DRAFT
TOXICOLOGICAL PROFILE FOR
WOOD CREOSOTE, COAL TAR CREOSOTE, COAL TAR, COAL TAR PITCH, AND COAL TAR PITCH VOLATILES

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

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UPDATE STATEMENT

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, N.E.
Mail Stop E-29
Atlanta, Georgia 30333

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

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

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

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

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

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 2.7	**Children's Susceptibility**
Section 5.6	**Exposures of Children**

Other Sections of Interest:

Section 2.8	**Biomarkers of Exposure and Effect**
Section 2.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 639-6357 ***Fax:*** (404) 639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Gangadhar Choudhary, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

A. Rosa McDonald, Ph.D
Syracuse Research Corporation, North Syracuse, NY

Cheryl A. Sutton, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Dr. Gary Pascoe, EA Engineering, Science and Technology Inc., 1019 23rd Street, Port Townsend, Washington 98368;

2. Dr. Rosalind Schoof, Exponent, 15375 SE 30th Place, Suite 250, Bellevue, Washington 98007;

3. Dr. Lee Shull, NewFields, Inc., 1550 Harbor Boulevard, Suite 130, West Sacramento, California 95691.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about wood creosote, coal tar creosote, coal tar, coal tar pitch and coal tar pitch volatiles and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Coal tar creosote, coal tar, and coal tar pitch have been found in at least 59 of the 1,591 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at.which coal tar creosote, coal tar, and coal tar pitch are found may increase. This information is important because exposure to coal tar creosote, coal tar, coal tar pitch or coal tar pitch volatiles may harm you and because these sites may be sources of exposure.

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

If you are exposed to wood creosote, coal tar creosote, coal tar, coal tar pitch or coal tar pitch volatiles, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CREOSOTE?

Wood creosote, coal tar creosote, coal tar, coal tarpitch, and coal tar pitch volatiles are rarely formed in nature. Creosote is the name used for a variety of products that are mixtures of many chemicals. Coal tar creosote, coal tar, and coal tar pitch are similar in composition. For this reason, many times throughout the profile, we will refer to coal tar creosote, coal tar, and coal tar

pitch simply as creosote. Creosotes are created by high-temperature treatment of beech and other woods (beechwood creosote) or coal (coal tar creosote), or from the resin of the creosote bush (creosote bush resin). Wood creosote is a colorless to yellowish greasy liquid with a characteristic smoky odor and sharp burned taste. It is relatively soluble in water. Creosote prepared from coal tar is the most common form of creosote in the workplace and at hazardous waste sites in the United States. Coal tar creosote is a thick, oily liquid that is typically amber to black in color. It is easily set on fire and does not dissolve easily in water. Coal tar and coal tar pitch are the by-products of the high-temperature treatment of coal to make coke or natural gas. They are usually thick, black, or dark brown liquids or semisolids with a smoky or aromatic odor. Coal tar residues can also be found in the chimneys of homes heated with coal, especially if insufficient oxygen is present. Chemicals in the coal tar pitch can be given off into the air as coal tar pitch volatiles when coal tar pitch is heated.

Beechwood creosote has been used as a disinfectant, a laxative, and a cough treatment. In the past, treatments for leprosy, pneumonia, and tuberculosis also involved eating or drinking beechwood creosote. It is rarely used today in the United States by doctors since it has been replaced by better medicines, and is no longer produced by businesses in the United States. It is still available as an herbal remedy, and is used as an expectorant and a laxative in Japan. The major chemicals in beechwood creosote are phenol, cresols, and guaiacol.

Coal tar creosote is the most widely used wood preservative in the United States. It is also a restricted use pesticide, so it can only be used by people who have been trained to use it safely. Coal tar products are ingredients in medicines used to treat skin diseases such as psoriasis. These products are also used as animal and bird repellents, insecticides, animal dips, and fungicides, Coal tar, coal tar pitch, and coal tar pitch volatiles are used or produced in several industries, including road paving, roofing, aluminum smelting, rubber producing, and coking. The major chemicals in coal tar creosote, coal tar, and coal tar pitch that can cause harmful health effects are polycyclic aromatic hydrocarbons (PAHs), phenol, and cresols. Coal tar pitch volatiles vary depending on the makeup of the coal tar product that is being heated. About 300 chemicals have been identified in coal tar creosote, but there may be as many as 10,000 other chemicals in this mixture. Because coal tar creosote is the major type found in the environment

and at hazardous waste sites in the United States, we will emphasize its effects on human health in this profile. The health effects of coal tar and coal tar pitch will also be described.

This profile is specifically about the toxicity of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, so we will not discuss in detail the health effects of individual chemicals in them, such as PAHs or phenol. In the chapters describing what happens to creosote in the environment and exposure to creosote, we will discuss some of the individual chemicals or groups of chemicals (such as PAHs) because many of the tests done in the scientific laboratories can tell us which chemicals are present in the soil, water, and air.

The Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995), the ATSDR *Toxicological Profile for Cresols* (ATSDR 1992), and the ATSDR *Toxicological Profile for Phenol* (ATSDR 1998) provide more information on these chemicals. For more information on the chemica1 and physical properties of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles, see Chapter 3. For more information on these substances in the environment, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO CREOSOTE WHEN IT ENTERS THE ENVIRONMENT?

No information is available on what happens to wood creosote when it enters the environment. Coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles do not occur in the environment naturally, but are by-products produced in coke or gas manufacturing plants using high-temperature processes. Coal tar creosote is released to water and soil mainly as a result of its use in the wood preservation industry. In the past, waste water from wood treatment facilities was often discharged to unlined lagoons where it formed a sludge. Also, companies that preserve wood with coal tar creosote may treat their water wastes in treatment plants or release the waste water to the municipal water treatment system. This is still the largest source of coal tar creosote in the environment. However, new restrictions from the EPA have caused changes in the treatment methods that have decreased the amount of creosote available to move into soil from waste water effluents. Coal tar creosote contains some components that dissolve in water and some that do not. Coal tar creosote components that dissolve in water may move through

the soil to eventually reach and enter the groundwater, where they may persist. Once in the groundwater, breakdown may take years. Most of the components that are not water soluble will remain in place in a tar-like mass. Migration from the site of contamination is not extensive. Breakdown in soil can take months for some components of coal tar creosote, and much longer for others. Sometimes, the small amounts of chemical remaining in the soil or water that take a long time to break down are still toxic to some animals and possibly to humans. Coal tar creosote components may also be found in the soil as a result of leaking or seeping from treated timber. More complete information on how creosote enters the environment and what happens to creosote in the environment can be found in Chapters 4 and 5 of this profile.

Volatile chemicals in coal tar creosote may evaporate and enter the air. About 1-2% of the coal tar creosote applied to treated wood is released to the air. This is a small amount compared to the amount of coal tar creosote found in waste water or soil. Volatile chemicals in coal tar and coal tar pitch are released into the environment in a similar way. They are most often found in and around coke or natural gas-producing factories, in industrial plants where coal tar and coal tar sludges are used, or at abandoned coke or gas factory sites. Water or soil surrounding these areas may contain detectable levels of coal tar or coal tar pitch.

Once coal tar creosote is in the environment, both plants and animals can absorb parts of the creosote mixture. Some components of coal tar creosote have been found in plants exposed to creosote-treated wood in nearby soil. The plants absorb very little (less than 0.5% of the amount available to the plant). Animals such as voles, crickets, snails, pill bugs, and worms take up coal tar creosote components from the environment that are passed into the body through skin, lungs, or stomachs. Animals that live in the water, such as crustacea, shellfish, and worms, also take up coal tar creosote compounds. For instance, mussels attached to creosote-treated pilings, and snails and oysters living in water near a wood-treatment plant, had creosote in their tissues. Coal tar creosote components are also broken down by microorganisms living in the soil and natural water, The components of coal tar and coal tar pitch move in the environment in a similar way.

1.3 HOW MIGHT I BE EXPOSED TO CREOSOTE?

Most people are exposed to very low levels of creosote. People who are exposed to higher concentrations than the general population are those that are exposed to creosote in their jobs and those that use products that contain creosote to improve a health problem such as eczema or psoriasis.

Some people are exposed to creosote through shampoos for psoriasis which contain creosote. Herbal remedies containing the leaves from the creosote bush (chaparral) are available as a dietary supplement and act as a source of exposure to wood creosote. The drinking of chaparral tea is a source of human exposure to wood creosote. Hazardous waste sites are a major source of contamination with creosote, coal tar, and coal tar pitch. Individuals working in the wood-preserving industry make up the largest part of the population that might be exposed to coal tar creosote. Individuals who live in areas that used to be sites of wood preserving facilities may be exposed if the soil was never cleaned up. The most common way that creosote will enter the body when it is present in soils is through the skin. Children may also have creosote enter their bodies by swallowing if they put their unwashed hands in their mouths after touching soil or wood that is contaminated with creosote. The most common way that it will enter the body for individuals in the wood preserving industry is through the lungs.

Asphalt workers; rubber, aluminum, iron, steel, and tire factory workers; and people working in the coke-producing industries are also at risk for potential exposure to coal tar pitch and coal tar pitch volatiles. They may breathe in vapors from or have direct skin contact with wood-preservation solutions, freshly treated wood, asphalt mixtures, or other products of coke-producing industries. Workers who use creosote-treated wood in building fences, bridges, or railroad tracks or installing telephone poles may be exposed; those who inspect or maintain these materials, or apply asphalt or other coal tar pitch-containing materials, may also be exposed. Homeowners, farmers, or landscapers who apply coal tar creosote to wood in noncommercial settings using a brush or dip procedure (which is no longer allowed by law unless you have been trained to safely use creosote as a wood preservative), or who use railroad ties or telephone poles in landscaping, or who reclaim scrap lumber from a treated structure may also be exposed. In

addition, people who work or live in treated-wood houses (log cabins) may be exposed through the air or by direct contact with the wood. Exposure to coal tar products may also occur in the natural gas and aluminum smelting industries. You can be exposed by any contact with water, soil, air, or plant and animal tissues that contain creosotes, coal tar, coal tar pitch, or its volatile components. Intentional or accidental eating of coal tar creosote has resulted in poisoning. If your activities bring you into contact with these mixtures, such as at hazardous waste sites, in contaminated groundwater, in wood products treated with creosote, or in contaminated shellfish, you will be exposed to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Drinking water contaminated by a hazardous waste site may also be a source of exposure. For more information on human exposure to these substances, see Chapter 5.

1.4 HOW CAN CREOSOTE ENTER AND LEAVE MY BODY?

Creosotes and coal tar products can enter your body through the lungs, stomach, intestines, and skin. There is no information that describes how fast or how much of creosote or its components might enter the body after one or many exposures. The amount that enters the body depends on how you come in contact with it (air, food, water, skin), how much of the mixture is present, and how long you are exposed to it. Many of the parts of the coal tar creosote mixture (for example, PAHs) are rapidly absorbed through the lungs, stomach, and intestines. Prolonged exposure through the skin, without washing, may increase the amount of the creosotes or coal tar products absorbed into the bloodstream. Individual components of coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles may be stored in body fat. Some studies indicate that creosotes may cross the placenta into the tissue of the developing fetus. Because coal tar products may be stored in body fat, they may be found in breast milk. Creosotes are excreted primarily in the stool; a smaller amount is excreted in the urine. See Chapter 2 for more information on how creosotes and coal tar products enter and leave the body.

1.5 HOW CAN CREOSOTE AFFECT MY HEALTH?

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

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

Exposure to creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles may be harmful to your health. Eating food or drinking water contaminated with a high level of these compounds may cause a burning in the mouth and throat as well as stomach pains. Taking herbal remedies containing creosote bush leaves may result in damage to the liver or kidney. Reports describing coal tar creosote poisoning in workers, or accidental or intentional eating of coal tar creosote, indicate that adverse reactions may occur. These reports indicate that brief exposure to large amounts of coal tar creosote may result in a rash or severe irritation of the skin, chemical burns of the surfaces of the eye, convulsions and mental confusion, kidney or liver problems, unconsciousness, or even death. Longer exposure to lower levels of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles by direct contact with skin or by exposure to the vapors from these mixtures can also result in sun sensitivity and cause damage to skin, such as reddening, blistering, or peeling. Longer exposures to the vapors of the creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles can also cause irritation of the respiratory tract. Skin cancer and cancer of the scrotum have also resulted from long exposure to low levels of these chemical mixtures, especially through direct contact with skin during wood treatment or manufacture of coal tar creosote-treated products, or in coke or natural gas factories. Cancer of the scrotum in chimney sweeps has been associated particularly with prolonged skin exposure to soot and coal

tar creosote. These levels are much higher than the levels that you are likely to be exposed to in groundwater, food, air, or soil.

Rats and mice fed a large amount of wood creosote at one time had convulsions and died. Rats fed a smaller amount of wood creosote for a long period developed kidney and liver problems, and died. Exposure to coal tar products through the skin has resulted in skin cancer in animals. Laboratory animals which ate food containing coal tar developed cancer of the lungs, liver, and stomach and animals exposed to coal tar in the air developed lung and skin cancer.

The International Agency for Research on Cancer (IARC) has determined that coal tar is carcinogenic to humans and that creosote is probably carcinogenic to humans. The EPA has also determined that coal tar creosote is a probable human carcinogen.

1.6 HOW CAN CREOSOTE AFFECT CHILDREN?

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

Children are generally exposed to very low levels of creosote, but intentional or accidental eating of coal tar creosote has resulted in poisoning. Children who live in hazardous waste areas contaminated with creosote may be exposed by drinking contaminated water or from contact with soil. The most common way that creosote will enter the body when it is present in soils is through the skin. However, children may also swallow creosote if they eat dirt or put their unwashed hands in their mouths after touching soil or wood that is contaminated with creosote. In addition, children may be exposed to creosote compounds if they eat fish and shellfish from contaminated areas. Children may also be exposed to creosote if they use products that contain creosote to improve a health problem such as dandruff, eczema, or psoriasis, or if they are given a herbal remedy containing the leaves from the creosote bush (chaparral).

Children may also be exposed to creosote if they breathe in vapors from or have direct skin contact with freshly treated wood found in fences, bridges, railroad ties, or telephone poles. In

addition, children who live in treated-wood houses (log cabins) may be exposed through the air or by direct contact with the wood. The use of creosote to protect wooden playground equipment or wooden decks for the yard is not recommended, but children may be exposed to creosote if it has been applied to wood in or around the home in the past. Children could also be exposed to creosote from clothing or shoes that have been contaminated with creosote at the workplace. Children are not more likely to be exposed to creosote than adults and there is no unique exposure of children to creosote.

Children who played on soil contaminated with creosote had more skin rashes than children from other areas. Apart from this, the health effects of creosote have not been studied in children, but they would likely experience the same health effects seen in adults exposed to creosote. We do not know whether children differ from adults in their susceptibility to health effects from creosote. Children could be more susceptible to cancer because they might have a longer time in which to develop it, but this has not been studied.

No effects have been reported for children exposed to creosote before birth. Experiments in laboratory animals have shown birth defects, such as cleft palates, in the young of mothers exposed to high levels of creosote during pregnancy, but it is not known if this could also occur in humans. Some animal studies indicate that creosotes may cross the placenta into the tissue of the developing fetus. Because coal tar products may be stored in body fat, they may be found in breast milk, but this has not been measured. For more information on the effects of creosote on children, see Section 2.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CREOSOTE?

If your doctor finds that you have been exposed to significant amounts of creosote, coal tar, coal tar pitch, or coal tar pitch volatiles, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Families may reduce the risk of exposure to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles in several ways if they find that they are at risk of such exposures. If you live in a

residential area that used to have a wood preservation facility or gas manufacturing plant located on or near the site, you should use precautions to decrease or limit the amount of creosote in the soil or water that comes into contact with your skin. This may include wearing long-sleeved shirts and long pants when working or playing outside. If the soil in your yard was contaminated by creosote in the past, you should probably not grow food in it. You will need to wash your hands and any other exposed skin carefully after you are in contact with the contaminated soil or water outside. This is especially true for children since they have a tendency to put their hands in their mouths. Some children eat a lot of dirt. It is not fully understood how much of the creosote bound to dirt may come off the dirt when it is inside your body. You should discourage children from eating dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or other hand-to-mouth activity. If your local water supply is near such a site, you should drink less tap water.

Children may be exposed to creosote during their outdoor play activities. You should encourage your children not to play in contaminated areas, particularly in those that may be abandoned waste sites or waste sites undergoing cleanup. Some children will ignore signs posted at the sites which alert the public to possible dangers and declare the areas off limits. Encourage your children to follow the instructions on the signs and to play elsewhere. Children may come into contact with creosote-treated wood when playing on or near railroad tracks, in ditches close to utility poles, when playing in old barns or other farm structures, or on bridges or piers. Children may also be exposed to creosote through ingestion if they chew or place their mouths on creosote-treated objects such as fence posts or pier railings. You should discourage your children from such behavior and from putting foreign objects in their mouths.

The drinking of chaparral tea may result in exposure to wood creosote by swallowing. If you drink chaparral tea in a practice unique to your heritage, then you are using creosote and may expose your child, Creosote is also found in coal tar shampoos used for anti-dandruff therapy, in coal tar ointments used for treatment of eczematous dermatitis, and in mineral coal tar for the treatment of psoriasis. You may expose your child to creosote if you use any of these products. Ask your doctor if there are alternative treatments that do not involve the use of these products.

It is sometimes possible to carry creosote into the home on work clothing or shoes that may have been exposed to coal tar creosote, coal tar, or coal tar pitch at the workplace. This may be of more importance for people who work in the wood preserving industry or in jobs such as roofing, paving, and chimney cleaning than for people who work in the coking industry, or,in other plants which use coal tar-derived products and where the main route of exposure is through breathing in contaminated dust. You can contaminate your car, home, or other locations outside work where children might be exposed to creosote. You should know about this possibility if you work with creosote. Long-term exposure to low levels of creosote through direct contact with skin has resulted in skin cancer. For workers in wood preservation facilities, the American Wood Preservers Institute (AWPI) recommends washing work clothes separately from other household clothing if oily creosote residues or sawdust from creosote-treated wood are present on the clothes. Adults with contaminated work clothes should wash them before reusing them. If you work in an industry in which creosote is used, your occupational health and safety officer at work should tell you whether this or other chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Your employer should have Material Safety Data Sheets (MSDSs) for many of the chemicals used at your place of work, as required by the Occupational Safety and Health Administration (OSHA). Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in an emergency. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHA-approved state occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your OSHA-approved state occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

Your children may be exposed to creosote compounds by eating certain types of fish and shellfish caught from certain locations. Certain states, Native American tribes, and U.S. territories have issued freshwater fish advisories to warn people about creosote-contaminated fish. Each state, Native American tribe, or U.S. territory sets its own criteria for issuing fish advisories. A fish advisory will specify which bodies of water have restrictions. The advisory will tell you what types and sizes of fish are of concern. The advisory may completely ban eating fish or tell you to limit your meals of a certain fish type. For example, an advisory may tell you to eat a certain type of fish no more than once a month. The advisory may tell you only to eat certain parts of the fish and how to prepare or cook the fish to decrease your exposure to creosote. The fish advisory may be stricter to protect pregnant women, nursing mothers, and young children. Chemicals in creosote have been found in breast milk and may cross the placenta. To reduce your child's exposure to creosote, obey fish advisories, Information on Fish and Wildlife Advisories in your home state is available from your state health or natural resources department. Signs might also be posted in certain fishing areas.

Creosote is a "Restricted Use Pesticide," meaning that it is only supposed to be applied by people who are trained to use it safely and who have been tested and approved to use it. It is not a pesticide that is available over-the-counter for use in the home or garden. The American Wood Preservers Institute does not recommend the use of creosote to protect wooden playground equipment or wooden decks for the yard. Other pesticides are generally used for the preservation of playground equipment and decks. Your children may be exposed to creosote if an unqualified person applies it to wood in or around your home, such as sundecks, or to wooden equipment your children play on. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and, if appropriate (as is the case for creosote), certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides according to EPA standards and further certifies each person who is qualified to apply "restricted use" pesticides. Ask to see the license and certification. Also ask for the brand name of the pesticide, an MSDS, the name of the product's active ingredient (the chemical which makes the pesticide work), and the EPA registration number. Ask whether EPA has designated the pesticide "for restricted use" and

what the approved uses are. This information is important if you or your family react to the product.

If you buy over-the-counter pesticide products to apply yourself, be sure the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions on the label. If you plan to use the pesticide in the home, make sure that it is intended for indoor use.

If you feel sick after a pesticide has been used in your home, consult your doctor or local poison control center.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CREOSOTE?

There is no medical test to determine if you have been exposed to wood creosote, coal tar creosote, coal tar, coal tar pitch mixtures, or coal tar pitch volatiles. However, chemicals contained in creosote (such as PAHs or phenol) can be found in the body and can be measured in body tissues (organs, muscle, or fat) or blood after exposure to creosote. Exposure to the low levels of these substances found in groundwater, food, air, and soil may not be detected with the test. Chemicals in coal tar creosote and its breakdown products can also be measured in the urine of exposed individuals. Urine tests are commonly done for employees in industry who work with coal tar creosote, coal tar, and coal tar pitch to monitor their exposure. For example, the metabolite 1-hydroxypyrene, which can be detected in urine after exposure to specific PAHs (for example, benzo[a]pyrene) contained in creosote, can be used to detect exposure to creosote.

This test is available at a doctor’s office and may require that a specimen be sent to a laboratory where special equipment for detecting the compound is available. These tests can confirm that a person has been exposed to the chemicals found in coal tar creosote and other coal tar products, but cannot accurately predict whether you will experience any health effects. Also, these tests cannot tell whether the chemicals came from creosote or other sources. Since the chemicals in coal tar products remain in body tissues for long periods, these tests may not be useful in

determining when you were exposed. Tests that determine levels of breakdown products may be more accurate in predicting exposure within days. For more information on tests to measure coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles in the body, see Chapters 2 and 6.

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

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

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

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for creosote include the following:
The Food and Drug Administration (FDA) has issued a public warning against consumption of herbal products derived from the leaves of the creosote bush (chaparral) because of reports of acute toxic hepatitis after use as a dietary supplement.

The federal government has not developed regulatory standards and guidelines to protect people from the potential health effects of exposure to coal tar creosote in drinking water and food. Regulatory standards and guidelines for air and water exist for the most important individual PAHs and phenols contained in wood creosote, coal tar creosote, coal tar, and coal tar pitch. The EPA has declared coal tar creosote a restricted use pesticide. This means it can only be bought and used by certified applicators and only for those uses covered by the applicator's certification. In addition, coal tar creosote has been identified as a hazardous waste.

The federal government has developed regulatory standards and guidelines to protect workers from the potential health effects of other coal tar products in air. OSHA has set a legal limit (Permissible Exposure Limit or PEL) of 0.2 milligrams of coal tar pitch volatiles per cubic meter of air in workroom air to protect workers during an 8-hour shift.

For more information on regulations and advisories for coal tar creosote, coal tar, and coal tar pitch exposure, see Chapter 7.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: l-888-42-ATSDR (l-888-422-8737)
Fax: (404) 639-6359

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

* To order toxicological profiles. contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

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 on the toxicology of creosote. 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. Th,e 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 (LOAEL) 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.

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

This profile addresses the toxicological and toxicokinetics database for several substances, wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, whose production stems from the incomplete combustion or pyrolysis of carbon-containing materials. Creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles are composed of many individual compounds of varying physical and chemical characteristics. In addition, the composition of each, although referred to by specific name (e.g., wood creosote or coal tar creosote) is not consistent. For instance, the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for combustion.

Wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles differ from each other with respect to their composition. Wood creosotes are derived from beechwood (*Fagus*, referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin). Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol. It is a colorless or pale yellowish liquid, and has a characteristic smoky odor and burnt taste (Miyazato et al. 1981). It had therapeutic applications in the past as a disinfectant, a laxative, and a stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States.
Coal tars are by-products of the carbonization of coal to produce coke or natural gas. Physically, they are usually viscous liquids or semisolids that are black or dark brown with a naphthalene-like odor. The coal tars are complex combinations of polycyclic aromatic hydrocarbons (PAHs), phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. By comparison, coal tar creosotes are distillation products of

coal tar. They have an oily liquid consistency and range in color from yellowish-dark green to brown. The coal tar creosotes consist of aromatic hydrocarbons, anthracene, naphthalene, and phenanthrene derivatives. At least 75% of the coal tar creosote mixture is PAHs. Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. The pitch is a shiny, dark brown to black residue which contains PAHs and their methyl and polymethyl derivatives, as well as heteronuclear compounds (American Wood Preserver's Association 1988). Coal tar creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants (EPA 1981a, 1984a). Volatile components of the coal tar pitch can be given off during operations involving coal tar pitch, including transporting, and in the coke, aluminum, and steel industries (Bender et al. 1988; Mazumdar et al. 1975; NIOSH 1983; Rönneberg 1995b; Riinneberg and Anderson 1995).

Although beechwood creosote and coal tar creosote have some components in common (e.g., phenols), and some of the adverse effects associated with exposure to beechwood creosote may be due to the phenol component, it is not known whether coal tar creosote will induce these same effects. Furthermore, coal tar creosote contains PAHs, some of which are carcinogenic to animals, and beechwood creosote does not. Thus, the relevance of health effects data on beechwood creosote to risk associated with exposure to coal tar creosote is not known.

Creosote bush resin consists of phenolics (e.g., flavonoids and nordihydroguaiaretic acid), neutrals (e.g., waxes), basics (e.g., alkaloids), and acidics (e.g., phenolic acids). The phenolic portion comprises 83-91% of the total resin. Nordihydroguaiaretic acid accounts for 5-10% of the dry weight of the leaves (Leonforte 1986). Again, it is not known if the health effects associated with creosote bush resin are due to the phenolic components common to coal tar creosote and if these effects would be expected to occur following exposure to coal tar creosote.

Throughout this profile, every attempt will be made to specify the characteristics of the creosote, coal tar, coal tar pitch, or coal tar pitch volatiles under discussion, and to indicate which effects may be expected to be common to two or more forms. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. Therefore, the health effects of the individual components (e.g., PAHs, phenol, or others) will not be discussed in great detail even though it is likely that the toxicity of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles is due largely to these major individual components. However, it is understood that the toxicity of the individual components may not be representative of the actual toxicity of the'mixtures because of the possibility of synergistic and/or

antagonistic interactions in the mixture. For more information on the health effects of these components, the reader can refer to the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons (ATSDR 1992, 1995, 1998).

2.2.1 Inhalation Exposure

This section describes the health effects observed in humans and laboratory animals associated with inhalation exposure to coal tar pitch or coal tar pitch volatiles, for which reliable exposure levels could be determined. All reliable exposure levels have been stated, where possible. No studies were located regarding the health effects in humans exposed solely by inhalation to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Studies of occupational exposure of humans (Armstrong et al. 1994; Bender et al. 1988; Bertrand et al. 1987; Bolt and Golka 1993; CEOH 1997; Costantino et al., 1995; Finkelstein 1989; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kromhout et al.., 1992; Kunze et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; NIOSH 1982; Park and Mirer 1996; Persson et al. 1989; Petsonk et al. 1988; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rijnneberg 1995b; Rijnneberg and Andersen 1995; Sakabe et al. 1975; Schildt et al. 1999; Siemiatycki et al. 1994; Spinelli et al. 1991; Swaen and Slangen 1997; TOMA 1978, 1979, 1982; Tremblay et al. 1995; Ward 1988; Wu et al. 1998; Yadav and Seth 1998) did not attempt to distinguish between inhalation, oral, or dermal exposure. Several studies were found describing health effects in animals of inhalation exposure to aerosols of coal tar or coal tar pitch (Heinrich et al. 1994a, 1994b; Hueper and Payne 1960; MacEwen et al. 1977; Ptitzer et al. 1965; Springer et al. 1982, 1986b, 1987). Although beechwood creosote, creosote bush resin, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have some components in common (e.g., phenols), it is not known which components of the mixtures produce the toxic effects.

2.2.1.1 Death

No studies were located connecting death in humans following exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles solely by inhalation. A mortality study of human exposure during employment at eight coal tar plants indicated significant increases in cancer-related deaths, compared to the general population (TOMA 1982). No clear relationship between inhalation of coal tar and increased mortality could be established since exposure routes in addition to .inhalation (e.g., dermal and oral) were likely and subjects were also exposed to other chemicals and cigarette smoke. Since the study was retrospective, no attempt was made to estimate occupational

exposure levels from any source (TOMA 1982). Limitations of the study included absence of data on smoking habits, short cut-off date of 10 days of employment, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and mixed chemical exposure. The same study population was used as the basis for a nested cancer case-control study (CEOH 1997). Fifty lung-cancer cases were identified and matched with controls from the same cohort. There were three controls per case, and individuals were matched for plant, gender, race, date of hire, and age at hire. Smoking history, work and medical history data were gathered by telephone interviews with the subjects or their next of kin and used to assign workers to various exposure classes. Odds ratios for lung cancer were increased in persons assessed as highly exposed to coal tar compared with those having low or no exposure, but the difference was not significant, and the risk associated with working for more than 20 years in production was lower than that of short-term employees. Controlling for smoking (data analyzed for smokers only) did not change the results, but no nonsmoking cases were identified and so it was not possible to assess the effects of coal tar exposure without concurrent cigarette smoking.

In a mortality study of steelworkers employed in a coke oven plant in 1953, increased mortality from respiratory neoplasms (monitored from 1953 to 1961) was observed in coke oven workers compared to expected mortality rates (Lloyd 197I). Specifically, 20 deaths from respiratory neoplasms were observed, compared to the expected 7.5 deaths. The increase in mortality was linked to an increase in mortality from respiratory neoplasms in nonwhite oven workers who had been employed for 5 years or more. No increase in deaths from respiratory neoplasms was observed in nonoven workers. In a series of follow up studies of these same coke oven workers in Allegheny County, Pennsylvania, similar associations between coal tar or coal tar pitch volatile exposure and mortality, primarily from lung cancer, were observed (Redmond 1976; Redmond et al. 1972, 1976). An increase in death due to kidney cancer was observed at the plant, although this was not limited to the coke oven workers at the steel plant (Redmond et al. 1976). Lung cancer mortality was higher in men exposed to coal tar in an aluminum smelter plant for more than 21 years, with an increased risk of 2.2-2.4 compared to persons not exposed to tar (Gibbs 1985; Gibbs and Horowitz 1979). Increased risk of mortality from pancreatic cancer and leukemia of more than 30% was observed for workers in the potrooms and carbon departments of 14 aluminum reduction plants, who had worked for more than 5 years (Rockette and Arena 1983).

Spinelli et al. (1991) examined mortality and cancer incidence over a 30-year period among a cohort of 4,213 workers exposed to coal tar pitch volatiles emitted during the production of aluminum. A significant increase in the mortality rate for brain cancer was observed. However, no exposure response was seen for deaths from any form of cancer in direct relation to cumulative coal tar pitch volatile

exposure. Mortality in a Norwegian aluminum smelter plant was investigated in a cohort of 1,085-l) 137 men who worked between 1922 and 1975 (Rönneberg 1995b; Rönneberg and Andersen 1995). An increase in mortality from atherosclerosis and chronic obstructive lung disease were associated with 40 or more years of exposure or 20-39 years exposure to pot emissions, respectively (Rönneberg 1995b). When cancer incidence was analyzed, associations were found between tar exposure and increases in bladder, prostatic, and lung cancer (Rönneberg and Andersen 1995). In a study of exposure to coal tar pitch volatiles in coke oven plants in France, mortality due to lung cancer was 2.5 times higher in the coke plant workers (534 males) exposed for periods from <5 to >l0 years compared to the French national male population (Bertrand et al. 1987). In another study of coal tar pitch volatile exposure in coke oven plants, mortality was monitored in coke oven workers in Pennsylvania who had been employed for >l0 years (Mazumdar et al. 1975). An increase in mortality due to lung cancer was positively correlated with coal tar pitch volatile exposure. In a study of coal tar pitch volatile exposure in the aluminum industry, four workers from the same area of the plant died of lung cancer (Bolt and Golka 1993). Duration of exposure to coal tar pitch volatiles ranged from 3.5 to 23 years. Costantino et al. (1995) carried out an epidemiological study of 5,321 coke oven workers and 10,497 nonoven workers. Statistically significant excess mortality was present among coke workers for several categories of death. The relative risk (RR) for all causes of death was 1.11 ($P<0.001$) The increase in overall mortality was primarily due to increased deaths from cancers. There were highly significant trends ($P<0.00l$) for increased cancer risk with increasing duration of employment and increasing exposure. The study did not control for excess mortality due to smoking. However, the similar socioeconomic status of the controls and exposed workers suggests that it is unlikely that there was a substantial difference in smoking habits between the two groups. Further discussion of retrospective human cancer/mortality studies can be found in Section 2.2.1.8.

Animal studies were also limited in number for this route of exposure. One study was located in which rats were exposed for 1 hour to saturated vapors of coal tar creosote (Pfitzer et al. 1965). In this study, no specific concentration level was stated and no deaths were observed. In a study in Wistar rats, female rats were exposed to 1.1 or 2.6 mg/m^3 coal tar pitch aerosol for 10 months, 5 days/week, 17 hours/day, followed by exposure to clean air for 20 months (Heinrich et al. 1994a, 1994b). Increased mortality was observed in the high-concentration group, due to lung tumors (no mortality data shown). Increased mortality was also observed in Wistar rats exposed to 1.1 or 2.6 mg/m^3 coal tar pitch aerosol for 20 months, 5 days/week, 17 hours per day, followed by clean air exposure for 10 months (Heinrich et al. 1994a, 1994b). New Zealand white rabbits exposed to 10 mg/m^3 coal tar pitch aerosol in a mixture of benzene, toluene, and xylene for 18 months, 5 days/week, 6 hours/day exhibited higher mortality than the

control animals (89 versus 33%), although the authors attributed death to chronic respiratory infection (MacEwen et al. 1977). Further evaluation of these animals was not provided, so it is not known whether the inhalation exposure affected the susceptibility of the animals to respiratory infection. Kock et al. (1994) reported death of 7 of 20 black rhinoceroses that had been held in creosote-treated holding pens. The animals that died had oral and gastric ulcers, widespread hemorrhages and hematoma, and uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. However, doses and routes of exposure were not established in this study.

The LOAEL values for death in each species are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

No studies were located regarding the gastrointestinal, musculoskeletal, hepatic, endocrine, or body weight effects in humans or musculoskeletal effects in animals after inhalation exposure to creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles. The systemic effects that have been observed in humans and animals are discussed below. LOAEL and NOAEL values for systemic effects are recorded in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. A single case report describes acute bronchoconstriction in an asthmatic patient exposed to coal tar vapor while being treated with coal tar occlusive bandages for a skin condition (Ibbotson et al. 1995). The authors conclude that the effect was probably due to inhalation of coal tar vapor leading to a nonspecific irritant response. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, respiratory effects, including reduced lung function, were noted in 24% (44 of 257) of the employees examined (TOMA 1978). Workers in 9 coal tar plants had a 33% (150 of 453) incidence of reduced lung function (TOMA 1979). Industrial hygiene surveys of coal tar pitch volatiles at the 4 wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1978). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1978). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., dermal and oral) were likely. Also, the ability to relate respiratory effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1978, 1979). Additional limitations of the studies included geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Systemic							
1	Human	8 hr	Ocular		0.18 M (conjunctivitis)		Emmett 1986 CTPV
2	Rat (CD)	5 d Gd 12-16 6 hr/d	Resp	84 F	660 F (significant increase in lung weight)		Springer et al. 1982 coal tar aerosol
			Hepatic	660 F			
			Renal	660 F			
			Endocr	660 F			
			Bd Wt	84 F	660 F (significant decrease in body weight)		
Immunological/Lymphoreticular							
3	Rat (CD)	5 d Gd 12-16 6 hr/d		84 F	660 F (significant decrease in thymus weight and increase in spleen weight)		Springer et al. 1982 coal tar aerosol
Reproductive							
4	Rat (CD)	5 d Gd 12-16 6 hr/d		84 F	660 F (significant increase in the incidence of mid- and late-gestational resorptions)		Springer et al. 1982 coal tar aerosol
Developmental							
5	Rat (CD)	5 d Gd 12-16 6 hr/d		84	660 (reduced fetal size, weight and lung size, reduced ossification)		Springer et al. 1982 coal tar aerosol

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Death							
6	Rat (Wistar)	10 mo 5 d/wk 17 hr/d				2.6 F (increased mortality)	Heinrich et al. 1994a, b coal tar pitch
Systemic							
7	Rat (Fischer-344)	6 wk 5 d/wk 6 h/d	Cardio		700 M (20% elevation in arterial blood pressure)		Sasser et al. 1989 coal mixture
			Bd Wt		700 M (17.5 % decrease in body weight)		

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
8	Rat (Fischer- 344)	5 wk 5 d/wk 6 hr/d	Resp		30 (histiocytosis of lung)		Springer et al. 1986b coal tar aerosol
			Cardio	690			
			Gastro	140 M 690 F	690 M (epithelial hyperplasia and chronic inflammation in cecum)		
			Hemato	30	140 (significant decrease in red blood cells, hemoglobin, and volume of packed red cells, significant increase in reticulocytes)		
			Hepatic	140 M	690 M (significant increase in 30 F relative weight of liver and serum cholesterol)		
			Renal	30 F	30 M (significant increase in 140 F relative weight of kidney)	690 M (pelvic epithelial hyperplasia)	
			Endocr	690			
			Bd Wt	30	140 (7% decrease in body weight)		

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
9	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp		30 (histiocytosis of lung)	690 (lesions of olfactory epithelium)	Springer et al. 1986b coal tar aerosol
			Cardio	690			
			Gastro	140	690 (epithelial hyperplasia, ulcers and chronic inflammation of cecum)		
			Hemato	30 M 140 F	140 M 690 F (significant decrease in red blood cells, hemoglobin, and volume of packed red cells)		
			Hepatic	30 F	30 M 140 F (significant increase in relative liver weight)	690 (presence of liver lesions, elevated cholesterol, blood urea nitrogen and alteration in activities of SGPT and LDH)	
			Renal	30	140 (significant increase in relative kidney weight)	140 M 690 F (pelvic epithelial hyperplasia and pigmentation of cortical tubules)	
			Endocr	690			
			Bd Wt	30	140 (10% decrease in body weight)		

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
10	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d	Resp	140	690 (lesions of olfactory epithelium)		Springer et al. 1987 coal tar aerosol
			Cardio	690			
			Gastro	690			
			Hemato	140	690 (significant decrease in red blood cells, hemoglobin, reticulocytes and volume of packed red cells)		
			Hepatic	29 M 140 F	140 M 690 F (significant decrease in liver weight)		
			Renal	690			
			Endocr	690			
			Bd Wt	690			
11	Rabbit (New Zealand)	9 mo 5 d/wk 6 hr/d	Bd Wt			10 F (31% decrease in body weight)	MacEwen et al. 1977 coal tar
Immunological/Lymphoreticular							
12	Rat (Fischer- 344)	5 wk 5 h/d 6 hr/d		140	690 (decreased number of megakaryocytes in spleen)		Springer et al. 1986b coal tar aerosol
13	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30	140 (significant reduction in weight of thymus)	690 (atrophy of thymus, hypocellular bone marrow, and decreased number of megakaryocytes in marrow and spleen)	Springer et al. 1986b coal tar aerosol

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
14	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		140 M 29 F	690 M (significant decrease in 140 F weight of thymus)		Springer et al. 1987 coal tar aerosol
	Neurological						
15	Rat (Fischer- 344)	5 wk 5 d/wk 6 hr/d		140 M 690 F	690 M (significant increase in relative brain weight)		Springer et al. 1986b coal tar aerosol
16	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30	140 (significant increase in relative brain weight)		Springer et al. 1986b coal tar aerosol
17	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		690			Springer et al. 1987 coal tar aerosol
	Reproductive						
18	Rat (Fischer- 344)	5 wk 5 h/d 6 hr/d		690 M 140 F	690 F (decreased luteal tissue)		Springer et al. 1986b coal tar aerosol

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
19	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30 M 140 F	140 M (significant increase in relative weight of testis) 690 F (significant decrease in relative weight of ovary and amount of luteal tissue)		Springer et al. 1986b coal tar aerosol
20	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		690 M 140 F	690 F (significant decrease in ovary weight)		Springer et al. 1987 coal tar
Cancer							
21	Rat (Wistar)	10 mo 5 d/wk 17 hr/d				2.6 F (CEL: 39% incidence broncho-alveolar adenomas & adenocarcinomas)	Heinrich et al. 1994a, b coal tar pitch
22	Mouse ICR CF-1	90 d 24 hr/d				2 F (CEL: 14/75 skin tumor, controls = 3/225)	MacEwen et al. 1977 coal tar
23	Mouse CAF1- JAX	90 d 24 hr/d				10 F (CEL: 18/43 skin tumor, control = 0/225) (CEL: 27/50 lung tumor, control = 0/225)	MacEwen et al. 1977 coal tar

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL mg/m3	LOAEL Less serious mg/m3	LOAEL Serious mg/m3	Reference Chemical Form
CHRONIC EXPOSURE							
Death							
24	Rat (Wistar)	20 mo 5 d/wk 17 hr/d				2.6 F (increased mortality)	Heinrich et al. 1994a coal tar pitch
Systemic							
25	Monkey (Macaca mulatta)	18 mo 5 d/wk 6 hr/d	Bd Wt	10			MacEwen et al. 1977 coal tar
26	Rat (Sprague-Dawley)	18 mo 5 d/wk 6 hr/d	Bd Wt		10 (15% decrease in body weight)		MacEwen et al. 1977 coal tar
Cancer							
27	Rat (Wistar)	20 mo 5 d/wk 17 hr/d				1.1 F (CEL: 33% incidence broncho-alveolar adenomas & adenocarcinomas)	Heinrich et al. 1994a, b coal tar pitch

