, Satake S, Itoh S, et al. 1990. Multiple-dosing effects of benzo[a]pyrene in the mouse bone marrow micronucleus test. Mutat Res 234(3-4): 179-181.

*Shimada H, Suzuki H, Itoh S, et al. 1992. The micronucleus test of benzo[a]pyrene with mouse and rat peripheral blood reticulocytes. Mutat Res 278(2-3):165-168.

Shimkin MB, Stoner GD. 1975. Lung tumors in mice: Application to carcinogenesis bioassay. In: Klein G, Weinhouse S, eds. Advances in cancer research. Vol. 12. New York, NY: Raven Press, 1.

*Shiraishi H, Pilkington NH, Otsuki A, et al. 1985. Occurrence of chlorinated polynuclear aromatic hydrocarbons in tap water. Environ Sci Technol 19:585-590.

*Shmahl D, Schmidt KG, Habs MK. 1977. Syncarcinogenic action of polycyclic aromatic hydrocarbons in automobile exhause gas condensates. In: Air Pollution and Cancer in Man. IARC Publication 16. (U. Mohr, D. Schmahl, and L. Tomatis, eds.). World Health Organization.Lyon France, 53-59.

Shubik P, Hartwell JL. 1957. Survey of compounds which have been tested for carcinogenic activity. Washington, D.C: Government Printing Office, Public Health Service publication no. 149, supplement 1.

Shubik P, Hartwell JL. 1969. Survey of compounds which have been tested for carcinogenic activity. Washington, D.C: Government Printing Office, Public Health Service publication no. 149, supplement 1.

*Shubik P, Porta GD. 1957. Carcinogenesis and acute intoxication with large doses of polycyclic hydrocarbons. Am Med Assoc Arch Pathol 64:691-703.

8. REFERENCES

Shubik P, Pietra G, Della Porta G. 1960. Studies of skin carcinogenesis in the Syrian golden hamster. Cancer Res 20:l00.

*Shugart L. 1986. Quantifying adductive modification of hemoglobin from mice exposed to benzo(a)pyrene. Anal Biochem 152:365-369.

*Shugart L, Holland JM, Rahn RO. 1983. Dosimetry of polycyclic aromatic hydrocarbon skin carcinogenesis: Covalent binding of benzo(a)pyrene to mouse epidermal DNA. Carcinogenesis 4:195-198.

*Shum S, Jensen NM, Nebert DW. 1979. The murine HA Hh locus: In utero toxicity and teratogenesis associated with genetic differences in benzo[a]pyrene metabolism. Teratology 20:365-376.

Siebert D, Marquardt H, Friesel H, et al. 1981. Polycyclic aromatic hydrocarbons and possible metabolites: Convertogenic activity in yeast and tumor initiating activity in mouse skin. J Cancer Res Clin Oncol 102:127-139.

Simmon VF. 1979a. *In vitro* assays for recombinogenic activity of chemical carcinogens and related compounds with Saccharomyces *cerevisiae* D3. J Nat1 Cancer Inst 62:901-910.

Simmon VF. 1979b. *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium.* J Nat1 Cancer Inst 62893-900.

*Simmon VF, Rosenkranz HS, Zeiger E, et al. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J Nat1 Cancer Inst 62:911-918.

*Simonich SL, Hites RA. 1994b. Importance of vegetation in removing polycyclic aromatic hydrocarbons from the atmosphere. Nature 370:49-51.

*Simonsick WJJ, Hites RA. 1985. Charge exchange chemical ionization mass spectrometry: A tool for PAH isomer differentiation. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Mechanisms, methods and metabolism. Columbus, OH: Battelle Press, 1227-1237.

Sims P. 1982. The metabolic activation of some polycyclic hydrocarbons: The role of dihydrodiols and diol-epoxides. Adv Exp Med Biol 136:487-500.

*Sims RC. 1990. Soil remediation techniques at uncontrolled hazardous waste sites, a critical review. J Air Waste Man Assoc 40(5):704-732.

*Sims RC, Overcash MR. 1983. Fate of polynuclear aromatic compounds (PNAs) in soil-plant systems. Res Rev 88:1-68.

*Sims RC, Doucette WJ, McLean JE, et al. 1988. Treatment potential for 56 EPA-listed hazardous shemicals in soil. Robert Kerr Environmental Research Laboratory, Ada, OK. Epa dot. no. EPA/600/6-88/001.

*Singer B, Grunberger. 1983. Metabolic activation of carcinogens and mutagens. In: Molecular biology of mutagens and carcinogens. New York, NY: Plenum Press, 97-141.

8. REFERENCES

*Singh R and Weyand EH. 1994. Studies on the binding of various polycyclic aromatic hydrocarbons to mouse hemoglobin and serum proteins. Polycyclic Aromatic Hydrocarbons 6:135-142.

Sinsheimer JE, Giri AK, Hooberman BH, et al. 1991. Mutagenicity in Salmonella and sister chromatid exchange in mice for 1,4-dimethylphenanthrenes 1,3-,2,4-dimethylphenanthrenes and 3,4-dimethylphenanthrenes. Environ Mol Mutagen 17(2):93-97.

Sirianni SR, Huang CC. 1978. Sister chromatid exchange induced by promutagens/carcinogens in Chinese hamster cells cultured in diffusion chambers in mice. Proceedings of the Society for Experimental Biology and Medicine 158:269-274.

Sisovic A, Fugas M. 1991. Comparative evaluation of procedures for the determination of PAH in low-volume samples. Environ Monit Assess 18(3):235-241.

*Slaga TJ, diGiovanni J. 1984. Inhibition of chemical carcinogenesis. In: Searle CE, ed. Chemical carcinogens. ACS Monograph #182. Vol. 2, 2nd ed. Washington, D.C: American Chemical Society.

*Slaga TJ, Jecker L, Bracken WM, et al. 1979. The effects of weak or non-carcinogenic polycyclic hydrocarbons on 7,12- dimethylbenz(a)anthracene and benzo(a)pyrene skin tumor-initiation. Cancer Lett 751-59.

*Slaga TJ, Gleason GL, Wells G. 1980a. Comparison of the skin tumor-initiating activities of dihydrodiols and diol-epoxides of various polycyclic aromatic hydrocarbons. Cancer Res 40:1981-1984.

*Slaga TJ, Triplett LL, Nesnow S. 1980b. Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: Two-stage carcinogenesis in skin tumor sensitive mice (SENCAR): Health effects of diesel engine emissions. Proceedings of An International Symposium. Cincinnati, OH: US Environmental Protection Agency. EPA 600/9-80-057b., 874-897.

Smolarek TA, Baird WM. 1984. Benzo[e]pyrene-induced alterations in the binding of benzo[a]pyrene to DNA in hamster embryo cell cultures. Carcinogenesis 5(8):1065-1069.

*Smolarek TA, Moynihan C, Salmon CP, et al. 1986. Benz(a)anthracene-induced alterations in the metabolic activation of benzo[a]pyrene by hamster embryo cell cultures. Cancer Lett 30:243-249.

*Smolarek TA, Baird WM, Fisher EP, et al. 1987. Benzo(e)pyrene-induced alterations in the binding of benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene to DNA in Sencar mouse epidermis. Cancer Res 47(14):3701-3706.

Snell KC, Stewart HL. 1962. Pulmonary adenomatosis induced in DBA/2 mice by oral administration of dibenz[a,h]anthracene. J Nat1 Cancer Inst 28:1043.

*Snell KC, Stewart HL. 1963. Induction of pulmonary adenomatoses in DBA/2 mice by the oral administration of dibenz[a,h]anthracene. Acta Un Int Cancer 19:692-694.