Table 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL			Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)		
28	Rat (Sprague-Dawley)	18 mo 5 d/wk 6 hr/d				10 M (CEL: 38/38 squamous cell carcinoma)		MacEwen et al. 1977 coal tar
						10 F (CEL: 31/38 squamous cell carcinoma and 3/38 mammary fibroadenoma)		

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

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CTPV = coal tar pitch volatiles; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Creosote - Inhalation

Acute (≤14 days)

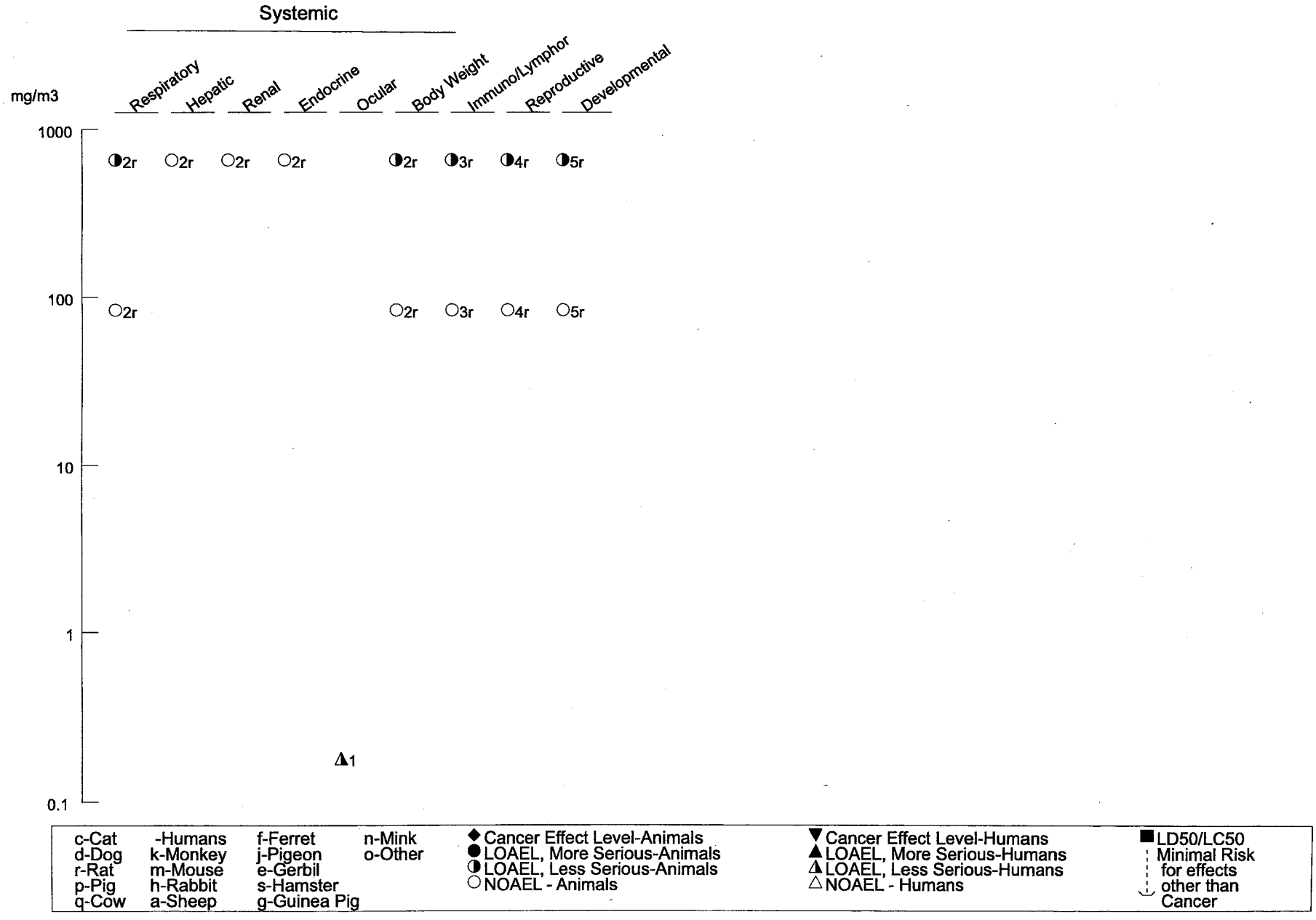


Figure 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Intermediate (15-364 days)

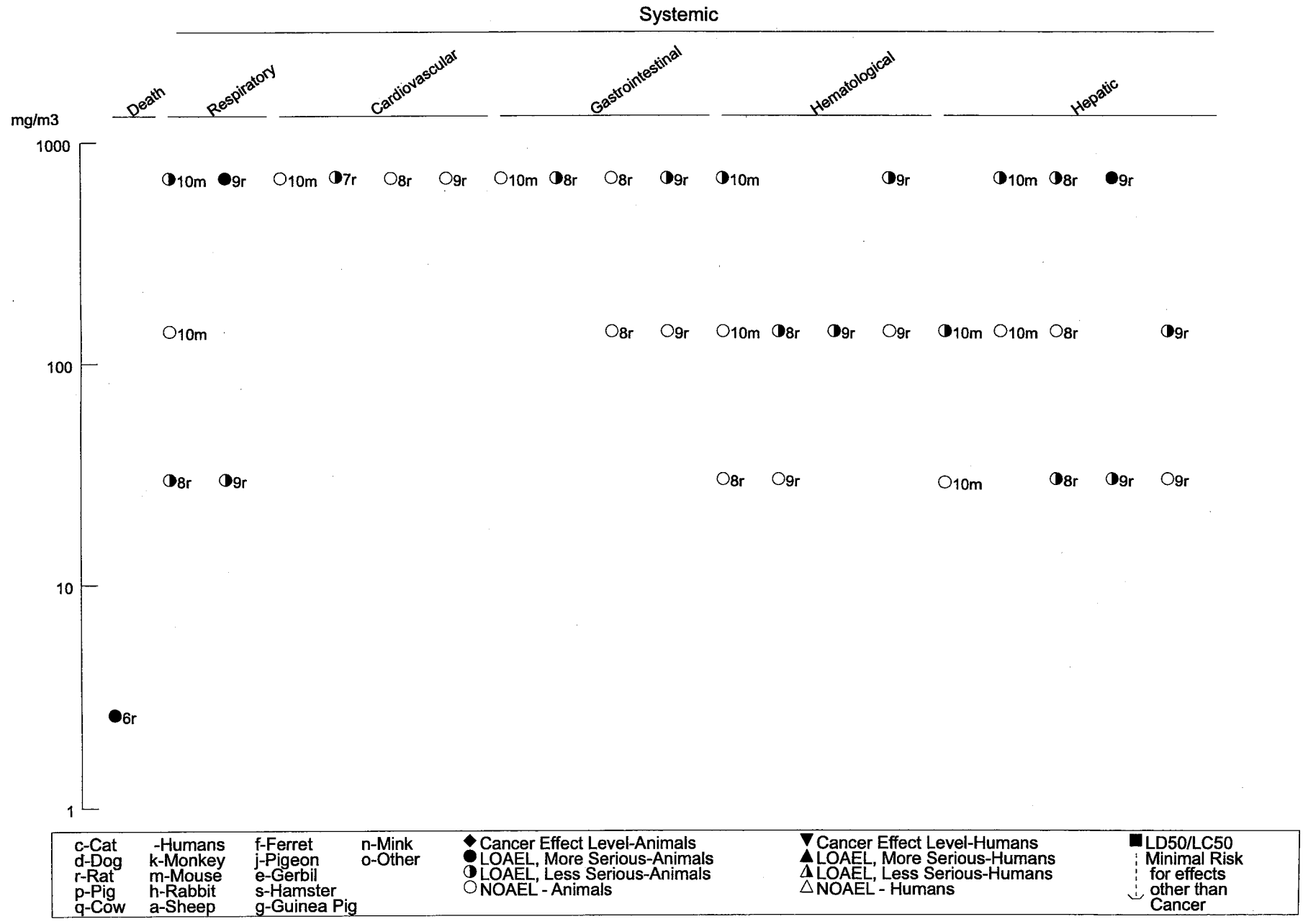


Figure 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Intermediate (15-364 days)

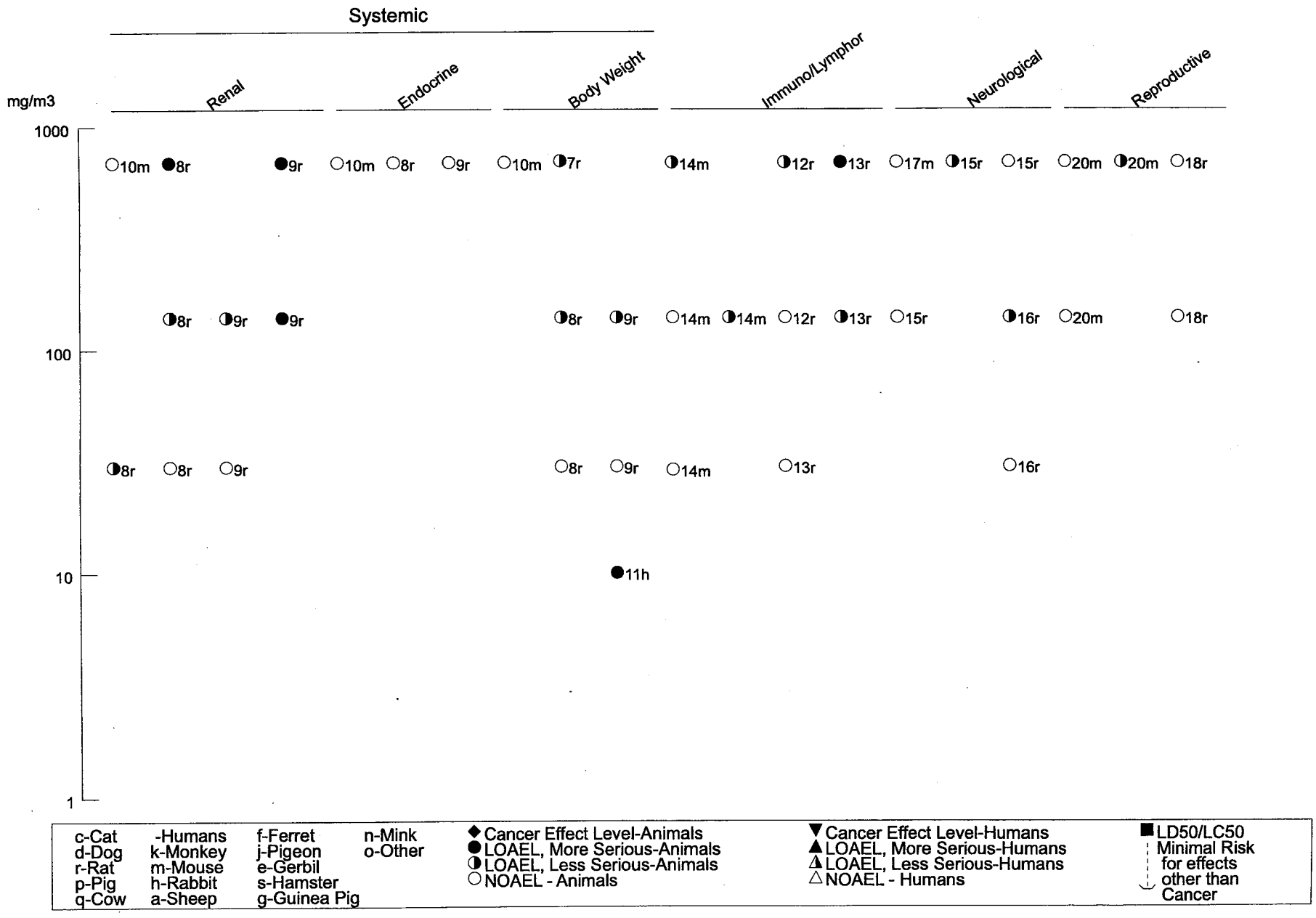
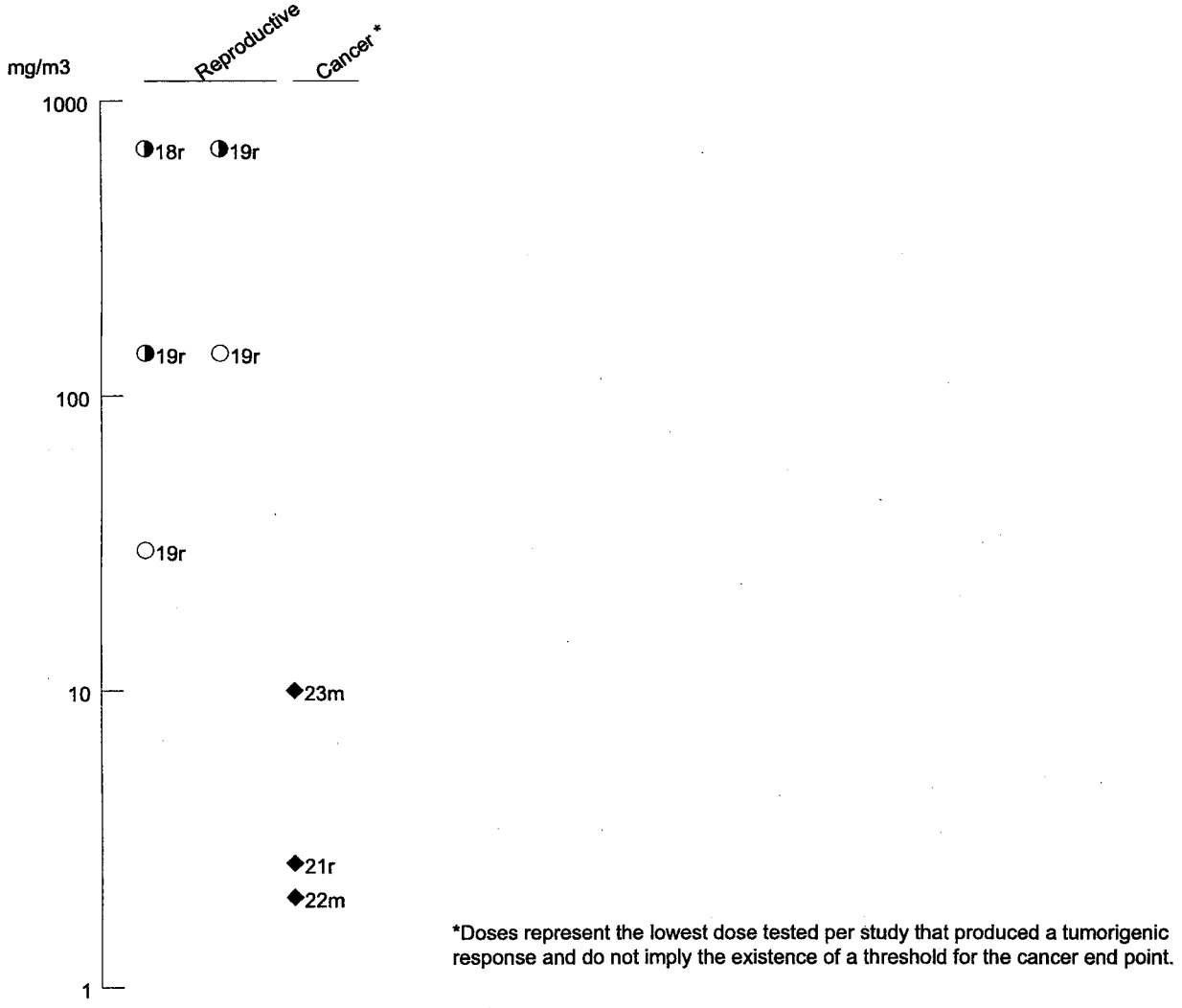


Figure 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Intermediate (15-364 days)

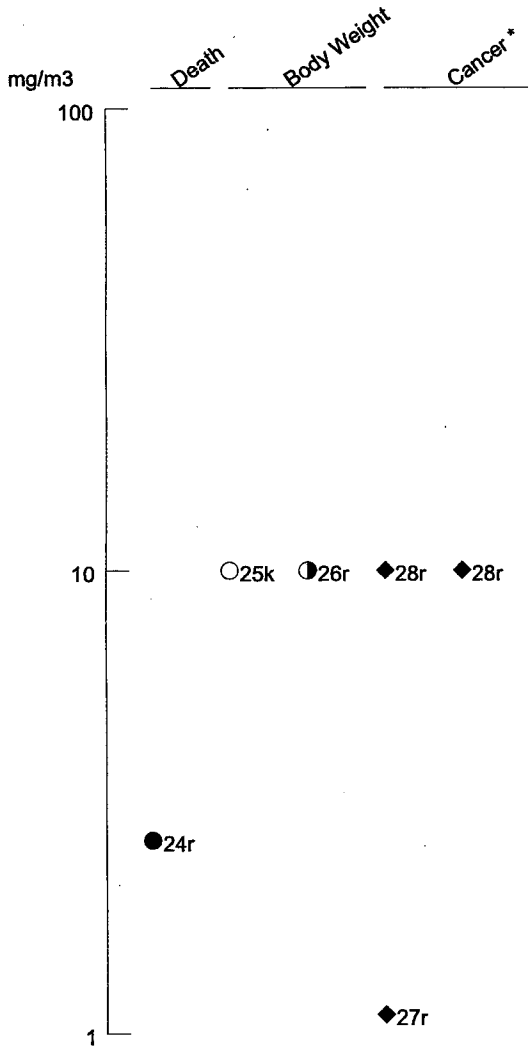


*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 2-1. Levels of Significant Exposure to Creosote - Inhalation (continued)

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat	-Humans	f-Ferret	n-Mink	◆Cancer Effect Level-Animals	▼Cancer Effect Level-Humans	■LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	●LOAEL, More Serious-Animals	▲LOAEL, More Serious-Humans	Minimal Risk for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑LOAEL, Less Serious-Animals	◭LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○NOAEL - Animals	△NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

workers, lack of statistical analyses, lack of adequate controls, use of only current employees, and testing confined to a single season (winter). In an industrial health survey of five workers in an electrode manufacturing plant, respiratory symptoms were observed, including pneumonoconiosis, respiratory obstruction, impaired gas exchange, and lung fibrosis with interstitial tissue alveoli filled with black pigment (Petsonk et al. 1988). These workers had been exposed to coke dust, pitch fumes, pitch dust, and other dusts for >15 years, which could be associated with the respiratory symptoms. Increased chronic obstructive lung disease was associated with 20-39 years of exposure to pot emissions in an aluminum smelter (Rönneberg 1995b). Similar increases in respiratory diseases have been noted in other studies of the aluminum industry (Gibbs 1985).

A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (ATSDR 1994). The plant had ceased creosoting activities in 1961, after operating for 51 years. A sand and gravel company had operated on part of the abandoned site during the 1970s and 1980s. Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the National Priorities List (NPL) in 1984. Several residential lots were observed to have soil concentrations of benzo[a]pyrene (B[a]P) in excess of 325 mg/kg, or oily-stained areas, and were subject to emergency resodding by the EPA. Contaminated soils were scheduled to be treated for clean-up. A total of 214 residents (123 males, 91 females) of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents (122 males, 93 females) from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. With regard to respiratory effects, there was no statistically significant increase in the reported incidence of bronchitis in residents from the Koppers area compared to the regional comparison group, when data were adjusted for health belief (i.e., the belief that health was affected by chemicals in or near their homes). Similarly, there was no significant increase in the incidence of bronchitis in the Koppers population compared to the 1990 National Health Interview Survey.

Pfitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for 1 day. The rats exhibited dyspnea and slight nasal irritation. The actual exposure level was not determined (Ptitzer et al. 1965). A significant increase in lung weight was reported for female Fischer

rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12-16, but not for females exposed to 84 mg/m^3 (Springer et al. 1982). Lesions of the olfactory epithelium were reported for Fischer rats and CD-l mice exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but not for animals exposed to 140 mg/m^3 (Springer et al. 1986b, 1987). Rats exposed to concentrations of coal tar ≥30 mg/m^3 for 5 or 13 weeks also showed histiocytosis of the lung tissue (Springer et al. 1986b). No lesions of the olfactory epithelium were reported for rats exposed to up to 690 mg/m^3 coal tar aerosol for 5 weeks (Springer et al. 1986b). Respiratory symptoms, consisting of extensive chronic tibrosing pneumonitis with peribronchial adenomatosis, were observed in female Bethesda rats and guinea pigs (sex not specified) exposed to coal tar or roofing asphalt vapors (exposure level not specified) for 4 days/week for a total period of 2 years (Hueper and Payne 1960).

Cardiovascular Effects. In an industrial health survey of employees in 4 wood preservative plants in which coal tar creosote and coal tar were the main treatments used, cardiovascular effects, including increased diastolic blood pressure, were noted in 21% (24 of 113) of the employees examined (TOMA 1978). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1978). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1978). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate cardiovascular effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1978). Additional limitations of the study are noted above (see “Respiratory Effects”). However, in another industrial study, an increase in mortality from atherosclerosis was associated with cumulative tar exposure and ≥40 years of exposure to pot emissions in the aluminum industry (Rdnneberg 1995b).

The susceptibility of the rat cardiovascular system to high-boiling coal liquid (heavy distillate, HD) administered by inhalation (700 mg/m^3, for 6 hours/day, 5 days/week for 6 consecutive weeks) was studied in male Fischer 344 rats (Sasser et al. 1989). Ten days after treatment was stopped, the cardiovascular assessments were made. The most striking observation was a 20% increase in arterial blood pressure of HD-exposed rats over that of sham-exposed rats. Heart rate was also elevated in the HD-treated animals. The causal relationship (i.e., direct or secondary) between HD and the elevation of blood pressure and heart rate is not clear since physiological disturbances of other systems, whose activity influence pressure and rate parameters (e.g., pulmonary and renal systems) might have produced the observed changes in cardiovascular activity. No change in heart weight or the histology of the heart or

aorta was found for Fischer rats or CD-l mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for up to 13 weeks (Springer et al. 1986b, 1987).

Gastrointestinal Effects. No change in histology of the gastrointestinal tract was found in female Fischer rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks or CD-l mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Male rats exposed to exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and male and female rats exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar for 13 weeks showed epithelial hyperplasia and chronic inflammation of the cecum (Springer et al. 1986b).

Hematological Effects. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, hematological effects, including increased number of white blood cells (basophils), were noted in 6% (15 of 257) of the employees examined (TOMA 1978). Similarly, 12% of the employees in eight of nine coal tar plants surveyed had increased white blood cells (eosinophils) (TOMA 1979). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1978). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1978). No determination of exposure was made at the nine coal tar plants (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate hematological effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke. Additionally, some effects were attributed to an infectious etiology at some plants, and not the result of exposure to toxic chemicals (TOMA 1979). Other limitations of the studies are noted above (see "Respiratory Effects").

In two studies by Springer et al. (1986b, 1987) Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice. Male rats exposed to 140 mg/m^3, but not to 30 mg/m^3, of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks had decreased red blood cell counts, hemoglobin concentration, white blood cells, lymphocytes, eosinophils, monocytes, and increased reticulocytes (Springer et al. 1986b). Female rats also had decreased red blood cell counts, hemoglobin concentration, white blood cells, lymphocytes, eosinophils, monocytes, and increased reticulocytes when exposed to 140 mg/m^3 coal tar for 5 weeks or 690 mg/m^3 for 13 weeks, but there was no significant

difference from controls for females exposed to 30 mg/m^3 coal tar for 5 weeks or 140 mg/m^3 coal tar for 13 weeks. Red blood cell counts, hemoglobin concentration, and the volume of packed red cells were also significantly decreased in CD-l mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but other hematologic parameters such as erythrocyte, leukocyte, and reticulocyte counts were unaffected by exposure (Springer et al. 1987). Kock et al. (1994) reported death of 7 of 20 black rhinoceroses which had been held in creosote-treated holding pens. The animals which died had widespread hemorrhages and anemia which may reflect the effects of hemolysis, but doses and routes of exposure were not established in this study.

Hepatic Effects. No change in liver weight was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12 to 16 (Springer et al. 1982). In two other studies by Springer et al. (1986b, 1987) Fischer rats appeared to be slightly more sensitive to the effects of inhaled coal tar aerosol than CD-l mice. Relative liver weights were significantly increased in male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) and female rats exposed to ≥30 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and in male rats exposed to ≥30 mg/m^3 and female rats exposed to ≥140 mg/m^3 (but not 30 mg/m^3) coal tar aerosol for 13 weeks (Springer et al. 1986b). Subtle changes in liver histology were also noted for males and females exposed to 690 mg/m^3 compared with controls. These included a slight increase in cytoplasmic basophilia, slightly more variability in hepatocellular size, the presence of hepatomegalocytes, increased variability in nuclear size and minimal loss of cording and lobular pattern. Minimal scattered focal necrosis was also observed in liver tissue of some exposed animals, but not in controls. Similar changes in weight and histology were also noted in mice exposed to 690 mg/m^3 (females) or ≥140 mg/m^3 (males) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1987). No changes in weight or histology were observed for female mice exposed to 140 mg/m^3 or male mice exposed to 29 mg/m^3 for 13 weeks (Springer et al. 1987). Kock et al. (1994) reported death of 7 of 20 black rhinoceroses which had been held in creoso-tetreated holding pens. The animals which died had uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. Serum levels of aspartate transaminase (AST) and bilirubin were also elevated. However, doses and routes of exposure were not established in this study.

Renal Effects. In an industrial health survey of employees in nine coal tar plants in which coal tar creosote and coal tar were the main treatments used, renal effects, including protein and cells in the urine were noted in l-8% (3-34 of 452) of the employees examined (TOMA 1979). These effects were attributed to urinary tract infections resulting from inadequate personal hygiene, and not to industrial exposure to toxic chemicals. No determination of exposure was made at the nine coal tar plants (TOMA

1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate renal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke. Additional limitations of the study included seasonal and geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy workers, lack of statistical analyses, lack of adequate controls, and use of only current employees.

No change in kidney weight was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12-16 (Springer et al. 1982). In another two studies by Springer et al. (1986b, 1987), Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD- 1 mice. Relative kidney weights were increased in female rats exposed to ≥140 mg/m^3 (but not 30 mg/m^3) and in male rats exposed to 230 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and in male rats and female rats exposed to ≥ 140 mg/m^3 (but not 30 mg/m^3) for 13 weeks (Springer et al. 1986b). Male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) for 5 weeks or 140 mg/m^3 (but not 30 mg/m^3) for 13 weeks and female rats exposed to 690 mg/m^3 (but not 140 mg/m^3) for 13 weeks also showed pelvic epithelial hyperplasia and pigmentation of the cortical tubules (Springer et al. 1986b). Relative kidney weights were also increased in mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but the difference between exposed and control animals was not significant and no histological changes were reported (Springer et al. 1987).

Endocrine Effects. No adverse effect on the adrenal glands was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12 to 16 or on the adrenal, pancreas, parathyroid, pituitary, or thyroid glands in Fischer rats exposed to up to 690 mg/m^3 for 5 or 13 weeks or in CD-l mice exposed to up to 690 mg/m^3 for 13 weeks (Springer et al. 1982, 1986b, 1987).

Dermal Effects. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, dermal effects, including skin irritation, eczema, folliculitis, and benign growths on the skin were noted in 33% (82 of 251) of the employees examined (TOMA 1978). Workers in nine coal tar plants had a 20% (86 of 419) incidence of these same dermal effects (TOMA 1979). The incidence of benign growths, eczema, and folliculitis was greater than that observed in the general U.S. population. Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble

components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1978). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1978). No determination of exposure was made at the nine coal tar plants (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation were likely (e.g., through direct contact with coal tar creosote and coal tar vapors in the air, and oral). Also, the ability to relate dermal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals (TOMA 1978, 1979). Additional limitations of the studies are noted above (see "Respiratory Effects"). In other industrial studies, dermal effects were also noted (Bolt and Golka 1993; NIOSH 1982). Four workers in an aluminum reduction plant, who had been exposed to coal tar pitch volatiles for a period of 3.5-23 years showed tar-related skin changes, including hyperkeratosis and telangiectasis (Bolt and Golka 1993). Skin lesions that were possibly pitch-related were observed in four workers involved in the transfer and transport of coal tar pitch, who had been exposed to coal tar pitch and asphalt for 2-8 years (NIOSH 1982). Warts and other lesions on the hands and face were described. Workers transferring coal tar pitch from a river barge to an ocean barge, or from a railroad car to an ocean barge were observed for 2 days to evaluate exposure conditions and health complaints after exposure to coal tar pitch volatiles (NIOSH 1982). Skin irritation, described as redness like a sunburn, lasting 2-3 days, with drying and peeling, and photosensitivity, was described by the workers. Personal air samples from the workers indicated respirable coal tar pitch vapors in concentrations up to 0.18 mg/m^3.

Dermal effects were noted in a site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (ATSDR 1994). Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the NPL in 1984. A total of 214 residents of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. Residents living on or near the Koppers area reported a higher prevalence of skin rashes (27.9%) during the first year of the surveillance than the comparison neighborhood (4.9%), with a RR of 5.72. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results, and similar results were obtained, with 34 Koppers residents reporting skin rashes, compared to an expected incidence of 4. Rashes were associated with

digging in the yard, having contact with the soil, or wading in or having contact with a creek in the area. Most rashes were associated with itching or burning. The recommendation of the Texas Department of Health was that residents in the Koppers area should wear protective clothing when having contact with the soil, and should wash their skin thoroughly when contact with the soil occurs. Other dermal effects of coal tar creosote, coal tar, or coal tar pitch exposure are mentioned in Sections 2.2.3 and 2.3.1.3.

Ocular Effects. Workers transferring coal tar pitch from a river barge to an ocean barge, or from a railroad car to an ocean barge, were observed for two days to evaluate exposure conditions and health complaints after exposure to coal tar pitch volatiles (NIOSH 1982). Eye irritation, including burning, redness, swelling, and watering of the eyes lasting about two days was described, occasionally associated with photophobia. Personal air samples from the workers indicated respirable coal tar pitch vapors in concentrations up to 0.18 mg/m^3. However, all of the workers were wearing protective equipment, including respirators and therefore the measurements taken do not represent actual exposures. Conjunctivitis was observed in roofers exposed to coal tar pitch volatiles at levels ≤0.18 mg/m^3, compared to no incidence of conjunctivitis in workers exposed to levels <0.18 mg/m^3 (Emmett 1986).

Pfitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for one day. The rats exhibited slight eye irritation. The actual exposure level was not determined.

Body Weight Effects. Body weight changes were monitored in monkeys, rats, and rabbits after inhalation exposure to 10 mg/m^3 coal tar aerosol (MacEwen et al. 1977). No other systemic effects were reported in this article. No change in body weight was observed in male or female Mucaca mulatta monkeys after exposure for 18 months, 5 days/week, 6 hours/day, but when male and female Sprague Dawley rats were exposed to the same concentration of coal tar aerosol for the same period of time, a 14-15% decrease in body weight was observed. Female New Zealand white rabbits exhibited a 31% decrease in body weight after 9 months of exposure to 10 mg/m^3 for 6 hours/day, 5 days/week.

Male Fischer 344 rats were exposed high-boiling coal liquid (heavy distillate, HD) administered by inhalation (700 mg/m^3) for 6 hours/day, 5 days/week for 6 consecutive weeks (Sasser et al. 1989). During treatment, the growth of the HD-exposed animals was suppressed significantly relative to the control group. Subsequently, growth was resumed after the treatment was stopped, although HD-treated rats weighed 17.5% less than control rats at necropsy. A significant decrease in body weight was reported for female Fischer rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12-16, but not for female rats exposed to 84 mg/m^3 (Springer et al. 1982). In two other studies by Springer et al.

(1986b, 1987), Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD-l mice. Body weights were significantly decreased in rats exposed to ≥ 140 mg/m^3 (but not 30 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks, but not in mice exposed to up to 690 mg/m^3 coal tar aerosol for 13 weeks (Springer et al. 1986b, 1987).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to wood creosote, coal tar creosote, coal tar pitch, or coal tar pitch volatiles. A significant increase in spleen weight and a significant decrease in thymus weight was reported for female rats exposed to 660 mg/m^3 (but not 84 mg/m^3) of a coal tar aerosol for 6 hours/day on gestational days 12-16 (Springer et al. 1982). In two other studies by Springer et al. (1986b, 1987), Fischer rats appeared more sensitive to the effects of inhaled coal tar aerosol than CD-l mice. Relative thymus weights were significantly decreased in female rats exposed to 690 mg/m^3 coal tar aerosol 6 hours/day for 5 weeks and both males and females exposed to ≥140 mg/m^3 for 13 weeks (Springer et al. 1986b). Males exposed to up to 690 mg/m^3 and females exposed to 30 mg/m^3 for 5 weeks, and both sexes exposed to 30 mg/m^3 for 13 weeks, showed no change in thymus weight. The thymus was atrophied in male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar aerosol for 6 hours/day for 5 weeks and in both male and female rats exposed for 13 weeks (Springer et al. 1986b). Examination of bone marrow smears showed that rats exposed to 690 mg/m^3 coal tar aerosol for 13 weeks had hypocellular marrows with a marked decrease in the number of megakaryocytes (Springer et al. 1986b). The number of megakaryocytes in the spleens of animals exposed to 690 mg/m^3 coal tar aerosol for 5 or 13 weeks was also decreased relative to controls. Both absolute and relative thymus weights were also significantly decreased in male mice exposed to 690 mg/m^3 (but not 140 mg/m^3) or in female mice exposed to ≥140 mg/m^3 (but not 29 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but no histological changes were observed (Springer et al. 1987).

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following inhalation exposure to wood creosote, coal tar creosote, coal tar pitch, or coal tar pitch volatiles. Inhalation of up to 690 mg/m^3 coal tar aerosol by CD-1 mice for 13 weeks had no effect on brain weight or histology (Springer et al. 1987). Inhalation of 690 mg/m^3 coal tar aerosol by male Fischer rats for 5 weeks and inhalation of ≥140 mg/m^3 by male and female rats for 13 weeks produced a significant increase in relative

brain weights, but no change in absolute brain weight or histological abnormalities (Springer et al. 1986b). There was no change in relative brain weight for male rats exposed to up to 140 mg/m^3 or for female rats exposed to up to 690 mg/m^3 for 5 weeks or for male and female rats exposed to 30 mg/m^3 for 13 weeks. The rats had significant reduction in body weight compared to controls, so it seems likely that the change in relative brain weight reflects the body weight loss rather than an adverse neurological effect.

2.2.1.5 Reproductive Effects

No adverse effects on sperm characteristics, including sperm count and morphology, were noted in workers exposed to coal tar pitch volatiles in an aluminum reduction plant (Ward 1988). No adverse reproductive effects were reported for residents at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant and was studied as a site surveillance program by the Texas Department of Health (ATSDR 1994). There was no difference in the overall reproductive outcome of female residents of the Koppers area compared to the comparison neighborhood or the 1990 National Health Interview Survey. In particular, there was no effect on the number of pregnancies, live births, premature births, spontaneous abortions, or still births. Koppers women who reported having problems becoming pregnant during the first year of surveillance had an average of 1.3 pregnancies compared to an average of 3.4 pregnancies for women in the comparison neighborhood who also reported difficulty in becoming pregnant, but no difference in pregnancy outcome was noted during the second year of surveillance.

No studies were located regarding reproductive effects in animals following inhalation exposure to wood creosote, coal tar creosote, coal tar pitch, or coal tar pitch volatiles. A significant increase in the incidence of mid- and late-gestational resorptions was reported for female rats exposed to 660 mg/m^3 (but not 84 mg/m^3) of a coal tar aerosol for 6 hours/day on gestational days 12-16 (Springer et al. 1982). Animals exposed to 660 mg/m^3 coal tar showed some signs of maternal toxicity. The thymus weight was significantly reduced and the weights of the lungs and spleen were significantly increased, but maternal body weights (without the products of conception) were not significantly reduced compared to controls and the weights of the liver, kidney, and adrenal glands were similar to controls. No change in the relative weights of ovary or testis were recorded for Fischer rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks (Springer et al. 1986b). Relative ovary weights were significantly decreased in Fischer rats and CD-l mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Testis weight in

rats exposed to ≥140 mg/m^3 (but not 30 mg/m^3) coal tar for 13 weeks was significantly increased relative to controls, while testis weight in male mice exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar was decreased relative to controls, but the difference was not significant. Examination of ovarian sections showed a significant decrease in the amount of luteal tissue in animals exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar for 5 or 13 weeks.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to wood creosote, coal tar pitch, or coal tar pitch volatiles. A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant on soil contaminated with creosote revealed no adverse developmental effects on the residents (ATSDR 1994). Specifically, there was no difference in the number of low birth weight births or birth defects.

In a study by Springer et al. (1982) mated female rats were exposed to 0, 17, 84, or 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12-16. There was a significant increase in the incidence of mid- and late-gestational resorptions in the 660 mg/m^3 group compared with controls. Crown-rump length, fetal weight, fetal lung weight and placental weights were significantly reduced, and there was a significantly increased incidence of reduced ossification in the 660 mg/m^3 group and a significant trend for reduced ossification with increased coal tar concentration. Cleft palates were also observed in this group, but the increased incidence was not significant. No significant changes in the number of resorptions, size of fetuses, or incidence of abnormalities were observed for animals exposed to less than 660 mg/m^3. Animals exposed to 660 mg/m^3 coal tar showed some signs of maternal toxicity. The thymus weight was significantly reduced and the weights of the lungs and spleen were significantly increased, but maternal body weights (without the products of conception) were not significantly reduced compared to controls and the weights of the liver, kidney, and adrenal glands were similar to controls.

2.2.1.7 Genotoxic Effects

In vivo genotoxicity has been evaluated in humans after inhalation exposure to coal tar and coal tar pitch volatiles. Genotoxic effects on peripheral lymphocytes were compared for 49 workers exposed to coal tar and 50 age-matched nonexposed controls (Yadav and Seth 1998). Significantly increased mitotic indexes were observed in exposed workers compared with controls. The increase was greatest for workers exposed for 6-10 years. Chromosome aberrations and sister chromatid exchanges were also significantly increased in exposed workers compared with controls.

Blood samples from 30 steelworkers exposed to coal tar pitch volatiles were analyzed for chromosomal abnormalities, sister chromatid exchange, and first mitoses (Bender et al. 1988). Industrial exposure levels were not specified. There was a significant increase in the frequency of chromatid aberrations, chromosomal aberrations, and sister chromatid exchange compared to the control samples. Blood samples from 24 workers (20 males, 4 females) exposed to coal tar pitch for 7-32 years were compared with samples from 10 individuals who had never been exposed to coal tar pitch (Wu et al. 1998). Serum P21 (the protein product of the ras oncogene) levels and sister chromatid exchange were significantly increased in exposed workers compared with controls. Analysis of exposed worker data showed that there was no significant difference in P21 level of sister chromatid exchange frequency between smokers and nonsmokers. Later analysis showed that P21 levels in the exposed group increased after 2 years further exposure, but the change was not statistically significant. Urine samples from 30 coke oven workers were shown to have significantly greater mutagenic and cytotoxic activity in the Ames Salmonella test compared with urine from 26 workers not exposed to coal tar volatiles or PAHs (Mielzynska and Snit 1992). Workers were divided into smokers and nonsmokers, and smoking was not found to affect the results of the mutagenicity assay.

No studies were located regarding *in vivo* genotoxic effects in animals following inhalation exposure to creosotes, coal tar, or coal tar pitch, or coal tar pitch volatiles. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A number of studies have provided evidence of an association between occupational exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles and increased incidence of cancer-related mortalities and cancer in humans (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Finkelstein 1989; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; Spinelli et al. 1991; TOMA 1982; Tremblay et al. 1995), although other industrial chemicals were present. Other studies have not shown a significant association between occupational exposure to creosote and increased incidence of cancer (CEOH 1997; Kromhout et al. 1992; Kunze et al. 1992; Schildt et al. 1999; Swaen and Slangen 1997). In some cases, there was a non significant increase in risk associated with creosote exposure (CEOH 1997; Kunze et al. 1992; Swaen and Slangen 1997), but interpretation of the data from these studies is limited by a variety of factors including small study populations, concurrent cigarette smoking, and poor exposure data.

Industrial populations that have been studied include coke oven workers, aluminum smelters, steelworkers, and people exposed to creosote through other activities (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; CEOH 1997; Costantino et al. 1995; Gibbs and Horowitz 1979; Kromhout et al. 1992; Kunze et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; Spinelli et al. 1991; Swaen and Slangen 1997; TOMA 1982; Tremblay et al. 1995). Following occupational inhalation exposure to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, cancer was observed involving a number of tissues which included the respiratory tract, lips and skin, lung, pancreas, kidney, scrotum, prostate, rectum, bladder, and central nervous system; leukemia and Iymphoma were also diagnosed (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Finkelstein 1989; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Liu et al. 1997; Lloyd 1971; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; TOMA 1982; Tremblay et al. 1995). Exposure levels in these studies were not consistently quantified. In addition, there were confounding factors. In all cases of occupational exposure, the workers were not exposed to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles as single agents, but in combination with other chemicals. For instance, some employees exposed themselves to

additional carcinogens via cigarette smoking (TOMA 1982). In other studies, exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles was generally combined with other substances such as chrysotile asbestos (Finkelstein 1989). Some studies had significant limitations (e.g., TOMA 1982, see Section 2.2.1.1).