*Snider EH, Manning FS. 1982. A survey of pollutant emission levels in waste waters and residuals from the petroleum refining industry. Environment International 7:237-258.

8. REFERENCES

Solt DB, Polverini PJ, Calderon L. 1987. Carcinogenic response of hamster buccal pouch epithelium to 4 polycyclic aromatic hydrocarbons. J Oral Pathol 16:294-302.

*Sorrel RK, Brass HJ, Reding R. 1980. A review of occurrences and treatment of polynuclear aromatic hydrocarbons. EPA-600/D-8l-066.

*Southworth GR. 1979. The role of volatilization on removing polycyclic aromatic hydrocarbons from aquatic environments. Bull Environ Contam Toxicol 21:507-514.

*Southworth GR, Beauchamp JJ, Schmeider PK. 1978. Bioaccumulation potential of polycyclic aromatic hydrocarbons in *Daphnia pulex.* Water Res 12:973-977.

*Soyka LF. 1980. Hepatic drug metabolizing enzyme activity and tumorigenesis in mice following perinatal exposure to benzo(a)pyrene. Pediatr Pharmacol 1:85-96.

*Spacie A, Landruff PF, Leversee GJ. 1983. Uptake, depuration and biotransformation of anthracene and benzo[a]pyrene. Ecotoxicol Environ Safety 7:330.

*Sparnins VL, Mott AW, Baraney G, et al. 1986. Effects of ally1 methyl trisulfide on glutathione-S-transferase activity. Nutr Cancer 8:211-215.

*SRI. 1992. SRI International. Directory of chemical producers. United States of America. Menlo Park, CA.

*SRI. 1994. Directory of chemical producers: United States of America. Menlo Park, Ca: SRI International.

*Srivastava V, Chauhan W, Srivastava P, et al. 1986. Fetal translocation and metabolism of PAH obtained form coal fly ash given intratracheally to pregnant rats. J Toxicol Environ Health 18:459-469.

*Stahl RG, Liehr JG, Davis EM. 1984. Characterization of organic compounds in simulated rainfall runoffs from model coal piles. Arch Environ Contam Toxicol 13:179-190.

Stanton MF, Miller E, Wrench C, et al. 1972. Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. J Nat1 Cancer Inst 49:867-877.

*Staples CA, Werner AF, Hoogheem TJ, et al. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ Toxicol Chem 4:131-142.

*Stavenow L, Pessah-Rasmussen H. 1988. Effects of polycyclic aromatic hydrocarbons on proliferation, collagen secretion and viability of arterial smooth muscle cells in culture. Artery 15:94-108.

Steiner PE. 1955. Carcinogenicity of multiple chemicals simultaneously administered. Cancer Res 15:632-635.

Steiner PE, Edgecomb JH. 1952. Carcinogenicity of 1,2-benzanthracene. Cancer Res 12:657-659.

8. REFERENCES

Steiner PE, Falk HL. 1951. Summation and inhibition effects of weak and strong carcinogenic hydrocarbons: 1,2-Benzanthracene, chrysene, 1,2,5,6-dibenzanthracene and 20-methylcholanthrene. Cancer Res 11: 56-63.

*Stenback F, Rowland J. 1979. Experimental respiratory carcinogenesis in hamsters: Environmental, physiochemical and biological aspects. Oncol 36:63-71.

Stenback F, Sellakumar A, Shubik P. 1975. Magnesium oxide as carrier dust in benzo[a]pyrene-induced lung carcinogenesis in Syrian hamsters. J Natl Cancer Inst 54:861-867.

*Stenback F, Rowland J, Sellakumar A. 1976. Carcinogenicity of benzo[a]pyrene and dusts in the hamster lung (instilled intratracheally with titanium oxide, aluminum oxide, carbon and ferric oxide). Oncol 33:29-34.

Stora C. 1980. Comparative study of the cellular localization of three polycyclic hydrocarbons differing in their carcinogenicity. Oncology 37(1):23-26.

*Storer JS, DeLeon I, Millikan LE, et al. 1984. Human absorption of crude coal tar products. Arch Dermatol 120:874-877.

*Strickland A, Szczeklik J, Galuszka Z, et al. 1994a. Humoral immunosuppression in men exposed to polycyclic aromatic hydrocarbons and related carcinogens in polluted environments. Environ Health Perspect 102(3):302-304.

*Strickland PT, Kang D, Bowman ED, et al. 1994b. Identification of 1-hydroxypyrene glucuronide as a major pyrene metabolite in human urine by synchronous fluorescence spectroscopy and gas chromatography-mass spectrometry. Carcinogenesis 15(3):483-487.

*Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradfor Communications Corporation, 298-299.

Su SY, Lai EPC, Winefordner JD. 1982. Determination of polynuclear aromatic hydrocarbons by a spiked mobile fluorescence HPLC detector. Anal Lett 15:439-450.

*Sullivan PD, Calle LM, Shafer K, et al. 1978. Effects of antioxidants of benzo[a]pyrene free radicals. In: Freudenthal RI, Jones PW, eds. Polynuclear aromatic hydrocarbons: 2nd International Symposium on Analysis, Chemistry, and Biology (Carcinogenesis - a comprehensive survey). Vol. 3. New York, NY: Raven Press, l-3.

*Sullivan TJ, Mix MC. 1985. Persistence and fate of polynuclear aromatic hydrocarbons deposited on slash bum sites in the Cascade Mountains and Coast Range of Oregon (USA). Arch Environ Contam Toxicol 14:187-192.

*Sun JD, Wolff RK, Kanapilly GM. 1982. Deposition, retention, and biological fate of inhaled benzo[a]pyrene adsorbed onto ultrafine particles as a pure aerosol. Toxicol Appl Pharmacol 65:231-244.

*Swartz WJ, Mattison DR. 1985. Benzo[a]pyrene inhibits ovulation in C57BL/6N mice. Anatomical Record 212:268-276.

8. REFERENCES

*Symons RK, Crick I. 1983. Determination of polynuclear aromatic hydrocarbons in refinery effluent by high-performance liquid chromatography. Anal Chim Acta 151:237-243.

*Szczeklik A, Szczeklik J, Galuszka Z, et al. 1994. Humoral immunosuppression in men exposed to polycyclic aromatic hydrocarbons and related carcinogens in polluted environments. Environ Health Perspect 102(3):302-304.

*Szepesy L, Lakszner K, Akermann L, et al. 1981. Rapid method for the determination of polycyclic aromatic hydrocarbons in environmental samples by combined liquid chromatography and gas chromatography. J Chromatogr 206:611-616.

*Tan YL. 1988. Analysis of polynuclear aromatic hydrocarbons in shale oil and diesel particulates. Anal Lett 21:553-562.

*Tan YL, Quanci JF, Borys RD, et al. 1992. Polycyclic aromatic hydrocarbons in smoke particles from wood and duff burning. Atmos Environ 26(6):1177-1181.

*Tanaka K, Saito M. 1988. High-performance liquid chromatographic separation and synchronous fluorimetric determination of polycyclic aromatic hydrocarbons in soils. The Analyst 113:509-510.

*Teranishi K, Hamada K, Watanabe H. 1975. Quantitative relationship between carcinogenicity and mutagenicity of polyaromatic hydrocarbons in *Salmonellu typhimurium* mutants. Mutat Res 31(2):97-102.

*Thomas W. 1986. Accumulation of airborne trace pollutants by arctic plants and soil. Water Sci Technol 18:47-57.

*Thomas AO, Lester JN. 1993. The microbial remediation of former gasworks sites: a review. Environ Technol 14(1): l-24.