Spinelli et al. (1991) evaluated the mortality and cancer incidence over a 30-year period among a cohort of workers exposed to coal tar pitch volatiles emitted during production of aluminum. Aluminum is produced by one of two electrolytic processes wherein petroleum and coal tar pitch are baked in pots. These processes result in a continuous generation of coal tar pitch volatiles, which include PAHs. For analysis of these data, the assignment of exposure level was based on data of coal tar pitch volatiles from recent plant monitoring, as well as knowledge of historical operational and engineering changes. Based on the threshold limit value (TLV) for coal tar pitch volatiles of 0.2 mg/m^3 benzene soluble material (BSM) averaged over 8 hours, 4 coding systems were adopted:

(1) no exposure to coal tar pitch volatiles (0 mg/m^3 BSM),

(2) low exposure to coal tar pitch volatiles (<.2 mg/m^3 BSM),

(3) medium exposure to coal tar pitch volatiles (0.2-1.0 mg/m^3 BSM), and

(4) high exposure to coal tar pitch volatiles (>1.0 mg/m^3 BSM).

According to Spinelli et al. (1991), jobs with the highest exposure to coal tar pitch volatiles primarily occurred before 1970 and included jobs located within the potrooms. The primary findings of this study were a significantly elevated incidence of bladder cancer in the cohort and the significant trend toward higher risk with greater lifetime exposure to coal tar pitch volatiles. Also observed was a nonstatistically significant association between lung cancer and coal tar pitch volatiles. Adjusting for smoking did not change the observed association. The authors state that the apparent discrepancy between the results of this study (Spinelli et al. 1991) and those performed previously which found a strong association between lung cancer and exposure to coal tar pitch volatiles (Anderson et al. 1982; Gibbs 1985; Gibbs and Horowitz 1979) might relate to the latency period and the levels of coal tar pitch volatiles, both of which were lower relative to the previous studies.

Costantino et al. (1995) carried out an epidemiological study of 5,321 coke oven workers and 10,497 nonoven workers matched for place of work and socioeconomic status. The average daily exposure to coal tar pitch volatiles was determined in previously published studies as 3.15 mg/m^3 for topside full time jobs, 1.99 mg/m^3 for topside part time jobs and 0.88 mg/m^3 for side jobs. Mortality was

assessed by race for 33 categories of cause of death. All RR were adjusted for age, race, coke plant, and period of follow up as appropriate. Statistically significant excess mortality was present among coke workers for several categories of death. The RR for all causes of death was 1.11 (P<0.001). The increase in overall mortality was primarily due to increased deaths from the following cancers; all cancers RR=1.38 (P<0.001), respiratory cancer RR=2.07 (P<0.00l) (elevated risk of cancer of the lungs, bronchus, and trachea), and genito-urinary cancer RR=1.49 (P<0.00l) (elevated risk of prostate cancer RR=1.60 (P<0.00l)). These findings were consistent across racial categories, but excess risk was higher among nonwhite than white workers. There were highly significant trends (P<0.00l) for increased cancer risk with increasing duration of employment and increasing exposure. The study did not control for smoking. However, the similar socioeconomic status of the controls and exposed workers suggests that it is unlikely that there was a substantial difference in smoking habits between the two groups.

Elevated risk of death from cancer and from lung cancer was reported in a retrospective cohort study of 6,635 male workers employed for more than 15 years during the period 1970-1985 in seven factories in China (Liu et al. 1997). The main chemical exposure was to coal tar pitch volatiles. Significantly elevated SMRs were observed in highly exposed workers for all causes of death (SMR 1.69, P<0.0l), all cancers (SMR 2.53, P<0.0l), digestive cancer (SMR 1.97, P<0.0l), esophageal cancer (SMR 3.97, P<0.05), liver cancer (SMR 2.25, P<0.0l), and lung cancer (SMR 4.3, P<0.01). The SMRs for highly exposed nonsmokers were also elevated for all cancers (SMR 2.1, P<0.01) and lung cancer (SMR 3.0, P<0.0l), and there was a significant correlation between deaths from lung cancer and exposure to coal tar pitch volatiles.

In a study of coal tar pitch exposure of the respiratory system, Wistar rats received 10 weekly intratracheal instillations of 0.648, 13.56, and 20.0 mg of coal tar pitch (equivalent to 5.18, 109.2, and 160.0 mg/kg) or 20 mg charcoal powder (control group) and were sacrificed and examined at 1, 3, 6, 12, and 18 months after treatment (Chang et al. 1992). The treatment produced inflammation, hyperplastic, and metaplastic changes. All rats with lung cancer were found in the two highest treatment groups. The pathogenesis of coal tar pitch-induced lung carcinomas seems to start from hyperplasia of bronchiole alveolar epithelium, progressing through squamous metaplasia and/or different stages of dysplasia to carcinomas (Chang et al. 1992). According to Chang et al. (1992), the effects produced with coal tar pitch were consistent with the effects reported after similar treatment with PAHs and tobacco smoke condensate. Although the findings presented by Chang et al. (1992) suggest a correlation between coal tar pitch and lung cancer, the relevance of this relationship to. potential exposures by inhalation is equivocal. Specifically, the treatment levels used in this study were excessively high. If the level of coal

tar pitch administered was normalized to the average wet weight of the rat lung (0.5% body weight), then exposure of the pulmonary tissues at the two highest doses (i.e., 55.74 and 81.63 mg/kg/day), which were carcinogenic, was equivalent to 28.5 and 41.7 mg coal tar pitch/g of lung tissue. The lowest concentration administered (5.18 mg/kg), which was noncarcinogenic, yielded a pulmonary exposure of 1.35 mg coal tar pitch/g of lung tissue. Also at these concentrations, none of the treated animals exhibited any overt signs of toxicity. Comparing these data to the LD_{50} values determined for rats exposed orally (i.e., single oral administration of 2.9 or 6.8 mg/g of body weight [estimated for an absolute body weight of 250 g]) or 725 or 1,700 mg/kg of body weight (Ptitzer et al. 1965; RTECS 1994), those doses used for intratracheal instillation were many fold higher. Also, based on the LD_{50} values (Pfitzer et al. 1965; RTECS 1994) and the lung wet weight (% body weight), and assuming that the coal tar pitch distributes evenly to all tissues after oral gavage, the lung tissue might contain 3.62-8.5 mg/g following exposure to the median lethal dose. Thus, it appears that the route of administration may significantly influence the toxic outcome of exposure.

In a study by Heinrich et al. (1994a, 1994b), groups of female Wistar rats were exposed to 0, 1.1, or 2.6 mg/m^3 coal tar pitch aerosol for 10 months, 5 days/week, 17 hours/day. This exposure was followed by 20 months of clean air exposure. The lung tumor rates of animals exposed to 1.1 and 2.6 mg/m^3 coal tar pitch aerosol for 10 months were 4.2 and 38.9%, respectively. Most of the tumors were benign and malignant keratinizing squamous cell tumors. Some broncho-alveolar adenomas and adenocarcinomas were also found. No exposure-related tumors were found in other organs. No lung tumors were found in the control animals. Similar results (i.e., increased incidence of benign lung tumors) were also observed in Wistar rats exposed to 1.1 and 2.6 mg/m^3 (increased incidence of tumors 33.3 and 97.2%, respectively) coal tar pitch aerosol for 20 months, 5 days/week, 17 hours/day, followed by clean air exposure for 10 months (Heinrich et al. 1994a, 1994b).

In a study by MacEwen et al. (1977), groups of 40 male and 40 female Sprague Dawley rats were exposed to 10 mg/m^3 coal tar aerosol 6 hours/day, 5 days/week for 18 months. Control animals were held in a vivarium. After exposures, the animals were returned to the vivarium and held for an additional 6 months of observation prior to necropsy. The tumors found in rats exposed to coal tar aerosol showed 31 of 38 females and all males (38 of 38) with squamous cell carcinoma (lung) and 3 of 38 females with mammary fibroadenoma. Overall tumor incidences for controls were 0% for males and 13% for females. Overall tumor incidences for exposed animals were 100% for males and 82% for females.

MacEwen et al. (1977) indicated that tumor-susceptible ICR CF-1 female mice and tumor-resistant CAFl-JAX female mice exposed to coal tar aerosol-BTX (benzene, toluene, xylene) mixture continuously for 90 days at concentrations of 0, 0.2, 2, and 10 mg/m^3 developed skin tumors at 2 and 10 mg/m^3, respectively. In the ICR CF-1 strain mice, tumors continued to develop for as long as 86 weeks postexposure. Skin tumor incidences in ICR CF-1 mice exposed to 0, 0.2, 2, and 10 mg/m^3 coal tar aerosol-BTX mixture for 90 days were 3 of 225 (1%), 1 of 61 (2%), 14 of 75 (19%), and 44 of 55 (80%), respectively. Skin tumor incidences in CAFl-JAX mice exposed to 0, 0.2, 2, and 10 mg/m^3 coal tar aerosol-BTX mixture for 90 days were 0 of 225 (0%), 0 of 75 (0%), 3 of 65 (5%), and 18 of 43 (42%), respectively. Tumors were confirmed by histological examination. Tumor-susceptible ICR CF-1 female mice and tumor-resistant CAF1-JAX female mice were exposed to 0 or 10 mg/m^3 coal tar aerosol-BTX mixture intermittently for 18 months (MacEwen et al. 1977). For animals exposed intermittently, skin tumor incidences were 5 of 75 in ICR CF-1 mice and 3 of 75 in controls, and 2 of 50 in CAFl-JAX mice as compared to 1 of 50 in controls. Calculation of total exposure indicated the amount of coal tar reaching the skin of the animals was the same as in the 90-day continuous exposure study. However, the intermittent exposure allowed daily normal cleaning of the fur. The incidence of tumors was less in the animals subjected to intermittent exposure. Tumors found in control and exposed mice of both strains included alveolargenic carcinoma, alveolargenic adenoma, bronchogenic carcinoma, squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, hemangiosarcoma, hemopoietic tumors, and subcutaneous sarcoma.

Levels of exposure associated with CELs of creosote are indicated in Table 2-l and plotted in Figure 2-l.

2.2.2 Oral Exposure

This section describes the health effects observed in humans and laboratory animals associated with oral exposure to coal tar and beechwood creosote at varying times and exposure levels. All reliable exposure levels have been reported. Although beechwood creosote, creosote bush resin, and coal tar creosote have some components in common (e.g., phenols), and some of the adverse effects associated with exposure to beechwood creosote may be due to the phenol component (e.g., acute and/or subacute toxicity), it is not known whether coal tar creosote will induce these same effects. Furthermore, coal tar creosote contains a complex mixture of animal and human carcinogenic/co-carcinogenic PAHs that probably accounts for the cancer risk associated with chronic exposure, and the other forms of creosote (i.e., wood creosote) do not.

2.2.2.1 Death

A 70-year-old man died following ingestion of an unspecified amount of "industrial" creosote (presumably coal tar creosote) (Bowman et al. 1984). Death was attributed to multi-organ failure and occurred 30 hours after admission to the hospital. It is not known if this man had a history of prior coal tar creosote ingestion. Death has been reported to occur in adults and children 14-36 hours after the ingestion of about 7 g and l-2 g coal tar creosote, respectively (Lewin 1929). Thus, ingestion of creosote can be fatal to humans, but the dose level required to produce death cannot be accurately estimated from these reports.

The acute toxicity of beechwood creosote in both rats and mice was studied following single gavage administration of a 10% aqueous solution (Miyazato et al. 1981). The oral LD_{50} of beechwood creosote in Wistar rats was 885 mg/kg (males) and 870 mg/kg (females). The highest dose at which no death occurred was 600 mg/kg. There was no significant difference between male and female rats with respect to mortality, and most animals died within 24 hours. However, no treatment-related deaths were observed when rats were given doses of beechwood creosote in the feed of up to 812 mg/kg/day (males) or 768 mg/kg/day (females) for 3 months (Miyazato et al. 1981). Male and female Wistar rats fed diets that contained up to 313 or 394 mg/kg/day beechwood creosote for 96 weeks exhibited deaths in all groups (Miyazato et al. 1984b). There was no treatment-related increase in mortality in the females; the major cause of death in the females including controls was bronchopneumonia and leukemia. The highdose males had a slightly higher incidence of death than controls and low-dose males, and this was due to chronic progressive nephropathy.

Mice appeared to be more susceptible to the lethal effects of beechwood creosote. The oral LD_{50} values in gavaged ddY mice were 525 mg/kg (male) and 433 mg/kg (female) (Miyazato et al. 1981). The highest dose at which no death occurred was 376 mg/kg (male) and 433 mg/kg (female). The mortality in female mice was significantly higher than in male mice. Most animals died within 5 hours. However, no treatment-related deaths were observed when mice were given doses of beechwood creosote in the feed of up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) for 3 months (Miyazato et al. 198 1). These results indicate that the acute oral toxicity of beechwood creosote is relatively low, and is influenced by the method of administration. Some species and sex differences exist.

The oral LD_{50} for coal tar creosote is reported to be 725 mg/kg in rats and 433 mg/kg in mice (RTECS 1998). However, another study reported an acute oral LD_{50} of 1,700 mg/kg in male Wistar rats (Ptitzer et

al. 1965). No deaths were reported in $B6C3F_1$ mice after oral treatment with doses of mgP residue (coal tar) up to 462 mg/kg/day (males) or 344 mg/kg/day (females) for 94 or 185 days (Weyand et al, 1994). Cases of lethal poisoning resulting from ingestion of large amounts of coal tar creosote have been reported in larger farm animals (Cribb 1968; Davis and Libke 1968; Giffee 1945; Graham et al. 1940; Harrison 1959; Luke 1954). Some of the reports are anecdotal and do not include quantification of the amount of creosote ingested (Cribb 1968; Giffee 1945; Graham et al. 1940; Luke 1954). Experimental feeding of powdered clay pigeon targets containing an unspecified amount of coal tar pitch (15-30 g of powdered material daily for up to 15 days) caused death in 8 of 9 pigs (Davis and Libke 1968). The acute fatal doses are 4 g/kg for sheep and over 4 g/kg for calves (Harrison 1959). Based on these data, coal tar creosote can be classified as mildly to moderately toxic.

Mated female Sprague Dawley CD rats (25-36 per group) were gavaged on gestational days 12-16 with 0, 90, 140, 180, 370, or 740 mg/kg/day coal tar (Hackett et al. 1984). Ten of the females receiving 740 mg/kg/day died within 4 days of the initial dose, but no deaths occurred at lower doses. In a feeding study 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). Coal tar 1 was a mixture of samples from seven waste sites and coal tar 2 was a mixture from two of the sites included in coal tar 1 plus a third site with a very high benzo[a]pyrene content. This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day of coal tar 2. Dietary levels 20.3% (333 mg/kg/day coal tar 1 or 346 mg/kg/day coal tar 2) coal tar produced a significant increase in early mortality compared with controls, while lower levels did not.

The LD_{50} and LOAEL values for death from each reliable study for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

There is relatively little information available regarding the systemic effects of ingested wood creosote, coal tar creosote, coal tar, or coal tar pitch. The database consists primarily of old anecdotal reports or animal studies that would be considered inadequate by current standards. Some clinical reports describe oral exposure of humans to wood creosote, but the amounts ingested are estimated (Alderman et al. 1994; Clark and Reed 1992; Gordon et al. 1995). Three studies published by Miyazato et al. (1981, 1984a, 1984b) that evaluated the acute, intermediate, and chronic effects of beechwood creosote in rats and mice comprise the bulk of reliable information on the systemic effects of ingested beechwood creosote. Based

Table 2-2. Levels of Significant Exposure to Creosote - 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 Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (CD)	5 d Gd 12-16 1x/d (G)				740 F (10 of 16 animals died)	Hackett et al. 1984 coal tar
2	Rat (Wistar)	once (G)				885 M (LD_{50}) 870 F (LD_{50})	Miyazato et al. 1981 beechwood
3	Rat (Wistar)	once (G)				1700 M (LD_{50})	Pfitzer et al. 1965 coal tar
4	Mouse (ddY)	once (G)				525 M (LD_{50}) 433 F (LD_{50})	Miyazato et al. 1981 beechwood
	Systemic						
5	Rat (CD)	5 d Gd 12-16 1x/d (G)	Hepatic	370 F			Hackett et al. 1984 coal tar
			Renal	370 F			
			Endocr		90 F (significant increase in adrenal weight)		
			Bd Wt	140 F	180 F (significant decrease in body weight gain)		

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
6	Rat (Wistar)	once (G)	Gastro	53 F	106 F (significant decrease in peristaltic movement of intestine)		Ogata et al. 1993 wood creosote
7	Mouse (ICR)	5 d Gd 5-9 1 x/d (G)	Resp	400 F			Iyer et al. 1993 petroleum
			Hepatic	400 F			
			Renal	400 F			
			Endocr	400 F			
			Bd Wt		400 F (16.1% decreased maternal body weight)		
8	Mouse (CD-1)	once (G)	Gastro		0.08 M (significant reduction in propulsive motility of the colon)		Ogata et al. 1999 wood creosote
Immunological/Lymphoreticular							
9	Rat (CD)	5 d Gd 12-16 1x/d (G)			90 F (significant increase in adrenal weight and decrease in thymus weight)		Hackett et al. 1984 coal tar
Neurological							
10	Rat (Wistar)	once (G)				600 (convulsions)	Miyazato et al. 1981 beechwood
11	Mouse (ddY)	once (G)		313 M		376 M (convulsions) 313 F	Miyazato et al. 1981 beechwood

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
	Reproductive								
12	Rat (CD)	5 d Gd 12-16 1x/d (G)		140	180	(significant increase in the number of resorptions)	370	(significant decrease in number of live fetuses/litter and increase in the number of resorptions)	Hackett et al. 1984 coal tar
13	Rat (Sprague-Dawley)	3 d Gd 12-14 1x/d (G)		740					Springer et al. 1986a coal tar
14	Mouse (ICR)	5 d Gd 5-9 1x/d (G)		400 F					Iyer et al. 1993 creosote
	Developmental								
15	Rat (CD)	5 d Gd 12-16 1x/d (G)		90	140	(significant decrease in relative fetal lung weight and a significant increase in anomalous fetuses)	370	(significant increase in the incidence of cleft palate, syndactyly/ectrodactyly and missing toenails on hind feet)	Hackett et al. 1984 coal tar
16	Rat (Sprague-Dawley)	3 d Gd 12-14 1x/d (G)					740	(significant increase in early mortality, increased incidence of cleft palate and small lungs)	Springer et al. 1986a coal tar
17	Mouse (ICR)	5 d Gd 5-9 1x/d (G)			400	(12% decreased fetal weight, increased incidence of missing sternbrae)			Iyer et al. 1993 creosote

Table 2-2. Levels of Significant Exposure to Creosote - 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 Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
18	Rat (Fischer- 344)	3-5 wk 1x/d (GO)	Gastro	50 M			Chadwick et al. 1995 coal tar
			Bd Wt	50 M			
19	Rat (Wistar)	3 mo (F)	Resp	812			Miyazato et al. 1981 beechwood creosote
			Cardio	812			
			Hemato	812			
			Hepatic	163 F	168 M (increased relative liver weight) 215 F		
			Renal	168 M	210 M (increased relative kidney weight) 163 F		
			Endocr	812			
			Bd Wt	534	768 F (11% decreased body weight)	812 M (22% decreased body weight)	
20	Mouse (B6C3F1)	28 d (F)	Bd Wt	410 M	693 M (approx 16% decreased body weight)		Culp and Beland 1994 coal tar
			Other	410 M	693 M (significantly decreased food intake)		

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
21	Mouse (ddY)	3 mo (F)	Resp	1427			Miyazato et al. 1981 beechwood creosote
			Cardio	1427			
			Hemato	1427			
			Hepatic	1127 F 768 M	314 F 1065 M (significant increase in relative liver weight)		
			Renal	1427			
			Endocr	1427			
			Bd Wt	450 M 1127 F	768 M (16% decreased body weight) 1427 F (11% decreased body weight)		
22	Mouse	15 d ad lib (F)	Bd Wt	659 M	1871 M (12.5% decreased body weight)		Weyand et al. 1991 coal tar
			Other	659 M	1871 M (decreased food consumption)		
23	Mouse (B6C3F1)	94 d (F)	Resp	462			Weyand et al. 1994 coal tar
			Cardio	462			
			Gastro	462			
			Hemato	462			
			Hepatic	462			
			Renal	462			
			Endocr	462			
			Bd Wt	462			

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Mouse (B6C3F1)	185 d (F)	Resp	462			Weyand et al. 1994 coal tar
			Cardio	462			
			Gastro	462			
			Hemato	462			
			Hepatic	462			
			Renal	462			
			Endocr	462			
			Bd Wt	462			
25	Mouse A/J	260 d (F)	Bd Wt	236 F			Weyand et al. 1995 coal tar
Immunological/Lymphoreticular							
26	Rat (Wistar)	3 mo (F)		317 M 768 F	805 M (increased relative spleen weight)		Miyazato et al. 1981 beechwood
27	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
28	Mouse (B6C3F1)	94 d (F)		462			Weyand et al. 1994 coal tar
29	Mouse (B6C3F1)	185 d (F)		462			Weyand et al. 1994 coal tar

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
30	Rat (Wistar)	3 mo (F)		768 F	257 M (increased relative brain weight)		Miyazato et al. 1981 beechwood
31	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
	Reproductive						
32	Rat (Wistar)	3 mo (F)		317 M 768 F	805 M (increased relative testes weight)		Miyazato et al. 1981 beechwood
33	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
34	Mouse (B6C3F1)	94 d (F)		462			Weyand et al. 1994 coal tar
35	Mouse (B6C3F1)	185 d (F)		462			Weyand et al. 1994 coal tar
	Cancer						
36	Mouse A/J	260 d (F)				100 F (significant increase in incidence of lung tumors CEL: 70%/0%)	Weyand et al. 1995 Coal tar

Table 2-2. Levels of Significant Exposure to Creosote - 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 Chemical Form
	CHRONIC EXPOSURE						
	Death						
37	Rat (Wistar)	96 wk (F)				313 M (30/51 died)	Miyazato et al. 1984b beechwood
38	Mouse (B6C3F1)	2 yrs (F)				333 F (significantly increased incidence of early mortality)	Culp et al. 1998 Coal tar
	Systemic						
39	Rat (Wistar)	96 wk (F)	Cardio	143 M 394 F	313 M (increased relative heart weight)		Miyazato et al. 1984b beechwood creosote
			Hepatic		143 M (increased relative liver weight and serum cholesterol) 179 F (increased serum cholesterol)		
			Renal		143 M (increased relative kidney weight, increased BUN, 179 F nephrosis)		
			Endocr	143 M 394 F	313 M (increased relative weight of adrenal glands)		
			Bd Wt	394			
40	Mouse (B6C3F1)	2 yrs (F)	Bd Wt	628 F	1364 F (decrease in body weight)		Culp et al.1996a coal tar

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Mouse (B6C3F1)	2 yrs (F)	Resp	117 F	333 F (significantly decreased lung weight)		Culp et al. 1998 coal tar
			Gastro	1300 F			
			Hepatic	117 F	333 F (40% increase in liver weight)		
			Renal	33 F	117 F (significantly decreased kidney weight)		
			Bd Wt	117 F	333 F (20% decrease in body weight gain)		
			Other	117	346 F (significantly reduced food consumption)		
42	Mouse (ddY)	52 wk (F)	Resp	532			Miyazato et al. 1984a beechwood creosote
			Hemato	532			
			Hepatic	532			
			Renal	532			
			Bd Wt	532			
	Immunological/Lymphoreticular						
43	Rat (Wistar)	96 wk (F)		394			Miyazato et al. 1984b beechwood
44	Mouse (ddY)	52 wk (F)		532			Miyazato et al. 1984a beechwood
	Neurological						
45	Rat (Wistar)	96 wk (F)		179 F	143 M (increased relative brain 394 F weight)		Miyazato et al. 1984b beechwood

Table 2-2. Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
46	Mouse (ddY)	52 wk (F)			247 M (increased relative brain weight) 297 F		Miyazato et al. 1984a beechwood
Reproductive							
47	Rat (Wistar)	96 wk (F)		394			Miyazato et al. 1984b beechwood
48	Mouse (ddY)	52 wk (F)		532			Miyazato et al. 1984a beechwood
Cancer							
49	Mouse (B6C3F1)	2 yrs (F)				200 F (increased incidence of tumors of the forestomach CEL: 61%: 0% in controls)	Culp et al.1996a Coal tar
50	Mouse (B6C3F1)	2 yrs (F)				333 F (significantly increased incidence of neoplasms of the liver, lung and forestomach and of hemangiosarcomas and histiocytic sarcomas, CEL: 27/47 alveolar/bronchiolar adenomas)	Culp et al. 1998 Coal tar

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

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Hemtao = hematological; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; RBC = red blood cells; Resp = respiratory; wk = week(s); x = times

Figure 2-2. Levels of Significant Exposure to Creosote - Oral

Acute (≤14 days)

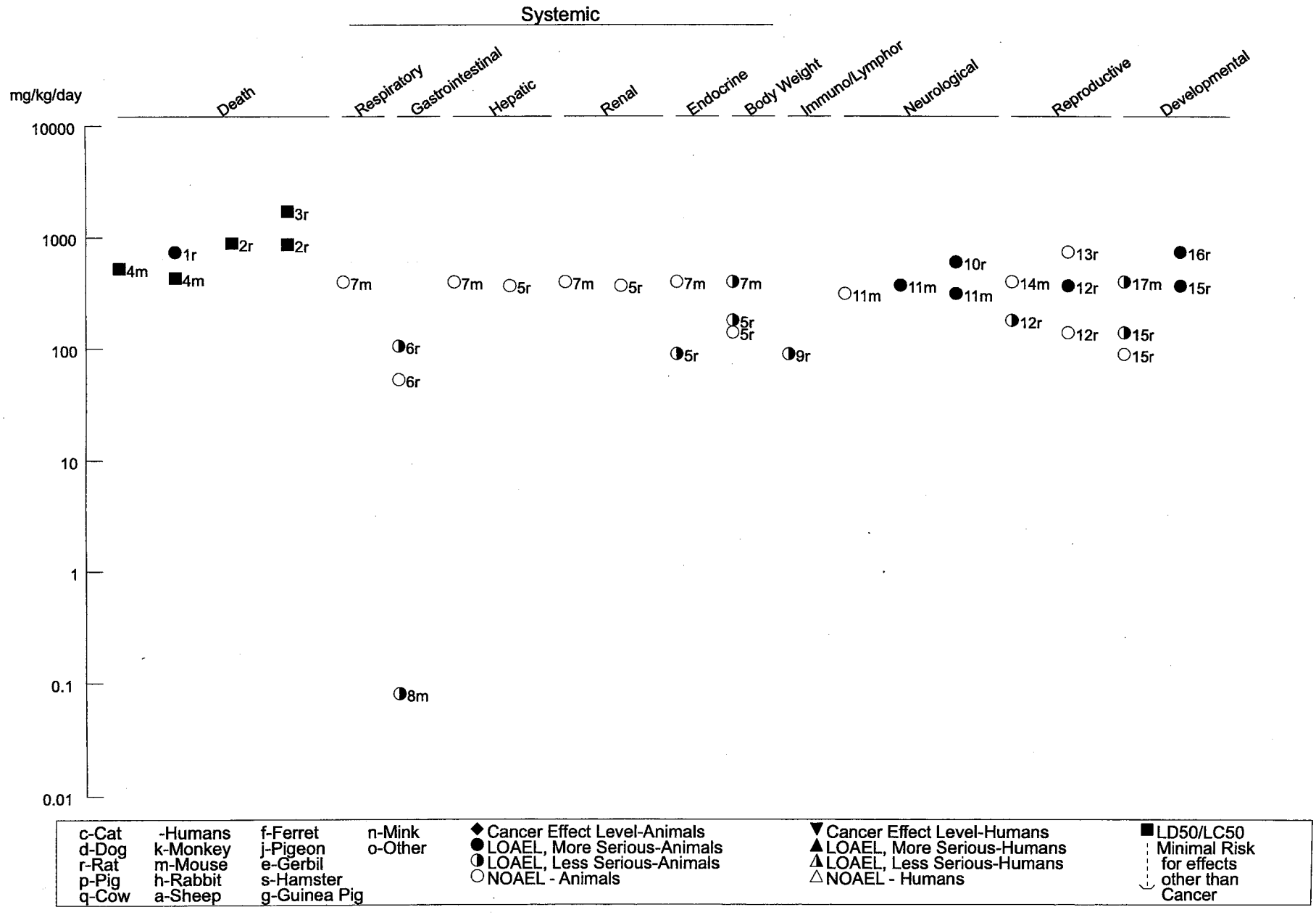


Figure 2-2. Levels of Significant Exposure to Creosote - Oral (Continued)

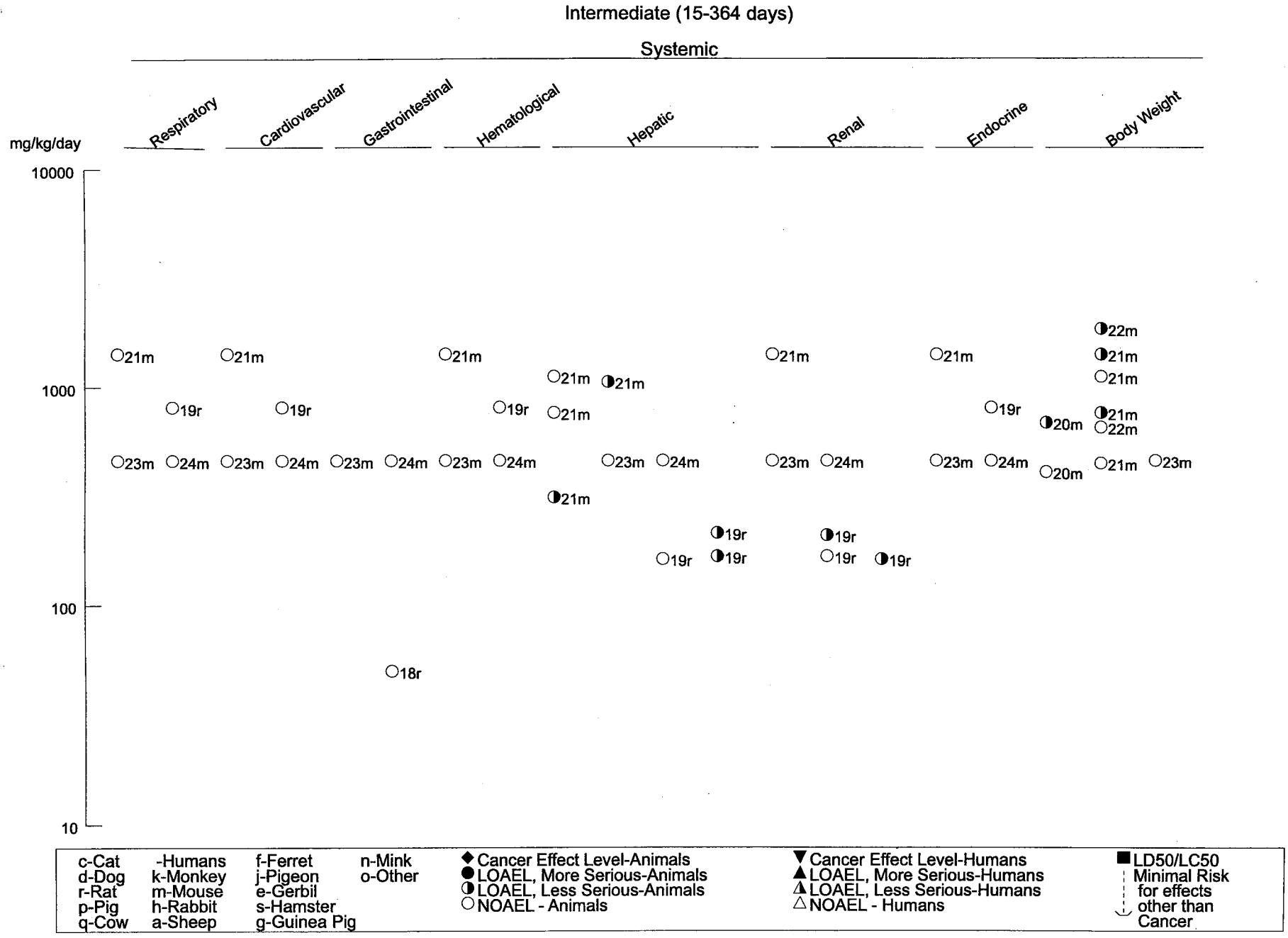
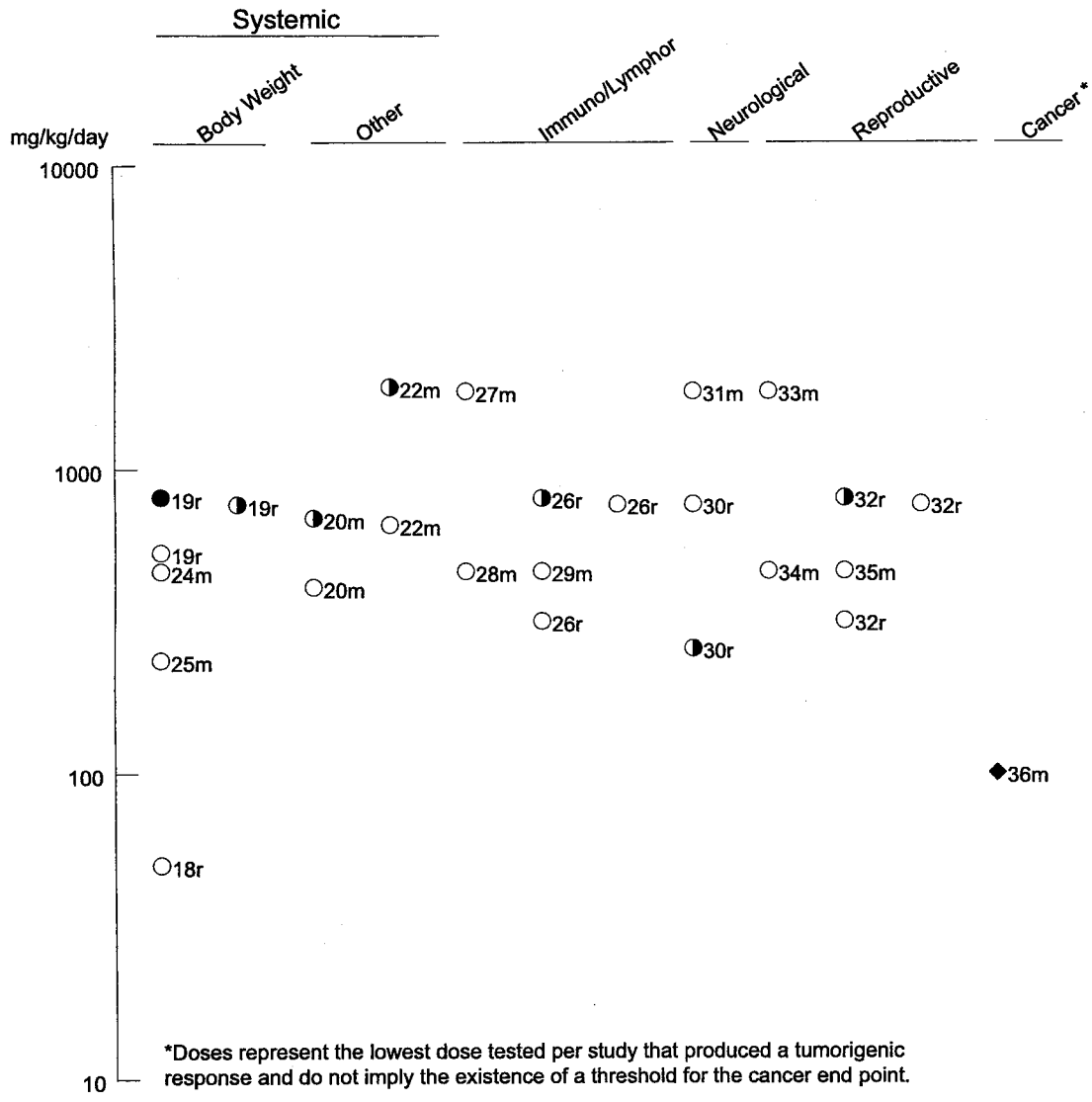


Figure 2-2. Levels of Significant Exposure to Creosote - Oral (Continued)

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

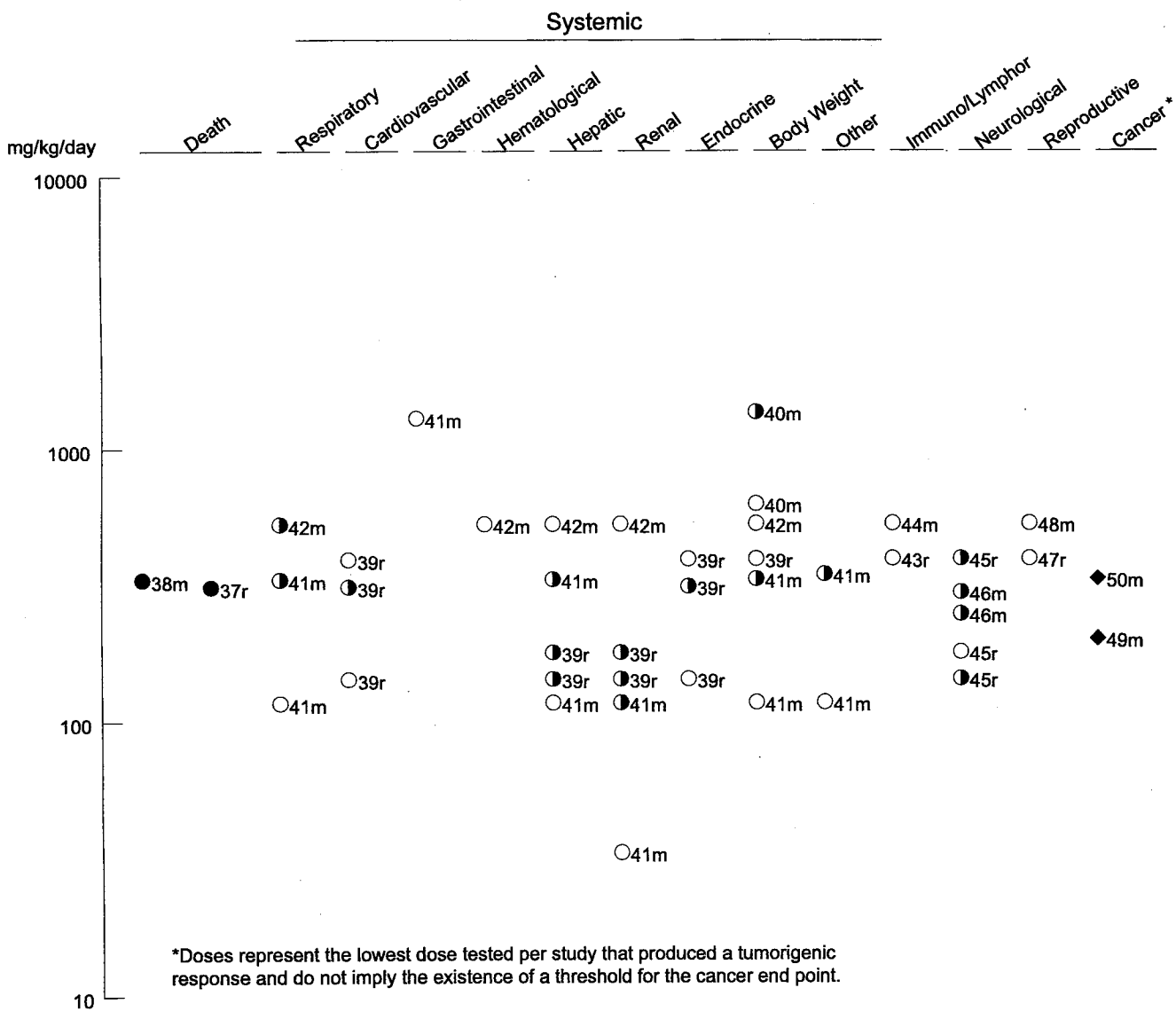
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk for effects other than Cancer

Figure 2-2. Levels of Significant Exposure to Creosote - Oral (Continued)

Chronic (≥365 days)



on the results of these studies, the liver, kidney, and central nervous system appear to be target organs of creosote toxicity. Effects have also been observed in the gastrointestinal, respiratory, and cardiovascular systems. No studies were located regarding musculoskeletal, endocrine, ocular, or body weight effects in humans or musculoskeletal, dermal, or ocular effects in animals after oral exposure to creosote. Studies regarding systemic effects that have been observed in humans and animals after oral exposure to coal tar creosote or coal tar are discussed below. Culp et al. (1996a, 1998), Goldstein et al. (1998), Hackett et al. (1984), Iyer et al. (1993) and Weyand et al. (1994, 1995) comprise the bulk of the data for these compounds. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to coal tar creosote, coal tar, or coal tar pitch. A report was found in the literature describing the medical condition of a 60-year-old woman hospitalized after taking l-2 capsules of chaparral (prepared by grinding leaves of an evergreen desert shrub known as creosote bush or "greasewood;" active ingredient is nordihydroguaiaretic acid [NDGA]) daily for 10 months (Gordon et al, 1995). The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission. She developed aspiration pneumonia requiring antibiotic therapy and endotracheal intnbation.

Beechwood creosote has been and continues to be used therapeutically on a limited basis in Asia as an expectorant/cough suppressant based on its presumed ability to increase the flow of respiratory fluids. The efficacy of creosote (type not specified, but presumably beechwood creosote) as an expectorant was studied by measuring the output of respiratory tract fluids in cats given a single oral dose of 0.1 or 5 mL/kg (concentration not specified) (Stevens et al. 1943). Creosote produced a slight increase in the output of respiratory tract fluid under these conditions. This is not considered a toxic effect. Given the limitations of this study (e.g., no dose information, no other respiratory effects evaluated), it provides no useful information on the potential respiratory effects of beechwood creosote after oral exposure.

No adverse effect on lung weight was noted for Wistar rats given up to 8 12 mg/kg/day (males) or 768 mg/kg/day (females) beechwood creosote or ddY mice given up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981). A slightly higher incidence of bronchitis or thickening of the tracheal mucous membrane was observed in ddY mice who ingested feed that contained 0.3% (equivalent to 247 mg/kg/day for males and 297 mg/kg/day for females) and 0.6% (equivalent to 474 mg/kg/day for males and 532 mg/kg/day for females) beechwood creosote for 52 weeks (Miyazato et al. 1984a). However, the authors attributed

this to irritation from long-term inhalation exposure to volatile components of beechwood creosote in the feed, and not to a direct toxic effect on the respiratory tissue from oral exposure.

No adverse effect on lung weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in dimethyl sulfoxide (DMSO) on gestational days 5-9 (Iyer et al. 1993). Five groups of $B6C3F_1$ mice (24 males, 24 females) were fed a control gel diet or adulterated diets containing 0.05, 0.25, or 0.50% mgP residue, a type of coal tar formed as a by-product of coal gasification (Weyand et al. 1994). Consumption was equivalent to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females. Half of the animals in each group were sacrificed after 94 days of treatment and all organs examined for gross lesions. The remaining animals from each group were maintained on diets for an additional 91 days. After a total of 185 days of treatment, the remaining animals were sacrificed and all organs examined for gross and microscopic lesions. There was no adverse effect of treatment on the lung. In another feeding study 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day of coal tar 2. The dietary level of 0.3% coal tar produced a significant decrease in lung weight compared with controls, but lower dietary levels did not (Culp et al. 1998).

Two pigs that died after ingesting an unknown amount of coal tar pitch exhibited pyrogenic pneumonia (Luke 1954). Heavy respiration was observed in a Hereford bull that had accidentally ingested creosote from an open drum; the actual amount ingested could not be estimated (Cribb 1968).

Cardiovascular Effects. The case of a 52-year-old woman who had been taking creosote (type and dose not specified) for 9 years to treat chronic bronchitis was reported by Robinson (1938). The woman was found to be weak, dizzy, light-headed, and hypertensive (blood pressure=206/140). A modified diet and diuretic therapy relieved all of these symptoms. Upon reinstitution of creosote therapy, her blood pressure rose to 235/130. The author concluded that creosote was responsible for the woman's hypertension. This study provides anecdotal evidence of creosote-induced cardiovascular effects, but the limited sample size, lack of detail on exposure, and possibility of confounding factors limit its usefulness.

No studies were located regarding the cardiovascular effects in animals following oral exposure to coal tar creosote. No adverse effect on heart weight was noted for rats given up to 812 mg/kg/day (males) or 768 mg/kg/day (females) beechwood creosote or mice given up to 1,065 mg/kg/day (males) or

1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981), or female rats given up to 394 mg/kg/day and male rats given 143 mg/kg/day beechwood creosote for 96 weeks (Miyazato et al. 1984b). Male rats given 313 mg/kg/day beechwood creosote for 96 weeks exhibited an increase in heart weight (Miyazato et al. 1984b).

In a feed study of mgP coal tar by Weyand et al. (1994) using B6C3F, mice, there was no adverse effect of treatment on the aorta after 94 or I85 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). One pig that died after ingesting an unknown amount of coal tar pitch exhibited pericarditis (Luke 1954).

Gastrointestinal Effects. Ulceration of the oropharynx and petechial hemorrhages over the gastrointestinal serosal surfaces were noted at autopsy in the case of a 70-year-old man who died following ingestion of industrial (presumably coal tar) creosote (Bowman et al. 1984). However, the esophagus and stomach were intact. The actual amount ingested was not specified. The authors attributed these effects to acute tissue damage resulting from phenol-induced corrosive effects, since phenol is a component of coal tar creosote.

The antidiarrheal effect of beechwood creosote was studied in rats (Ogata et al. 1993, 1999). Female Wistar rats were dosed orally with creosote in concentrations of 0, 7, 13, 27, 53, 107, 213, and 427 mg/kg mixed with 7.7 mg/kg of saline (Ogata et al. 1993). After 1 hour, 5.6 mg/kg castor oil was administered through the stomach cannula to all groups of rats to induce diarrhea. Feces excreted were then observed at 1 hour intervals during the next 7 hours. To assay antimotility effects, female Wistar rats were given creosote at the same concentrations as above. After 1 hour, 0.2 mL of a charcoal meal (12% wet weight [w/w] charcoal powder and 2% [w/w] gum arabic in water) was administered through the stomach cannula and the rats sacrificed 20 minutes later; the small intestine was examined to determine how far the charcoal meal had traveled from the stomach. Creosote administered 1 hour before the castor oil treatment prevented diarrhea with an ED_{50} of 53 mg/kg. The gastrointestinal transit time of the charcoal meal given to rats was significantly suppressed by 106 and 213 mg/kg (but not by 53 mg/kg) creosote, which showed creosote inhibited peristaltic propulsive movement of the intestine.

In a second study by Ogata et al. (1999), the effect of orally administered wood creosote on propulsive motility of the intestine and the colon were tested in male CD-l mice using a charcoal meal test and a colonic bead expulsion test. The effect of treatment with wood creosote was compared with untreated mice or mice treated with loperamide (a known antidiarrheal agent). Postdose plasma samples were

removed from mice 30 minutes after dosing and tested for the ability to suppress colonic propulsive movement. Wood creosote showed only a slight inhibitory effect on the propulsive motility of the small intestine at administered doses of 0.08 and 0.4 mg/kg, but not at an ordinary human therapeutic dose level (2-10 mg/kg). In the colonic bead expulsion test orally administered wood creosote significantly (pc0.05) increased bead expulsion time at doses of 0.08, 0.4, and 2 mg/kg; it was most marked at the dose of 2 mg/kg. The reduction in colonic propulsive motility produced by wood creosote occurred within 15 minutes of dosing. Postdose plasma samples from creosote treated mice produced a significant reduction in colonic propulsive motility when injected into untreated mice. This suggests that the effect is mediated by wood creosote (or its metabolites) in the blood rather than wood creosote from the lumen of the colon as the time period would not be sufficient for creosote to have reached the colon.

Wistar rats that died following the administration of single gavage doses of coal tar creosote in an acute range-finding study (doses ranged from 613 to 5,000 mg/kg) exhibited hyperemia and distention of the stomach upon necropsy (Pfitzer et al. 1965). No adverse gastrointestinal effects were noted in male Fischer 344 rats treated with 50 mg/kg/day creosote by gavage for l-5 weeks, including no change in the weight of the small intestines, large intestines, or caecum (Chadwick et al. 1995). In a feed study of mgP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the glandular stomach or forestomach after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). In another feeding study, 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day of coal tar 2. No effect on the weight or histology of the stomach or small intestine was observed at any dose (Culp et al. 1998). Pigs that died after ingesting an unknown amount of coal tar pitch exhibited blood-stained fluid in the abdominal cavity (Luke 1954).

Hematological Effects. No studies were located regarding hematologic effects in humans following oral exposure to coal tar creosote, coal tar, or coal tar pitch. A report was found in the literature describing a 45-year-old woman who developed painless jaundice, fatigue, anorexia, and pruritus after taking chaparral tablets, 160 mg/day for around 2 months (Alderman et al. 1994). Complete blood count, platelet count, and clotting times were normal. A 60-year-old woman was hospitalized with a l-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking l-2 capsules of chaparral daily for the past 10 months. The patient developed “flulike

syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission, The patient's prothrombin time increased from 15.9 to 28 seconds (normal values 10.9-13.7 seconds).

Various hematological parameters (red blood cell, white blood cell, lymphocyte and neutrophil counts, hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit) were measured by Miyazato et al. (1981, 1984a, 1984b) in Wistar rats and ddY mice fed beechwood creosote in the daily diet for 3 months, 52 weeks (mice), or 96 weeks (rats). No significant treatment-related changes were noted in mice of either sex fed doses of up to 1,065 mg/kg/day (male) or 1,427 mg/kg/day (female) for 3 months (Miyazato et al. 1981). These doses are considerably higher than the oral LD_{50} values reported for mice by the same authors. One possible explanation for this discrepancy is that the LD_{50} values were determined by bolus gavage injections and in the intermediate study, the beechwood creosote was administered in the feed. A slight reduction in red blood cells (RBCs) was noted in male and female rats following dietary exposure to doses of 210 (male) or 163 (female) mg/kg/day for 3 months, but this reduction was not observed in mice exposed to higher doses [812 (male) or 768 (female) mg/kg/day], and was therefore not considered to be toxicologically significant (Miyazato et al. 1981). Chronic (52 weeks) dietaryexposure of mice to up to 474 mg/kg/day (males) or 532 mg/kg/day (females) beechwood creosote resulted in statistically significant dose-related differences in mean cell volume, mean corpuscular hemoglobin, and absolute lymphocyte and neutrophil counts when compared to the corresponding control values. These changes were not considered by the authors to be toxicologically significant; they claimed that the values were within normal physiological ranges (Miyazato et al. 1984a).

In a feed study of mgP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the bone marrow after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females).

Hepatic Effects. Acute toxic hepatitis has been attributed to ingestion of chaparral, an herbal nutritional supplement product derived from the leaves of the creosote bush (Clark and Reed 1992). A 42-year-old man had icterus and jaundice after consuming three 500 mg capsules of chaparral a day for 6 weeks. Serum chemistry tests showed elevated bilirubin, gamma glutamyltranspeptidase (GGT), AST, and lactate dehydrogenase. His illness was diagnosed as hepatic dysfunction secondary to chaparral ingestion. Three weeks after discontinuing the chaparral ingestion, his serum chemistry was normal, and he had no other symptoms. The same article noted the case of a 41-year-old woman who had abdominal pain and jaundice after consuming 150 tablets of chaparral over an 11 -week period. Serum chemistry

tests revealed elevated bilirubin, AST, alanine aminotransferase (ALT), GGT, and lactate dehydrogenase. Six weeks after discontinuation of chaparral ingestion, serum chemistry tests were normal, and there were no other symptoms reported.

A 45-year-old woman developed painless jaundice, fatigue, anorexia, and pruritus after taking chaparral, 160 mg/day, for around 2 months (Alderman et al. 1994). Physical examination confirmed jaundice and a 14-cm liver with a smooth, nontender border. Serum enzyme levels were elevated; serum ALT was 1,611 IU (normal 0-65 IU); AST was 957 IU (normal 0-50 IU); alkaline phosphatase was 265 IU (normal 35-130 IU); GGT was 993 IU (normal 0-65 IU), and total bilirubin was 11.6 mg/dL (normal <l.4 mg/dL). Tests for anti-hepatitis A IgG and IgM, hepatitis B surface antigen, antibody against hepatitis B surface antigen and hepatitis B core antigen, and acute antibody against hepatitis virus were all negative. Ultrasonography showed no abnormality. Endoscopic retrograde cholangiopancreatigraphy (ERCP) showed sparse, smooth, but severely narrowed biliary ducts without sclerosing cholangitis, distal obstruction, tumor, or stenosis. Specimens from percutaneous liver biopsy showed prominent acute inflammation with neutrophil and lymphoplasmocytic infiltration, diffuse hepatocyte disarray and necrosis, focal acute pericholangitis, some ductal dilatation, and proliferation of bile ductules in portal-periportal regions. The patient was started on Prednisone at 60 mg/day, tapered to 10 mg/day and discontinued in 7 weeks; the patient remained well with normal laboratory findings. The patient was diagnosed with chaparral-induced toxic hepatitis after reports of two cases of chaparral hepatotoxicity were published. In another report, a 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking l-2 capsules of chaparral daily for the past 10 months. The patient developed “flulike syndrome” and increased her chaparral intake to 6 capsules a day 3 weeks before admission. Jaundice occurred 2 weeks later. On admission, she was confused and deeply jaundiced. Her total serum bilirubin increased from 212 mmol/L (12.4 mg/dL) to 607 mmol/L (35.5 mg/dL) (normal values 2-20 mmol/L [0.l-l.2 mg/dL]). The patient’s liver failure was considered to be chaparral-induced toxic hepatitis. Viral hepatitis was ruled out because antibodies to hepatitis A virus IgM, antibody to hepatitis B core antigen, and hepatitis C virus were undetectable. An exploratory laparotomy performed 1 week after admission showed ascites and a nodular liver. Liver biopsy showed severe acute hepatitis with areas of lobular collapse and nodular regeneration, mixed portal inflammation and marked bile ductular proliferation. Her total serum bilirubin increased to 607 mmol/L. The patient underwent orthotopic liver transplantation. The patient slowly recovered and was discharged.

Degeneration and necrosis of hepatocytes were observed at autopsy in the case of a 70-year-old man who ingested industrial (coal tar) creosote (Bowman et al. 1984). The actual amount ingested was not specified. Given the advanced age of this man and the lack of comparison data, it is not possible to definitively attribute these effects to coal tar creosote ingestion.

Liver-to-body-weight ratios tended to increase in male Wistar rats exposed to doses of beechwood creosote >168 mg/kg/day in the diet for 3 months or in females exposed to ≥215 mg/kg/day (but not 163 mg/kg/day) (Miyazato et al. 198 1). A similar increase in relative liver weight was observed for rats exposed to ≥143 (male) or 179 (female) mg/kg/day beechwood creosote for 96 weeks (Miyazato et al. 1984b). Increased relative liver weights were observed in female ddY mice fed beechwood creosote at doses ≥314 mg/kg/day (but not 164 mg/kg/day) and in male mice fed 1,065 mg/kg/day (but not 768 mg/kg/day) for 3 months and in female mice fed ≥297 mg/kg/day, but not in male mice fed up to 474 mg/kg/day for 52 weeks (Miyazato et al. 1981). Although this response is considered to be of minimal pathologic significance, it may be an early indication of adverse changes since the liver is a known target organ. No treatment-related histopathological alterations were observed.

A significant increase in serum glutamic-oxaloacetic transferase (GOT, currently known as AST) and glutamic-pyruvic transferase (GPT, currently known as ALT) levels was also observed in the chronically exposed female mice, but these levels were still within normal physiological range (Miyazato et al. 1981). A slight increase in serum cholesterol was noted in male and female rats following dietary exposure to 210 (male) or 578 (female) mg/kg/day beechwood creosote for 3 months (Miyazato et al. 1981). The significance of the serum cholesterol changes is not known. Increases in serum cholesterol were also noted in rats exposed to beechwood creosote in the diet for 96 weeks at doses of 143 (male) and 179 (female) mg/kg/day and above (Miyazato et al. 1984b). There was no effect of treatment on liver weight or serum cholesterol in mice exposed to up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) in the diet for 3 months or for mice exposed to up to 474 mg/kg/day (males) or (532 mg/kg/day (females) beechwood creosote in the diet for 52 weeks (Miyazato et al. 1984a). Taken together, these early changes indicate that if increased doses of beechwood creosote are used, more clear cut hepatotoxic effects would be expected to occur.

No adverse effect on liver weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5-9 (Iyer et al. 1993). In a feed study of mgP coal tar by Weyand et al. (1994), B6C3F_1 mice were exposed to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females) in the feed for 94 or 185 days. Plasma clinical chemistry parameters

determined were as follows: glucose, creatine, blood urea nitrogen, total protein, ALT, ALT, and alkaline phosphatase activity. Tissues obtained from the animals were examined for microscopic lesions. There was no adverse effect of treatment on liver histopathology or serum enzymes.

Anecdotal reports of mortality in pigs after ingestion of clay pigeons containing coal tar pitch from pastures formerly used for target shooting were found in the literature (Giffee 1945; Graham et al. 1940). Lack of appetite, sluggishness, rough coat, and weakness, followed by death were reported. Autopsy revealed degenerative hepatic changes. Experimental feeding of powdered clay pigeon targets containing an unspecified amount of coal tar pitch (15-30 g powdered material daily for up to 15 days) caused death in 8 of 9 pigs (Davis and Libke 1968). Twenty-four to 48 hours prior to death, a decrease in hemoglobin, packed blood cell volume, and blood sugar concentration was noted. Autopsy revealed centrilobular hepatic necrosis and hemorrhage of the liver. Four pigs that ingested an unknown amount of coal tar pitch exhibited, at necropsy, marked enlargement of the liver (Luke 1954). The hepatic surface was pitted, the lobules very prominent and the whole organ extremely friable. Fibrinous strands were found on the liver, the cut surface of which presented a mottled mosaic-like pattern. Three pigs were fed a small quantity of pitch ground up in their feed (Luke 1954). These 3 pigs received 2 pounds (approximately 0.38 ounces/day) of pitch over a period of 28 days. At the end of the 28th day, the pigs were sacrificed and examined. The addition of pitch did not interfere with their appetite and no marked symptoms were observed. Enlargement of the liver was seen together with a varying degree of liver damage. The liver lesions were extensive and there was a marked excess of peritoneal fluid. Histological examination of the affected liver tissue showed marked central necrosis of the lobules which, in some cases, had completely destroyed the normal liver cells. These liver changes had a somewhat patchy distribution with badly affected and normal lobules often occurring side by side. The factors in the pitch responsible for the lesions were not identified.

No change in liver weight was observed in female rats gavaged on gestational days 12-16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984). In a feeding study 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day of coal tar 2. The dietary level of 0.3% coal tar produced a significant increase in liver weight (40%) compared with controls, exposure to lower doses had no effect on the liver (Culp et al. 1998).

Renal Effects. A 45-year-old woman who took 160 mg/kg/day chaparral for approximately 2 months was diagnosed with chaparral-induced toxic hepatitis (Alderman et al. 1994). No adverse renal effects were noted. A 60-year-old woman was hospitalized with a l-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking l-2 capsules of chaparral daily for the past 10 months. The patient increased her chaparral intake to 6 capsules a day 3 weeks before admission. Renal failure ensued which required hemodialysis. The patient underwent cadaveric renal transplantation. The patient slowly recovered and was discharged.

A 70-year-old man who ingested a fatal dose of industrial (coal tar) creosote became acidotic and anuric before he died, indicating probable kidney failure (Bowman et al. 1984). The actual amount ingested was not specified. Acute renal tubular necrosis was revealed at necropsy. However, the acute tubular necrosis may have been due to vascular insufficiency rather than a direct toxic effect on the kidney.

Kidney-to-body-weight ratios were significantly increased in Wistar rats exposed to ≥210 (male) or ≥163 (female) mg/kg/day or more beechwood creosote in the diet for 3 months or to ≥143 (males) or ≥179 (females) mg/kg/day or more for 96 weeks (Miyazato et al. 1981, 1984b), although the trend was not strictly dose-related. No effect on the relative weight of the kidney was observed in mice exposed to up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) for 3 months, mice exposed to 474 mg/kg/day (males) or 532 mg/kg/day (females) for 52 weeks, or male rats exposed to 168 mg/kg/day for 3 months (Miyazato et al. 1981). This response is of minimal pathologic significance in the intermediately treated rats of both sexes and the chronically treated female rats since no treatment-related changes were noted at histopathological evaluation. Blood urea nitrogen and serum inorganic phosphorus were elevated in the chronically treated male rats, which is indicative of uremia. Chronic progressive nephropathy, which occurs spontaneously in old male rats, was also observed at a higher incidence in the chronically treated male rats than in the control male rats, and probably accounts for the biochemical changes observed. The authors concluded that long-term exposure to beechwood creosote at the high dose (1.2% in feed or 534 mg/kg/day) accelerated the occurrence of chronic progressive nephropathy in male rats (Miyazato et al. 1984b). These results suggest that beechwood creosote has the potential to induce adverse effects in the kidney.

No adverse effect on kidney weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5-9 (Iyer et al. 1993). No change in kidney weight was observed in female CD rats gavaged on gestational days 12-16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984). In a feed study of mgP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there

was no adverse effect of treatment on the kidney or bladder after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). In another feeding study 5-week-old female B6C3F_1 mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1,0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day of coal tar 2. The dietary level of 0.1% coal tar produced a significant decrease in kidney weight compared with controls, but lower dietary levels did not (Culp et al. 1998).

Postmortem examination on 4 pigs that had ingested an unknown amount of pitch showed cystic kidneys (Luke 1954).

Endocrine Effects. No adverse effect on adrenal weight was noted for Wistar rats given up to 812 (males) or 768 mg/kg/day (females) beechwood creosote or ddY mice given up to 1,065 (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981). Male rats given 313 mg/kg/day beechwood creosote for 96 weeks exhibited an increase in relative adrenal weight, but males receiving 143 mg/kg/day and females receiving up to 394 mg/kg/day did not (Miyazato et al. 1984b).

Adrenal weights were significantly increased in pregnant rats gavaged with ≥90 mg/kg/day coal tar on gestational days 12-16 (Hackett et al. 1984). No adverse effect on adrenal weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5-9 (Iyer et al. 1993). Weyand et al. (1994) conducted a feed study of mgP coal tar using B6C3F, mice. There was no adverse effect of treatment on the salivary glands, pancreas, thymus, parathyroid, or adrenal glands after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females.

Dermal Effects. A 45-year-old woman developed pruritus, probably secondary to chaparral-induced toxic hepatitis, after taking 160 mg/kg/day chaparral for around 2 months (Alderman et al. 1994).

Body Weight Effects. No adverse effect on body weight was noted in male Fischer 344 rats treated with 50 mg/kg/day coal tar creosote by gavage for 3-5 weeks (Chadwick et al. 1995). However, body weight was significantly decreased in female CD rats gavaged on gestational days 12-16 with 180 mg/kg/day (but not 140 mg/kg/day) coal tar (Hackett et al. 1984). A 16% decrease in body weight was also observed in female ICR mice after gavage treatment with 400 mg/kg petroleum creosote in

DMSO on gestational days 5-9 (Iyer et al. 1993). In another study, male B6C3F$_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). Food consumption and change in body weights were monitored for the coal-tar-fed animals. Dose-related decreases in body weight were observed in all dose groups. Animals treated with 693 and 1,067 mg/kg/day coal tar showed average body weights significantly decreased by approximately 16%. Body weights for other treated groups were not significantly different from those of controls.

The relationship between coal tar creosote ingestion and systemic availability of coal tar components in male mice was evaluated by measuring whole animal body weight, DNA adduct formation binding in several soft tissues, and urinary excretion of PAH metabolites (Weyand et al. 1991). Coal tar creosote samples collected from four different coal gasification sites were incorporated separately at varying concentrations into the diet and fed to the mice for 15 days. Animal body weight was not affected in groups fed up to 0.2% (659 mg/kg/day) coal tar creosote, but body weight was significantly reduced in animals fed diets containing 0.5% (1,871 mg/kg/day) coal tar because the animals refused to eat.

Five groups of B6C3F$_1$ mice (24 males, 24 females) were fed a control gel diet or adulterated diets containing 0.05, 0.25, or 0.50% mgP (Weyand et al. 1994). Consumption was equivalent to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females. Half the animals in each group were sacrificed after 94 days of treatment and all organs examined for gross lesions. The remaining animals from each group were maintained on diets for an additional 91 days. After a total of 185 days of treatment, the remaining animals were sacrificed and all organs examined for gross and microscopic lesions. Differences in weight gain did not show any clear dose response. Control and treated males ingesting 51 mg/kg/day feed had the highest weight gain. Body weight gains in the 251 and 462 mg/kg/day groups were considerably lower (statistical analysis not performed). Females exposed to 42 mg/kg/day diets had the highest body weight gains, while females on the 196 mg/kg/day diets had the lowest. In a similar study Weyand et al. (1995) fed female A/J mice with a control diet or a diet containing 0.1 or 0.25% coal tar samples from manufactured gas plant waste sites for 260 days. This diet provided approximately 100 or 236 mg/kg/day coal tar. Consumption of coal tar did not significantly alter body weight gain since mice fed the control and 0.25% coal tar diets had equally low body weight gain compared to mice fed the 0.1% coal tar diet.

Gulp et al. (1996a) fed diets containing 0, 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar to female B6C3F$_1$ mice for 2 years and noted a decrease in body weight (data not shown) at the two highest doses (1,364 and 2,000 mg/kg/day) compared with controls. No decrease was noted for animals exposed to

≤0.3% (628 mg/kg/day) compared with controls. In another feeding study, 5-week-old female B6C3F$_1$ mice were fed a control gel diet or diets containing 0.0 1,0.03,0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333,739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mglkglday of coal tar 2. The dietary level of 0.3% coal tar (333 mg/kg/day coal tar 1 or 346 mg/kg/day coal tar 2) produced a significant decrease in body weight gain (20%) compared with controls, but lower dietary levels did not (Culp et al. 1998).

Body weight gain was decreased 1l-22% in Wistar rats given 768 (males) or 812 (females) mg/kg/day beechwood creosote, and 1l-16% in ddY mice given respectively 768 (males) or 1,427 (females) mg/kg/day beechwood creosote in the feed for 3 months (Miyazato et al. 1981). No effect on body weight was observed in rats or mice exposed to lower doses (534 mg/kg/day, male rat; 578 mg/kg/day, female rat; 450 mg/kg/day, male mouse; 1,127 mg/kg/day, female mouse) of beechwood creosote for 3 months. No effect on body weight was observed in rats or mice exposed to up to 313 (males) or 394 (females) mg/kg/day for 96 weeks, or to 474 (males) or 532 (females) mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b).

Other Systemic Effects. Consumption of food containing coal tar creosote was evaluated in male B6C3F, mice by measuring whole animal body weight and food consumption (Weyand et al. 1991). Coal tar creosote samples collected from four different coal gasification sites were incorporated separately at varying concentrations into the diet and fed to the mice for 15 days. Food consumption was not affected in groups fed up to 0.2% (659 mg/kg/day) coal tar creosote. However, animals fed diets containing 0.5% (1,871 mg/kg/day) or 1.0% (3,125 mg/kg/day) coal tar refused to eat for 2 or 4 days respectively, while animals fed 2% or more coal tar continued to refuse to eat for the duration of the experiment. In another feeding experiment, male B6C3F$_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). Dose-related decreases in food consumption were observed in all treated groups. Animals treated with 693 and 1,067 mg/kg/day coal tar showed significantly decreased food consumption compared to controls over a period of 28 days, animals receiving lower doses did not. Similar reductions in food consumption were seen in another study of female B6C3F$_1$ mice fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day of coal tar 2. Mice fed coal tar 1 ate significantly less food than controls. The reduction in food consumption was approximately

30% for mice fed 1% coal tar 1 and 25% for mice fed 0.6% coal tar 1. Mice fed 0.3% coal tar 2 also ate significantly less food than controls and had approximately a 20% reduction in food consumption.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunologic/lymphoreticular effects in humans after oral exposure to, wood creosote, coal tar creosote, coal tar, or coal tar pitch.

In rats, the spleen may be affected by beechwood creosote exposure, although the data are not conclusive (Miyazato et al. 1981). In particular, exposure to beechwood creosote at 805 mg/kg/day in the diet for 3 months resulted in increased relative spleen weight of male Wistar rats. Spleen weights of male rats exposed to lower levels of beechwood creosote in the diet and female rats at doses up to 768 mg/kg/day indicated no consistent trend of either increase or decrease (Miyazato et al. 1981). In companion experiments using ddY mice, no effect on relative spleen weight was seen at doses up to 1,810 (male) or 1,570 (female) mg/kg/day, in the feed (Miyazato et al. 1981). No effect on spleen weight was observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, or mice exposed to doses of 532 mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b).

Coal tar may affect the spleen and thymus in rats, but not in mice. A significant decrease in thymus weight and increase in adrenal weight was observed in female CD rats gavaged on gestational days 12-16 with 90 mg/kg/day coal tar (Hackett et al. 1984). B6C3F_1 mice fed a control gel diet or diets containing 0, 51, 251, or 462 mg/kg/day coal tar (males) and 0, 42, 196, or 344 mg/kg/day (females) coal tar, exhibited no adverse gross or histopathological effects for the spleen, thymus, or bone marrow after treatment for 94 or 185 days (Weyand et al. 1994).

All reliable NOAEL and LOAEL values for immunological and lymphoreticular effects for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to coal tar creosote, coal tar, or coal tar pitch. A 45-year-old woman developed fatigue and anorexia after taking 160 mg/kg/day chaparral for around 2 months (Alderman et al. 1994). The patient was diagnosed with chaparral-induced toxic hepatitis. In another report, a 60-year-old woman was hospitalized with a l-week

history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking l-2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission. On admission, she was confused; her encephalopathy worsened, and she developed seizure activity. The patient was diagnosed with toxic hepatitis secondary to chaparral ingestion.

In rats and mice, the first sign of poisoning following the gavage administration of single high doses (600 mg/kg in Wistar rats; 378 [male] or 313 [female] mg/kg in ddY mice) of beechwood creosote was muscle twitching followed by convulsions within l-2 minutes. This was followed by asphyxiation, coma, and death (Miyazato et al. 1981). These effects were not observed in male mice gavaged once with 313 mg/kg beechwood creosote (Miyazato et al. 1981). Dose-related increased brain-to-body-weight ratios were observed in male rats exposed to doses of ≥257 mg/kg/day beechwood creosote in the diet for 3 months, but not female rats exposed up to 768 mg/kg/day or male and female mice exposed to up to 1,8 10 (male) or 1,570 (female) mg/kg/day (Miyazato et al. 198 1). Increased relative brain weights were observed in male and female mice exposed to doses up to 247 (male) or 297 (female) mg/kg/day for 52 weeks in the diet, and in male rats exposed to 143 mg/kg/day and female rats exposed to 394 mg/kg/day (but not 179 mg/kg/day) for 96 weeks in the diet (Miyazato et al. 1984b). This response is of questionable toxicological significance because of the lack of a dose-response trend and/or the lack of treatment-related pathological findings at necropsy.

Several cases of acute poisoning in cattle have been attributed to ingestion of coal tar creosote. Six cattle believed to have licked creosote-treated electrical light poles as evidenced by burning over the mucosa of the mouth, tongue, and lips showed the following symptoms: extremely rapid respiration, contracted pupils, cold skin, apparent severe pain, and coma (Hanlon 1938). However, it is probable that some of these effects may have been due to ingestion of pentachlorophenol. Pentachlorophenol, like creosote, is an oil-borne wood preservative with extensive use in the public utility industry for treatment of utility poles. Some of the effects observed by Hanlon (1938) are more compatible with the metabolic effects (i.e., uncoupling of phosphorylative oxidation) associated with pentachlorophenol. For more information on the effects of pentachlorophenol, please refer to the ATSDR *Toxicological Profile for Pentachlorophenol* (ATSDR 1999). Thus, it is not possible to determine conclusively whether coal tar creosote is toxic to the central nervous system of animals based on this report. In another report, a bull that had ingested an unknown amount of creosote was observed to be walking stiffly (Cribb 1968). The animal recovered fully.

All reliable NOAEL and LOAEL values for neurological effects for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to creosotes, coal tar, or coal tar pitch.

A significant decrease in both the number of live fetuses/litter and the number of resorptions was observed in female Sprague Dawley CD rats gavaged with 370 mg/kg/day coal tar on gestational days 12-16 (Hackett et al. 1984). A significant increase in resorptions was also observed in rats treated with 180 mg/kg/day (but not 140 mg/kg/day) coal tar, but there was no decrease in the number of live fetuses/litter. Some maternal toxicity was observed in the body weight (minus the products of gestation) of the dams was significantly reduced for the three highest dose groups and the weight of the adrenal glands was significantly increased. However, the weights of the spleen, liver, kidneys, and ovaries of all dosed groups were similar to controls.

No significant difference in the number of live births was observed in female Sprague Dawley rats gavaged with 740 mg/kg/day coal tar on gestational days 12-14 (Springer et al. 1986a). Only moderate maternal toxicity was observed. Body weight gain was significantly reduced in treated dams, but the estimated weights of the products of conception were similar for control and treated animals, and no significant reduction in litter size was observed. No adverse effects on reproductive indices, including the number of live fetuses, dead fetuses, and resorptions were observed in female ICR mice dosed by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5-9 (Iyer et al. 1993). Moderate maternal toxicity in the form of reduced body weight gain was observed for both creosote-treated and vehicle control mice compared with untreated controls, but no differences in organ weights were observed for any group. B6C3F, mice fed a control gel diet or adulterated diets containing 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females) MCP residue, a type of coal tar formed as a by-product of coal gasification, exhibited no adverse effect on the epididymides, preputial gland, ovaries, uterus, or clitoral gland after treatment for 94 or 185 days (Weyand et al. 1994).

An increase in relative testis weight was observed in Wistar rats administered 805 mg/kg/day beechwood creosote in the diet for 3 months, but not in rats receiving 317 mg/kg/day or in mice treated with up to 1,810 mg/kg/day beechwood creosote for 3 months (Miyazato et al. 1981). There were no accompanying

gross or histopathological lesions of the testes in these animals. No adverse effects on ovary weight were noted in female rats (768 mg/kg/day) or mice (1,570 mg/kg/day) in the same study. No effect on testis or ovary weight was observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, or mice exposed to doses of up to 532 mg/kg/day beechwood creosote for 52 weeks (Miyazato et al. 1984a, 1984b).

All reliable NOAEL and LOAEL values for reproductive effects for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects .

No studies were located regarding the developmental effects in humans following oral exposure to wood creosote, coal tar, or coal tar pitch.

A significant decrease in relative fetal lung weight and a significant increase in anomalous fetuses was observed in female CD rats gavaged with 140 mg/kg/day (but not 90 mg/kg/day) coal tar on gestational days 12-16 (Hackett et al. 1984). Further abnormalities, a significant increase in the incidence of cleft palate, syndactyly/ectrodactyly and missing toenails on hind feet, were observed in offspring of females treated with 370 mg/kg/day coal tar. Some maternal toxicity was observed in that the body weight (minus the products of gestation) of the dams was significantly reduced for the three highest dose groups and the weight of the adrenal glands was significantly increased. However, the weights of the spleen, liver, kidneys, and ovaries of all dosed groups were similar to controls.

In another developmental study, female Sprague Dawley rats were gavaged with 740 mg/kg/day coal tar on gestational days 12-14 and allowed to deliver their pups (Springer et al. 1986a). Only moderate maternal toxicity was observed. Body weight gain was significantly reduced in treated dams, but the estimated weights of the products of conception were similar for control and treated animals, and no significant reduction in litter size was observed. Pup development was followed for 21 days after birth. Early mortality was significantly increased in treated pups; within the first 3 days after birth, 54% of the treated pups died compared with 9% of the untreated pups. Body and lung weights of treated pups that died or were sacrificed at 1 or 3 days postdelivery were significantly reduced compared with controls. Body weight gain was significantly reduced (15%) for treated pups compared with controls at all time points. Treated pups that died showed signs of severe dehydration and this became more pronounced as the time to death increased. Thymus and lung weights in treated animals were significantly lower than in the corresponding control animals. Lungs were defined as “small lungs” if their size was more than two

standard deviations below the mean of the control group. No controls had small lungs or cleft palates. In treated pups that died, the incidence of small lungs was 27% (in 90% of litters), 10% (in 80% of litters) had cleft palates, and 33% of pups (in 80% of litters) had both small lungs and cleft palates. Median survival times for pups with cleft palate, both cleft palate and small lungs, and only small lungs were 2, 2, and 10 hours respectively. No malformations were detected in 30% of the treated pups that died and microscopic examination of fetal lung tissue revealed no overt histological differences between treated and control animals.

A decrease of 12% in mean fetal body weight was observed in the offspring of female ICR mice dosed by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5-9, although this difference was not statistically significant when compared to the vehicle control group (Iyer et al. 1993). Similarly, an increase in the incidence of a skeletal variation (i.e., missing sternebrae) was also observed in the creosote-treated litters, but the difference in the frequency of occurrence was not significant compared to the control group. Moderate maternal toxicity in the form of reduced body weight gain was observed for both creosote-treated and vehicle control mice compared with untreated controls, but no differences in organ weights were observed for any group.

Four sows were confined to wooden farrowing crates for 2-10 days before delivery. The platforms of the crates were coated with 3 brush applications of a commercial wood preservative containing 98.5% coal tar creosote (Schipper 1961). Following contact with creosote, 24 of the 41 pigs delivered were dead at birth, and 11 pigs died by day 3 postfarrowing. The surviving pigs had rough skin and suffered from dehydration and severe diarrhea. The pigs failed to gain weight until they were 5-6 weeks old. No toxic effects on the sows were reported. However, 4 sows confined to untreated lumber crates at least 24 hours before farrowing delivered 36 pigs; 1 died within 24 hours and 3 died postfarrowing. No toxic effects were noted in mothers or baby pigs.

The LOAEL and NOAEL values for developmental effects in mice and rats after oral exposure to creosote are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding *in vivo* genotoxic effects in humans following oral exposure to wood creosote, coal tar creosote, coal tar, or coal tar pitch.

Male Fischer 344 rats received daily oral treatment of 50 mg/kg creosote in peanut oil for 1 week (Chadwick et al. 1995). Controls were dosed with the vehicle. After treatment with creosote, 6 control and 6 treated rats were administered 75 mg/kg 2,6-dinitrotoluene (DNT) in DMSO by gavage and 24-hour urine was collected. Urine was also collected from 2 control and 2 treated rats dosed with DMSO. The same protocol was employed after 1,3, and 5 weeks of treatment using the same 16 animals, Hydrolyzed urines were tested for mutagenicity in a microsuspension bioassay using *Salmonella typhimurium (S. typhimurium)*, strain TA98 without rat liver S9 activation. The 6 control and 6 treated animals were sacrificed after 1, 3, and 5 weeks of treatment and the liver, small intestine, large intestine, and cecum were examined. The rat livers were removed for the determination of DNA adduct formation. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. After 1 week of treatment, a significant increase in adduct 3 was detected in the hepatic DNA from the creosote with DNT-treated rats. No significant differences were found after 3 weeks. After 5 weeks of treatment, the contents of adducts 1, 2, 3, and 4 were all significantly increased in the hepatic DNA of the creosote with DNT-treated rats. Total adduct formation in the animals treated with creosote plus DNT increased by 66%. The microbial flora population in the small intestine, large intestine, or cecum was not significantly altered by pretreatment with creosote. The genotoxicity of DNT was potentiated by coal tar creosote.

In another study, male B6C3F$_1$ mice (8 per group) were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-postlabeling. The adduct levels were then compared with those obtained by feeding benzo[a]pyrene to mice for 3 weeks at concentrations corresponding to the amount of benzo[a]pyrene in the coal tar doses. DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene. DNA adduct levels were in the order forestomach > liver > lung at lower dose groups, while the order changed to liver > forestomach > lung at the highest dose group. Total DNA adduct formation was greater in the coal tar fed mice than in the benzo[a]pyrene fed animals (≈10- to 30-fold greater in the liver and forestomach, and over 90-fold greater in the lungs at the lower doses).

A 28 day feeding experiment in which female B6C3F$_1$ mice were fed 0, 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar found that ^{32}P-postlabeling of DNA from forestomach tissue of mice fed coal tar gave a diffuse adduct pattern within which a number of discrete adducts were discemable (Culp et al. 1996a). The major one of these was identified as an adduct of benzo[a]pyrene. The adduct level increased in a relatively linear manner throughout the dose range. DNA adducts in small intestine tissue were similar and also increased with dose until 0.6% (1,364 mg/kg/day), but at the 1% dose level (2,000 mg/kg/day) the adduct level decreased. This decrease may have been due to decreased food consumption by the high dose animals (with a consequent decrease in delivered dose) since in a subsequent 2-year feeding study by the same authors (Culp et al. 1998), food consumption was significantly decreased in animals receiving this dose level.

Weyand et al. (1991) evaluated the relationship between coal tar creosote ingestion and systemic availability of coal tar components in male mice by measuring whole animal body weight, DNA adduct formation binding in several soft tissues, and urinary excretion of PAH metabolites. Coal tar creosote samples collected from 4 different coal gasification sites were incorporated separately at varying concentrations into the diet and fed to the mice for 15 days. DNA adduct levels were 4 times greater in animals fed a 0.5 or 1% diet relative to the levels detected in the 0.1 and 0.2% dietary groups. A dose-related increase in DNA adduct level was observed in the lung, which exhibited the highest levels of adducts relative to the other tissues. In contrast, no dose-related differences were exhibited in the forestomach. The levels of DNA adducts formed in lung, forestomach and spleen did not correlate with the total PAH content of the coal tar creosote samples (Weyand et al. 1991).

In another study by Weyand et al. (1994), live groups of B6C3F$_1$ mice were fed a control gel diet or adulterated diets containing 0.05, 0.25, or 0.50% mgP for 94 or 185 days. Consumption was equivalent to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females. The ^{32}P-postlabeling assay was used to evaluate mgP DNA adduct formation in lung and forestomach tissue from 2 animals of each sex after 94 days of treatment. The remaining animals (12 males, 12 females) from each group were maintained on diets for an additional 91 days. After a total of 185 days of treatment, two additional animals of each sex were used for DNA adduct analysis. A dose-related increase in DNA adduct levels was observed in both lung and forestomach tissue after 94 and 185 days of mgP ingestion. The levels of adducts ranged from 0.03 to 8.41 pmol/mg DNA; the highest DNA adduct levels were detected in animals treated with 0.50% mgP. The levels of DNA adducts detected in lung tissue were consistently higher than the levels observed in forestomach tissue.