*Thomas DH, Delfino JJ. 1991. A gas chromatographic/chemical indicator approach to assessing ground water contamination by petroleum products. Ground Water Monit Rev 11(4):90-100.

*Thomas JF, Mukai M, Tebbens, et al. 1968. Fate of airborne benzo[a]pyrene. Env Sci Technol 2:33-39.

*Thomas W, Ruehling A, Simon H. 1984. Accumulation of airborne pollutants (polycyclic aromatic hydrocarbons, chlorinated hydrocarbons, heavy metals) in various plant species and humus. Environ Poll (Series A) 36:295-310.

Thompson JI. 1971. Survey of compounds which have been tested for carcinogenic activity. Washington, D.C: Government Printing Office, Public Health Service publication no. 149, 1968-1969.

*Thony C, Thony J, LaFontaine M, et al. 1976. Hydrcarbeures polycycliques aromatique cancerogens dans les produits petroliers prevention possibles du cancer des huiles minerales. Inserm Symp Ser 52:165. (French)

Thrane KE, Makalsen A, Stray H. 1985. Monitoring method for airborne polycyclic aromatic hydrocarbons. Int J Environ Anal Chem 23:111-134.

8. REFERENCES

*Thruston ADJ. 1978. High pressure liquid chromatography techniques for the isolation and identification of organics in drinking water extracts. J Chromatogr Sci 16:254-259.

*Thyssen J, Althoff JKG, Mohr U. 1981. Inhalation studies with benzo[a]pyrene in Syrian golden hamsters. J Nat1 Cancer Inst 66:575-577.

*Tokiwa H, Sera N, Horikawa K, et al. 1993. The presence of mutagens/carcinogens in the excised lung and analysis of lung cancer induction. Carcinogenesis 14(9):1933-1938.

*Tolos WP, Shaw PB, Lowry LK, et al. 1990. 1-Pyrenol: A biomarker for occupational exposure to polycyclic aromatic hydrocarbons. Appl Occup Environ Hyg 5(5):303-309.

*Tolos WP, Lowry LK, MacKenzie BA. 1991. 1-pyrenol in urine: A biological monitoring method to assess exposure to polynuclear aromatic hydrocarbons containing pyrene. In: Cooke M, Dennis AJ, Fisher GL, eds. Polynuclear aromatic hydrocarbons: physical and biological chemistry. New York, NY: Springer-Verlag, 913-926.

*Tomingas R, Pott F, Dehnen W. 1976. Polycyclic aromatic hydrocarbons in human bronchial carcinoma. Cancer Lett 1:189- 195.

*Tomkins BA, Griest WH. 1987. Liquid chromatographic determination of benzo(a)pyrene at part-per-billion concentrations in highly refined coal- and petroleum-derived fuels. J Chromatogr (Netherlands) 386: 103-110.

*Tomkins BA, Griest WH, Caton JE, et al. 1982. Multicomponent isolation and analysis of polynuclear aromatics. In: Cooke M, Dennis AJ, Fisher GL, eds. Polynuclear aromatic hydrocarbons: Physical and biological chemistry. New York, NY: Springer-Verlag, 813-824.

*Tomkins BA, Buchanan MV, Reagan RR, et al. 1986. The isolation, identification, and quantitation of the four- and five-ring dermal tumorigen PAH in petroleum crude oils and distillate fractions using normal-phase isolation HPLC and GC/MS in the single-ion monitoring mode. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Chemistry, Characterization, and carcinogenesis. Proceedings of the Ninth International Symposium. Columbus, OH: Battelle Press, 917-932.

*Tomkins BA, Greist WH, Caton JE, et al. 1991. Multicomponent isolation and analysis of polynuclear aromatics. In: Cooke M, Dennis AJ, Fisher GL, eds. Polynuclear aromatic hydrocarbons: physical and biological chemistry. New York, NY: Springer-Verlag, 813-824.

Tong C, Brat SV, Williams GM. 1981. Sister-chromatid exchange induction by polycyclic aromatic hydrocarbons in an intact cell system of adult rat-liver epithelial cells. Mutat Res 91:467-473.

Topham JC. 1980. Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens? Mutat Res 74:379-387.

*Topping DC, Martin DH, Nettesheim P. 1981. Determination of cocarcinogenic activity of benzo[e]pyrene for respiratory tract mucosa. Cancer Lett 11(4):315-321.

*Topping DC, Pal BC, Martin DH, et al. 1978. Pathologic changes induced in respiratory tract mucosa by polycyclic hydrocarbons of differing carcinogenic activity. Am J Pathol 93(2):311-324.

8. REFERENCES

*Torronen R, Nousiainen U, Hanninen O. 1981. Induction of aldehyde dehydrogenase by polycyclic aromatic hydrocarbons in rats. Chem-Biol Interact 36:33-44.

*Toussaint G, Walker EA. 1979. Use of high-performance liquid chromatography as a clean-up procedure in analysis of polycyclic aromatic hydrocarbons in alcoholic beverages. J Chromatogr 171:448-452.

Tracer-Jitco. 1973a. Survey of compounds which have been tested for carcinogenic activity. Washington, D.C: Government Printing Office. Public Health Service publication no. 149, 1961-1967.

Tracer-Jitco. 1973b. Survey of compounds which have been tested for carcinogenic activity. Washington, D.C: Government Printing Office. Public Health Service publication no. 149, 1970-1971.

*Traynor GW, Apte MG, Sokol HA, et al. 1990. Selected organic pollutant emissions from unvented kerosene space heaters. Environ Sci Technol 24(8):1265-1270.

*TRI90. 1992. Toxic Chemical Release Inventory. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC.

*TRI92. 1994. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Tromberg BJ, Sepaniak MJ, Alarie JP, et al. 1988. Development of antibody-based fibre-optic sensors for detection of a benzo(a)pyrene metabolite. Anal Chem 60(18):1901-1908.

*Tsuda H, Farber E. 1980. Resistant hepatocytes as early changes in liver induced by polycyclic aromatic hydrocarbons. Int J Cancer 25:137-139.

Tsuge S, Nishimura K, Suzuki M, et al. 1988. Determination of benzo(a)pyrene in airborne particulates by automated thermal-desorption gas chromatography. Anal Sci 4(1):115-116.

Tuominen J, Pyysalo H, Laurikko J, et al. 1987. Application of GLC-selected ion monitoring (SIM)-technique in analyzing polycyclic organic compounds in vehicle emissions. Sci Total Environ 59:207-210.

*Tuominen JP, Pyysalo HS, Sauri M. 1988. Cereal products as a source of polycyclic aromatic hydrocarbons. J Agric Food Chem 36(1):118-120.

*Tumey GL, Goerlitz DF. 1990. Organic contamination of ground water at Gas Works Park, Seattle, Washington. Ground Water Monit Rev 19(3):187-198.

Turusov VS, Nikonova TV, Parfenov YuD. 1990. Increased multiplicity of lung adenomas in five generations of mice treated with benz(a)pyrene when pregnant. Cancer Lett 55(3):227-231.

Tweats DJ. 1981. Activity of 42 coded compounds in a differential killing test using *Escherichia coli* strains WP2, WP67 (uvrA polA), and CM871 (uvrA 1exA recA): Evaluation of shot-term tests for carcinogens: Report of the International Collaboratorive Program. Prog Mutat Res 1:199-209.

8. REFERENCES

*Ueng T-H, Alvares AP. 1993. Metabolism of benzo(a)pyrene by lung microsomes from rabbits pretreated with polychlorinated biphenyls and 2,3,4,7,8-pentachlorodibenzofuran. Life Sci 52:163-169.

*United Nations. 1985. Traetment and disposal methods for waste chemicals (IRPTC file). Data profile series no. 5. Geneva, Switzerland: United Nations Environmental Programme.

*Ursa P, Gengozian N. 1980. Depressed humoral immunity and increased tumor incidence in mice following in utero exposure to benzo[a]pyrene. J Toxicol Environ Health 6:569-576.

*Ursa P, Johnson RA. 1987. Early changes in T lymphocytes and subsets of mouse progeny defective as adults in controlling growth of a syngeneic tumor after in utero insult with benzo(a)pyrene. Immunopharmacology 14:1-10.

Urso P, Johnson RA. 1988. Quantitative and functional change in T cells of primiparous mice following injection of benzo(a)pyrene at the second trimester of pregnancy. Immunopharmacol Immunotoxicol 10:195-217.

*Ursa P, Gengozian N, Rossi RM, et al. 1986. Suppression of humoral and cell-mediated immune responses *in vitro* by benzo(a)pyrene. J Immunophatmacol 1986, 8(2):223-241.

Urso P, Ryan MC, Bennett JS. 1988. Changes in peripheral blood cells in mice after injection with benzo[a]pyrene during pregnancy. Immunopharmacol Immunotoxicol 10:179-193.

*Ursa P, Zhang W, Cobb JR. 1992. Immunological consequences from exposure to benzo(a)pyrene during pregnancy. Stand J Immunol 36(Suppl 11):203-206.

*USDA. 1980. The biologic and economic assessment of pentachlorophenol, inorganic arsenicals, creosote. Volume 1: Wood preservatives. US Department of Agriculture, Washington, D.C. Technical bulletin no. 1658-1, 193-227.

*USDOC. 1985. U.S. Imports for Consumption and General Imports. TSUSA Commodity by Country of Origin. FT246/Annual 1985. Washington, D.C.: US Department of Commerce.

*Uziel M, Ward RJ, Vo-Dinh T. 1987. Synchronous fluorescence measurement of benzo(a)pyrene metabolites in human and animal urine. Anal Lett 20:761-776.

*Vahakangas K, Trivers G, Rowe M, et al. 1985. Benzo[a]pyrene diolepoxide-DNA adducts detected by synchronous fluorescence spectrophotometry. Environ Health Perspect 62:101-104.

*Vainiotalo S, Matveinen K. 1993. Cooking fumes as a hygienic problem in the food and catering industries. Am Ind Hyg Assoc J 54(7):376-382.

Valencia R, Houtchens K. 1981. Mutagenic activity of 10 coded compounds in the Drosophila sex-linked recessive lethal test. Evaluation of short-term tests for carcinogens: Report of the Intemation Collaborative program. Prog Mutat Res 1:652-659.

*van de Wiel JAG, Fijneman PHS, Duijf CMP, et al. 1993. Excretion of benzo[a]pyrene and metabolites in urine and feces of rats: influence of route of administration, sex, and long-term ethanol treatment. Toxicology 80: 103-l15.

8. REFERENCES

Van Duuren BL, Sivak A, Segal A, et al. 1966. The tumor producing agents of tobacco leaf and tobacco smoke condensate. J Natl Cancer Inst 37519.

*Van Duuren BL, Langseth L, Goldschmidt BM. 1967. Carcinogenicity of epoxides, lactones and peroxy compounds: VI. Structure and carcinogenic activity. J Nat1 Cancer Inst 39:1217-1227.

*Van Duuren BL, Katz C, Goldschmidt BM, et al. 1973. Brief communication: cocarcinogenic agents in tobacco carcinogenesis. J Nat1 Cancer Inst 51:703-705.

*Van Heddeghem A, Huyghebaert A, De Moor H. 1980. Determination of polycyclic aromatic hydrocarbons in fat products by high pressure liquid chromatography. Z Lebensm Unter Forsch 171(1):9-13.

*Van Hummelen P, Gennart JP, Buchet JP, et al. 1993. Biological markers in PAH exposed workers and controls. Mutat Res 300:231-239.

*Van Rooij JGM, Bodelier-Bade MM, Jongeneelen FJ. 1993a. Estimation of individual dermal and respiratory uptake of polycyclic aromatic hydrocarbons in 12 coke oven workers. Br J Ind Med 50:623-632.

*Van Rooij JGM, Van Lieshout EMA, Bodelier-Bade MM, et al. 1993b. Effect of the reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. Stand J Work Environ Health 19:200-207.

*Van Rooij JGM, De Roos JHC, Bodelier-Bade MM, et al. 1993c. Absorption of polycyclic aromatic hydrocarbons through human skin: differences between anatomical sites and individuals. J Toxicol Environ Health 38:355-368.

*Van Rooij JGM, Veeger MMS, Bondelier-Bade MM, et al. 1994. Smoking and dietary intake of polycyclic aromatic hydrocarbons as sources of inter-individual variability in the baseline excretion of 1 -hydroxypyrene in urine. Int Arch Occup Environ Health 66(1):55-65.

*Van Schooten FJ, Hillebrand MJX, Scherer E, et al. 1991. Immunocytochemical visualization of DNA adducts in mouse tissues and human white blood cells following treatment with benzo(a)pyrene or its diol epoxide: A quantitative approach. Carcinogenesis 12(3):427-434.

*Van Schooten FJ, Hillebrand MJX, Van Leeuwen FF, et al. 1992. Polycyclic aromatic hydrocarbon-DNA adducts in white blood cells from lung cancer patients: No correlation with adduct levels in lung. Carcinogenesis 13(6):987-993.

Vanio RS. 1976. The fate of intratracheally installed benzo[a]pyrene in the isolated perfused rat lung of both control and 20-methylcholanthrene pretreated rats. Res Commun Chem Pathol Pharmacol 13:259-272.

*Varanasi U, Gmur DJ. 1980. Metabolic activation and covalent binding of benzo[a]pyrene to deoxyribonucleic acid catalyzed by liver enzymes of marine fish. Biochem Pharmacol 29:753-762.

8. REFERENCES

*Varanasi U, Gmur DJ. 1981. *In vivo* metabolism of naphthalene and benzo[a]pyrene of flatfish. In: Cooke M, Dennis AJ, eds. Chemical analysis and biological fate: Polynuclear aromatic hydrocarbons. Fifth International Symposium. Columbus, OH: Battelle Press, 367-376.

*Varanasi U, Reichert WL, Stein JE, et al. 1985. Bioavailability and biotransformation of aromatic hydrocarbons in benthic organisms exposed to sediment from an urban estuary. Environ Sci Technol 19:836-841.

*Vassilaros DL, Stoker PW, Booth GM, et al. 1982. Capillary gas chromatographic determination of polycyclic aromatic compounds in vertebrate fish tissue. Anal Chem 54: 106-112.

*Vaughan BE. 1984. State of research: Environmental pathways and food chain transfer. Environ Health Perspect., 353-371.

Veith GD, Kuehl DW, Leonard EN, et al. 1981. Polychlorinated biphenyls and other organic chemical residues in fish from major United States watersheds near the great lakes, 1978. Pestic Monit J 15:1-8.

*Verschueren K. 1983. Handbook of data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Co.

*Viau C, Vyskocil A, Tremblay C, et al. 1993. Urinary excretion of 1-hydroxypyrene in workers exposed to polycyclic aromatic hydrocarbon mixtures. J Occup Med Technol 2(3):267-276.

VIEW. 1989. Agency of Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA. June 20, 1989.

*Vo-Dinh T. 1981. A new passive dosimeter for monitoring personnel exposure to polycyclic aromatic vapors. 182nd American Chemical Society National Meeting, New York, NY, August 23-28.