In a study by Weyand and Wu (1995), female A/J and CD-l mice were fed either basal gel diets or diets to which had been added 0.25% (636 mg/kg/day) manufactured gas plant residue (MGP). Animals were sacrificed after 14 days. Lung and forestomach tissue was removed, pooled for group and examined for the presence of DNA adducts by 32P-postlabeling. Mice (A/J or CD1) which ingested MGP showed a high production of DNA adducts within lung tissue, but a much lower production of adducts within forestomach tissue. Treatment with MPG produced a range of DNA adducts (with three major components) similar to those seen with other complex mixtures. Two of the adducts produced by treatment with MPG were identified as those produced by benzo[a]pyrene (10% of the lung adducts, 47% of forestomach adducts) and benzo[b]fluoranthene (13% of the lung adducts); the identity of the third (41% of lung adducts, 32% of forestomach adducts) was unknown.

Goldstein et al. (1998) fed coal tar samples from manufactured gas plant waste sites to 7-week-old female A/J mice. MGP-M7 was a mixture of samples from seven waste sites and MGP-M3 was a mixture from two of the sites included in MGP-M7 plus a third site with a very high benzo[a]pyrene content. The coal tar samples were added to the feed at the following concentrations; 0.01, 0.03, 0.1, 0.3, 0.6, and 1% MGP-M7 and 0.01, 0.03, 0.1, and 0.3% MGP-M3. Animals received doses ranging from 25 to 2,778 mg/kg/day. Controls were fed unadulterated feed. After 2 weeks, DNA adduct formation was evaluated in lung tissue using 32P-postlabeling. In a second experiment, male $B6C3F_1$ mice were fed MPG-M7 at 0.1 to 2% (655 to 5,833 mg/kg/day) for 4 weeks. DNA adducts were examined in lung, liver, and forestomach tissue using ^{32}P-postlabeling. DNA adducts were detected in lung, liver, and forestomach of all mice fed MGP-M3 or MGP-M7. Adduct maps for mice fed coal tar gave a diffuse pattern typical of the patterns seen with complex organic mixtures. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located that dealt directly with an association between cancer and ingested coal tar or coal tar pitch in humans. A 56-year-old woman who had been consuming 3-4 cups daily of chaparral tea (an infusion of the leaves of the creosote bush) for a period of 3 months approximately 15 years prior to surgery was found to have cystic renal disease and cystic adenocarcinoma of the kidney (Smith et al. 1994). One of the components of chaparral tea is nordihydroguaiaretic acid. This chemical has been shown to produce cystic nephropathy in rats fed a 2% concentration for 6 weeks (Evan and Gardner 1979; Goodman et al. 1970). The concentration of nordihydroguaiaretic acid in chaparral tea is considerably

higher than that used to cause cystic nephropathy in animals and the authors conclude that the renal disease seen in their patient was most likely to have been due to consumption of chaparral tea.

A common Japanese folk remedy under the generic name “seirogan” and its relationship to stomach cancer is reported in a study by Weiner (1986). This preparation was used as a treatment for stomach aches, taken 3 times/day and the dose was equivalent to 260 mg creosote daily. The cancer distribution in Japan shows the highest incidence of stomach cancer reported in Toyoma where seirogan was produced and in prefectures close to Toyoma. However, the author notes that there may be other factors in addition to seirogan. At the time of the report, 35 different digestive remedies contained creosote.

Excess cases of breast cancer have been observed in St. Louis Park, Minnesota, that were tentatively associated with coal tar creosote contamination of the water supply (Dean et al. 1988). Coal tar creosote-derived PAHs were first detected in the water supply of St. Louis Park .in November 1978, but may have been there for decades. A l00-acre plot of coal tar creosote-contaminated soil on which stood a plant that used coal tar creosote and operated from 1917 to 1972 is believed to be the source of contamination. The levels of coal tar creosote or creosote-derived PAHs in the contaminated drinking water of St. Louis Park were not specified. There were 113 cases per 100,000 of breast cancer in St. Louis Park compared to 78 cases per 100,000 in the metropolitan Minneapolis-St. Paul area during 1969-l971. An attempt was made to demonstrate that these excess cases could be explained by known risk factors for breast cancer, such as age at first birth, parity, age at menarche and menopause, body mass index, history of benign breast disease, and familial history, and thus had no association with environmental exposure variables (Dean et al. 1988). The authors presented a method to adjust the breast cancer morbidity in St. Louis Park using data from a larger population with documented risk factors for breast cancer (“standard population”). These more stable rates based on breast cancer risk factors were determined in a larger study conducted by Helmrich et al. (1983). Dean et al. (1988) determined that the attributable risk due to the risk factors was higher for the breast cancer cases in St. Louis Park (0.598) than in the metropolitan Minneapolis-St. Paul area (0.311). They then used these attributable risks to calculate an adjusted morbidity ratio to estimate expected numbers of breast cancer cases in the community. After this adjustment, there appeared to be a higher expected number of breast cancer cases (n=134 per 100,000) than the observed number (113 per 100,000) in St. Louis Park, thereby negating any association with creosote in the water supply. It is necessary when using any standardization method in adjusting rates to ensure comparability among the groups in the study population that are being compared and between the study population and the standard population. It would appear that differences do exist between women in St. Louis Park, the metropolitan Minneapolis-St. Paul area, and the larger cohort studied by Helmrich

et al. (1983). These differences were not thoroughly examined by Dean et al. (1988) and could include differences in demographic, economic, and/or environmental factors. However, Dean et al. (1988) did note a difference in religious backgrounds between the study population described by Helmrich et al. (1983) and that of the St. Louis Park area. These dissimilarities indicate that the populations were not directly comparable and, therefore, adjustment of rates was not appropriate. The authors did not attempt to incorporate coal tar creosote contamination of water as an independent variable in their analysis.

The Minnesota Department of Health (1985) also reviewed the St. Louis Park data and concluded that this study did not provide adequate evidence to associate breast cancer with coal tar creosote-contaminated groundwater. They supported this conclusion with the following observations. It is not possible to classify individuals or residences within St. Louis Park according to their relative degree of historical exposure to PAH contaminants in drinking water because the pattern and history of municipal well contamination are not known; contaminant levels were measured at the well head and not at the tap; water treatment, storage, and distribution effects on contaminant concentration are not known; and much of the water distribution system is lined with coatings made of coal tar or asphalt. Furthermore, given the ubiquitous nature of PAHs, it is probable that exposures to PAHs from food would significantly exceed exposures from contaminated St. Louis Park well water. In addition, it was found that the specific PAHs (e.g., 3-methyl-cholanthrene) that have been shown to induce mammary tumors in rats (Dao 1964; Dao and Sunderland 1959) were either not present in contaminated wells or were detected very rarely even in the most highly contaminated wells. Furthermore, the many published case-control and cohort studies of breast cancer have not demonstrated clear-cut evidence of an association between breast cancer and smoking, which is a significant source of exposure to PAHs. These studies have also identified a number of risk factors that account for some of the observed variations in rates among different groups of women, and the women of St. Louis Park differ from those in the general Metro area with respect to several of the factors that are known to influence breast cancer rates.

In another analysis of the St. Louis Park data, cancer incidence rates in St. Louis Park were compared with those in Edina and Richfield and in the entire Minneapolis-St. Paul Standard Metropolitan Statistical Area (SMSA), using data from the Third Cancer Survey for 3 years, 1969-1971 (Dusich et al. 1980). Richfield was selected because it was a SMSA suburb similar to St. Louis Park in social and economic characteristics such as median school years completed, percentage high school graduates, occupation and median family income. Edina was selected because the creosote contamination was believed at that time to be moving toward Edina. The entire SMSA was used as a major comparison area. For males, no cancer rates in St. Louis Park were statistically significant from those in the three comparison areas.

Among females, age-adjusted rates for all cancers, cancers of the gastrointestinal tracts and breast cancer were higher in the St. Louis Park than in Edina, Richfield and the SMSA. The excess in gastrointestinal cancer rates for females was only slightly significant but all cancer combined and breast cancer had differences with a high degree of statistical significance.

Dietary exposure of male and female ddY mice to beechwood creosote at concentrations up to 532 mg/kg/day (which induced signs of toxicity) for 52 weeks induced no treatment-related increase in the incidence of tumors (Miyazato et al. 1984a). This study is limited, in that 52 weeks may not be a sufficient treatment duration to observe. an increase in the incidence of tumors in mice. However, these same authors reported that dietary exposure of male and female rats to 394 mg/kg/day beechwood creosote (which induced signs of toxicity) for 96 weeks also failed to result in any treatment-related increase in the incidence of tumors (Miyazato et al. 1984b). Based on these results, there is no evidence that ingested beechwood creosote is carcinogenic to mice or rats.

A feeding study in female A/J mice examined tumor induction after 260 days (Weyand et al. 1995). Treated mice ate diets to which had been added 0.25% coal tar (236 mg/kg/day) or 0.1% coal tar (100 mg/kg/day), while controls received either unadulterated food (negative control) or a diet containing benzo[a]pyrene (positive control). Mice that ingested coal tar had a significant increase in the incidence of lung tumors (70%) compared with controls (0%), but ingestion of coal tar did not produce any tumors of the forestomach. This is in contrast to ingestion of benzo[a]pyrene which produced a significant increase in incidence of tumors of the forestomach (but not lung tumors) compared with controls.

The most extensive studies of coal tar carcinogenicity to date are 2-year cancer bioassays carried out by Culp et al. (1996a, 1998). In the earlier of these two studies, female B6C3F_1 mice (5 weeks of age) were allocated to 14 dose groups consisting of 48 mice per group (Culp et al. 1996a). Coal tar was added to the animals feed at the following concentrations; 0, 0.01, 0.03, 0.1, 0.3, 0.6 (15 mg coal tar/day), and 1% (22 mg coal tar/day). Three groups of mice received feed with the following concentrations of benzo[a]pyrene; 5, 25, and 100 ppm. The coal tar was a mixture of samples from seven waste sites and corresponds to coal tar 1 in the later study (Culp et al. 1998). Feeding was continued for 2 years. All mice, including those that died during the experiment were examined grossly at necropsy. Forestomach tumors were found in all groups of mice fed coal tar or benzo[a]pyrene and incidence increased with dose. Tumors of the small intestine were only seen in mice fed 0.6 or 1.0% coal tar.

In the later study, coal tar samples from manufactured gas plant waste sites were added to the feed of 5-week-old female B6C3F$_1$ mice at the following concentrations; 0.01, 0.03, 0.1, 0.3, 0.6, and 1% (12, 33, 117, 333, 739, and 1,300 mg/kg/day) coal tar 1 and 0.01, 0.03, 0.1, and 0.3% (40, 120, or 346 mg/kg/day) coal tar 2 (Culp et al. 1998). Coal tar 1 was a mixture of samples from seven waste sites and coal tar 2 was a mixture from two of the sites included in coal tar 1 plus a third site with a very high benzo[a]pyrene content. Control mice received either unadulterated feed (negative control) or feed containing 5, 25, or 100 ppm benzo[a]pyrene. Mice fed coal tar 1 or 2 showed a significant concentration-related increase in incidence of neoplasms of the liver, lung, and forestomach and of hemangiosarcomas, histiocytic sarcomas, and sarcomas. Mice treated with coal tar 1 also showed a significant concentration-related increase in incidence of neoplasms of the small intestine. In contrast mice treated with benzo[a]pyrene showed a significant concentration-related increase in incidence of neoplasms of the forestomach, esophagus, tongue, and larynx. The authors concluded that the forestomach neoplasms produced by coal tar treatment may be due to the presence of benzo[a]pyrene, but that the other tumors produced by coal tar are likely to be due to the presence of genotoxic compounds other than benzo[a]pyrene. The small intestine-tumors produced by coal tar 1 may be due to chemical-lyinduced cell proliferation that occurred at high doses of coal tar.

A risk assessment based on the data from Culp et al. (1998) discussed the validity of using the concentration of a single component of coal tar (benzo[a]pyrene) to estimate the relative cancer risk for coal tar (Gaylor et al. 2000). The authors conclude that, in this experiment, benzo[a]pyrene dominated the cancer risk for coal tar when it was present at concentrations <6,300 ppm in the coal tar mixture, and in this case, the forestomach was the most sensitive tissue site. However, when benzo[a]pyrene was present in concentrations <6,300 ppm, the lung was the most sensitive site and benzo[a]pyrene did not contribute to the risk. In general, the concentration of benzo[a]pyrene in coal tar is unlikely to be as high as 6,300 ppm and, therefore, it probably should not be used as a measure of the cancer risk for coal tar.

Levels of exposure associated with CELs of creosote are indicated in Table 2-2 and Figure 2-2.

2.2.3 Dermal Exposure

This section describes the health effects observed in humans and laboratory animals associated with dermal exposure to coal tar creosote. All reliable exposure levels have been reported. Coal tar creosote exerts its toxic effects primarily via dermal exposure. Several reports were found that describe the occurrence of dermal and ocular irritation, burns, and “warts” (i.e., squamous papillomas) following acute

or prolonged skin contact with coal tar creosote. Coal tar creosote also induces phototoxicity of the skin, and has been demonstrated to be a skin carcinogen in animals. Conclusions that can be drawn from the results of animal studies are limited by the possibility of concurrent oral ingestion of creosote from the skin via normal preening behavior and by the fact that few studies reported accurate doses. Details of these reports are given below.

2.2.3.1 Death

No studies were located regarding death in humans following dermal or skin contact with creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles solely by this route. Evaluations of human exposure during employment in coal tar plants indicated significant increases in cancer-related deaths (TOMA 1982). No specific type of cancer was predominant. Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate death to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1982). Additional limitations were identified in this study, including absence of data on smoking habits, short cut-off date of 10 days of employment, unknown race classification for 20 of participants, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and the relationship between the cohort and production history was not explored.

In test animals, a dermal LD_{50} in rabbits of >7,950 mg/kg was estimated following a 24-hour application of coal tar creosote to both intact and abraded skin; two of four rabbits died at the high dose of 15,800 mg/kg (Plitzer et al. 1965). This LOAEL value is recorded in Table 2-3. Additional reports of deaths in test animals, after dermal application of coal tar or coal tar pitch volatiles, can be found in the literature, although specific details of the studies are missing (Bonser and Manch 1932; Deelman 1962). Wallcave et al. (1971) treated groups of Swiss albino mice topically with 9% benzene solutions of 2 coal tar pitches of known PAH content. An additional group of 15 male and female mice were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Mean survival time for animals painted with coal tar pitch and control animals was 3 1 and 82 weeks, respectively. Asphalt (500 mg/mL) and coal tar pitch (30-84 mg/mL) were the materials used in assessing skin carcinogenesis in nonpigmented Swiss CD-l and pigmented C3H/HeJ male mice (Niemeier et al. 1988). The mean survival time for treated C3H/HeJ ranged from 44.3 to 68.7 weeks compared to 65.6-73.9 for the controls. The mean

Table 2-3. Levels of Significant Exposure to Creosote - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Rabbit	once				15800 (2/4 died)	Pfitzer et al. 1965 coal
Systemic						
Rat (Sprague-Dawley)	4 d Gd 11-15 1x/d	Hepatic		500 F (significant increase in relative liver weight)		Zangar et al. 1989 coal tar
		Renal		500 F (significant increase in relative kidney weight)		
		Endocr	1500 F			
		Bd Wt		500 F (15% decrease in body weight)	1500 F (30% decrease in body weight)	
Mouse (t.o.)	1-3 wk 7 d/wk 1 x/d	Dermal		5% M (irritation)		Wrench and Britten 1975 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d	Hepatic		500 F (significant increase in relative liver weight)		Zangar et al. 1989 coal tar
		Renal		500 F (significant increase in relative kidney weight)		
		Endocr	1500 F			
		Bd Wt	1500 F			
Rabbit (New Zealand White)	once	Ocular		0.1 mL M (conjunctival redness)		Pfitzer et al. 1965 coal tar

Table 2-3. Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Rabbit (New Zealand White)	once	Gastro	7950 M	15800 M (intestinal hyperemia)		Pfitzer et al. 1965 coal tar
Immunological/Lymphoreticular						
Rat (Sprague-Dawley)	4 d Gd 11-15 1x/d			500 F (significant decrease in relative weight of thymus)		Zangar et al. 1989 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d			500 F (significant increase in relative weight of spleen)		Zangar et al. 1989 coal tar
Reproductive						
Rat (Sprague-Dawley)	4 d Gd 11-15 1x/d				500 F (significant increase in resorptions and decrease in uterine weight)	Zangar et al. 1989 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d			500 (significant decrease in uterine weight)	1500 F (significant increase in resorptions)	Zangar et al. 1989 coal tar
Developmental						
Rat (Sprague-Dawley)	4 d Gd 11-15 1x/d				500 (significantly increased incidence of small lungs, cleft palate, edema, midcranial lesion and reduced cranial ossification)	Zangar et al. 1989 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d				500 (significantly increased incidence of cleft palate, dilated ureter and renal pelvic cavitation).	Zangar et al. 1989 coal tar

Table 2-3. Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg)	LOAEL Less serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
Cancer						
Mouse (CD-1)	once				5555 M (initiation of skin tumors)	Mahlum 1983 coal tar
Mouse (CD-1)	once				203 F (initiation of skin tumors)	Springer et al. 1989 coal tar
INTERMEDIATE EXPOSURE						
Systemic						
Rabbit (Australian albino)	3 wk 5 d/wk	Dermal	0.01% M	0.1% M (comedogenicity)		Kligman and Kligman 1994 coal tar
Rabbit (Australian albino)	10 wk 5 d/wk	Dermal		10% M (small visible comedones in 2 wks)		Kligman and Kligman 1994 birch tar
Cancer						
Mouse (Sutter)	4-28 wk 2 x/wk				0.025 F mL (CEL: papillomas and carcinomas)	Boutwell and Bosch 1958 coal tar
Mouse (Swiss-albino)	31 wk 2 x/wk				1.7 mg (CEL: squamous cell carcinoma and papillomas in 53/58)	Wallcave et al. 1971 coal tar pitch volatiles
Rabbit (Australian albino)	15 wk 3 x/wk				10% M (CEL: papillomas, squamous cell carcinoma,s keratoacanthomas & cutaneous horns)	Kligman and Kligman 1994 coal tar

Table 2-3. Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE						
Death						
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				30-84 M mg/mL (mean survival time for C3H/HeJ; treated = 44.3-68.7 wks, control = 65.6-73.9 wks; for CD-1; treated = 52.6-67.8 wks, control = 63.9-67.8 wks)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				500 M mg/mL (mean survival time for C3H/HeJ; treated = 44.3-68.7 wks, control = 65.6-73.9 wks; for CD-1; treated = 52.6-67.8 wks, control = 63.9-67.8 wks)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				500 M mg/mL asphalt + 30-84 mg/mL coal tar pitch (deaths)	Niemeier et al. 1988 CTPV
Systemic						
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2x/wk	Bd Wt	30-84 M mg/ml			Niemeier et al. 1988 CTPV

Table 2-3. Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL	LOAEL		Reference Chemical Form
				Less serious	Serious	
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2x/wk	Bd Wt	500 M mg/ml			Niemeier et al. 1988 CTPV
Cancer						
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				30-84 M mg/mL (CEL: skin tumors)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				500 M mg/mL (CEL: skin tumors)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				500 M mg/mL asphalt + 30-84 mg/mL coal tar pitch (CEL: tumors)	Niemeier et al. 1988 CTPV
Mouse (C57L)	lifetime 3 x/wk				20% F (CEL: papillomas 100% incidence)	Poel and Kammer 1957 coal tar

Bd Wt = body weight; CEL = cancer effect level; CTPV = coal tar pitch volatiles; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; wk = week(s); x = times

survival time for the treated CD-l mice ranged from 52.6 to 67.8 weeks compared to 63.9-67.8 weeks for controls.

2.2.3.2 Systemic Effects

No studies were located regarding the musculoskeletal, endocrine, or body weight effects in humans or respiratory, musculoskeletal, or endocrine effects in animals after dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Studies regarding the systemic effects that have been observed in humans and animals after dermal exposure to creosotes are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-3.

Respiratory Effects. In an industrial health survey of employees in 4 wood preservative plants in which coal tar creosote and coal tar were the main treatments used, decreased pulmonary function was noted (TOMA 1978). Restrictive deficits in pulmonary function, as indicated by decreases in forced vital capacity (FVC), were noted in 44 of 257 employees (10 of 47 nonsmokers). Obstructive deficits, as indicated by decreases in percentage forced expiratory volume in one second (FVEl) were noted in 19 of 257 employees (3 of 54 nonsmokers). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate respiratory effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1978). Additional limitations of the studies included seasonal and geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy workers, lack of statistical analyses, lack of adequate controls, and use of only current employees.

A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (ATSDR 1994). The plant had ceased creosoting activities in 1961, after operating for 51 years. A sand and gravel company had operated on part of the abandoned site during the 1970s and 1980s. Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the National Priorities List (NPL) in 1984. Several residential lots were observed to have soil concentrations of benzo[a]pyrene in excess of 325 mg/kg, or oily-stained areas, and were subject to emergency resodding by the EPA. Contaminated soils were scheduled to be treated for clean-up. A total of 214 residents (123 males, 91 females) of the

contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents (122 males, 93 females) from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results. There was no statistically significant increase in the incidence of bronchitis in residents from the Koppers area compared to the regional comparison group, when data were adjusted for health belief (i.e., the belief that health was affected by chemicals in or near their homes). Similarly, there was no significant increase in the incidence of bronchitis in the Koppers population compared to the 1990 National Health Interview Survey.

Cardiovascular Effects. In an industrial health survey of employees in 4 wood preservative plants in which coal tar creosote and coal tar were the main treatments used, cardiovascular effects, including increased diastolic blood pressure, were noted in 21% (24/l13) of the employees examined (TOMA 1978) Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate cardiovascular effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1978). Additional limitations of the study are listed above under Respiratory Effects.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to creosotes, coal tar, or coal tar pitch. In an acute animal study, New Zealand white rabbits that died following single dermal applications of undiluted coal tar creosote (15,800 mg/kg) exhibited hyperemia of the intestines, but animals treated with 7,950 mg/kg did not (Ptitzer et al. 1965). Hematological Effects. In an industrial health survey of employees in 4 wood preservative plants in which coal tar creosote and coal tar were the main treatments used, hematological effects, including increased number of white blood cells (basophils), were noted in 6% (15 of 257) of the employees examined (TOMA 1978). Similarly, 12% of the employees in 8 of 9 coal tar plants surveyed had increased white blood cells (eosinophils) (TOMA 1979). Industrial hygiene surveys of coal tar pitch volatiles at the 4 wood preservative plants indicated that in 94% of the samples, airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 (TOMA 1978). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1978).

No determination of exposure was made at the nine coal tar plants (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate hematological effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1978, 1979). Additional limitations of the studies are noted above (see "Respiratory Effects").

In a clinical study, 15 patients (Group A) with chronic plaque psoriasis were treated with increasing concentrations (14%) of topical coal tar paste (Gilmour et al. 1993). These patients did not receive ultraviolet (UV) therapy and served as controls. Seventeen subjects (Group B) received UV-B phototherapy and four subjects (Group C) received psoralen photochemotherapy (PUVA). Another control group (Group D) consisted of 4 nonpsoriatic subjects who were receiving UV-B as part of another study. Samples of blood were collected before irradiation and 48 hours after irradiation, and full blood counts were determined. Samples taken from Group A were taken before treatment and again 4 weeks later. Samples taken from Group B and C were taken before treatment, 4 weeks after treatment (48 hours after irradiation), and finally 4 weeks after irradiation. The blood counts were all normal. A similar lack of adverse effect on the hematological system was observed by Tham et al. (1994) in psoriasis patients who applied a total of 120 g of coal tar over a period of 2-6 weeks to the skin of one side of their body.

Hepatic Effects. Fifteen patients (Group A) with chronic plaque psoriasis were treated with increasing concentrations (l-4%) of topical coal tar paste (Gilmour et al. 1993). An additional 17 subjects (Group B) received UV-B phototherapy and 4 subjects (Group C) received psoralen photo-chemotherapy (PUVA). Another control group (Group D) consisted of 4 nonpsoriatic subjects who were receiving UV-B as part of another study. Liver function was determined. Samples taken from Group A were taken before treatment and again 4 weeks later. Samples taken from Group B and C were taken before treatment, 4 weeks after treatment (48 hours after irradiation), and finally 4 weeks after irradiation. Liver function was within normal limits. A similar lack of adverse effect on liver function was observed by Tham et al. (1994) in psoriasis patients applying 120 g of coal tar to their skin twice daily for 2-6 weeks.

In a developmental study of Sprague Dawley rats and CD-1 mice exposure to 500, or 1,500 mg/kg coal tar on gestational days 11-15, resulted in significant increases in maternal liver to body weight ratios for treated animals from both species compared with controls (Zangar et al. 1989).

Renal Effects. In an industrial health survey of employees in 9 coal tar plants in which coal tar creosote and coal tar were the main treatments used, renal effects, including protein and cells in the urine were noted in l-8% (3-34 of 452) of the employees examined (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate renal effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979). A study performed by Wright et al. (1992b) evaluated the nephrotoxic effects of commercial coal tar preparation for the scalp. The preparation was applied to healthy human subjects either for 15 minutes, twice a week, for 8 weeks to uncovered skin, or for 30 minutes, every second day for 4 weeks under occlusive bandage. The preparations tested contained 5 or 10% beechwood tar. The concentration of coal tar in the preparation was not specified. Renal function and urinary phenol levels were assayed before, during, and after treatment. No impairment of renal function was detected, nor was urinary phenol content found to be related to the coal tar treatment (Wright et al. 1992b). No adverse effect on urinalysis was observed for 15 patients with chronic plaque psoriasis were treated with increasing concentrations (l-4%) of topical coal tar paste in urine samples taken before treatment and 4 weeks after treatment (Gilmour et al. 1993).

In a developmental study of Sprague Dawley rats and CD-1 mice exposed to 500, or 1,500 mg/kg coal tar on gestational days 11-15, exposure of rats or mice to coal tar resulted in significant increases in maternal kidney to body weight ratios for treated animals compared with controls (Zangar et al. 1989).

Renal effects were also noted in a study conducted by Deelman (1962), in which mice were exposed dermally to an unspecified amount of tar applied 6-l8 times over 6-7 weeks. “Seriously affected” kidneys were noted, although no details or data were presented. Ten groups of Swiss albino mice received topical applications of 10% benzene solutions of 8 petroleum asphalts of known polynuclear aromatic hydrocarbon content (Wallcave et al. 1971). An additional group of 15 males and females were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of asphalt were painted in this area 2 times/week with 25 mL of solution (approximately 2.5 mg asphalt per treatment). Amyloidosis was frequently observed in animals receiving asphalt, particularly in the kidney.

Endocrine Effects. In a developmental study of Sprague Dawley rats and CD-l mice exposure to 500 or 1,500 mg/kg coal tar on gestational days 11-15, produced no change in weight of the adrenal glands of treated animals from both species compared with controls (Zangar et al. 1989).

Dermal Effects. Burns and irritation of the skin are the most frequent manifestations of coal tar creosote toxicity following dermal exposure. Creosote burns were observed in construction workers who handled wood treated with creosote (presumably coal tar creosote) (Jonas 1943). Exposure levels were not specified. It was found that 70% of the burn cases were mild and were characterized by erythema of the face. These symptoms were more marked on the cheeks, nose, forehead, and posterior part of the neck. The remainder of the burn cases (30%) were more severe and were characterized by intense burning, itching, and considerable subsequent pigmentation followed by desquamation. There is no way to determine, given the information provided, whether this response was due to primary irritation or an allergenic response. Other reports of skin irritation after contact with coal tar (Cusano et al. 1992) or the creosote bush (Leonforte 1986; Smith 1937) were found. Patients admitted over a 4-month period to the dermatology wards of Manchester Skin Hospital for the treatment of psoriasis were patch tested with 3% coal tar (Burden et al. 1994). A positive reaction to coal tar was followed by dilution series testing down to a 0.1% concentration of coal tar. Patients were asked about previous psoriasis treatment and adverse reactions from topical preparations. Mean duration of psoriasis was 20 years and many patients had been treated as inpatients previously on numerous occasions; 91% of patients recalled previous treatment with coal tar. Thirteen patients showed clinical intolerance to coal tar and two had positive patch test reaction to coal tar confirmed by serial dilutions. In another study, 5% crude coal tar (CCT) was applied to the backs of eight subjects in six distinct sites for 15, 30, 60, 90, 120, and 180 minutes (Diette et al. 1983). Tar was then vigorously removed with a washcloth, Ivory soap, and water. Immediately following tar removal, the minimal phototoxic dose (MPD) of UV-A was determined at each site using l-cm diameter apertures. In all subjects, the minimal erythema dose (MED) and MPD were defined as the minimal dose of UV-A causing 1+ erythema with distinct borders read at 24 hours after exposure. In addition, 5% CCT was applied to four separate sites on the backs of 13 subjects for 1 hour. The following methods of tar removal were compared: (1) water, (2) Ivory soap and water, (3) mineral oil, and (4) Ivory soap and water followed by mineral oil. Immediately after tar removal all sites were exposed to UV-A and the MPD of UV-A was determined. UV-A exposure doses were identical to those used above. A 5% CCT ointment was applied to the backs of 19 subjects and removed 1 hour later with a washcloth, Ivory soap, and water, The subjects were informed prior to testing about the photosensitizing effect of tar plus UV-A in producing a burning, stinging, or smarting reaction at an unspecified time during UV-A exposure. These subjects would signal the onset of symptoms and were encouraged not to wait until the burning

sensation became unbearable. Subjects were tested immediately and at 0.5, 2, 4, 6, 24, and 30 hours following tar removal. At least 8 subjects were tested at each time; only at 24 and 30 hours were <10 subjects tested. Using the same UV-A exposure times, the MED of UV-A was determined in those eight subjects tested at 24 and 30 hours. The minimal UV-A dose required to induce delayed erythema (the MPD) and the minimal UV-A dose required to induce an immediate smarting reaction (minimal smarting dose or MSD) were recorded. The effects of the following variables on MPD were noted: (1) interval of time tar is left on the skin (TA); (2) methods of tar removal; and (3) time between removal of tar and UV-A irradiation. Tar application for 30 minutes was photosensitizing in all eight subjects; six of the subjects showed photosensitization after only 15 minutes of tar application. The photosensitizing effect of tar increased rapidly up to 60 minutes of application. MPD increased from 3.77±1.55 to 6.1± 4.0 J/cm^2 after 30 minutes of application. Longer time intervals between tar removal and UV-A exposure were accompanied by more gradual, but consistent, increases in MPD. The MSD also significantly increased with increasing intervals between tar removal and UV-A exposure. At times the smarting reaction was associated with an immediate erythema which faded in several hours; this was not a consistent finding with 1 MSD of UV-A. No urticarial response was noted at this dose level.
Other studies confirm that coal tar creosote is capable of inducing phototoxicity of the skin.

Phototoxicity is an exaggerated response to sun exposure characterized by excessive sunburn. The usual sunburn is produced by UV-B light, whereas a phototoxic skin response occurs following absorption of UV-A light by chemicals in or on the skin (NIOSH 198la). Coal tar creosote exposure was evaluated in six male dock builders of Scandinavian descent with fair skin and an average of 16.6 years work as pile-drivers (NIOSH 1981a). The dermal burning and irritation experienced by these workers upon dermal contact with wood treated with coal tar creosote was exacerbated on hot or sunny days. Skin examinations of these dermally exposed workers revealed erythema and dry peeling skin on the face and neck with irritation and folliculitis on the forearms. These symptoms were worse on hot or sunny days, at which time red, swollen, and puffy eyes were observed. Thus, phototoxicity compounds the irritative response of the skin to coal tar creosote. No skin tumors were observed. Similar effects were noted in workers transferring coal tar pitch from a river barge to an ocean barge (NIOSH 1982). Exposure levels of coal tar pitch volatiles measured were considered to represent the minimum ambient air exposure in the barge area because of unusual environmental sampling conditions. These levels ranged from below the detectable limit to 0.06 mg/m^3 for breathing zone samples and from below the detectable limit to 0.02 mg/m^3 for area samples. Other studies have been published that describe similar effects of coal tar exposure, although exposure levels are not specified (Emmett 1986).

Coal tar creosote has been reported to produce types of noncancerous skin lesions other than burns and irritation following dermal exposure (Haldin-Davis 1935; NIOSH 1982; Schwartz 1942; Shambaugh 1935). Haldin-Davis (1935) described the case of a man employed in the activity of dipping wood in creosote tanks who received "heavy" dermal exposure to coal tar creosote (level not determined) on the face, trunk, and thighs. He subsequently developed a number of lesions on the hands, forearms, and thighs. One of these lesions was excised and examined, and classified as a benign squamous cell papilloma. A study was made of the cases of cancer of the lip at various New England hospitals (Shambaugh 1935). Men who were constantly exposed to tars were those who worked in "net lofts" where the fishing nets are repaired and tarred. It was common practice to hold the large wooden shuttle-like needle in the mouth while the tarred nets are being mended. The needle soon becomes smeared with the tar, which is thus carried to the lip. It was found that the older workers who had been exposed to the tar for many years showed typical tar warts on the hands and forearms. An irritative condition on the forearms which they call "pinginitis," evidently a pustular folliculitis (not cancerous), was observed. Three workers in factories erected for manufacturing armaments developed symptoms a week or two after beginning work that were attributed to the creosote which evaporated off the wooden floors (Schwartz 1942). It was likely that the fresh creosote on the blocks came in contact with the ends of the trousers and rubbed against the ankles. These employees noticed that their ankles began to itch above the shoe tops and later an erythematous, papular, and vesicular eruption appeared. The lesion extended 4 or 5 inches above the shoe tops, and when seen, presented the appearance of a scratched eczematoid dermatitis. Their condition improved over the weekend. One patient, before the etiology of the condition was discovered, had been treated with a coal tar ointment and the dermatitis became worse. Patch tests were not performed with scrapings from the wooden blocks.

In an industrial health survey of employees in 4 wood preservative plants in which coal tar creosote and coal tar were the main treatments used, dermal effects, including skin irritation, eczema, folliculitis, and benign growths on the skin were noted in 33% (82 of 251) of the employees examined (TOMA 1978). Workers in nine coal tar plants had a 20% incidence of these same dermal effects (TOMA 1979). The incidence of benign growths, eczema, and folliculitis was greater than that observed in the general U.S. population. However, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate dermal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1978, 1979). Additional study limitations are noted above under "Respiratory Effects."

The National Institute for Occupational Safety and Health (NIOSH) has investigated potential employee-related health effects in mixers and laborers exposed to coal tar/coal tar creosote/clay products in a refractory cement factory (NIOSH 1980a). Six of seven environmental samples collected exceeded the Permissible Exposure Limit (PEL) for coal tar products (cyclohexane solubles, which include creosote) of 0.1 mg/m'. Exposures were reported to be as high as 1.42 mg/m^3. Because environmental levels significantly exceeded the PEL, it is likely that considerable dermal exposure occurred. One worker reported the need for medical treatment when coal tar creosote splashed in his eye, and another claimed that he was hospitalized for 3 days after experiencing convulsions following an incident where he was splashed with coal tar creosote. The medical records for these two men were not reviewed.

A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant revealed dermal effects of creosote exposure in the residents (ATSDR 1994). Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. Residents living in or near the Koppers area reported a higher prevalence of skin rashes (27.9%) during the first year of the surveillance than the comparison neighborhood (4.9%), with a RR of 5.72. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results, and similar results were obtained, with 34 Koppers residents reporting skin rashes, compared to an expected incidence of 4. Rashes were associated with digging in the yard, having contact with the soil, or wading in or having contact with a creek in the area. Most rashes were associated with itching or burning. The recommendation was that residents in the Koppers area should wear protective clothing when having contact with the soil, and should wash their skin thoroughly when contact with the soil occurs.

Beechwood creosote has been found to irritate tissue other than skin. The effects of beechwood creosote (dose not specified) on the periapical tissue (the connective tissue surrounding the apex of the tooth) were studied in 10 teeth from 4 different dogs 7 days after its application following root canal surgery (Attalla 1968). Beechwood creosote application resulted in localized inflammatory changes and occasional abscess formation in the periapical region, presumably due to tissue damage caused by coagulation of proteins. Bone resorption was observed in the alveolar process. The authors concluded that beneficial disinfectant properties of beechwood creosote may be outweighed by irritant effects following root canal surgery.

Skin irritation is also observed in laboratory animals following dermal exposure to coal tar creosote. The effects of dermally applied coal tar fractions, derived from creosote and anthracene oils by high-temperature boiling, were studied in mouse tail skin at concentrations of 5 and 10% (acids) in paraffin by Wrench and Britten (1975). Several of the fractions caused irritation, and some caused peeling and epidermal thickening. The authors concluded that the acids that boiled in the range from 280 to 340 ºC have a more specific action in inducing granular layers than the parent tars, oils, or whole acids at similar concentrations. This study is of limited value because the chemical composition of the acid fractions was not defined, and no dose levels could be quantified. It can only be concluded that certain fractions of coal tar creosote irritate mouse skin. Three samples of Scottish blast-furnace tar (I, II, and III), one sample of English tar, and an ether extract of English tar were applied in a clipped area of skin in the region between the shoulder blades of 60 mice (Bonser and Manch 1932). Tar was applied biweekly for the first 14 weeks, and thereafter once weekly. This change in the frequency of the tar applications was necessitated by the rather marked tendency to ulceration of the skin exhibited by many of the mice. This experiment was continued for 56 weeks, by which time all mice had died. At 30 weeks, 35 of 60 mice applied with ether extract of English tar died and among the 25 survivors, 50% bore tumors. The first appearances of warts in mice applied with Scottish tar (samples I, II, & III), English tar sample, and ether extract of English tar was in 16 (7 of 60 animals), 21 (8 of 60 animals), and 12 (24 of 60 animals) weeks, respectively. Warts were confirmed histologically in 4, 3, and 16 mice (per sample), treated with Scottish tar (samples I, II, and III), English tar, and ether extract of English tar, respectively. The skin of 10 groups of Swiss albino mice was treated with 9% benzene solutions of two coal tar pitches of known PAH content (Wallcave et al. 1971). An additional group of 15 males and females were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Animals exhibited hyperplasia of the epidermis as a general phenomenon, frequently accompanied by inflammatory infiltration of the dermis and on several occasions ulceration with formation of small abscesses. This effect was also seen after application of a 10% solution of petroleum asphalts (Wallcave et al. 1971). Guinea pigs also exhibited phototoxicity after dermal treatment with coal tar pitch distillates and UV light (Emmett 1986). In addition, the histological effects of coal and birch tar on guinea pig teat epidermis treated over a period of 22 days have been investigated (Schweikert and Schnyder 1972a, 1972b). Preparations of both coal and birch tar induced a proliferate acanthosis.

Rabbits given single dermal applications of undiluted coal tar creosote exhibited slight to moderate erythema and moderate edema followed by severe hyperkeratosis (Pfitzer et al. 1965).

Birch tar (10%) or coal tar (0-l.0%%), was applied to the ear of male Australian albino rabbits for 3 weeks, 5 days/week (Kligman and Kligman 1994). Cornedones were visible on the ear after 2 weeks of treatment with the birch tar, and after 3 weeks of treatment with 0.1 or 1.0% coal tar.

In summary, dermal application of either coal tar or beechwood creosote results in mild-to-severe irritation of the skin, and other exposed tissues, as well as benign skin lesions in both humans and animals. Coal tar creosote also induces phototoxicity, so exposure to the sun exacerbates its irritant effects.

Ocular Effects. Direct exposure of the eye to coal tar creosote is irritating to the superficial tissues. Factory and construction workers, roofers, and other workers who handle coal tar, or wood treated with coal tar creosote have experienced conjunctiva burns and irritation resulting from accidental exposure (Birdwood 1938; Emmett 1986; Jonas 1943; NIOSH 1980a, 1981a). Exposure to the sun exacerbated eye irritation from exposure to creosote or coal tar fumes. Specific length of exposure or amount of creosote was not included in these articles.

Similar effects (tearing, phototoxicity, and keratoconjunctivitis) have been observed in animals, including C3H/HeJ mice and New Zealand rabbits (Emmett 1986). Instillation of 0.1 mL undiluted coal tar creosote in the eyes of New Zealand white rabbits produced a redness of the conjunctiva with congested vessels that resolved within 7 days (Ptitzer et al. 1965).

Body Weight Effects. In a developmental study of Sprague Dawley rats and CD-1 mice, exposed to 0, 500, or 1,500 mg/kg coal tar on gestational days 11-15, exposure of rats to coal tar resulted in significant decreases in extragestational body weight for treated animals compared with controls while exposure of mice to coal tar produced no significant change in extragestational body weight for treated animals compared with controls (Zangar et al. 1989). Body weight effects were noted in a study conducted by Deelman (1962), in which mice were exposed dermally to an unspecified amount of tar applied 6-l8 times over 6-7 weeks. “Diminished weight” was noted, although no details or data were presented. Asphalt (50 µL of a 500 mg/mL solution) and coal tar pitch (50 µL of a 30-84 mg/mL solution) applied to an unspecified area of the skin of Swiss CD-l and pigmented C3H/HeJ male mice 2 times/week for 78 weeks had no adverse effect on body weight (Niemeier et al. 1988).

2.2.3.3 Immunological and Lymphoreticular Effects

Several cases of acute allergic dermatitis have been reported following contact with the creosote bush. Smith (1937) described the case of a patient who presented with erythematous and vesicular dermatitis of the face, the upper part of the neck, and the backs of the hands after collecting creosote bush. Patch tests confirmed the existence of an allergy to this plant. Leonforte (1986) reported six cases of acute allergic dermatitis subsequent to contact with a creosote bush and confirmed by a patch test. Two cases were a result of "casual occupations," two were a result of household remedies, and two were a result of burning the bush. Based on his findings, the author concluded that the allergens are probably contained in the plant's perfume, are volatile, and are not destroyed by heat. The relevance of these findings to individuals who live in areas surrounding hazardous waste sites and who will most likely be exposed to coal tar creosote is questionable. Creosote bush resin differs from creosote extracted from coal and wood tar, but all contain phenolic derivatives. It is not known whether these derivatives are the allergens in creosote bush resin.

Contact dermatitis has also been reported after short-term contact with coal tar (Cusano et al. 1992). No adverse immunological effects were observed in patients with chronic plaque psoriasis who were treated with increasing concentrations (l-4%) of topical coal tar paste (Gilmour et al. 1993). Autoantibodies, serum immunoglobulin and complement levels were measured; two patients with psoriasis had slightly elevated IgE levels and several had slightly raised concentrations of serum immunoglobulin isotopes and complement components, but these were within normal ranges in most psoriasis patients. Percentages of subsets of peripheral blood mononuclear cells (PBMC) were normal and were not altered by treatment. Lymphocytic infiltration was noted in the pathological evaluation of a tar carcinoma excised from the eyelid of a tar and pitch worker (Goulden and Stallard 1933).

There is very little information describing immunological and lymphoreticular effects of wood or coal tar products in animals after dermal exposure. In a developmental study of Sprague Dawley rats and CD-l mice exposure of rats to 500, or 1,500 mg/kg coal tar on gestational days 11-15, resulted in significant decreases in maternal thymus to body weight ratios for treated animals compared with controls while spleen weights were similar in control and treated animals (Zangar et al. 1989). Exposure of mice to coal tar produced a significant increase in maternal spleen to body weight ratios for treated animals compared with controls, while thymus weights were similar in control and treated animals (Zangar et al. 1989). Amyloidosis of the spleen and inflammatory infiltration of the dermis were observed in Swiss mice after

topical application of 2.5 mg asphalt in 10% benzene solutions twice weekly for 81-82 weeks (Wallcave et al. 1971).

2.2.3.4 Neurological Effects

A worker who was splashed with coal tar creosote in a refinery claimed that he was hospitalized for 3 days after experiencing convulsions (NIOSH 1980b). The medical records for this man were not reviewed, so it cannot be concluded that creosote exposure was responsible for his convulsions. No additional information was provided. Observations were made of the effect of coal tar creosote on workers constructing buildings with treated wood (Jonas 1943). Complications observed in 2.4% of the workers included neurological symptoms including headache, weakness, confusion, vertigo, and nausea. No studies were located regarding neurologic effects in animals following dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.

2.2.3.5 Reproductive Effects

No studies on the reproductive effects produced by dermal exposure to wood creosote, coal tar pitch, or coal tar pitch volatiles in human or animals were located. One retrospective human study of dermal exposure to coal tar was located in which 64 women who had been treated with coal tar for psoriasis or dermatitis were issued questionnaires (Franssen et al. 1999). Fifty-six of the women returned the questionnaires. The ratio of dermatitis to psoriasis was 1:2 with a mean percentage treated body area of 78-90%, and the women were between 18 and 35 years of age for the period of the study (1981-1985). In total the women had been pregnant 103 times. In 59 out of 103 pregnancies, no coal tar had been used; in 21 pregnancies, it was unclear whether coal tar had been used or not, and in the remainder, coal tar had been used at some point during pregnancy. Untreated pregnancies resulted in 19% spontaneous abortion while treated pregnancies resulted in 26% spontaneous abortion. The authors did not consider this to be a significant increase in spontaneous abortion compared with the general population, but pointed out that their sample size was small and this study probably did not have sufficient resolution to detect a modest increase in risk.

A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant revealed no adverse reproductive effects in the residents (ATSDR 1994).

There was no difference in the reproductive outcome of female residents of the Koppers area compared to the comparison neighborhood or the 1990 National Health Interview Survey. In particular, there was no effect on number of pregnancies, live births, premature births, spontaneous abortions, or still births. Koppers women who reported having problems becoming pregnant during the first year of surveillance had an average of 1.3 pregnancies compared to an average of 3.4 pregnancies from women in the comparison neighborhood who also reported difficulty in becoming pregnant. No difference in pregnancy outcome was noted during the second year of surveillance.

In a developmental study of Sprague Dawley rats and CD-l mice, exposure to 500, or 1,500 mg/kg coal tar on gestational days 1l-l 5, resulted in significant decreases in uterine weight (Zangar et al. 1989). No difference in extragestational body weight gain of the mouse dams was observed, but some maternal toxicity in the form of significantly increased weights of the liver, kidney, and spleen was seen. The extragestational body weights of treated rats were significantly decreased compared to controls and the relative weights of maternal liver and kidney were significantly increased while those of the thymus were significantly decreased. The relative weights of the spleen and adrenal glands were unaffected by treatment. Resorptions were significantly increased for all exposed rats and high dose mice compared to controls. Early resorptions (occurred before dosing) were similar in all groups, but middle resorptions (which corresponded to the dosing period) were significantly increased in exposed rats and high dose mice. Late resorptions were also significantly increased in exposed rats.

2.2.3.6 Developmental Effects

No studies on the developmental effects produced by dermal exposure to wood creosote, coal tar, coal tar pitch, or coal tar pitch volatiles in humans were located. A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant (ATSDR 1994). There was no difference in the number of low birth weight births or birth defects. One retrospective human study of dermal exposure to coal tar was located in which 64 women who had been treated with coal tar for psoriasis or dermatitis were issued questionnaires (Franssen et al. 1999). Fifty-six of the women returned the questionnaires. The ratio of dermatitis to psoriasis was 1:2 with a mean percentage treated body area of 78-90%, and the women were between 18 and 35 years of age for the period of the study (1981-1985). In total, the women had been pregnant 103 times. In 59 out of 103 pregnancies no coal tar had been used, in 21 pregnancies it was unclear whether coal tar had been used or not and in the remainder coal tar had been used at some point during pregnancy. Untreated

pregnancies resulted in 5% congenital disorders while treated pregnancies resulted in 4% congenital disorders. The authors pointed out that their sample size was small and this study probably did not have sufficient resolution to detect a small increase in risk.

In a developmental study of Sprague Dawley rats and CD-l mice exposed to 0, 500, or 1,500 mg/kg coal tar on gestational days 11-15, exposure of rats and mice to coal tar resulted in significant increases in developmental defects (Zangar et al. 1989). Both rats and mice exposed to coal tar showed a significant decrease in uterine weight compared with controls. No difference in extragestational body weight gain of the mouse dams was observed, but some maternal toxicity in the form of significantly increased weights of the liver, kidney, and spleen was seen. The extragestational body weights of treated rats were significantly decreased compared to controls and the relative weights of maternal liver and kidney were significantly increased while those of the thymus were significantly decreased. The relative weights of the spleen and adrenal glands were unaffected by treatment. Fetal and placental weights and crown-rump lengths decreased in a dose dependant manner and fetal lung weights were decreased on absolute and relative weight basis for both low and high dose rat groups. There was no significant difference between fetal weight, placental weight, and fetal lung weights and crown-rump lengths in control and exposed mouse fetuses. A significantly increased incidence of small lungs, cleft palate, edema, midcranial lesion, and reduced cranial ossification was observed in exposed rat fetuses and a significantly increased incidence of cleft palate, dilated ureter, and renal pelvic cavitation was observed in exposed mouse fetuses.

Another animal study reported that dermal contact with coal tar creosote-treated wood produced fetotoxic effects in pregnant sows (Schipper 1961). Four sows were confined to wooden farrowing crates for 2-l0 days before delivery. The platforms of the crates were coated with three brush applications of a commercial wood preservative containing 98.5% coal tar creosote. Following contact with creosote, 24 of the 41 pigs delivered were dead at birth, and 11 pigs died by day 3 postfarrowing. The surviving pigs had rough skin and suffered from dehydration and severe diarrhea. The pigs failed to gain weight until they were 5-6 weeks old. No toxic effects on the sows were reported. However, 4 sows confined to untreated lumber crates at least 24 hours before farrowing delivered 36 pigs; 1 died within 24 hours and 3 died postfarrowing. No toxic effects were noted in mothers or baby pigs.

2.2.3.7 Genotoxic Effects

The *in vivo* genotoxic risk associated with dermal exposure to coal tars has been addressed in human subjects. Sarto et al. (1989) examined peripheral blood lymphocytes collected before, during, and after coal tar therapy of male, nonsmoking subjects treated for psoriasis with topical applications of pure coal tar or 4% coal tar-containing ointment. The lymphocytes were assayed for sister chromatid exchanges and chromosomal aberrations. The results suggest that the frequency of chromosomal aberrations and sister chromatid exchange in lymphocytes were related to the levels of exposure to coal tar, thus demonstrating that both the pure coal tar and the 4% coal tar ointment were genotoxic mixtures.
In addition to mutagenic evaluations, preparations of coal tar and juniper tar (cade oil) that are used for the treatment of psoriasis have been evaluated for covalent binding to DNA by components of the tars in human skin, mouse skin and lung tissue. Schoket et al. (1990) evaluated the DNA sampled from (1) human skin biopsy samples from 12 psoriasis patients receiving therapy with these agents, (2) human skin explants maintained in organ culture and treated topically with the tars, and (3) the skin and lungs of mice treated with repeated doses of the formulations (Schoket et al. 1990). Treatment of each test system produced elevated levels of adducts relative to corresponding control levels. The findings that components of these mixtures produce covalent DNA adducts in human skin is evidence of the occurrence of events characteristic of tumor initiation (Schoket et al. 1990). However, as described by the authors, conclusive evidence of this relationship in psoriasis patients is equivocal since there is a virtual absence of control subjects with more than very mild symptoms who have not received any treatment for their disorder. In addition, this is further complicated by the recurrent nature of the disease, which means that most patients have received a number of different remedies or combinations of therapies.

Zhang et al. (1990) detected benzo[a]pyrene diol epoxide (B[a]PDE) adducts in human skin biopsies sampled from psoriasis patients following single and multiple 24-hour exposures to the entire body surface with 3-5% coal tar compounds. The findings further demonstrate that topical application of crude coal tar preparations produces detectable levels of DNA adducts in the skin of psoriasis patients.

Male psoriatic patients hospitalized in the Dermatology Clinic of the University of Padora in Italy were selected in a study by Pavane110 and Levis (1994). Data collected included age, smoking habits, occupational or consistent environmental exposure to PAH, medical history, domiciliary treatments for psoriasis and drugs taken during the coal tar therapy. During hospitalization, some patients were treated

with crude coal tar (CT) either alone or in association with a CT-based paste (TP) containing 50% coal tar, sometimes in association with UV-irradiation, or with 2% coal tar ointment (TO). Controls were healthy males who were not taking prescribed medications, and not exposed to ionizing radiation or industrial chemicals at work. Smokers were individuals consuming 15 or more cigarettes/day at least 3 months prior to donating blood and non smokers were individuals who never smoked. Peripheral blood lymphocytes were used to evaluate the *in vivo* formation of B[a]PDE)-DNA adducts by an ELISA (Enzyme-Linked Immuno-Sorbent Assay) technique and by the ^{32}P-postlabeling method. The levels of B[a]PDE-DNA adducts determined by an ELISA assay in the peripheral blood lymphocytes of 23 psoriatic patients during CT treatment and 2-5 months later showed a mean adduct level of 7.7±4.9 adducts/10^8 nucleotides. This level was comparable to 4 subjects occupationally exposed to PAH. A lower mean adduct level of 3.3±2.4 adducts/l0^8 nucleotides was found in 9 of 10 patients examined 2-5 months after CT treatment, which suggested a relatively short presence of the DNA damage induced by PAH in human peripheral blood lymphocytes. Data showed no correlation between the exposure to CT and the levels of PAH-DNA adducts. The PAH-DNA adducts quantified by the ^{32}P-postlabeling method used both nuclease P1 enrichment and butanol extraction procedures. In both procedures used, no statistically significant difference was found in the mean total DNA adduct levels before clinical therapy with TP, after 8 days of TP treatment and 16 days after TP treatment. No significant difference in the mean total DNA-adduct levels was detected by the nuclease Pl method (0.58±0.3 1 adducts/10^8 nucleotides) and by the butanol method (0.73±0.30 adducts/10^8 nucleotides). The autoradiograms of 18 DNA samples obtained by the butanol procedure showed the presence of additional radioactive spots not detected by the nuclease Pl method. In a similar study by Santella et al. (1995), patients diagnosed with plaque stage psoriasis were treated with an ointment and/or a gel based coal tar product applied to the entire body surface once a day followed by UV-B treatment. Precise dose determinations were not possible since treatments were self-applied with variable efficiency. The estimated exposure was 20-100 g tar/day. Healthy volunteers with no previous exposures to coal tar shampoos or ointments served as controls. Blood was collected into heparinized tubes and separated within 4 hours of sampling. White blood cells (WBC), red blood cells and plasma were also collected. The assays included measurement of PAH diol epoxide-DNA adducts in the blood cells by competitive enzyme-linked immunosorbent assay (ELISA) with fluorescence end point detection, PAH-albumin adducts by competitive ELISA with color end point detection and serum levels of antibodies recognizing B[a]PDE-DNA adducts by noncompetitive color ELISA. PAH-DNA adducts by ELISA were elevated in patients (6.77±12.05 adducts/10^8 nucleotides) as compared to controls (4.90±8.81 adducts/10^8 nucleotides). Days of treatment before sampling collection were unrelated to adduct levels; nor was there an effect of smoking on adducts in either patients or controls. There was no

difference in PAH-albumin adducts between patients and controls. Glutathione S-transferase Ml genotype was also determined but no relationship was found between the presence of the gene and either DNA or protein adduct levels. Measurement of WBC PAH-DNA adducts appeared to be the most sensitive biomarker of PAH exposure in highly exposed coal tar treated psoriasis patients.

A study by Pavane110 and Levis (1992) assessed the effect of coal tar treatment on DNA adduct formation in human lymphocytes. Four male psoriatic patients 25-70 years old were treated for 4-10 days with a paste containing 50% coal tar. Nine control subjects (healthy individuals not taking any medication) were also included. Human peripheral blood lymphocytes were collected before and after treatment and treated *in vitro* with 4 uM [3H]-benzo[a]pyrene and 2 uM (-)-B[a]P-7,8-dihydrodiol in order to verify if the coal tar influenced the formation of benzo[a]pyrene-DNA adducts or the metabolism of benzo[a]pyrene. No significant difference was detected in the amount of total benzo[a]pyrene DNA adducts between patients and controls or between patients before and after treatment.

In a study by Gabbani et al. (1999), 15 nonsmoking patients being treated for skin complaints were treated with an ointment containing 2% coal tar for at least 3 days. At the end of this time, urine and blood samples were collected. The patients were typed for glutathione S-transferase Ml (GSTMl) genotype and their urine was assessed for mutagenicity and the presence of 1-pyrenol (used as a marker of coal tar exposure). The mutagenicity test used was the Ames test on *S. typhimurium* strains TA98 and YG1024 in the presence of microsomal enzyme. Mutagenicity on YG1024 was correlated with l-pyrenol levels using Spearman's rank correlation coefficient. The mean value of urinary mutagenicity of subjects with genotype GSTMl-null was greater than that of GSTMl-positive subjects, but the difference was not significant. Correcting the data for coal tar exposure, the mean value of urinary mutagenicity of subjects with genotype GSTMl null was double that of GSTM1-positive subjects and the difference was significant. The results of this study suggest that GSTMl may be of importance in the detoxification of coal tar.

Groups of male Parkes mice were treated topically with 30 mg of pharmaceutical coal tar solution (20% in ethanol) (Hughes et al. 1993). Mice were also treated with the synthetic mixtures of PAH in Group A (all PAHs present in coal tar), Group B (those PAHs present in coal tar for which evidence of carcinogenicity in experimental animals is sufficient) and Group C (those PAHs present in coal tar for which there is inadequate or limited evidence of carcinogenicity in experimental animals). Mice were sacrificed 24 hours after treatment and treated skin areas were taken and stored until the DNA was isolated. Characterization of PAHs responsible for the DNA binding of coal tar were analyzed by

^{32}P-postlabeling. Application of 30 mg of coal tar to mouse skin showed an apparent band of radioactivity with discrete spots in areas 2, 4, and 6 and diffuse radioactivity in areas 1, 3, 5, and 7. By comparing the pattern of adducts formed by coal tar with those formed by the synthetic PAH mixtures, it appeared that PAHs in Group B contributed to the formation of coal tar-DNA adduct spots 4, and 6 and that adduct spot 2 was formed by PAHs in Group C.

Hexaneiacetone extracts of two samples from a wood preserving waste site were applied to the shaved skin of female ICR mice (Randerath et al. 1996). Groups (three mice per group) received 150 uL extract/day for 2 days (total of 6 mg residue per animal or 48 mg/cm^2/kg). Control animals received acetone only. Tissue samples from lung, skin, liver, kidney, and heart were removed from the animals after they were sacrificed by cervical dislocation. DNA was extracted from the tissues and DNA adducts were analyzed by ^{32}P-postlabeling and thin layer chromatography. Adduct profiles were tissue specific and displayed a multitude of nonpolar DNA adducts. Based on their chromatographic properties these adducts are most likely derived from polycyclic aromatic hydrocarbons. One of the major adduct fractions was identified as an adduct of benzo[a]pyrene. Total adduct levels were highest in the skin, lung and liver and benzo[a]pyrene adduct levels were linearly correlated with total adduct levels for all five tissues.

Groups of three rats (7-8 week old BD4, sex not stated) were shaved on the top central part of the back on Monday, treated on Tuesday with approximately 100 mg bitumen (collected at 160 or 210 ºC) or coal tar (collected at 110 or 160 ºC) fume condensates (Genevois et al. 1996). Rats were rested on Wednesday, treated again on Thursday, and sacrificed on Friday. Control rats received no treatment. Lymphocyte DNA was extracted from blood collected by cardiac puncture, and DNA was also extracted from lung and skin tissue, DNA adducts were analyzed by ^{32}P-postlabeling. Fume condensates were rapidly absorbed through the skin and DNA adducts were found in the skin, lungs, and lymphocytes of all treated animals. Relative adduct labeling was lower for the bitumen condensate than the coal tar condensate and the pattern of adducts produced by the two fume condensates was very different. Relative adduct labeling was also reduced in the high temperature coal tar fume condensate than the low temperature condensate, but the pattern of adducts formed was similar. There was no correlation between 1-hydroxypyrene excretion and adduct formation.

Female CD-l mice (4 per group) were either untreated, treated topically with 1.5% coal tar ointment (‘initiator’, 50 mg/treatment) 5 times/week for 2 weeks or treated with a single dose of 50 mg benzo[a]pyrene (Phillips and Alldrick 1994). Animals were sacrificed 9 days after treatment with

benzo[a]pyrene and 12 days after the final application of coal tar. Another group of animals was given three doses of 0.1% diathranol cream (50 mg/treatment) and sacrificed 3 days after the final dose. DNA was isolated from the treated areas of the epidermis and the presence of DNA adducts detected by autoradiography. A series of adduct spots in a diagonal band was detected with DNA from coal tar treated mice. A single adduct spot and a number of very minor spots were detected in benzo[a]pyrene-treated mice. There were no DNA adducts formed in diathranol treated and untreated animals.

Charles River CD-l female mice (3-4 per group) were treated with benzo[a]pyrene and a variety of coal derived complex mixtures in an assay for DNA binding and adducts (Springer et al. 1989). Mice were treated with 100 uL of an acetone:methylene chloride (1:1, v/v) solution of the following test materials: 25 µg radiolabeled benzo[a]pyrene ([3H]BaP (430 µCi; 2.2 µg from radiolabeled BaP+22.8 µg nonradiolabeled BaP); 5 mg of coal tar fractions (boiling points; 300-700,700-750,750-800, 800-850, or >850 ºF) +25 µg radiolabeled benzo[a]pyrene. The three lower boiling-point coal tar fractions did not contain benzo[a]pyrene, while the other two fractions contributed 8.5 µg benzo[a]pyrene towards the total dose. Twenty-four hours after dosing, mice were sacrificed, and DNA was isolated from the treated skin. DNA adducts were isolated and the amount of radioactivity counted in a scintillation counter. The production of DNA adducts by benzo[a]pyrene was reduced by approximately 50% in the presence of any of the coal tar fractions. The binding of benzo[a]pyrene to mouse skin DNA was also decreased by co-administration of coal tar fractions, with the high temperature fractions (800-850 and >850 ºF) giving the greatest reduction (approximately 7-fold). The authors suggest that the reduction in benzo[a]pyrene-DNA adduct formation by coal tar fractions is caused by altered rates or routes of metabolism of benzo[a]pyrene due to the presence of various components of the coal tar.

Crude coal tar (5%) in petrolatum was applied to the backs of the hairless HRS/J mice and the animals immobilized for 2 hours (Walter et al. 1978). Vehicles for tar preparations applied to the skin were used as controls. The area was then washed with soap, rinsed with distilled water and gently patted dry. The animals were then exposed to the light source for 1 or 4 hours. After 1 or 4 hours light exposure, the animals were injected intraperitoneally with 25 mCi titrated thymidine (6 mg thymidine) and sacrificed 1 hour after injection. Samples were taken at the treated site for the determination of specific activity of epidermal DNA and determination of mitotic index or labeling index. Results showed that 5% crude coal tar alone and 5% crude coal tar plus UV-A significantly depressed DNA synthesis in the essential fatty deficient (EFAD) epidermis model as compared to the vehicle alone. Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote (coal tar) exposure with the development of skin cancer (Cookson 1924; Goulden and Stallard 1933; Henry 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935). These papers reported similar neoplastic skin lesions for different groups of workers exposed to creosote. Lesions included the development of dermatoses (e.g., squamous papillomas) which progressed to carcinoma, usually squamous-cell carcinoma. Tumor locations included regions of the face, head and neck, and upper limb. Cancer of the scrotum has also been associated with prolonged exposure to coal tar creosote (Henry 1946). The latency period for the development of dermatoses, such as squamous papillomas, was varied, ranging from several months to 16 years or more (Cookson 1924; Henry 1946, 1947; O'Donovan 1920; Shambaugh 1935). Worker exposure in the past was much greater than it is now because of less-sophisticated industrial practices, the lack of knowledge concerning occupational hygiene, and the current recognition of the dangers of excessive exposure to the health of workers. For example, chimney sweeps had a lower incidence of scrotal cancer after limiting their exposure to coal tar creosote by regular washing of their skin. Other factors that should be considered when extrapolating the findings of this older literature to present conditions are the role of exposure to UV radiation in the form of sunshine in these workers (UV radiation is now known to be a major cause of skin cancer), the composition of the creosote products, and other health factors that differ in Great Britain prior to 1940 and the present. Although these studies lack information concerning specific exposures and do not consider other risk factors for the development of skin cancer, when taken as a group, they suggest a relationship between chronic dermal coal tar creosote exposure, phototoxicity, and the development of skin carcinoma in humans.

The effect of treatment with tar and/or artificial UV radiation on the risk of developing cutaneous carcinoma was evaluated on skin cancer patients (59 cases) with severe psoriasis (Stern et al. 1980); 924 subjects without skin cancer were selected as unmatched controls. A matched group (58 cases and 126 matched controls) was also selected from the same group of controls. Patients were categorized according to amount of tar use (<30, 30-90, or >90 months) and levels of radiation exposures (low, moderate, or high). The relationship between tar exposure and UV radiation treatment and the development of skin cancer both before and after 8-methoxypsoralen photochemotherapy (PUVA) were evaluated. The estimated crude relative rate of cutaneous carcinoma for all patients with high exposure to tar or UV radiation, or both, was 2.4, compared with patients without high exposure. The reported relative rates were 1.8 for high-exposure groups of the prevalence cases and 3.0 for incidence cases. For

the matched set of cases and controls, the estimated relative rate for all cases was 4.7. Prevalence and incidence cases in matched sets showed significantly increased risk.

In contrast, several studies are available that suggest that there is no association between exposure to coal tar creosote or other coal tar products and cancer in humans. Data from a population-based case-control interview study of 1,867 white men (622 cases and 1,245 controls) in Iowa and Minnesota conducted during 1980-83 were examined (Blair et al. 1993). Interviews were conducted with individuals or their next of kin to obtain information on agricultural exposures, residential history, medical history, family history of cancer, and a detailed occupational history. White men without hematopoietic or lymphatic malignancy were selected as controls. Risks of non-Hodgkin's lymphoma (NHL) were evaluated by intensity or probability of exposure to specific substances. No increased risk was noted with exposure to creosote or asphalt. No increased incidence of nonmelanoma skin cancer was observed in 426 patients 25 years after they had undergone 4 years of coal tar medicinal therapy in combination with UV light for the treatment of atopic dermatitis and neurodermatitis (Maugham et al. 1980). This study is limited in that follow up occurred in only 72% of the patients, and there was no discussion of recall bias or of the effects of mobility (i.e., relocation of the study participants) on the results. In a 25-year retrospective study of 280 psoriatic patients treated with crude coal tar in combination with UV radiation at the Mayo clinic, it was found that the incidence of skin cancer in these patients was not significantly increased above the expected incidence for the general population (Pittelkow et al. 1981). Chemical and biological analysis of coal tar-based therapeutic agents and industrial grade coal tar indicated that the therapeutic agents and the industrial materials were similar (Wright et al. 1985). The authors suggest that the lack of carcinogenic effects after therapeutic exposure may be due to the presence of solvents and surfactants in the preparations which may alter deposition and absorption by the skin. Reducing the contact with the therapeutic agents by regular washing may also be a factor (Wright et al. 1985). A case-control study was carried out on 24 PUVA-treated patients with squamous cell cancer of the skin and 96 PUVA-treated patients as matched controls (Lindelof and Sigurgeirsson 1993). Information on past therapies was obtained by questionnaire designed to determine if previous therapy was a risk factor for skin cancer in PUVA-treated patients. For subjects using previous tar therapy, there were 17 of 24 cases of skin cancer (70% exposed) with an estimated RR of 1.3; for control subjects reported 62 of 96 cases (64% exposed). Prior treatment with tar was not considered to be a risk factor for skin cancer in PUVA-treated patients.

Another study was located that reported that there was no increase in the risk of skin, bladder, or lung cancer in wood treatment plant workers, where coal tar creosote and coal tar pitch were the chemicals used (TOMA 1980). Nevertheless, these findings are of limited value since the study population was

limited to those currently working at the plant, was small, and comprised of 46.5% blacks, who experience a very low incidence of skin cancer compared to whites. In addition, the exposure and follow up periods did not allow a long enough latency period for tumor development and there was no verification provided that those studied were actually exposed to coal tar creosote or coal tar.

A large body of evidence exists to show that coal tar creosote is carcinogenic when applied to the skin of laboratory animals. Many of the early studies are limited in that they lack appropriate negative control data, the dose of creosote and the chemical composition of the fractions studied were not quantified, and no other tissues were generally examined (Bonser and Manch 1932; Deelman 1962; Hueper and Payne 1960; Watson and Mellanby 1930). The results from later studies that include appropriate control groups are consistent with the earlier studies that found that creosote is carcinogenic following dermal application to rodent skin. The more detailed dermal carcinogenicity studies are reviewed below, and the relevant CELs are presented in Table 2-3.

The tumor-promoting potential of coal tar creosote was evaluated by applying various fractions (e.g., basic, phenolic, and neutral) to the skin of albino mice in conjunction with benzo[a]pyrene (Cabot et al. 1940). The various fractions of creosote oil were prepared by distillation and separation; 90% of the creosote oil distilled between 160 and 300 ºC. The basic fraction was removed with aqueous hydrochloric acid. The phenolic fraction was removed with aqueous sodium hydroxide. The remaining neutral fraction was then steam distilled. The composition of the various fractions was not specified. Four of the test solutions antagonized the tumorigenic effects of benzo[a]pyrene, but in three instances this antagonistic effect was considered secondary to skin damage. Only the phenolic fraction seemed to exhibit a primary antagonistic effect. Three fractions (basic, neutral, and neutral distillate) exhibited apparent promoting effects.

Ten groups of Swiss albino mice were exposed topically with 9% benzene solutions of two coal tar pitches of known PAH content (Wallcave et al. 1971). An additional group of 15 males and females was painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Animals were weighed once a week (no data shown) and all tumors arising in the skin were charted. Animals were sacrificed when moribund or when they developed highly advanced tumors on the skin. A complete autopsy was performed on all animals, and sections of the skin as well as all grossly pathological organs were studied histologically. Coal tar-painted animals developed squamous cell carcinomas and benign

tumors in the form of squamous cell papillomas and keratoacanthomata; 91.4% of animals bore some kind of skin tumor.

Weanling C3H/HeJ mice were exposed to 50 mg solutions containing 25 mg of rooting materials (traditional coal tar pitch, coal tar bitumen, standard asphalt from roofing operation, coal tar bitumen from roofing operation, or roofing dust) 2 times/week for 80 weeks, or until a skin lesion was diagnosed as a papilloma (Emmett et al. 1981). The material was dissolved or suspended in redistilled toluene in a 1:1 ratio (w/w) and applied to the intrascapular region of their backs, where hair had been previously removed. A vehicle control group received 50 mg of toluene 2 times/week, and a positive control group received 50 mg of 0.1% solution of benzo[a]pyrene in toluene 2 times/week. When the papilloma progressed and was diagnosed grossly as a carcinoma, the mouse was sacrificed and autopsied. Selected histopathologic examination of tumors was made to confirm the gross diagnosis. It was found that traditional coal tar pitch and dust from removal of an old roof were significantly more carcinogenic than coal-derived roofing bitumen, but all were strongly carcinogenic. The average times of the appearance of papillomas (and percentage of mice developing tumors) were at 18 (98%), 21.5 (98%), 20.5 (93%), 16.5 (86%), and 31.8 (79%) weeks for traditional coal tar pitch, coal tar bitumen, coal tar bitumen from roofing operation, roofing dust, and positive control, respectively. No tumors were caused by standard roofing asphalt or toluene. The percentage of benzo[a]pyrene in the materials was as follows: traditional coal tar pitch, 0.064%; coal tar bitumen, 0.072%; standard asphalt, <0.004%; coal tar bitumen from roofing operation, 0.064%; roofing dust 0.08%; toluene, 0%; and positive control, 0.1%.

Asphalt and coal tar pitch were the materials used in assessing skin carcinogenesis in nonpigmented Swiss CD-l and pigmented C3H/HeJ male mice (Niemeier et al. 1988). Animals were divided into 48 experimental groups and treated as follows: (a) 32 groups treated for the primary factorial experiment (i.e., 2 strains x 4 materials x 2 generation temperatures (232 and 316 ºC) x 2 light exposure conditions [presence or absence of simulated sunlight]); each animal dosed 2 times/week with 50 µm of the appropriate test material; (b) 4 groups for the solvent control (i.e., 2 strains x 2 light exposure conditions; each animal dosed 2 times/week with 50 µL of cyclohexane/acetone [1:1] vehicle); (c) 2 groups for cage control (i.e., 2 strains x 2 light exposure conditions, dosed 2 times/week with 50 mL solvent and not sham irradiated but always maintained in their individual cages); (d) 4 groups for the positive control (i.e., 2 strains x 2 light exposure conditions, dosed 2 times/week with 50 µL of the solution of 0.01% benzo[a]pyrene in cyclohexane:acetone [1:1]; (e) 4 groups for a combination treatment of asphalt and coal tar pitch fume condensate (i.e., 2 strains x 2 light exposure conditions; each animal dosed 2 times/week with the high temperature condensate from Type III asphalt and Type I coal tar pitch, on

alternate weeks); and (f) 2 groups (i.e., 2 strains, for light exposure 2 times/week with no skin painting treatment). Mice were observed daily for systemic toxicity and gross appearance of tumors. Mice found dead were necropsied and those that were moribund were sacrificed and necropsied. Surviving mice at the end of 78 weeks were also necropsied. Tissues were examined and skin lesions excised and prepared for microscopic examination. The theoretical air concentrations of PAH from coal tar pitch at 232 and 316 ºC were $5.0x10^8$ and $55.1x10^8$ mg/m^3, respectively. The theoretical air concentrations of benzo[a]pyrene from coal tar pitch at 232 and 316 ºC were $55.6x10^8$ and $366.7x10^8$ mg/m^3, respectively. The theoretical air concentrations of PAH from asphalt at 232 and 316 ºC were 3,300 and 15,000 mg/m^3, respectively. The theoretical air concentrations of benzo[a]pyrene from asphalt at 232 and 316 ºC were 21 and 122 mg/m^3, respectively.

Administration of condensed fumes from both types of coal tar pitches and both types of asphalt resulted in benign tumors (papillomas, kerato-acanthomas, fibromas, and unclassified benign epitheliomas) and malignant tumors such as squamous cell carcinoma and fibrosarcomas (seen more often in C3H/HeJ mice) (Niemeier et al. 1988). CD-l mice had a much lower incidence of malignant tumors than C3H/HeJ mice (about 5 versus 60%). The average latent period ranged from 39.5 to 56.1 weeks among C3H/HeJ groups and from 47.4 to 76.5 weeks among the CD-1 groups. The tumorigenic response of C3H/HeJ in the coal tar pitch Type III group with concomitant exposure to light increased with high temperature. Both strains when exposed to condensed coal tar pitch fumes or benzo[a]pyrene in the presence of simulated sunlight had inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and coal tar pitch showed increased tumorigenic response. In the CD-l strain, only the solar exposed pitch fume groups showed significantly increased tumorigenic response when compared to the positive control. The tumorigenic response of C3H/HeJ to the condensed asphalt fumes increased with high temperature, but no significant change in tumorigenic response was observed for CD-l mice exposed to fumes at the higher temperature. Simulated sunlight significantly inhibited tumorigenic response in C3H/HeJ mice to both types of asphalt fumes collected at the lower temperature and no overall significant effects were noted in the CD-l strain. Both strains when exposed to benzo[a]pyrene in the presence of simulated sunlight had inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and those exposed to the high temperature asphalt fumes showed increased tumorigenic response. In the CD-1 strain, only the nonsolar exposed asphalt fume exposed groups showed significantly increased tumorigenic response when compared to the positive control. In comparing the combination group to their respective controls, the C3H/HeJ strain showed no differences in latency, but the combination group showed a significantly increased response by the onset rate analysis method as compared to the asphalt group (Type III-316 ºC) without light. The responses in CD-l mice

were similar, in that the nonsolar exposed combination group had a significantly increased tumor response, as assessed by the onset rate method, compared with the asphalt group. They also died earlier (no data shown) and developed tumors at a significantly earlier time than the asphalt group. When the combination groups were compared to the responses of the pitch groups, onset rate analysis showed that the sham irradiated pitch group (Type I-316 ºC) had a significantly greater tumor response than the combination group. No other differences were noted. Both strains when exposed to benzo[a]pyrene or combination of pitch and asphalt in the presence of simulated sunlight showed inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and the combination groups and those exposed to the high temperature asphalt fumes showed increased tumorigenic response.

In conclusion, both coal tar pitch and asphalt produced benign and malignant skin tumors in mice (Niemeier et al. 1988), but C3H/HeJ mice were more susceptible to the formation of malignant tumors than CD-l mice. Concomitant exposure to sunlight reduced tumor production by coal tar pitch, or asphalt, or the combination of coal tar pitch and asphalt compared with nonsolar exposed animals. The combination of exposure to both asphalt and coal tar pitch increased tumor formation compared with asphalt alone, but was reduced compared with coal tar pitch alone.

The potential of basic fractions of coal tar creosote to accelerate tumor induction by known carcinogens was evaluated by Sal1 and Shear (1940). A 1% solution of the basic fraction of creosote oil in benzene was dermally applied to female strain A mice alone or in conjunction with 0.05 or 0.02% benzo[a]pyrene. The basic fraction alone did not induce skin tumors, but when applied in conjunction with either concentration of benzo[a]pyrene, skin tumors appeared more rapidly than when benzo[a]pyrene alone was applied. Maximum tumor induction was seen between 28 and 42 weeks; 19 of 20 mice developed tumors.

This is in contrast to the results of a tumor initiation study by Springer et al. (1989) in which Charles River CD-l female mice (30 per group) were treated with crude coal tar and a variety of coal tar fractions in an initiation assay. The backs of the mice were shaved and the skin treated with 50 µL of an acetone solution of the various test materials. Two weeks after initiation, the animals were promoted with twice-weekly applications of 5 µg of 12-O-tetradecanoylphorbol-13-acetate (TPA) (also known as phorbol myristate acetate or PMA) in 50 µL of acetone for 24 weeks. Tumors were identified visually and were not characterized further by histopathology. The time of tumor appearance and the number of tumors were recorded as measures of response. Test materials included: 5 mg (approximately 203 mg/kg body weight) crude coal tar (boiling point: 300-850 ºF); coal tar temperature fractions (boiling points:

300-700, 700-750, 750-800, 800-850, or >850 ºF); chemical fractions of the 750-800ºF temperature fraction (aliphatics and olefins, neutral PAH, nitrogen-containing polycyclic aromatic compounds, hydroxy-PAH); 25 ug benzo[a]pyrene; 5 mg crude coal tar +25 µg benzo[a]pyrene; coal tar temperature fractions +25 µg benzo[a]pyrene; chemical fractions +25 µg benzo[a]pyrene . The three lower temperature coal tar fractions did not contain benzo[a]pyrene, while the other two contributed 8.5 µg benzo[a]pyrene towards the total dose. Mice initiated with benzo[a]pyrene alone showed the greatest tumor response. Administration of the lowest boiling point coal tar fraction did not produce significantly more tumors than controls. Exposure to the crude coal tar or the 700-750 and 750-800 ºF fractions produced a small, but significant increase in tumors compared with controls. The two highest temperature fractions showed substantial initiating activity. The aliphatic fraction did not have tumor initiating activity, the other chemical fractions had some activity, with that of the PAH fraction being the highest and similar to that of crude coal tar. Co-administration of benzo[a]pyrene and coal tar or coal tar fractions resulted in a decrease in the initiation of tumors compared with benzo[a]pyrene alone. The authors suggest that the reduction in benzo[a]pyrene tumor initiation by coal tar fractions may be caused by altered rates or routes of metabolism of benzo[a]pyrene due to the presence of various components of the coal tar.

The ability of coal tar creosote to induce lung tumors after dermal application to mice was studied when it was observed that mice housed in coal tar creosote-treated wooden cages had a high incidence of lung tumors (Roe et al. 1958). Dermally applied coal tar creosote (0.25 mL undiluted twice weekly for 8 months) induced 5.8 lung adenomas/mouse in mice that were reared in stainless steel cages. Creosote ,treatment following the same regimen in mice reared in creosote-treated cages induced 10.8 lung adenomas per mouse. Untreated controls reared in untreated cages exhibited 0.5 lung adenomas per mouse. A high incidence of skin tumors was also observed in the creosote-treated mice reared in either type of cage. In a second experiment, topical application of “one drop” of coal tar creosote twice a week for only 4 weeks induced lung adenomas, but not skin tumors in mice reared in stainless steel cages. This study demonstrated that coal tar creosote induces tumors in the lungs and skin of mice when dermally applied. Rearing animals in coal tar creosote-treated wooden cages exacerbated the tumorigenic effect of dermally applied coal tar creosote. Based on this study, lung tumors may be a more sensitive end point of creosote tumorigenic activity than skin tumors after skin contact and inhalation exposure. However, this study did not take into account possible oral exposure due to normal preening behavior.

Seven groups of 30 female Sutter mice each were treated with 75 µL dimethylbenzanthracene (DMBA) and 25 µL coal tar creosote (undiluted creosote oil), alone and in combinations of the two to evaluate the

carcinogenic, initiating, and promoting activity of coal tar creosote on mouse skin (Boutwell and Bosch 1958). Coal tar creosote alone, DMBA and coal tar creosote, and coal tar creosote with 25 µL croton oil (0.5% in benzene) all induced the development of papillomas and carcinomas. Tumors first appeared at 10-20 weeks of application. DMBA pretreatment shortened the latent period and increased the tumor yield of coal tar creosote treatment, but since a nearly maximal tumor induction response (i.e., percentage of mice with papillomas just below 100) was seen with coal tar creosote alone, tumor-promoting activity of coal tar creosote could not be definitely proven. The initiating activity of coal tar creosote was demonstrated by its ability to induce tumors when applied prior to croton oil treatment (croton oil alone was without effect). Coal tar creosote alone or in combination with DMBA or croton oil induced papilloma formation more slowly, and carcinomas appeared by 14 weeks and accumulated more rapidly than in the DMBA plus croton oil group. Thus, this study demonstrated the carcinogenic and tumor-initiating activity of coal tar creosote on Sutter mouse skin.

The complete carcinogenic and tumor-promoting activity of undiluted coal tar creosote, a 10% solution of creosote oil, and 2% solution of the basic fraction of coal tar creosote was studied when dermally applied to mice (Lijinsky et al. 1957). Undiluted creosote alone induced 23 skin tumors (16 malignant) in 13 of 26 treated mice with a latent period of 50 weeks. The authors concluded that creosote alone has a carcinogenic activity comparable to a 0.01% solution of DMBA. When applied as a promoter following a single application of DMBA, 32 skin tumors (26 malignant) were observed in 17 of 30 mice with a latent period of 39 weeks. The basic fraction did not act as a tumor promoter when administered after a single application of DMBA. Thus, coal tar creosote appeared to enhance the carcinogenic activity of DMBA, but the promoting effect was not strong, when the results were compared to DMBA positive controls.