*Vo-Dinh T, Abbott DW. 1984. A ranking index to characterize polynuclear aromatic pollutants in environmental samples. Environ Int 10:299-304.

*Vo-Dinh T, Bruewer TJ, Colovos GC, et al. 1984. Field evaluation of a cost-effective screening procedure for polynuclear aromatic pollutants in ambient air samples. Environ Sci Technol 18:477-482.

*Vo-Dinh T, Alarie JP, Johnson RW. 1991. Evaluation on the fiber-optic antibody-based fluoroimmunosensor for DNA adducts in human placenta samples. Clin Chem 37(4):532-535.

Vogel EW, Zijlstra JS, Blijleven WGH. 1983. Mutagenic activity of selected aromatic amines and polycyclic hydrocarbons in *Drosophila melanogaster.* Mutat Res 107(1):53-78.

Vogt NB, Brakstad F, Thrane K, et al. 1987. Polycyclic aromatic hydrocarbons in soil and air: Statistical analysis and classification by the SIMCA method. Environ Sci Technol 21:35-44.

*Vreuls JJ, De Jong GG, Brinkman U. 1991. On-line coupling of liquid chromatography capillary gas chromatography and mass spectrometry for the determination and identification of polycyclic aromatic hydrocarbons in vegetable oils. Chromatographia 31(3-4)113-122.

8. REFERENCES

*Wachter RA, Blackwood TR. 1979. Water pollutants from coal storage areas. Coal Technology (Houston) 2:234-239.

*Wadler S, Fuks JZ, Wiemik PH. 1986. Phase I and II agents in cancer therapy: Part I. Anthracyclines and related compounds. J Clin Pharmacol 26:491-509.

*Waldeman JM, Lioy PJ, Greenberg A, et al. 1991. Analysis of human exposure to benzo(a)pyrene via inhalation and food ingestion in the total human environmental exposure study (THEES). J Expos Anal Environ Epidemiol 1(2):193-225.

*Wallace WE, Keane MJ, Hill CA, et al. 1987. Mutagenicity of diesel exhaust particles and oil shale particles dispersed. J Toxicol Environ Health 21:163-171.

*Wang DT, Meresz O. 1982. Occurrence and potential uptake of polynuclear aromatic hydrocarbons of highway traffic origin by proximally grown food crops. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Physical and biological chemistry. Columbus, OH: Battelle Press. 885-896.

*Wang J-S, Busby WF, Jr. 1993. Induction of lung and liver tumors by fluoranthene in a preweanling CD-l mouse bioassay. Carcinogenesis 14(9):1871-1874.

*Warshawsky D, Barkley W. 1987. Comparative carcinogenic potencies of 7H-dibenzo[c,g]carbazole, dibenz[a,j]acridine and benzo(a)pyrene in mouse skin. Cancer Lett 37:337-344.

*Warshawsky DT, Cody M, Raidke BA, et al. 1983. Toxicity and metabolism of benzo[a]pyrene in the green alga Selenastrum capricontum. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Formation, metabolism and measurement. Columbus, OH: Battelle Press, 1235-1245.

*Warshawsky D, Barkley W, Bingham E. 1993. Factors affecting carcinogenic potential of mixtures. Fundam Appl Toxicol 20:376-382.

Wattenberg LW, Bueding E. 1986. Inhibitory effects of 5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione (Oltipraz) on carcinogenesis induced by benzo[a]pyrene, diethylnitrosamine and uracil mustard. Carcinogenesis 7:1379-1381.

*Wattenberg LW, Leong JL. 1970. Inhibition of the carcinogenic action of benzo[a]pyrene by flavones. Cancer Res 30:1922-1925.

*Weast RC, ed. 1987. CRC handbook of chemistry and physics. 68th ed. Boca Raton, FL: CRC Press.

*Weast RC, Astle MJ, Beyer WH, eds. 1988. Handbook of chemistry and physics. Boca Raton, FL: CRC Press, Inc.

*Weibel FJ. 1980. Activation and inactivation of carcinogens by microsomal nonoxooxygenases: Modification by benzoflavones and polycyclic aromatic hydrocarbons. Carcinogenesis 5.: Modifiers of chemical carcinogenesis.

8. REFERENCES

*Weinberg CR, Wilcox AJ, Baird DD. 1989. Reduced fecundability in women with prenatal exposure to cigarette smoking. Am J Epidemiol 129:1072-1078.

*Weinstein D, Katz ML, Kazmer S. 1977. Chromosomal effects of carcinogens and non-carcinogens on WI-38 after short term exposures with and without metabolic activation. Mutat Res 46:297-304.

*Weissenfels WD, Beyer M, Klein J. 1990. Rapid testing system for assessing the suitability of the biological reclamation for PAH-contaminated soil. In: Christiansen C, Munck L, Villadsen J, eds. 5th European Congress on Biotechnology, proceedings volume 2. Copanhagen, Denmark: Munksgaard, 931-934.

*Weissenfels WD, Klewer HL, Langhoff J. 1992. Adsorption of polycyclic aromatic hydrocarbons (PAHs) by soil particles: Influence on biodegradability and biotoxicity. Appl Microbial Biotechnol 36(5):689-696.

Wenzel-Hartung R, Brune H, Grimmer G, et al. 1990. Evaluation of the carcinogenic potency of 4 environmental polycyclic aromatic compounds following intrapulmonary application in rats. Exp Pathol 40(4):221-227.

*Werner P, Brauch H-J. 1988. Aspects on the in-situ and on-site removal of hydrocarbons from contaminated sites by biodegradation. In: Wolf K, van den Brink WJ, Colon FJ, eds. Contaminated Soil ‘88. Boston, MA: Kluwer Academic Publishers, 69.5704.

*Wester RC, Maibach HI, Bucks DAW, et al. 1990. Percutaneous absorption of carbon-14 labelled DDT and carbon-14 labelled benzo(a)pyrene from soil. Fundam Appl Toxicol 15(3):510-516.

*Westerholm R, Li H. 1994. A multivariant statistical analysis of fuel-related polycyclic aromatic hydrocarbon emissions from heavy-duty diesel vehicles. Environ Sci Technol 28(5):965-972.

Weston. 1985. Comparative studies of the metabolic activation of chrysene in rodent and human skin. Chem Biol Interact 54:223-242.

*Weston A, Bowman ED. 1991. Fluorescence detection of benzo(a)pyrene-DNA adducts in human lung. Carcinogenesis 12(8):1445-1450.

*Weston A, Bowman ED, Shields PG, et al. 1993a. Detection of polycyclic aromatic hydrocarbon-DNA adducts in human lung. Environ Health Perspect 99:257-259.

*Weston A, Bowman ED, Carr P, et al. 1993b. Detection of metabolites of polycyclic aromatic hydrocarbons in human urine. Carcinogenesis 14(5):1053-1055.

*Weston A, Rowe M, Poirier M, et al. 1988. The application of immunoassays and fluorometry to the detection of polycyclic hydrocarbon-macromolecular adducts and anti-adduct antibodies in humans. Int Arch Occup Environ Health 60(3): 157-162.

*Weston A, Santella RM, Bowman ED. 1994. Detection of polycyclic aromatic hydrocarbon metabolites in urine from coal tar treated psoriasis patients and controls. Polycyclic Aromatic Compounds 5 :24l-247.

8. REFERENCES

*Weyand EH, Bevan DR. 1986. Benzo(a)pyrene disposition and metabolism in rats following intratracheal instillation. Cancer Res 46:5655-5661.

*Weyand EH, Bevan DR. 1987a. Covalent binding of benzo(a)pyrene to macromolecules in lung and liver of rats following intratracheal instillation. Cancer Lett 36:149-159.

*Weyand EH, Bevan DR. 1987b. Species differences in disposition of benzo(a)pyrene. Drug Metab Dispos 15:442-448.

*Weyand EH, Bevan DR. 1988. Benzo(a)pyrene metabolism *in vivo* following intratracheal administration. In: Cooke M, Dennis AJ, eds., Polynuclear aromatic hydrocarbons: A decade of progress. Columbus, OH: Battelle Press, 913-923.

*Weyand EH, LaVoie EJ. 1988. Comparison of PAH: DNA adduct formation and tumor initiating activity in newborn mice (meeting abstract). Proceeding of the Annual Meeting of the American Association for Cancer Res 29:A390.

*Weyand EH, Wu Y. 1994. Genotoxicity of manufactured gas plant residue (MGP) in skin and lung of mice following MGP ingestion or topical administration. Polycyclic Aromatic Compounds 6:35-42.

*Weyand EH, Rice JE, LaVoie EJ. 1987. 32P-postlabeling analysis of DNA adducts from non-altemant PAH using thin-layer and high performance liquid chromatography. Cancer Lett 37:257-266.

*Weyand EH, Geddie N, Rice JE, et al. 1988. Metabolism and mutagenic activity of benzo[k]fluoranthene and 3-, 8- and 9-fluorobenzo[k]fluoranthene. Carcinogenesis 9(7):1277-1281.

*Weyand EH, Pate1 S, LaVoie EJ, et al. 1990. Relative tumor initiating activity of benzo(a)fluoranthene, benzo(b)fluoranthene, naphthol(1 ,2-b)fluoranthene and naphtho(2,1-a)fluoranthene on mouse skin. Cancer Lett 52(3):229-234.

*Weyand EH, Wu Y, Pate1 S. 1991a. Urinary excretion and DNA binding of coal tar components on B6C3F_1 mice following ingestion. Chem Res Toxicol 4:93-100.

*Weyand EH, Wu Y, Pate1 S, et al. 1991b. Biochemical effects of coal tar in mice following ingestion. In: Garriques P, Lamotte M, eds. Polycyclic aromatic compounds. Synthesis, properties, analytical measurements, occurrence, and biological effects. Proceedings of the thirteenth international symposium on polynuclear aromatic hydrocarbons. Philadelphia, PA: Gordon and Breach.

*Weyand EH, Amin S, Sodhi R, et al. 1991~. Effects of methyl substitution on the metabolism and binding of benz[e]acephenanthrylene. In: Garriques P, Lamotte M, eds. Polycyclic aromatic compounds. Synthesis, properties, analytical measurements, occurrence, and biological effects. Proceedings of the thirteenth international symposium on polynuclear aromatic hydrocarbons. Philadelphia, PA: Gordon and Breach.

*Weyand EH, Amin S, Huie K, et al. 1992a. Effects of fluorine substitution on the DNA binding and tumorigenicity of benzo[b]fluoranthene in mouse epidermis. Chem Biol Interactions 7 1:279-290.

8. REFERENCES

*Weyand EH, He Z-H, Ghodrati Y, et al. 1992b. Effect of fluorine substitution on benzo(j)fluoranthene genotoxicity. Chem Biol Interact 84:37-53.

*Weyand EH, Bryla P, WuY, et al. 1993a. Detection of the major DNA adducts of benzo(j)fluoranthene in mouse skin: Nonclassical dihydrodiol epoxides. Chem Res Toxicol 6:117-124.

*Weyand EH, Cai Z-W, Wy Y, et al. 1993b. Detection of the major DNA adducts of benzo(b)fluoranthene on mouse skin: Role of phenolic dihydrodiols. Accepted for publication by Chem Res Toxicol.

*Weyand EH, Wu Y, Pate1 S. 1994. Biochemical effects of manufactured gas plant residue following ingestion by $B6C3F_1$ mice. J Toxicol Environ Health 4289-107.

*White CM, Lee ML. 1980. Identification and geochemical significance of some aromatic components of coal. Geochim Cosmochim Acta. 44: 1825-l 832.

White J, White A. 1939. Inhibition of growth of the rat by oral administration of methylcholanthrene, benzpyrene, or pyrene and the effects of various dietary supplements. J Biol Chem 131:149-161.

White JB, Vanderslice RR. 1980. POM source and ambient concentration data: Review and analysis. Washington, D.C. U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/7-80-044.

*White KJ, Holsapple MP. 1984. Direct suppression of *in vitro* antibody production by mouse spleen cells by the carcinogen benzo[a]pyrene but not by the congener benzo[e]pyrene. Cancer Res 44:3388-3393.

*White KJ, Lysy HH, Holsapple MP. 1985. Immunosuppression by polycyclic aromatic hydrocarbons: A structure-activity relationship in $B6C3F_l$ and DBA/2 mice. Immunopharmacology 9:155-164.

*WHO. 1971. International standards for drinking-water. Third Edition. Geneva, Switzerland: World Health Organization, 37.

*Wielgosz SM, Brauze D, Pawlak AL. 1991. Ah locus-associated differences in induction of sister-chromatid exchanges and in DNA adducts by benzo[a]pyrene in mice. Mutat Res 246(1):129-137.

*Wiencke JK, McDowell ML, Bode11 WJ. 1990. Molecular dosimetry of DNA adducts and sister chromatid exchanges in human lymphocytes treated with benzo(a)pyrene. Carcinogenesis 11(9):1497-1502

*Wilcox AJ, Baird DD, Weinberg CR. 1989. Do women with childhood exposure to cigarette smoking have increased fecundability? Am J Epidemiol 129: 1079- 1083.

Wild SR, Berrow ML, McGrath SP, et al. 1992. Polynuclear aromatic hydrocarbons in crops from long-term field experiments amended with sewage sludge. Environ Poll 76(1):25-32.

8. REFERENCES

*Wild SR, Jones KC. 1993. Biological and abiotic losses of polynuclear aromatic hydrocarbons (PAHs) from soils freshly amended with sewage sludge. EnvironToxicol Chem 12:5-12

*Wild SR, Mitchell DJ, Yelland CM, et al. 1992. Wasted municipal solid waste incinerator fly ash as a source of polynuclear aromatic hydrocarbons (PAHs) to the environment. Waste Manag Res 10(1):99-111.

*Willems MI, Roggeband R, Baan RA, et al. 1991. Monitoring the exposure of rats to benzo(a)pyrene by the determination of mutagenic activity in excreta, chromosome aberrations and sister chromatid exchanges in peripheral blood cells, and DNA adducts in peripheral blood lymphocytes and liver. Mutagenesis 6(2):151-158.

*Williams PT, Taylor DT. 1993. Aromatization of tire pyrolysis oil to yield polycyclic aromatic hydrocarbons. Fuel 72(11): 1469-1474.

Williams GM, Laspia MF, Dunkel VC. 1982. Reliability of the hepatocyte primary culture/DNA repair test in testing of coded carcinogens and noncarcinogens. Mutat Res 97:359-370.

*Williams R, Meares J, Brooks L, et al. 1994. Priority pollutant PAH analysis of incinerator emission particles using HPLC and optimized fluorescence. Int J Environ Anal Chem 54(4):299-314.

*Wilson JS, Holland LM. 1988. Periodic response difference in mouse epidermis chronically exposed to crude-oils or b(a)p males vs. females. Toxicology 50(1):83-94.

*Wilson SC, Jones KC. 1993. Bioremediation of soil contaminated with polynuclear aromatic hydrocarbons (PAHs): a review. Environ Pollut 81(3):229-249.