Three-month-old Charles River CD-1 male mice (30 per group) were treated with a variety of coal derived complex mixtures in an initiation/promotion assay (Mahlum 1983). The backs of the mice were shaved and the skin was treated with 50 µL of the various test materials. Groups of animals initiated with DMBA or benzo[a]pyrene served as positive controls, negative controls received 50 µL acetone. Two weeks after initiation, the animals were promoted with twice-weekly applications of 50 µL of phorbol myristate acetate (PMA) (also known as 12-O-tetradecanoylphorbol-13-acetate or TPA) for 6 months. Tumors were identified visually and were not characterized further by histopathology. The time of tumor appearance, the number of mice with tumors, and the number of tumors per mouse were recorded as measures of response. The following coal distillates were used as initiators: heavy distillate (HD) boiling point range 550-850ºF; 300-700ºF boiling point range fraction, and an 800-850ºF boiling point range fraction. In addition the following chemical fractions were prepared from HD: basic (BF), basic tar

(BTF), neutral tar (NTF), and polynuclear aromatic (PNA) fractions. The promoting activity of middle distillate (MD), boiling point range 380-550 °F, was tested by initiating with 50 µg DMBA, followed 2 weeks later, by twice weekly applications of a 50% solution (w/v) of MD in acetone. Animals that received no DMBA, but were treated twice weekly with MD, were used as controls. DMBA was a more potent initiator than benzo[a]pyrene. Initiation with HD resulted in about the same incidence of tumors as benzo[a]pyrene. NTF was almost as active an initiator as HD, while BTF was only slightly less active. BF and PNA were considerably less active initiators. The 800-850 ºF fraction showed a low degree of initiating activity, while the response of the 300-700 ºF group was the same as the acetone controls. MD showed a low level of promotion in animals initiated with DMBA. No uninitiated mice showed tumors after 12 months, 17% of initiated mice had tumors at 6 months, and incidence increased to 52% by 12 months.

The carcinogenic activity of two high-temperature-derived coal tar creosote oils ("light" and "blended") was studied by Poe1 and Kammer (1957). The principal components of light oil are benzene, toluene, xylene, and solvent naphtha. Blended oil is a mixture of creosote oil, anthracene oil and the oil drained from the naphthalene recovery operation. Its principal components are methylated naphthalenes, acenaphthene, fluorene, phenanthrene, anthracene, and carbazole. The oils were applied by drops to the skin of mice at concentrations of 20, 50, or 80% 3 times/week for life. Both oils induced skin tumors in every exposed mouse by 21-26 weeks of application. Several mice exhibited metastases to the lungs or regional lymph nodes. The fractions tested did not contain benzo[a]pyrene, so the authors concluded that the carcinogenic activity of the coal tar creosote oil used in the experiment was not due to benzo[a]pyrene.

Crude coal tar (10, 25, and 100%) in petrolatum was applied to the ear of male Australian albino rabbits (3 per group) 3 times/week for 15 weeks (Kligman and Kligman 1994). Crude coal tar was both comedogenic and carcinogenic at all doses tested (10, 25, or 100%). Tumors developed as early as l-2 weeks after 3 weeks of treatment with 10% coal tar. The tumors were classified as papillomas, squamous cell carcinomas, keratoacanthomas, and cutaneous horns, and became extremely numerous with longer treatment.

In conclusion, the results of these studies indicate that coal tar creosote and several of its fractions can be carcinogenic when applied to the skin of mice or rabbits. Dermally applied coal tar creosote can also act as a tumor-initiating agent. Thus, it is likely that individuals whose skin comes into contact chronically

with coal tar creosote would be at higher risk for skin cancer, particularly when exposure to other carcinogenic substances also occurs, as is a possible scenario in areas surrounding hazardous waste sites.

2.3 TOXICOKINETICS

Specific information regarding the toxicokinetics of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles is limited. Several compounds have been detected in coal tar creosote, yet there are no definitive data on which of these compounds people are exposed to in wood-treatment plants or at hazardous waste sites. Analyses have revealed that PAHs are the major components of the coal tar creosote mixture (TOMA 1979). Hence, pharmacokinetic studies on PAHs can be used as surrogates for coal tar creosote. However, this information is only speculative given the possible toxicokinetic interactions that occur among the PAHs and other components in the coal tar creosote mixture, and will be used only when data on coal tar creosote are not available. For more information on the toxicokinetics of PAHs, please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995). Phenols and cresols are also components of coal tar products. For more information on the toxicokinetics of these chemicals, please refer to the ATSDR *Toxicological Profile for Phenol* (ATSDR 1998) and the ATSDR *Toxicological Profile for Cresols* (ATSDR 1992).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located in humans or animals regarding the direct analysis of the extent or rate of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile absorption following inhalation exposure. However, there is evidence to suggest that inhalation absorption occurs. Employees of a coal tar creosote wood-impregnating plant, employees in a coal tar plant, and coke oven workers excreted 1-hydroxypyrene, a metabolite of the creosote component, pyrene, in their urine (Bos and Jongeneelen 1988; Jongeneelen et al. 1985, 1988). Similarly, workers asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Bos and Jongeneelen 1988; Jongeneelen et al. 1988). Increased levels of 1-hydroxypyrene were observed over the course of the workday for all groups of workers, indicating an accumulation of pyrene during the exposure period (Bos and Jongeneelen 1988). The presence of this metabolite in the urine suggested that coal tar creosote components were absorbed and metabolized following inhalation exposure. However, it is possible that some dermal exposure may have occurred as well.

Measurements were carried out in a creosote impregnation plant where 6 men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work-free period of 64 hours. All workers wore leather protective gloves and cotton overalls. Two employees worked overtime (until 6:30 a.m.) on Monday which was an exception to the regular &hour schedule. Particulate PAHs were collected during the whole shift and analyzed within 7 weeks. Workers were asked to collect all urine passed within the 24 hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentration was 4.77 (1.2-13.7) mg/m^3 (n=30) for total particulate PAHs (including pyrene), and 1,254 (370-4,200) mg/m^3 (n=30) for naphthalene. The PAH profile was similar in all samples. 1-Hydroxypyrene was found in the urine samples.

Exposure of assemblers (all smokers) handling creosote-impregnated wood railroad ties and one worker (smoker) chiselling coal tar pitch insulation to coal tar products was assessed by analyzing the breathing zone air for airborne PAHs, and assaying urinary excretion of 1-hydroxypyrene (Heikkila et al. 1995). The concentration of pyrene and 11 other PAHs in particulate matter had been measured both in the work room and in the breathing zone of the assemblers a year earlier during 2 working days. In the present setting the ties were impregnated with the same type of creosote as a year earlier, which contained 0.2 weight-percent (w%) of pyrene. Urine samples were collected during 3 working days (Monday, Wednesday and Friday) and over the following weekend. Urine samples from one chiseller were collected in the morning before work, during lunch time, at the end of the shift, in the evening and on the next morning. The total concentrations of PAH and of 4-6 aromatic ring-containing PAHs (when chiselling) were 440 $\mu g/m^3$ (50-fold higher than assemblers) and 290 $\mu g/m^3$ (200-fold higher than assemblers), respectively. The estimated mean of inhaled pyrene for assemblers measured on Monday, Wednesday, and Friday was found to be 0.009, 0.007, and 0.024 mmol/shift, respectively. The estimated inhaled pyrene measured on the chiseller was 1.2 mmol/shift. Excretion of urinary 1-hydroxypyrene was detected for all participants.

Four rotation crews of about 29 workers and one day crew of 22 workers worked in a 5-day shift, 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators which were renewed 4-5 times/day, thick cotton working clothes with long sleeves, safety shoes, safety glasses, gloves, and helmets. Other groups that worked occasionally in the potrooms were also included in this study. Some employees who worked in dusty environments also wore facial protective clothing. Personal breathing zone air samples taken randomly from 38 workers were sampled once. Measurements were done on 3 out of 5 working days for the rotation crews and on 4 days in 2 work weeks for the day

crew. The filter holders and the XAD-2 tubes used in sampling were analyzed. Urine samples were collected from 33 of 38 workers before and after the 5-day work week. Control urine samples were taken from 10 guards not exposed to coal tar pitch volatiles. 1-Hydroxypyrene in urine was determined by liquid chromatography (LC). Results showed that field blanks were not contaminated with coal tar pitch volatiles. No benzo[a]pyrene was found on XAD-tubes. Vapor phase measurement showed 48% pyrene and 24% total PAHs. The highest filter sample (particulate) concentration of pyrene was 170 mg/m^3, and the highest sorbent tube (vapor) concentration of pyrene was 94 mg/m^3. The correlation between these two variables was 0.70. Individuals who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging from 10-2,710 mg/m^3. Multiple regression analysis of increased urinary 1-hydroxypyrene was strongly related to the environmental PAH exposure. Increased urinary 1-hydroxypyrene was greater among those using facial protective clothing under their respirators; this was probably caused by poor fitting or by facial coverings becoming contaminated by PAH. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for coal tar pitch volatiles was 4.3 mmol/mol creatinine. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for benzo[a]pyrene, was 4.3 mmol/mol creatinine.

Data from studies of inhabitants of log homes that were built with logs treated with pentachlorophenol indicate inhalation exposure to pentachlorophenol fumes occurs (Hernandex and Stressman-Sundy 1980). Similar exposure may result from coal tar creosote-treated logs (Cammer 1982).

Tumor-susceptible ICR CF-1 and tumor-resistant CAFl -JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX (benzene, toluene, xylene) mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al. 1977). Coal tar used to generate the aerosol was of various samples from multiple coke ovens blended together with a 20% by volume amount of BTX fraction of the coke oven distillate. The coal tar-BTX mixture was comparable to the material inhaled by topside coke oven workers. Mice were serially sacrificed during the exposure period for the determination of coal tar lung burden and the time to tumor induction. Control animals were held in a vivarium. All animals were examined daily during the exposure and postexposure periods. Coal tar fluorescence retained in mouse lung and skin tissues (n=4) were measured. The amount of coal tar found on mouse skin did not change to any great degree after the first week of exposure. Lung tissue accumulated coal tar aerosol at a fairly steady rate during 18 months of intermittent exposure as compared to a high increased rate (from graph) during the 90 days of continuous exposure. The coal tar lung burden in mice was approximately equal for both exposure modes for the 180-day exposure period.

PAHs extracted from coal fly ash were intratracheally administered to pregnant Wistar rats at a dose of 20 mg/kg, once/day, on gestational days 18 and 19 (Srivastava et al. 1986). The presence of the PAHs in both the maternal and fetal lungs and livers on gestational day 20 indicated that pulmonary absorption occurred following intratracheal administration, but inhalation exposure was not examined.

Pulmonary absorption may be influenced by carrier particles, and by solubility of the matrix or vehicle in which the compounds are found. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of inhalation absorption studies conducted with pure PAHs is limited.

2.3.1.2 Oral Exposure

No studies were located regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile absorption following oral intake in humans or animals. However, the presence of coal tar creosote metabolites in the urine of humans and rabbits receiving calcium creosote (a calcium salt of creosote) tablets was evidence that this salt of creosote was absorbed following ingestion (Fellows 1937, 1939b). Furthermore, evidence exists that certain PAHs found in coal tar creosote such as anthracene (Rahman et al. 1986), benzo[a]pyrene (Hecht et al. 1979; Rahman et al. 1986; Rees et al. 1971; Yamazaki et al. 1987), chrysene (Chang 1943; Modica et al. 1983), and phenanthrene (Rahman et al. 1986) are absorbed following oral administration in animals.

Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote capsule and 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. Phenols in serum and urine were analyzed by high performance liquid chromatography (HPLC). Wood creosote used in this study as determined by gas chromatography (GC) contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). Concentrations found in peripheral venous blood and urine were 15 mg/L phenol, 32 mg/L guaiacol, 18 mg/L *p*-cresol, and 24 mg/L cresol. HPLC analysis of 30-minutes postdose serum detected low concentrations of guaiacol and *p*-cresol.

Male B6C3F$_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days (Culp and Beland 1994). At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-postlabeling. The adduct levels were then compared with those obtained by feeding benzo[a]pyrene to mice for 3 weeks at concentrations corresponding to the amount of benzo[a]pyrene in the coal tar doses. DNA adduct formation was found to increase as a

function of dose in each tissue with both coal tar and benzo[a]pyrene, indicating absorption after oral exposure. Five groups of $B6C3F_1$ mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% mgP (Weyand et al. 1994). The urinary excretion of 1-hydroxypyrene by male mice (12 per group) treated with 0.25 and 0.50% mgP was evaluated throughout the 185 days of diet administration. 1-Hydroxypyrene was detected in the urine, indicating absorption after oral exposure.

Based on data on PAHs, absorption of PAH components of coal tar products after oral exposure may be positively influenced by the presence of oils and fats in the stomach, and bile in the intestines (ATSDR 1995). Due to relative water insolubility of PAHs, absorption is enhanced by solubilization in an intermediate phase than can be metabolized during the process of lipid digestion and absorption. Excretion after oral exposure may be detected hours to days after exposure. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of oral absorption studies conducted with pure PAHs is limited.

2.3.1.3 Dermal Exposure

No studies were located in humans or animals regarding the direct analysis of the extent or rate of wood or coal tar creosote, coal tar, or coal tar pitch absorption following dermal exposure. However, reports of workers who developed cancer subsequent to dermal exposure suggested that coal tar creosote was absorbed through the skin (Cookson 1924; Henry 1946, 1947; Lenson 1956).

Human exposure studies demonstrate that coal tar creosote or its components are absorbed dermally in humans, based on excretion of metabolites after dermal exposure (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Hansen et al. 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995). Van Rooij et al. (1993a) examined differences in the absorption of PAH between anatomical sites and individuals following dermal exposure of volunteers to 10% coal tar in a vehicle of zinc oxide paste. The surface disappearance of PAH and the excretion of urinary 1-hydroxypyrene after coal tar application were used to assess dermal absorption following controlled exposures. Surface disappearance measurements show low but significant differences in dermal PAH absorption between anatomical sites: shoulder > forehead; forearm, groin > ankle, hand (palmar site). Differences between individuals in PAH absorption are small (7%) in comparison with differences between anatomical sites (69%). Urinary excretion of 1-hydroxypyrene verified that the coal tar creosote and its components were absorbed through the skin, but the site of application had no effect on the

excreted amount of 1-hydroxypyrene although the time to excrete half of the total metabolite varied between 8.2 and 18.9 hours. Another study of dermal absorption was conducted by Van Rooij et al. (1993b) in a wood preserving plant in the Netherlands in October 1991. Volunteers for this study worked near the impregnation cylinders (three subjects) and the assembly hall (seven subjects). Exposure measurements were performed in 2 consecutive weeks on a Monday after a weekend off. On one Monday, the workers wore protective clothing over their clothes and on the other Monday, no protective clothing was used. PAH contamination on the skin and PAH concentration was measured on the two Mondays tested for all workers. Urine samples were collected from Sunday morning up to and including Tuesday morning for the assessment of the internal exposure to PAH. For assessing PAH contamination on the skin, six exposure pads were pasted on the skin of the workers (jaw, shoulder, upper arm, wrist, groin, and ankle) during work hours. Immediately after exposure, the pads were removed, packed in aluminum foil and stored until analysis. Results showed that extra protective clothing reduced the PAH contamination on the pads of the shoulder, upper arm, and groin, At the other skin sites, no significant reduction was found. On the average, the coveralls reduced the pyrene contamination on the worker's skin by 35%. The excreted amount of 1-hydroxypyrene in urine decreased significantly from 6.6 to 3.2 mg (30.2-14.7 nmol), indicating a change in the extent of absorption with the change in protective clothing.

Another indication that coal tar components are absorbed transdermally was reported by Paleologa et al. (1992). In particular, these investigators evaluated the occurrence of B[a]PDE-DNA adducts in white blood cells of 23 psoriatic patients undergoing clinical coal tar therapy. Two to 5 months after therapy, 10 of the patients were reanalyzed. The actual dose levels varied among the treated individuals because the application ranged from pure coal tar to 4% coal tar-based paste or ointment. No relationship appeared to exist between exposure level and concentration of B[a]PDE-DNA adducts. The results show that the mean adduct level during the treatment period was 0.26±0.16 fmole benzo[a]pyrene/g DNA (7.7±t4.9 adducts/l0^8 nucleotides), while 2-5 months later the mean adduct level had decreased significantly to 0.11±0.08 fmole benzo[a]pyrene/g DNA (3.3±2.4 adducts/10^8 nucleotides).

A coal tar solution (crude coal tar diluted to 20% with ethanol and polysorbate 80) was applied to clinically unaffected skin of 3 patients with severe atopic dermatitis and 6 patients with generalized psoriasis (Bickers and Kappas 1978). Another skin area at least 10 cm away was not treated or was treated with 100 mL of the vehicle alone. Twenty-four hours later, a 6-mm punch biopsy was obtained from coal tar treated and control areas and the effect on aryl hydrocarbon hydroxylase (AHH) activity was determined. Application of coal tar to the skin caused induction of cutaneous AHH activity that varied

from 2.4- to 5.4-fold over the enzyme activity in untreated skin areas, suggesting absorption after topical application.

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. 1-Hydroxypyrene was detected in the urine of all patients, indicating absorption of a component of the coal tar.

Twenty-eight patients who required coal tar treatment on an area larger than two-thirds of the body surface were studied (Cernikova et al. 1983). Tar paste (10 and 20%) was used for treatment; in one application, approximately l-6 g of coal tar containing 0.6% acridine was spread on the patient's skin. Urine analysis was performed by thin-layer chromatography (TLC) to obtain information on polyaromatic and heterocyclic substances excreted in the urine. Further identification of the substance was performed by GC/mass spectrometry (GC/MS). The presence of acridine in urine after the coal tar application was identified by MS. The detection of acridine in urine provided proof of the absorption of a coal tar component through the skin.

Sixteen urine samples were collected from 4 male, nonsmoking psoriatic patients, undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar based ointment, followed by exposure to UV irradiation) in the Dermatology Clinic of the University of Padua (Clonfero et al. 1989). Patient A was treated with pure coal tar for 1 day; patients B, C, and D were treated with 4% coal tar based ointment for 2, 8, and 13 days, respectively. Body surface involved by psoriasis was 30, 40, 35, and 60% for patients A, B, C, and D, respectively. Total PAH (and pyrene) content of the two coal tar preparations was 28,800 (3,100) and 470 (104) ppm, respectively. The samples were collected at different times after the beginning of therapy (from 12 hours after the 1st application of coal tar to 72 hours after the last application). 1-Hydroxypyrene and other PAHs were detected in the urine, indicating absorption of components of the coal tar.

Santella et al. (1994) also observed urinary excretion of PAH metabolites after dermal application of coal tar, indicating absorption. Studies confirming that coal tar creosote is capable of inducing phototoxicity of the skin indicate dermal absorption after exposure (Diette et al. 1983).

It can also be concluded that dermal absorption occurred as evidenced by the development of skin tumors (Boutwell and Bosch 1958; Lijinsky et al. 1957; Poe1 and Kammer 1957; Roe et al. 1958) and lung tumors (Roe et al. 1958) in mice following the dermal application of coal tar creosote (see Section 2.2.3.8). Other studies in animals support absorption of coal tar products after dermal application. Coal tar solution (0.05 mL of a 20% solution) was applied to the skin of 6 neonatal rats (4-6 days of age) and 24 hours later AHH activity was measured in the skin and liver (Bickers and Kappas 1978). There was greater than a lo-fold induction of skin AHH activity (298±13 versus 26.3±19 pmol hydroxy-benzo[a]pyrene/mg protein/hour in controls) and marked increased hepatic AHH activity (16,300±899 versus 750±35 pmol hydroxy-benzo[a]pyrene/mg protein/hour in controls) after topical application of the coal tar solution.

Based on data on PAHs, absorption of PAH components of coal tar products after dermal exposure may be limited by binding and/or metabolism in the skin, thus leaving less for systemic absorption (ATSDR 1995). Excretion of PAHs following dermal application may be detected in hours or days, and is improved by solubilization of the compounds in a fat or oil mixture prior to application. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of dermal absorption studies conducted with pure PAHs is limited. A further problem with the use of individual PAHs to estimate absorption of coal tar is that individual PAHs differ in their rates of absorption. The concentrations of nine different PAHs were measured after topical application of coal tar to a blood-perfused pig-ear (VanoRooij et al. 1995). There was a variation of accumulations of the various PAHs in the perfused blood, ranging between 830 pmol cm^{-2} for phenanthrene to less than 4 pmol cm^{-2} for benzo[b]fluoranthene, benzo[a]pyrene, and indeno[123-cd]pyrene. These data show that different components of coal tar are absorbed at different rates, and that using a single PAH to represent absorption of the mixture is likely to over- or under-estimate the absorption of other components.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located in humans regarding the distribution of the creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation exposure. Because coal tar products are composed of hydrocarbons, they are likely to distribute to lipid-rich tissues. These may include breast milk and the placenta. Coal tar creosote is also likely to distribute to the liver as evidenced by the presence of metabolites in the urine.

Tumor-susceptible ICR CF-1 and tumor-resistant CAFl-JAX mice were exposed to 10 mg/m3 coal tar aerosol-BTX mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al. 1977). The coal tar-BTX mixture was comparable to the material inhaled by topside coke oven workers. Mice were serially sacrificed during the exposure period for the determination of coal tar lung burden and the time to tumor induction. Control animals were held in a vivarium. All animals were examined daily during the exposure and postexposure periods. Coal tar fluorescence retained in mouse lung and skin tissues were measured. The amount of coal tar found on mouse skin did not change to any great degree after the first week of exposure. Lung tissue accumulated coal tar aerosol at a fairly steady rate during 18 months of intermittent exposure as compared to a high increased rate (from graph) during the 90 days of continuous exposure. The coal tar lung burden in mice was approximately equal for both exposure modes around the 180-day exposure period.

When [^{3}H]-benzo[a]pyrene was administered intratracheally to rats at a dose of 0.001 mg/kg, radioactivity was distributed to all tissues (Weyand and Bevan 1987). During the 6 hours following administration, >20% of the dose was detected in the carcass. The activity steadily increased in the intestine and the intestinal contents over the 6 hours. Levels of activity in the liver and lung were moderate and declined over time. Trace amounts of activity were detected in other tissues (Weyand and Bevan 1987).

Intratracheal administration of [^{3}H]-benzo[a]pyrene, along with the benzene extract of coal fly ash, to pregnant rats (20 mg/kg/day) on days 18 and 19 of gestation resulted in their distribution to the maternal lung and liver (Srivastava et al. 1986): The amount of radioactivity found in the maternal liver was approximately 68% of the amount of radioactivity found in the maternal lung. The amounts of radioactivity found in the placenta, fetal lung, and fetal liver were approximately 4, 1.9, and 1.4%, respectively, of the amount of radioactivity found in the maternal lung. Much of the radioactivity was attributable to metabolites. These results in rats suggest that components of coal tar creosote and their metabolites can pass through the placenta and distribute to fetal tissue.

2.3.2.2 Oral Exposure

No studies were located in humans or animals regarding the distribution of, coal tar creosote, or coal tar pitch volatiles following ingestion. Based on chemical structure, it is likely that PAHs would have a strong affinity for adipose tissue. For example, benz[a]anthracene, chrysene, and triphenylene distributed to all tissues following oral administration (22.8 mg/kg) to female rats, but its greatest distribution was to

adipose tissue. In this study, benz[a]anthracene concentrations were 10 times higher in adipose than in other tissues (Bartosek et al. 1984).

The distribution of nonmetabolized PAHs is dependent on their water-solubility. The more water-soluble PAHs, such as triphenylene, are generally more available to tissues other than fat (Bartosek et al. 1984). In humans, distribution of coal tar creosote following ingestion is likely to be qualitatively similar to that seen in the animal studies. The lipophilicity of PAHs allows the chemicals to be readily absorbed and preferentially accumulated in fatty tissues. Furthermore, PAHs are likely to be present in adipose and highly perfused organs such as the lungs and liver.

Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. Phenols in serum and urine were analyzed by HPLC. Wood creosote used in this study as determined by GC contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). Concentrations found in peripheral venous blood and urine were 15 mg phenol, 32 mg guaiacol, 18 mg *p*-cresol, and 24 mg cresol. HPLC analysis of 30-minute postdose serum detected low concentrations of guaiacol and *p*-cresol.

Culp and Beland (1994) fed male B6C3F$_1$ mice 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days. A second group of mice was fed benzo[a]pyrene for 21 days at levels corresponding to those found in the coal tar-containing feed mixtures. At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-postlabeling. The adduct levels were then compared with those obtained from the mice fed benzo[a]pyrene. DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene. DNA adduct levels were in the order forestomach > liver > lung at lower dose groups, while the order changed to liver > forestomach > lung at the highest dose group. Total DNA binding was greater in the coal tar fed mice than in the benzo[a]pyrene fed animals (≈ l0- to 30-fold greater in the liver and forestomach, and over 90-fold greater in the lungs at the lower doses).

2.3.2.3 Dermal Exposure

No studies were located in humans or animals regarding the distribution of wood creosote, coal tar creosote, coal tar, or coal tar pitch following dermal exposure. Distribution of creosotes or coal tar products in humans following dermal exposure is expected to be qualitatively similar to that seen in animals or in humans following any route of exposure.

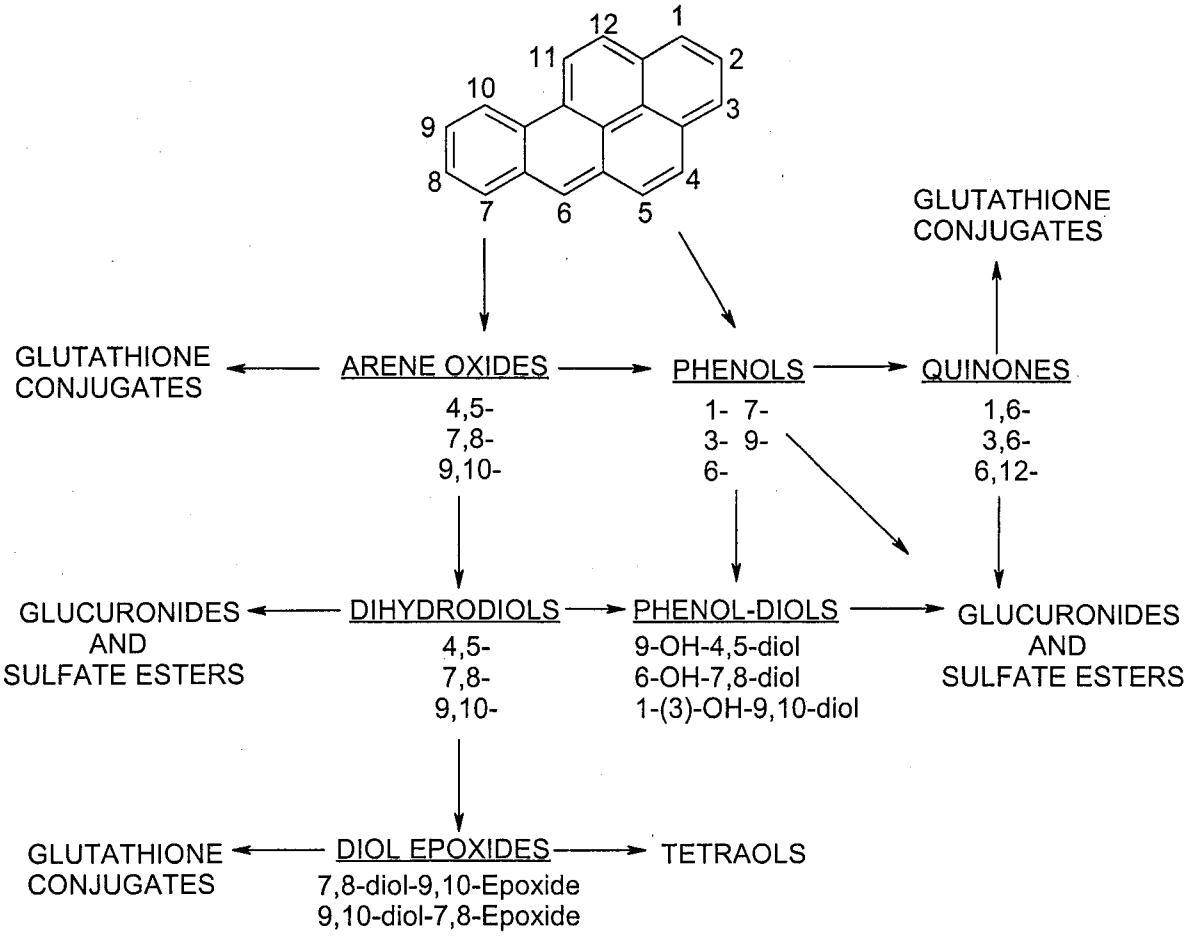
2.3.3 Metabolism

Generally, the PAH components of coal tar creosote, coal tar, and coal tar pitch are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The metabolic profiles vary among species and compounds, but the components follow the same reaction pathways. Hence, the metabolites are structurally very similar. The proposed metabolic scheme for a representative PAH, benzo[a]pyrene, is presented in Figure 2-3, The principal products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products (Autrup and Seremet 1986; Dahl et al. 1985; Fellows 1939b; Geddie et al. 1987; Hopkins et al. 1962; Jongeneelen et al. 1985, 1986, 1988; Ogata et al. 1995; Petridou-Fischer et al. 1988; Povey et al. 1987; Rice et al. 1986; Santella et al. 1994; Weyand and Bevan 1987).

Metabolic studies of creosote have generally been confined to measurements of metabolites in the blood or urine (Bieniek 1997; Bowman et al. 1997; Chadwick et al. 1995; Fellows 1939b; Grimmer et al. 1997; Heikkila et al. 1997; Jongeneelen et al. 1985, 1986, 1988; Malkin et al. 1996; Ogata et al. 1995; Santella et al. 1994; Weston et al. 1994). However, a number of studies have examined the role of individual enzymes in the metabolism of coal tar products. Experiments by Bickers and Kappas (1978), Li et al. (1995), Luukanen et al. (1997), and Genevois et al. (1998) assessed metabolic induction and activity of AHH, glucuronosyltransferase, and cytochrome P450 in response to coal tar.

Application of coal tar for 24 hours to the healthy skin of psoriasis and dermatitis patients caused a 2-5-fold induction of AHH activity compared to untreated skin from the same individuals (Bickers and Kappas 1978). Incubation of human skin with coal tar solution *in vitro* also caused induction of AHH, which reached a maximum after 24 hours. Application of coal tar to the skin of rats produced significant induction of AHH both in skin (10-fold) and in liver (>20-fold).

Figure 2-3. Proposed Metabolic Scheme for Benzo[a]pyrene



Dermal treatment of healthy volunteers with 10% coal tar for 4 days produced an 18-fold induction of CYPlAl mRNA levels in coal-tar-treated skin (Li et al. 1995). *In vitro* incubation of DNA with coal tar fume concentrates in the presence of mouse and yeast microsomes expressing various cytochrome P450 isoforms or the aryl hydrocarbon hydroxylase receptor (AHR) demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYPlA were involved in the metabolism of coal tar fume condensate. It was also shown that the reactive metabolites formed by CYP1A are substrates for microsomal epoxide hydrolase.

Microsome preparations from the livers of rats gavaged with coal tar creosote were used to assay the activities of two glucuronosyltransferases, 1-hydroxypyrene UGT and *p*-nitrophenol UGT, and to estimate the kinetic parameters of the two enzymes (Luukanen et al. 1997). Pretreatment with creosote increased the ratio of V_{max} / K_m for 1 hydroxypyrene UGT by 18-fold and by 2-3-fold for *p*-nitrophenol suggesting that a highly efficient form of glucuronosyltransferase was selectively induced by creosote.

2.3.3.1 Inhalation Exposure

Workers in a coal tar creosote wood-impregnating plant were exposed to coal tar creosote by inhalation during the course of their jobs (Jongeneelen et al. 1985, 1988). The creosote that these employees inhaled contained 19.8 mg pyrene/g creosote (approximately 2%). A metabolite of pyrene, 1-hydroxypyrene, was detected in their urine at levels that were above the mean values of controls (Jongeneelen et al. 1985, 1988). Similarly, workers asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Jongeneelen et al. 1988).

A study of workers occupationally exposed to coal tar creosote compared the concentration of 1-naphthol (a urinary metabolite of napthalene) in six workers from a creosote impregnation plant and five male smokers not occupationally exposed to creosote (Heikkila et al. 1997). Exposed workers wore gloves and cotton overalls to reduce dermal exposure to creosote, but did not wear respirators. The average concentrations of naphthalene in the workers air varied from 0.4 to 4.2 mg/m^3. There was a poor correlation between the amount of naphthalene in the air and the concentration of PAHs. However, the concentration of 1-naphthol was consistently greater in exposed workers than in unexposed controls and was highest for exposed workers at the end of the work shift. There was a correlation of r = 0.745 between the concentration of naphthalene in breathing zone air and urinary 1-naphthol concentrations at the end of the shift.

A similar study was carried out in a coke plant in Zabrze, Poland (Bieniek 1997). The concentrations of 1-naphthol and 2-naphthol in the urine of 102 workers from the coke plant were compared with those of 36 controls not occupationally exposed to coal tar volatiles. Significant differences were found between the concentrations of l- and 2-naphthols in the urine of exposed and unexposed workers ($P<0.05$). The correlation between the concentrations of naphthols in urine and napthalene in air were statistically significant ($P<0.00l$).

Another study of metabolites of coal tar volatiles was carried out by Grimmer et al. (1997). Urine samples were collected from workers at a coke plant over a period of four days. Two workers were exposed to high levels of PAH and two were exposed to lower levels. The concentration of metabolites of phenanthrene; fluoranthene, pyrene, chrysene, and benzo[a]pyrene (in total, about 25 compounds) in urine were measured by GC/MS. The urinary metabolite profile for each individual remained similar over the four days analyzed. However, there was a significant difference between individuals for the absolute amounts of metabolites excreted and also for the ratio of metabolites produced (e.g., only one worker formed the 3,4-dihydrodiol of phenanthrene, the other two did not).

Similar results were obtained for measurements of the concentrations of metabolites of phenanthrene, fluoranthene, pyrene, chrysene and benzo[a]pyrene in urine of female Wistar rats exposed to coal tar pitch aerosols (dose and duration not stated) (Grimmer et al. 1997). The urinary metabolite profile for each individual rat did not show significant variation during the course of the experiment, but there was a significant difference between individuals for both the absolute amounts of metabolites excreted and also for the ratio of metabolites produced.

2.3.3.2 Oral Exposure

Calcium creosotate was orally administered to humans at daily doses of 7-30 mg/kg for 3 days (Fellows 1939b). Calcium creosotate phenols were excreted in the urine. Also, large unspecified doses of calcium creosotate were orally administered to rabbits. Analysis of the rabbit urine revealed that free and conjugated phenols were excreted (Fellows 1939b).

Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. The metabolites in the serum started to rise 15 minutes after the oral dose, reaching the maximum 30 minutes after dosing. The maximum serum concentrations (Cmax)

of glucuronides were 0.18±0.07, 0.9l±0.38, 0.33±0.18, and 0.47±0.23 mg/L, and of sulfates were 0.16±0.06, 0.22±0.09, 0.17±0.07, and <0.04 mg/L for phenol, guaiacol, *p*-cresol, and cresol, respectively. The Cmax for unconjugated phenols were 0.06±0.01, 0.05±0.01, 0.12±0.05, and 0.04 mg/L for phenol, guaiacol, *p*-cresol and cresol, respectively. Rats receiving a single dose of either 0.0002, 0.002, 0.02, 0.2, or 2.0 mg pyrene/kg by gavage in olive oil excreted 1-hydroxypyrene in the urine in a dose-dependent manner (Jongeneelen et al. 1986). This metabolite could be detected up to 96 hours after administration. No unchanged pyrene was excreted.

Induction of glucuronosyltransferase activity in liver microsomes from male Wister rats treated with coal tar creosote (200 mg/4 mL olive oil/kg) by gavage 72 and 24 hours before death was compared with activity in microsomes from untreated control animals (Luukanen et al. 1997). Microsome preparations from the livers of these rats were used to assay the activities of 1-hydroxypyrene UGT and *p*-nitrophenol UGT and estimate the kinetic parameters of the two enzymes. Pretreatment with creosote lowered the apparent K_m value for 1-hydroxypyrene UGT and significantly increased the estimated maximum velocity V_{max} over 4-fold. The apparent K_m values of *p*-nitrophenol UGT were higher and the V_{max} values lower than the ones for 1-hydroxypyrene UGT, but again, treatment with creosote lowered the apparent K_m value and increased the estimated maximum velocity V_{max}. Pretreatment with creosote increased the ratio of V_{max}/K_m for 1-hydroxypyrene UGT by 18-fold and for *p*-nitrophenol 2-3-fold. These results suggest that a highly efficient form of glucuronosyltransferase was selectively induced by creosote.

Male Fischer 344 rats received 50 mg/kg coal tar creosote in peanut oil daily by gavage for 1 or 3-5 weeks (Chadwick et al. 1995). Controls were dosed with the vehicle. After treatment with creosote, 6 control and 6 treated rats were administered 75 mg/kg 2,6-DNT in DMSO by gavage and 24-hour urine was collected. Urine was also collected from two control and two treated rats dosed with DMSO. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. Low levels of mutagenic metabolites were also found in the urine of animals treated with creosote alone.

It is evident in both human and animal studies that hydroxylation is a principal oxidative pathway of PAH metabolism, and consequently, coal tar creosote metabolism. In these studies, there were no discussions to suggest that the researchers attempted to identify other metabolites.

2.3.3.3 Dermal Exposure

A number of studies have shown that PAH components of coal tar appear to be metabolized following dermal exposure in humans. Two patients suffering from eczema on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar) (Jongeneelen et al. 1985). The daily dermal dose was approximately 1 mg/kg. Analysis of the urine samples collected from these patients prior to treatment and in the morning and evening of the first 3 days of treatment showed that 1-hydroxypyrene was excreted at levels 200 times that which was detected before the treatment started (Jongeneelen et al. 1985).

Urine samples collected from 43 patients being treated in the hospital for psoriasis with a coal tar ointment and from 37 controls who had never been treated with coal tar were analyzed for the presence of 1-hydroxypyrene-glucuronide and r-7,t-8,t-9,c-l0-tetrahydroxy-7,8,9,10-tetrahydro-benzo[a]pyrene (Bowman et al. 1997). The metabolite, r-7,t-8,t-9,c-l0-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, was detected in urine of 20 (47%) of the patients, but only 4 (10%) of the controls. The other metabolite studied, 1-hydroxypyrene-glucuronide, was detected in all samples, but the mean level for patients was 40.96±72.62 pmol μmol^{-1} creatinine and that for control was 0.38±0.32 pmol μmol^{-1}; this difference was significant ($P<0.0001$). The ratio of urinary levels of the two metabolites was examined in the coal tar-treated patients and found to vary by approximately 6,000-fold, suggesting wide variation between individuals in the ability to metabolize benzo[a]pyrene and pyrene.

Similar results were obtained in another study of psoriasis patients (43 patients and 39 untreated controls) being treated with a coal tar ointment (Weston et al. 1994). The benzo[a]pyrene metabolite, r7,t8,t9,cl0-tetrahydroxy-7,8,9,l0-tetrahydrobenzo[a]pyrene, was detected in urine of 18 psoriasis patients (42%) and 4 untreated subjects (10%). There was a significant difference in the levels of r7,t8,t9,cl0-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene in patients and untreated individuals with levels varying from undetectable to 330 fmol/mL for patients and from undetectable to 40 fmol/mL for untreated individuals. A second metabolite 1-hydroxypyrene-glucuronidide was found in all urine samples, but levels were significantly higher in psoriasis patients than in untreated controls, ranging from 180 to 50,000 fmol/mL in patients and 36-650 fmol/mL in untreated individuals.

Patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure

was 20-100 g of tar/day. Twenty-four hour urine samples were collected from all subjects. Urinary 1-hydroxypyrene was analyzed by HPLC. Urinary PAH metabolites measured by PAH-ELISA were elevated in patients (mean 730±1,370 mmol) as compared to untreated volunteers (±90 mmol equivalents of B[a]P/mol creatinine). Urinary levels of 1-hydroxypyrene were also elevated in patients (mean 547±928 mmol/mol creatinine) as compared with untreated volunteers (mean 0.14±0. 17 mmol).

Metabolism of pyrene was reported for 18 workers from a coke oven included in a NIOSH environmental survey (Malkin et al. 1996). Personal breathing zone air was checked for the presence of PAHs and coal tar pitch volatiles (identity not specified). The levels of naphthalene, benzene and pyrene were specifically recorded. Sludge samples were also analyzed for the presence of PAHs. Preshift and postshift urine samples were collected from the workers and analyzed for the presence of 1 -hydroxypyrene, a metabolite of pyrene. Pyrene was found in analysis of the sludge samples at levels between 6.3 and 36 mg/g, but was detected in only one breathing zone air sample. Preshift 1-hydroxypyrene levels were significantly increased at the end of the work shift. Preshift levels varied from 0.16 to 3.0 µmol/mol creatinine (mean 1.0) and postshift levels ranged form 0.24 to 4.85 µmol/mol creatinine (mean 1.7). Smoking was not found to be significantly related to 1-hydroxypyrene levels in exposed workers, although preshift levels were slightly increased in smokers relative to nonsmokers.