*Wilson RH, DeEds F, Cox AJ. 1947. The carcinogenic activity of 2-acetaminofluorene: IV. Action of related compounds. Cancer Res 7:453-458.

*Wilson JT, McNabb JF, Cochran JW, et al. 1986. Influence of microbial adaptation on the fate of organic pollutants in ground water. Environ Toxicol Chem 721-726.

*Windholz M. 1983. The Merck index. 10th ed. Rahway, NJ: Merck and Co.

Windsor JG, Hites RA. 1979. Polycyclic aromatic hydrocarbons in Gulf of Maine sediments and Nova Scotia sils. Geochim Cosmochim Acta 43:27-33.

Wise SA, Chesler SN, Hilpert LR, et al. 1985. Characterization of polycyclic aromatic hydrocarbon mixtures from air particulate samples using liquid chromatography, gas chromatography, and mass spectrometry. In: Cooke M, Dennis AJ, eds. Polynuclear aromatic hydrocarbons: Mechanisms, methods and metabolism. Columbus, OH: Battelle Press, 1413-1427.

*Withey JR, Law FCP, Endrenyi L. 1991. Pharmacokinetics and bioavailability of pyrene in the rat. J Toxicol Environ Health 32(4):429-447.

*Withey JR, Shedden J, Law FCP, et al. 1992. Distribution to the fetus and major organs of the rat following inhalation exposure to pyrene. J Appl Toxicol 12(3):223-231.

8. REFERENCES

*Withey JR, Law FCP, Endrenyi L. 1993a. Percutaneous uptake, distribution, and excretion of pyrene in rats. J Toxicol Environ Health 40:601-612.

*Withey JR, Shedden J, Law FCP, et al. 1993b. Distribution of benzo[a]pyrene in pregnant rats following inhalation exposure and a comparison with similar data obtained with pyrene. J Appl Toxicol 13(3):193-202.

Wojciechowski JP, Kaur P, Sabharwal PS. 1981. Comparison of metabolic systems required to activate pro-mutagens/carcinogens *in vitro* for sister-chromatid exchange studies. Mutat Res 88:89-97.

*Wojdani A, Alfred LJ. 1984. Alterations in cell-mediated immune functions induced in mouse splenic lymphocytes by polycyclic aromatic hydrocarbons. Cancer Res Mar 44(3):942-945.

Wojdani AM, Attarzadeh G, Wolde-Tsadik, et al. 1984. Immunocytotoxicity effects of polycyclic aromatic hydrocarbons on mouse lymphocytes. Toxicology 31:18l-189.

*Wolfe JM, Bryan WR. 1939. Effects induced in pregnant rats by injection of chemically pure carcinogenic agents. Am J Cancer 36:359-368.

*Wolff RK, Griffith WC, Henderson RF, et al. 1989a. Effects of repeated inhalation exposures to 1-nitropyrene, benzo(a)pyrene, Ga_2O_3, particles, and SO, alone and in combinations on particle clearance, bronchoalveolar lavage fluid composition, and histopathology. J Toxicol Environ Health 27(1):123-138.

*Wolff RK, Sun JD, Bond JA, et al. 1989b. Repeated inhalation exposures to 1-nitropyrene (NP) or benzo(a)pyrene (BaP) in association with Ga203 particles and S02: Tissue distribution, binding, and metabolism of (^{14}C)NP and (^{14}C)BaP. Inhal Toxicol 1(1):79-94.

*Wolff MS, Herbert R, Marcus M, et al. 1989~. Polycyclic aromatic hydrocarbon (PAH) residues on skin in relation to air levels among roofers. Arch Environ Health 44(3):157-163.

*Woo CS, D'Silva AP, Fassel VA. 1980. Characterization of environmental samples for polynuclear aromatic hydrocarbons by an x-ray excited optical luminescence technique. Anal Chem 52:159-164.

Wood AW, Levin W, Ryan D, et al. 1977. High mutagenecity of metabolically activated chrysene 1,2-dihydrodiol: Evidence for bay region activation of chrysene. Biochem Biosphys Res Comm 78:847.

Wood AW, Levin W, Thomas PE, et al. 1978. Metabolic activation of dibenz(a,h)anthracene and its dihydrodiols to bacterial mutagens. Cancer Res 38:1967-1973.

*Wood AW, Chang RL, Levin W, et al. 1979a. Mutagenicity and tumorigenicity of phenanthrene and chrysene epoxides and diol epoxides. Cancer Res 39:4069-4077.

*Wood AW, Levin W, Thakker DR, et al. 1979b. Biological activity of benzo[e]pyrene: An assessment based on mutagenic activities and metabolic profiles of the polycyclic hydrocarbon and its derivatives. J Biol Chem 254(11):4408-4415.

8. REFERENCES

*Wood AW, Chang RL, Huang MT, et al. 1980. Mutagenicity of benzo(e)pyrene and triphenylene tetrahydroepoxides and diol-epoxides in bacterial and mammalian cells. Cancer Res 40:1985-1989.

Wu RM, Jiang Y-M, Ge N-C, et al. 1985. Determination of trace amounts of organic pollutants in the Yellow River by capillary column gas chromatography-mass spectrometry. Int J Environ Anal Chem 22:115-126.

*Wu Y, Kim SJ, Weyand EH. 1994. Bioavailability of manufactured gas plant residue (MPG) components in mice following ingestion: comparison of adulterated powder and gel diets. Polycyclic Aromatic Hydrocarbons 7: 175-182.

*Wynder EL, Hoffmann D. 1959a. A study of tobacco carcinogenesis: VII. The role of higher polycyclic hydrocarbons. Cancer 12:1079-1086.

*Wynder EL, Hoffmann D. 1959b. The carcinogenicity of benzofluoranthene. Cancer 12:1194.

*Wynder EL, Hoffmann D. 1967. Tobacco and tobacco smoke. New York, NY: Academic Press.

Wynder EL, Ritz LFN. 1957. Effect of concentrations of benzopyrene in skin carcinogenesis. J Natl Cancer Inst 19:361-370.

Wynder EL, Spranger JW, Fark MM. 1960. Dose-response studies with benzo[a]pyrene. J Natl Cancer Inst 13:106-l 10.

*Xiao Y, Von Tungein LS, Chou MW, et al. 1993. Effect of caloric restriction on the metabolism of 7-bromobenz[a]anthrecene and 7-fluorobenz[a]anthracene by male B6C3F$_1$ mouse liver microsomes: reduction of metabolic activation pathway. Age 17:160-165.

*Xu B-X, Fang Y-Z. 1988. Determination of polynuclear aromatic hydrocarbons in water by flotation enrichment and HPLC. Talanta 35(11):891-894.

Ya Khesina A, Shcherback NP, Shabad LM, et al. 1969. Benzpyrene breakdown by the soil microflora. Bull Exp Biol Med 68:70.

*Yabiku HY, Martins MS, Takahashi MY. 1993. Levels of benzo[a]pyrene and other polycyclic aromatic hydrocarbons in liquid smoke flavour and some smoked foods. Food Addit Contam 10(4):399-405.

*Yamagiwa K, Ichikawa K. 1918. Experimental study of the pathogenesis of carcinoma. J Cancer Res 3:1-29.

*Yamazaki H, Kakiuchi Y. 1989. The uptake and distribution of benzo(a)pyrene in rat after continuous oral administration. Toxicol Environ Chem 24(1/2):95-104.

*Yamazaki H, Terada M, Tsuboi A, et al. 1987. Distribution and binding pattern of benzo(a)pyrene in rat liver, lung and kidney constituents after oral administration. Toxicol Environ Chem 15:71-81.

*Yamazaki H, Imamura E, Kamei S, et al. 1990. Polycyclic aromatic hydrocarbons affect the calcium ionophore induced activation of rabbit platelet. Chemosphere 21(1/2):21-28.

8. REFERENCES

Yang SK. 1988. Stereoselectivity of cytochrome P-450 isozymes and epoxide hydrolase in the metabolism of polycyclic aromatic hydrocarbons. Biochem Pharmacol 37(1):61-70.

*Yang JJ, Roy TA, Mackerer CR. 1986. Percutaneous absorption of anthracene in the rat: Comparison of *in vivo* and *in vitro* results. Toxicol Ind Health 2:79-84.

*Yang JJ, Roy TA, Krueger AJ, et al. 1989. In-vitro and in-vivo percutaneous absorption of benzo-a-pyrene from petroleum crude-fortified soil in the rat. Bull Environ Contam Toxicol 43(2):207-214.

*Yang SYN, Connell DW, Hawker DW, et al. 1991. Polycyclic aromatic hydrocarbons in air soil and vegetation in the vicinity of an urban roadway. Sci Total Environ 102:229-240.

*Yang Y, Sjovall J, Rafter J, et al. 1994. Characterization of neutral metabolites of benzo[a]pyrene in urine from germfree rats. Carcinogenesis 15(4):681-687.

*Yanysheva NY, Balenko NV, Chemichenko IA, et al. 1993. Peculiarities of carcinogenesis under simultaneous oral administration of benzo[a]pyrene and o-cresol in mice. Environ Health Perspect 101(Supp 3):341-344.

*Yoshikawa T, Ruhr LP, Flory W, et al. 1987. Toxicity of polycyclic aromatic hydrocarbons: III. Effects of beta-naphtoflavone pretreatment on hepatotoxicity of compounds produced in the ozonation or NOZnitration of phenanthrene and pyrene in rats. Vet Hum Toxicol 29: 113-117.

*Zaleski J, Kwei GY, Thurman RG, et al. 1991. Suppression of benzo[a]pyrene metabolism by accumulation of triacylglycerols in rat hepatocytes: Effects of high-fat and food-restricted diets. Carcinogenesis (Eynsham) 12(11):2073-2080.

*Zepp RG, Schlotzhauer PF. 1979. In: Jones PW, Leber P, eds. Polynuclear aromatic hydrocarbons. Ann Arbor MI: Ann Arbor Science, 141.

*Zhao XL, Ho W, Shiu J-H, et al. 1990a. Effects of benzo(a)pyrene on the humoral immunity of mice exposed by single intraperitoneal injection. Chinese J Prevent Med 24(4):220-222.

*Zhao ZH, Quan WY, Tian DH. 1990b. Urinary 1-hydroxypyrene as an indicator of human exposure to ambient polycyclic aromatic hydrocarbons in a coal-burning environment. Sci Total Environ 92:145-154.

*Zheng G-Q, Kenney PM, Zhang J, et al. 1993. Chemoprevention of benzo[a]pyrene-induced forestomach cancer in mice by natural phthalides from celery seed oil. Nutr Cancer 19:77-86.

Zijlstra JA, Vogel EW. 1984. Mutagenecity of 7,12-dimethylbenz[a]anthracene and some other aromatic mutagens in *Drosophila melanogaster.* Mutat Res 125:243-261.

9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

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.

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.

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.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In vivo-Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose 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.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of 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.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

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 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 CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-l) 2-2, and 2-4) and figures (2-1, 2-2, and 2-3) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) 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 to 364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 " 18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [chemical x] via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint 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 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(I 2) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphical!y illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure 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, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the' entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

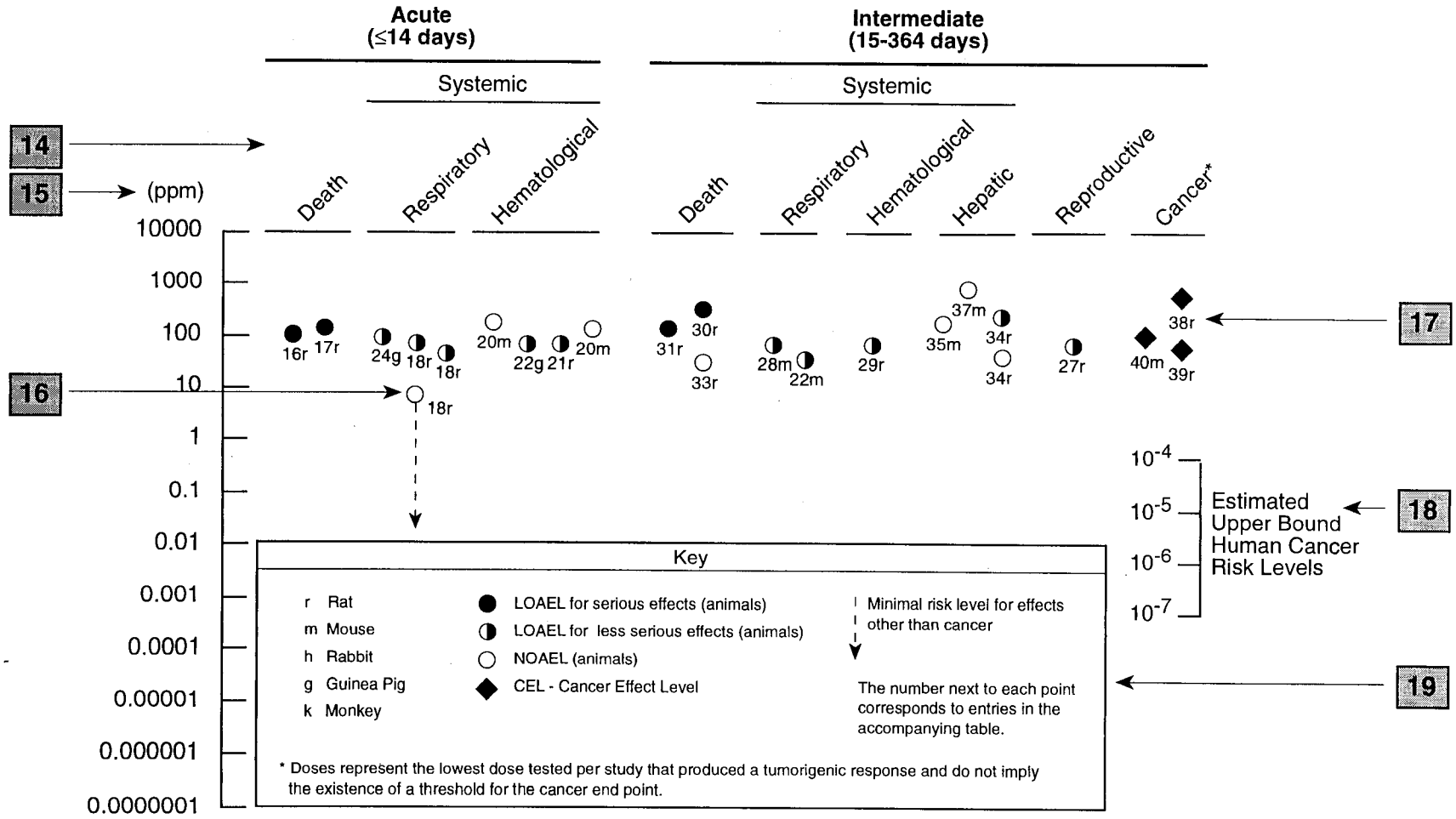
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 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).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section 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 endpoints 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 section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints 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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Chemicals”, and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
dL	deciliter
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient

K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram
μM	micromolar

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