Experiments by Bickers and Kappas (1978), Li et al. (1995) and Genevois et al. (1998) have examined the role of AHH and cytochrome P450 in the metabolism of coal tar products. A coal tar solution (crude coal tar diluted to 20% with ethanol and polysorbate 80) was applied to clinically unaffected skin of three patients with severe atopic dermatitis and six patients with generalized psoriasis (Bickers and Kappas 1978). Another skin area at least 10 cm away was not treated or was treated with 100 mL of the vehicle alone. Twenty-four hours later, a 6-mm punch biopsy was obtained from coal tar treated and control areas and the effect on AHH activity was determined. Application of coal tar to the skin caused induction of cutaneous AHH activity that varied from 2.4-5.4-fold over the enzyme activity in untreated skin areas. There were no sex differences in inducibility between patients with psoriasis and patients with atopic dermatitis. Relative inducibility of human skin AHH by coal tar did not appear to be a function of the basal level of the enzyme.

Coal tar solution (0.05 mL of a 20% solution) was applied to the skin of six neonatal rats (4-6 days of age), and 24 hours later, AHH activity was measured in the skin and liver (Bickers and Kappas 1978). There was greater than a 10-fold induction of skin AHH activity (298±13 versus 26.3±19 pmol hydroxy benzopyrene/mg protein/hour in controls) and marked increased hepatic AHH activity

(16,300±899 versus 750±35 pmol hydroxy benzopyrene/mg protein/hour in controls) after topical application of the coal tar solution.

Cytochrome P4501Al (CYPlAl) expression was increased in healthy volunteers treated dermally with 10% coal tar for 4 days producing an l8-old induction of CYPlAl mRNA levels in coal-tar-treated skin (Li et al. 1995). *In vitro* incubation of DNA with coal tar fume concentrates in the presence of mouse and yeast microsomes expressing various cytochrome P450 isoforms or the AHR demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYPlA were involved in the metabolism of coal tar fume condensate, but neither was absolutely required. The role of microsomal epoxide hydrolase was also tested, and it was shown that the reactive metabolites formed by CYPlA are substrates for epoxide hydrolase. Addition of epoxide hydrolase to the microsome preparations caused an 80% reduction in the relative level of DNA adducts produced from coal tar fume condensates by CYP1Al.

2.3.4 Elimination and Excretion

Excretion of the PAH compounds of coal tar creosote is controlled by their rate of metabolism. Excretion of these metabolites or any remaining parent compound is primarily in the urine, bile, and feces. Weyand and Bevan (1987) demonstrated this by cannulating the bile ducts of rats that received [^{3}H]-benzo[a]pyrene intratracheally. Those rats with the biliary cannulas had significantly lower levels of activity in their intestines, intestinal contents, and stomach than rats without biliary cannulas. Sanders et al. (1986) showed that PAHs were primarily removed in the feces after dermal administration of [^{14}C]-benzo[a]pyrene and [^{14}C]-7,12-dimethylbenz[a]-anthracene, suggesting hepatobiliary excretion. Urinary excretion of PAH metabolites also occurs, but to a lesser extent than by the other routes. Excretion of the major portion of experimental doses of PAHs suggests half-lives in hours to days, with inhalation exposure yielding the fastest elimination, followed by oral exposure and dermal exposure (ATSDR 1995). PAHs are also stored in the fat, so it is possible that they may appear in breast milk.

Studies of excretion of coal tar products have used urinary levels of PAHs and their metabolites as an estimate of excretion of the parent mixture. These studies give information as to the rates of elimination of individual PAHs, but not their extent, since a significant proportion of these chemicals is eliminated in the bile and feces. The conclusions that can be drawn from these studies are also limited by evidence that the rates at which individual PAHs are absorbed can vary by several orders of magnitude (VanøRooij et al. 1995) so that no individual PAH can be taken as representative of the entire coal tar mixture.

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion of wood creosote following inhalation exposure in humans or animals. Some studies were located that estimate excretion of individual PAHs or their metabolites in urine. Excretion of PAHs and their metabolites after inhalation exposure may be detected hours to days after exposure (ATSDR 1995).

Measurements were carried out in a creosote impregnation plant where 6 men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work free period of 64 hours. All workers wore leather protective gloves and cotton overalls. Two employees worked overtime (until 6:30 a.m.) on Monday which was an exception to the regular &hour schedule. Particulate PAHs were collected during the whole shift and analyzed within 7 weeks. Workers were asked to collect all urine passed within the 24-hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentration of total particulate PAHs (including pyrene) was 4.77 (1.2-13.7) mg/m^3 and that of naphthalene was 1,254 (370-4,200) mg/m^3. The PAH profile was similar in all samples. The lowest concentrations of 1-hydroxypyrene in creosote workers were found in the Monday morning urine samples after 64 hours off work. The highest concentrations were consistently found in the evening samples (6-9 hours after work) but lower at the end of the shift. The urinary 1-hydroxypyrene levels on Monday morning before work ranged from 4 to 22 mmol/mol creatinine; levels on Tuesday morning to Saturday morning ranged from 16 to 120 mmol/mol creatinine; and levels at end of shift ranged from 19 to 85 mmol/mol creatinine. The evening after work (taken on Monday, Wednesday and Friday) urinary levels of 1-hydroxypyrene ranged from 27 to 122 mmol/mol creatinine.

Exposure of assemblers (all smokers) handling creosote-impregnated wood and one worker (smoker) chiselling coal tar pitch insulation to coal tar products was assessed by analyzing the breathing zone air for airborne PAHs, and assaying urinary excretion of 1-hydroxypyrene (Heikkila et al. 1995). The concentration of pyrene and 11 other PAHs in particulate matter had been measured both in the work room and in the breathing zone of the assemblers a year earlier during 2 working days. In the present setting the ties were impregnated with the same type of creosote as a year earlier, which contained 0.2 w% of pyrene. Urine samples were collected during 3 working days (Monday, Wednesday, and Friday) and over the following weekend. Urine samples from one chiseller were collected in the morning before work, during lunch time, at the end of the shift, in the evening, and the next morning. The total concentrations of PAH and of 4-6 aromatic ring-containing PAH (when chiselling) were 440 (50-fold

higher than assemblers) and 290 (200-fold higher than assemblers) mg/m^3, respectively. The estimated mean of inhaled pyrene for assemblers measured on Monday, Wednesday, and Friday was found to be 0.009, 0.007, and 0.024 mmol/shift, respectively. The estimated inhaled pyrene measured on the chiseller was 1.2 mmol/shift. Excretion of urinary 1-hydroxypyrene for assemblers measured on Monday, Wednesday, and Friday for assemblers showed mean pyrene doses (pyrene doses=breathing volume [25 L/minute] x work period x pyrene concentration x 50% retention) of 0.010, 0.13, and 0.19 mmo1/24 hours, respectively. Excretion of urinary 1-hydroxypyrene measured on the chiseller showed a pyrene dose of 0.492 mmol/24 hours.

Four rotation crews of about 29 workers and one day crew of 22 workers worked a 5-day shift of 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators which were renewed 4-5 times/day, thick cotton working clothes with long sleeves, safety shoes, safety glasses, gloves, and helmets. Other groups that worked occasionally in the potrooms were also included in this study. Some employees who worked in dusty environments also wore facial protective clothing. Personal breathing zone air samples were taken randomly one time from 38 workers. Measurements were done on 3 of 5 working days for the rotation crews and on 4 days in 2 work weeks for the day crew. The filter holders and the XAD-2 tubes used in sampling were analyzed. Urine samples were collected from 33 of 38 workers before and after the 5-day work week. Control urine samples were taken from 10 guards not exposed to coal tar pitch volatiles. 1-Hydroxypyrene in urine was determined by liquid chromatography. Results showed that field blanks were not contaminated with coal tar pitch volatiles. No benzo[a]pyrene was found on XAD-tubes. Vapor phase measurement showed 48% pyrene and 24% total PAHs. The highest filter sample (particulate) concentration of pyrene was 170 mg/m^3 and the highest sorbent tube (vapor) concentration of pyrene was 94 mg/m^3. The correlation between these 2 variables was 0.70. Individuals who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging from 10-2,710 mg/m^3. Multiple regression analysis of increased urinary 1-hydroxypyrene was strongly related to the environmental PAH exposure. Increased urinary 1-hydroxypyrene was greater among those using facial protective clothing under their respirators; this was probably caused by poor fitting or by facial coverings becoming contaminated by PAH. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for coal tar pitch volatiles was 4.3 mmol/mol creatinine. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for benzo[a]pyrene was 4.3 mmol/mol creatinine.

Urine samples collected from two reference groups of nonoccupationally exposed individuals and four groups of workers were measured for urinary excretion of 1-hydroxypyrene (Viau et al. 1995). The study

groups are described as follows: reference group 1 (12 males, 9 females) was workers with no occupational exposure to PAH (single spot urine sample collected during the day); reference group 2 (7 males) was administrative workers in a silicon carbide plant (urine samples obtained Monday morning upon arrival at work); the silicon carbide group (83 males) worked in a silicon carbide plant involved in various occupations (urine samples collected at the beginning and end of work shift on a Monday and Friday); the creosote group (19 males) was workers exposed to creosote in a wood treatment plant (one urine sample collected towards the end of the work week and another sample obtained after at least 64 hours of exposure); the decontamination group (29 males) was workers in various occupations related to the removal of soil contaminated with PAH from the pyrolysis of used tires after a major tire at a dump (single urine sample collected at beginning of shiftj; and the brushwood cutting group (10 males) was workers responsible for the clearing of brushwood under electricity power lines (single urine sample collected at end of shift). Urine samples from reference group 1, creosote, decontamination, and brushwood cutting groups were analyzed by high performance chromatography; samples from reference group 2 and silicon carbide group were analyzed by GC/MS. Results showed that the creosote group was largely exposed to pyrene. Even after >64 hours without exposure, the mean (geometric) excretion of 1-hydroxypyrene was higher for the creosote group (0.53 mmol/mol creatinine) than for the reference groups 1 (0.08 mmol/mol creatinine) and 2 (0.10 mmol/mol creatinine). The mean (geometric) excretion in creosote workers during their working week was 1.63 (0.18-10.47) mmol/mol creatinine. The brushwood cutting workers excreted more 1-hydroxypyrene than the referents. These results were pooled with those of the nonoccupationally exposed reference groups yielding a total of 140 individuals having a mean (geometric) excretion of 0.08 mmol/mol creatinine and the 5th, 50th, and 95th percentiles of 0.02, 0.09, and 0.32 mmol/mol creatinine. The mean (geometric) excretion in the 95 nonsmokers and 45 smokers of this pool was 0.07 and 0.12 mmol/mol creatinine, respectively.

2.3.4.2 Oral Exposure

No studies were located regarding the excretion of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following oral exposure in humans. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Urine samples were collected at various time intervals. Phenols in urine were analyzed by HPLC. Wood creosote used in this study as determined by GC contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). The urinary recoveries of the sum of the conjugated and unconjugated forms of each phenolic compound were 75±35, 45±36, 103±51, and 74±36% for phenol, guaiacol, *p*-cresol, and cresol, respectively.

Weyand et al. (1991) fed male mice 0.25% coal tar in feed for 15 days. The coal tar mixtures were of five different compositions. Analysis of urine collected on the first and last day of exposure indicated that 1-hydroxypyrene was the major metabolite excreted by all groups. Urinary levels of 1-hydroxypyrene were greater on day 15 of ingestion compared to day 1 of ingestion. 1-Naphthol, 1-hydroxyphenanthrene, and 2-hydroxyphenanthrene were also detected in the urine. Animals fed coal tar with a high content of pyrene excreted more I-hydroxypyrene than animals fed coal tar with low pyrene content. In another study by Weyand et al. (1994), 5 groups of $B6C3F_1$ mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% mgP residue, a type of coal tar formed as a by-product of coal gasification. The urinary excretion of 1-hydroxypyrene by male mice (12 per group) treated with 0.25 and 0.50% mgP was evaluated throughout the 185 days of diet administration, Urine was collected overnight on days 1, 34, 64, 88, 116, and 182 of diet administration and analyzed by HPLC. Urine collected overnight on days 1, 34, 64, 88, 116, and 182 resulted in increased urinary excretion of 1-hydroxypyrene 19 (day 1) to 203 (day 182) mg/mL per mouse. This increase in concentration paralleled a notable decrease in the total volume of urine excreted by animals. Thus, the total amount of 1-hydroxypyrene excreted reached a maximum of 5-6 mg within 34 days of diet administration.

Male Fischer 344 rats received 50 mg/kg creosote in peanut oil daily by gavage for 1 week, or 3-5 weeks (Chadwick et al. 1995). Controls were dosed with the vehicle. After treatment with creosote, 6 control and 6 treated rats were administered 75 mg/kg 2,6-DNT in DMSO by gavage and 24-hour urine collected. Urine was also collected from 2 control and 2 treated rats dosed with DMSO. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. Low levels of mutagenic metabolites were also found in the urine of animals treated with creosote alone.

2.3.4.3 Dermal Exposure

Human exposure studies demonstrate that coal tar creosote or its components are absorbed dermally in humans, based on excretion of metabolites after dermal exposure (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Hansen et al. 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995). Van Rooij et al. (1993a) examined differences in absorption of PAH between anatomical sites and individuals following dermal exposure of volunteers to 10% coal tar in a vehicle of zinc oxide paste. Differences between individuals in PAH absorption are small (7%) in comparison with differences between anatomical sites (69%). Urinary excretion of

1-hydroxypyrene verified that the coal tar creosote and its components were absorbed through the skin, but the site of application had no effect on the excreted amount of 1-hydroxypyrene although the time to excrete half of the total metabolite varied between 8.2 and 18.9 hours. Another study of excretion after dermal absorption was conducted by Van Rooij et al. (1993b) in a wood preserving plant in the Netherlands in October 1991. Volunteers for this study were workers who worked near the impregnation cylinders (3 subjects) and the assembly hall (7 subjects). Exposure measurements were performed in 2 consecutive weeks on a Monday after a weekend off. On one Monday, the workers wore protective clothing over their clothes and on the other Monday, no protective clothing was used. PAH contamination on the skin and PAH concentration was measured on the two Mondays on all workers, Urine samples were collected from Sunday morning through Tuesday morning for the assessment of the internal exposure to PAH. The excreted amount of 1-hydroxypyrene in urine decreased significantly from 6.6 to 3.2 mg (30.2-14.7 nmol).

Sarto et al. (1989) examined the excretion of coal tar metabolites in male psoriatic patients treated dermally with an ointment containing 2 or 4%, or pure coal tar on 35-60% of the surface skin for 1-13 days. Coal tar content was reported to be 0.49 mg/g for the 4% coal tar ointment, and about 29 mg/g for the pure coal tar. PAHs appeared in the urine within a day after treatment, with peak concentrations.7-10 days after treatment.

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing l0% *pix lithanthracis dermata* (coal tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. High concentrations of toxic compounds in the urine samples were found and mutagenicity tests were not successful. One out of two nonsmoking patients excreted a large amount of thioether products during the beginning of the treatment: 19.6 mmol SH/mol creatinine was measured in the evening urine sample of the first day of treatment and 24.5 mmol SH/mol creatinine in the morning urine sample of the second day of treatment. The concentrations were within the normal range in urine samples measured on the evening of the second day (5.4 mmol SH/mol creatinine) and on the morning of the third day (3.3 mmol SH/mol creatinine). No similar increase in thioether excretion during coal tar treatment was found for other patients, whose values were within or slightly above the normal range. The concentration of 1-hydroxypyrene rose rapidly to 100 times the control value after the beginning of the treatment of these

patients reaching 50-500 μmol/mol creatinine. Pretreatment urine samples of the smoker patients contained somewhat higher levels of 1-hydroxypyrene than those for a separate group of control smokers.

Twenty-eight patients who required coal tar treatment on an area larger than two-thirds of the body surface were selected for this study (Cernikova et al. 1983). Tar paste (10 and 20%) was used for treatment; in one application approximately l-6 g of coal tar containing 0.6% acridine was spread on the patient's skin. Urine analysis was performed by TLC to obtain information on polyaromatic and heterocyclic substances excreted in the urine. Further identification of the substance was performed by GC/MS. The presence of acridine in urine after the coal tar application was identified by MS. Acridine was not quantitated.

Sixteen urine samples were collected from 4 male, nonsmoking psoriatic patients undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar based ointment, followed by exposure to UV irradiation) in the Dermatology Clinic of the University of Padua (Clonfero et al. 1989). Patient A was treated with pure coal tar for 1 day; patients B, C, and D were treated with 4% coal tar based ointment for 2, 8, and 13 days, respectively. Body surface involved by psoriasis was 30,40, 35, and 60% for patients A, B, C, and D, respectively. Total PAH (and pyrene) content of the two coal tar preparations was 28,800 (3,100) and 470 (104) ppm, respectively. The samples were collected at different times after the beginning of therapy (from 12 hours after the first application of coal tar to 72 hours after the last application). Levels of 1-hydroxypyrene ranged from 25.4 mg/g creatinine to 1,565 mg/g creatinine. Total PAH content in urine ranged from 6.4 mg/g creatinine to 64.2 mg/g creatinine. Baseline levels of total PAH and mutagenic activity were determined in evening urinary samples of 5 healthy, nonsmoking subjects, not exposed to PAH. The control group for the determination of 1-hydroxypyrene levels consisted of 52 nonsmokers who exhibited values of 1.3 mg/g creatinine. Results showed levels of 1-hydroxypyrene are 20 and 1,000 times higher in the exposed group than in controls; total PAHs were 3.5-20 times higher in the exposed group than in controls. In 5 of 15 cases, the urinary mutagenicity of the exposed group was not significantly higher than that of the controls, while in one case it was not evaluated due to toxic effects. The mutagenic activity of the urinary extracts of the exposed subjects was at most 8 times greater than the average mutagenicity of the controls.

Patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure was 20-100 g of tar/day. Twenty-four-hour urine samples were collected from all subjects. Urinary

1-hydroxypyrene was analyzed by HPLC. Urinary PAH metabolites measured by the PAH-ELISA were elevated in patients (mean 730±l,370 mmol) as compared to untreated volunteers (110±90 mmol equivalents of B[a]P/mol creatinine). Urinary levels of 1-hydroxypyrene were also elevated in patients (mean 547±928 mmol/mol creatinine) compared with untreated volunteers (mean 0.14±0.17 mmol).

No studies were located regarding the excretion of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following dermal exposure in animals.

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

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The

numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

The pharmacokinetics of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes. Information on individual components is not adequate to define the properties of the whole mixture and for this reason no PBPK models have been proposed for creosote.

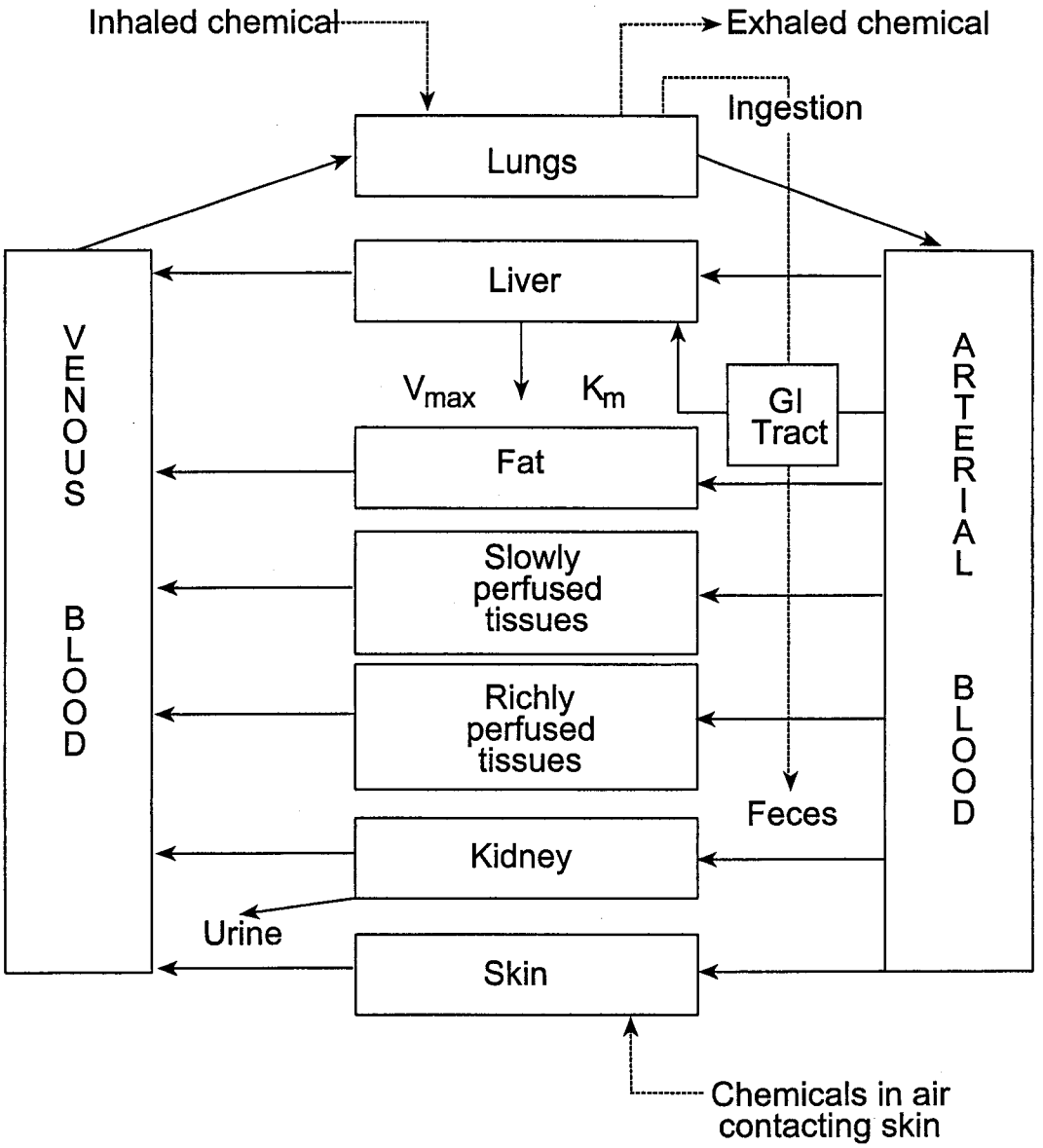
2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. No studies were located in humans or animals regarding the direct analysis of absorption of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles via the inhalation, oral, or dermal routes. Studies of humans exposed to coal tar creosote have measured increased levels of urinary metabolites of various components of coal tar creosote suggesting that at least some components of coal tar creosote are absorbed by all routes. However, these studies do not provide any information as

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance

Source: adapted from Krishnan et al. 1994



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

to the mechanism of absorption. PAHs are lipophilic compounds that are probably absorbed by passive diffusion, but no information was located for mechanism of absorption of other components of creosote. From data on individual PAHs (ATSDR 1995), gastrointestinal absorption of the PAH components of coal tar creosote may be increased by the presence of oils and fats in the stomach and bile in the intestines, while dermal absorption is affected by the anatomical site to which it is applied. Dermal absorption of PAHs may also be increased when they are solubilized in a fat or oil mixture prior to application or conversely may be reduced by binding and/or metabolism in the skin. However, due to the variable composition of coal tar creosote, coal tar pitch, and coal tar, the predictive value of studies carried out on single PAHs is limited. For further information on PAHs please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995).

Distribution. No studies were located in humans or animals regarding the distribution of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. Coal tar is composed of hydrocarbons which are lipophilic substances and are therefore likely to distribute to lipid-rich tissues including breast milk and the placenta. The frequent presence of metabolites of coal tar in the urine also suggests that it is likely to distribute to the liver. The distribution of nonmetabolized PAHs is dependent on their water-solubility. The most lipophilic PAHs may be preferentially distributed to fatty tissues where they may accumulate while more water-soluble PAHs may be more easily excreted. PAHs are distributed to tissues by transport through the blood, therefore, highly perfused tissues such as the lung and liver are likely to contain PAHs. This may also be the case with phenol and cresol as analysis of blood from volunteers who ingested wood creosote (Ogata et al. 1995) demonstrated the presence of phenol, guiacol, and cresols in the blood. A study of the distribution of intratracheally administered radioactive benzo[a]pyrene mixed with a benzene extract of coal fly ash in pregnant rats found that most radioactivity was distributed to the maternal lung, while 68% of the amount in lung was found in the maternal liver (Srivastava et al. 1986). A small amount of radioactivity was also distributed to the fetal lung and liver and to the placenta, respectively 1.9, 1.4, and 4% of the amount in maternal lung. The route of administration of creosote may affect distribution in that entry via the lungs may initially bypass metabolism in the liver so that parent compounds reach peripheral tissues in higher concentrations than would be seen after oral administration.

Metabolism. No studies were located in humans or animals which specifically addressed the metabolism of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. The PAH components of creosote are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules.

The metabolic profiles of these substances vary among species and compounds, but the components follow the same reaction pathways and so the metabolites are structurally similar. The major products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products. Enzymes involved in the metabolism of PAHs vary depending on tissue and the particular PAH, but can include various isoforms of cytochrome P450 (predominantly CYPlAl, but also CYPlA2, CYPlBl, or CYP2C) (Genevois et al. 1998), epoxide hydrolase, glutathione-S-transferases, glucuronidases, and AHH (ATSDR 1995). For more information on the metabolism of PAHs the reader is referred to the ATSDR *Toxicological Profile on Polycyclic Aromatic Hydrocarbons* (ATSDR 1995). Phenol is metabolized via three pathways in mammals; P450 catalyzed hydroxylation, sulphate conjugation, or glucuronide conjugation. The two conjugation pathways can be considered competitive pathways in most species of mammal. Thus, the relative amounts of each product formed depend on dose level as well as the relative abundance and kinetic parameters of the two enzyme systems. For further information on the metabolism of phenol the reader is referred to the ATSDR *Toxicological Profile on Phenol* (ATSDR 1998).

Excretion. No studies were located in humans or animals regarding the excretion of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. Phenol is a normal constituent of human urine and phenol administered via all routes of absorption is rapidly eliminated in the urine and the bile (ATSDR 1998). PAHs are lipophilic compounds that could remain indefinitely within fatty tissues, but metabolism of PAHs renders them more water soluble and more excretable. Excretion of the metabolites of PAHs is primarily in the urine, bile, and feces. Experimental data suggests half-lives of hours to days with elimination being fastest after inhalation exposure followed by oral and dermal exposure (ATSDR 1995). The lipophilic nature of PAHs suggests that it is possible that they are excreted in breast milk, although no studies were located that addressed this issue.

2.4.2 Mechanisms of Toxicity

Defining a general mechanism of toxicity for creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles is essentially impossible because of their diversity and variability in biological effect and composition. The creosotes vary tremendously in respect to their sources (wood or coal), components, and preparation conditions. Similarly, coal tar, coal tar pitch, and coal tar pitch volatiles will differ in composition depending on the source of the coal. Hence, mechanisms of action most likely differ among individual creosotes, coal tars, coal tar pitch, and coal tar pitch volatiles.

In addition, although a great deal is known about the mechanisms of action for many of the individual components of creosote, the use of individual components to define the properties of the whole mixture may or may not supply adequate information upon which risk from exposure to the whole can be appropriately assessed. An excellent example of this is presented by Warshawsky et al. (1993), who reported that the carcinogenicity for mice of specific coal tar creosote components mixed in different formulations differed in incidence and latency of appearance from their individual carcinogenicities. For instance, coal tar in toluene, which was determined to contain 0.0006% B[a]P, produced tumors in 51% of mice with a latent period of 73 weeks. In contrast, the same concentration of B[a]P administered in toluene without coal tar did not produce tumors. The addition of another solvent, n-dodecane, resulted in increased tumor incidence and reduced latency period. Solutions of methylbenz[a]anthracenes in toluene did not produce tumors, but did result in tumors when administered in n-dodecane. The findings of this study indicated that (1) low doses of noncarcinogenic PAHs could have an impact on the carcinogenic potential of B[a]P in mixtures, (2) the carcinogenic activity of coal tar cannot be accounted for by the level of B[a]P present, and (3) certain noncarcinogenic components of coal tar can have their carcinogenic potential altered by the presence of other aliphatic compounds.

Individual components of creosote are also metabolized by several different enzyme systems including cytochrome P450, epoxide hydrolase, glutathione-S-transferases, glucuronidases, AHH, phenol sulfotransferase, and glucuronyltransferase. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual which will again affect the relative toxicity of particular components of creosote for old or young individuals (for further discussion of age-related effects the reader is referred to Section 2.7 Children’s Susceptibility). Therefore, for creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles, it is not presently possible to define mechanisms of transport, distribution, or the precise chemical or physiological events that lead to toxic damage or carcinogenicity in the biological system.

2.4.3 Animal-to-Human Extrapolations

Animal-to-human extrapolations of the toxicity of creosote are complicated by the inherent chemical variety of these substances. Creosotes are complex mixtures of variable composition and the individual components are likely to show interspecies variation in toxicity. Only one study was located which treated more than one species of animal with the same sample of creosote (Miyazato et al. 198l), and although this study suggested that mice were more susceptible to the acute effects of beechwood creosote

than rats, the differential susceptibility observed with this particular sample cannot be applied to creosotes of different composition. In general, the adverse effects observed in animals are similar to those reported for humans with cancer being the most serious, but it is not possible at present to assess whether the doses required to produce adverse effects in animal systems are similar to those required to produce similar effects in humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview. Creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles are complex mixtures of organic substances. Creosote can be derived by distillation from wood (beechwood creosote) or coal (coal tar creosote). Another form is a resin from the leaves of the creosote bush. The chemical composition of creosote varies considerably depending on the source of the coal, wood, or plant, and the design and attendant operating conditions (e.g., temperature, gas distillation systems, etc.) used to produce the creosote.

Beechwood creosote consists mainly of phenol, cresol, guaiacol, xylenol and creosol. It has been used therapeutically as an expectorant and a disinfectant. The leaves of the creosote bush, consumed in tablets, capsules, or in tea (chaparral), are promoted as an herbal remedy for cancer, acne, and as an antioxidant free-radical inhibitor (Nightingale 1993). Creosote bush resin consists of phenolics (which account for 83-91% of the total resin), neutrals (e.g., waxes), basics (e.g., alkaloids), and acidics (e.g., phenolic acids) (Leonforte 1986).

Coal tar creosote is reported to contain over 300 compounds, many of which are in trace amounts (TOMA 1978), the major components of which are PAHs, tar acids (phenol, cresols and xylenols), and tar bases (pyridine and lutidine derivatives); coal tar and coal tar pitch are also mixtures of many compounds. Volatile components of coal tar pitch can be given off during operations involving coal tar pitch, including transporting, and by processes in the coke, aluminum, and steel industries (Bender et al. 1988; Mazumdar et al. 1975; NIOSH 1983; Riinneberg 1995b; Riinneberg and Anderson 1995). Coal tar creosote is used primarily as a wood preservative. Coal tar creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants (EPA 198la, 1984a). Given the current widespread use of coal tar creosote as a wood preservative and its past pesticidal applications, it is the form of creosote most likely to be present at hazardous waste sites.

No studies describing the health effects of wood (beechwood) creosote in humans or animals after inhalation exposure were found in the literature. The available information regarding health effects of coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatile exposure of humans by inhalation must be inferred from occupational surveys and retrospective health studies (Armstrong et al. 1994; ATSDR 1994; Bender et al. 1988; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Emmett 1986; Finkelstein 1989; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; NIOSH 1982; Park and Mirer 1996; Persson et al. 1989; Petsonk et al. 1988; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg 1995b; Riinneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; Spinelli et al. 1991; TOMA 1978, 1979, 1982; Tremblay et al. 1995; Yadav and Seth 1998). In many instances in these industrial studies, exposure levels were not known. The composition of coal tar creosote, coal tar, and coal tar pitch is known to vary depending on the source of the material and the process by which it is produced, and thus the volatile components to which people are exposed will vary depending on the specific composition of the material. Toxicity resulting from inhalation exposure may be different than oral or dermal exposure to the same material, since the more volatile components of the mixtures may have a different and more variable toxicological spectrum than the less volatile fractions of the materials. In addition, exposure to other substances in the workplace was generally not accounted for in these industrial studies, nor was any evaluation of concomitant dermal exposure made. However, with the addition of several animals studies (Chang et al. 1992; Heinrich et al. 1994a, 1994b; Hueper and Payne 1960; MacEwen et al. 1977; Pfitzer et al. 1965; Springer et al. 1986b, 1987), some conclusions can be drawn concerning the organ systems most likely to be affected by exposure. In particular, adverse respiratory, hepatic, dermal, and ocular effects, and cancer, may result from inhalation exposure to coal tar products. Little distinction be between coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles can be made, based on a lack of information concerning their composition.

There is relatively little information available regarding the systemic effects of ingested creosotes, coal tar, or coal tar pitch. However, oral exposure via ingestion of contaminated drinking water is not a highly significant route of exposure to creosotes, coal tar, or coal tar pitch at hazardous waste sites, given its low solubility in water. There is more information on the adverse effects of ingested beechwood creosote in both humans and animals (Alderman et al. 1994; Clark and Reed 1992; Gordon et al. 1995; Miyazato et al. 1981, 1984a, 1984b; Ogata et al. 1993, 1999). These studies indicate that the cardiovascular system, liver, kidney, and central nervous system may be adversely affected by beechwood creosote in sufficient doses, although the mechanism of action for these effects is not known.

The relevance of these findings in humans and animals exposed orally to beechwood creosote, to humans exposed to coal tar creosote is not known. Although the two forms of creosote contain some components in common (e.g., phenolic derivatives), it is not known whether the toxic effects observed after exposure to beechwood creosote can be attributed to the phenol components and thus, extrapolated to coal tar creosote. Oral exposure to coal tar creosote has been associated with death in both humans and animals (Bowman et al. 1984; Cribb 1968; Culp et al. 1998; Davis and Libke 1968; Giffee 1945; Graham et al. 1940; Hackett et al. 1984; Harrison 1959; Luke 1954; Ptitzer et al. 1965), and with adverse effects on the lung, liver, kidney thymus, adrenal glands, and colon (Bowman et al. 1984; Culp et al. 1998; Davis and Libke 1968; Hackett et al. 1984; Luke 1954; Ogata et al. 1999). Developmental effects in animals have also been seen after oral administration of coal tar (Hackett et al. 1984; Springer et al. 1986a). Increases in cancer incidence in humans and animals have been associated with oral exposure to coal tar creosote (Culp et al. 1996a; Dean et al. 1988; Dusich et al. 1980; Goldstein et al. 1998; Weyand et al. 1995), and genotoxicity has been observed after oral exposure of animals to coal tar products (Chadwick et al. 1995; Culp and Beland 1994; Culp et al. 1996a; Goldstein et al. 1998; Weyland and Wu 1995; Weyand et al. 1991, 1994).

Dermal irritation and allergic dermatitis have been reported after dermal contact with beechwood creosote (Leonforte 1986; Smith 1937). However, the majority of reports describing dermal exposure in humans and animals involve coal tar products. Coal tar creosote exerts its acute toxic effects in humans primarily via dermal contact, causing structural damage to the tissues that it comes in contact with, such as the skin and eyes (ATSDR 1994; Birdwood 1938; Diette et al. 1983; Emmett 1986; Jonas 1943; NIOSH 1980a, 1982; Schwartz 1942). Animals studies corroborate these observations (Attalla 1968; Emmett 1986; Pfitzer et al. 1965; Wrench and Britten 1975). Longer periods of dermal exposure to coal tar products seem to be associated with dermal irritation and noncancerous lesions, and skin cancer in both humans and animals (Bonser and Manch 1932; Boutwell and Bosch 1958; Cabot et al. 1940; Cookson 1924; Deelman 1962; Emmett et al. 1981; Goulden and Stallard 1933; Haldin-Davis 1935; Henry 1947; Kligman and Kligman 1994; Lenson 1956; Mackenzie 1898; Niemeier et al. 1988; O'Donovan 1920; Schweikert and Schnyder 1972a, 1972b; Shambaugh 1935; TOMA 1978, 1979; Wallcave et al. 1971; Wrench and Britten 1975). Developmental effects in animals have also been seen after dermal administration of coal tar (Zangar et al. 1989), but similar effects have not been reported for humans (ATSDR 1994; Franssen et al. 1999). The mechanism of action for coal tar creosote-induced toxicity is not defined, but is most likely due to the activity of the PAH components as indicated in Section 2.4.2, Mechanisms of Toxicity.

Much of the information available on the health effects of coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles must be inferred from experimental animal and *in vitro* data on the components of the mixtures (e.g., PAHs). Extrapolation of these results to possible human health effects following exposure to creosotes, coal tar, or coal tar pitch must consider the possible interactions of the mixtures, such as co-carcinogenicity, co-mutagenicity, additivity, promotion, and antagonism. The extent to which these interactions modify the expression of coal tar product toxicity in humans is not known.

Issues relevant to children are explicitly discussed in 2.7 Children's Susceptibility and 5.6 Exposures of Children.

Minimal Risk Levels for Creosote.

Minimum Risk Levels (MRLs) for wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles cannot be determined because available data are insufficient for acute, intermediate, and chronic exposures via the oral and inhalation routes. In addition, creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles are extremely complex chemical compositions, thereby further complicating the MRL derivation process. The MRL is an estimate of the daily human exposure to a substance (noncarcinogenic) that is likely to be without an appreciable adverse risk over a specified duration of exposure. The primary limitation to deriving the MRL for these agents is that the MRL is based on measured biological effects of a substance and not on the effects produced by mixtures of chemicals, which is the chemical nature of the creosotes, coal tar creosote, coal tar, and coal tar pitch. As stated in Section 1.1, creosote is a complex mixture originating from high temperature treatments of coal tar and beechwood or occurring in the resin of the creosote bush. About 300 chemicals have been identified in coal tar creosote, and there may be 10,000 other chemicals present in the mixture. Creosote derived from plants is composed of various organic compounds including phenols, cresols, and guaiacol.

The derivation of the MRL is further complicated by the variability of the mixture's composition among creosote samples. The mixture composition is dependent on the sources and preparation parameters of the creosote, and as a result the creosote components are rarely consistent in their type and concentration. Hence, toxicological evaluations of one creosote sample, for instance, are most likely inadequate for extrapolation to other creosote samples unless their compositions are similar. An example of the composition variability among creosote samples was presented by Weyand et al. (1991). In that study the concentrations of several PAHs were analyzed in 4 coal tars. All of the PAHs identified exhibited 2- to

nearly 20-fold differences in concentration among the 4 samples. Benzo[a]pyrene, a component whose individual toxicity has been examined extensively, ranged from nondetectable levels (detection limit 0.3 g/kg) to 1.7, 6.4, and 3.9 g/kg of coal tar. Other studies that illustrate the variability of samples include Wrench and Britten (1975), Niemeier et al. (1988), and Emmett et al. (1981).

The risk assessment of mixtures on human and environmental health has not been easily accomplished since little effort has been directed towards the development of approaches to assess environmental exposure and biological effects. Further difficulty is encountered when efforts are made to predict the toxicity of complex mixtures from available toxicity data which usually indicate biological effects of either a single component of the complex mixture or a simple mixture of several of the components. The relevance of these data to the actual biological effects of the complex mixture is usually not known; therefore, predictions of potential toxicity are highly speculative. It has been reported that the carcinogenicity of PAHs differed considerably depending on the components of the mixture (Warshawsky et al. 1993). For instance, when benzo[a]pyrene, a potent animal carcinogen, is added at noncarcinogenic levels to mixtures of carcinogenic or noncarcinogenic PAHs, the skin tumorigenicity of the noncarcinogenic and carcinogenic mixtures, as well as the latency of tumor incidence, is changed. Hence, unless the actual complex mixture is evaluated directly for toxicity, it is unlikely that its toxic potency can be interpreted from that of its components. Advancements of efforts to assess the human and environmental risks at waste sites will depend on the ability to evaluate the waste site. For example, assessments would be performed to determine the mixture(s) contained within the site, the level of release and contamination, air and soil surrounding the site and the movement of the contaminants into the food chain. By identifying these activities as real or conceptual concerns, we may establish a standardized approach to evaluating the toxicity of waste sites.

Inhalation MRLs

- No MRL has been derived for acute-duration inhalation exposure (14 days or less) to creosote.
- No MRL has been derived for intermediate-duration inhalation exposure (15-364 days) to creosote.
- No MRL has been derived for chronic-duration inhalation exposure (365 days or more) to creosote.

Oral MRLs

- No MRL has been derived for acute-duration oral exposure (14 days or less) to creosote.
- No MRL has been derived for intermediate-duration oral exposure (15-364 days) to creosote.
- No MRL has been derived for chronic-duration oral exposure (365 days or more) to creosote.

Death. No information was available on the lethal effects of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation exposure in humans. Although some industrial studies suggest increased mortality in workers exposed to coal tar creosote and coal tar pitch volatiles due to cancer (Lloyd 1971; Redmond 1976; Redmond et al. 1976; Rochette and Arena 1983; TOMA 1982), exposure of persons living near hazardous waste sites is unlikely to cause these effects. No deaths were observed in rats exposed to near saturated vapors of coal tar creosote for 1 hour (concentration estimated to be <0.033 mL/L) (Pfitzer et al. 1965). The exposed animals showed signs of slight eye and nose irritation, and slight dyspnea. All rats exhibited weight gains comparable to the control animals, and no treatment-related lesions were observed at necropsy. Heinrich et al. (1994a, 1994b) reported increased mortality in rats exposed to coal tar aerosol for 10-20 months.

No information was available on the lethal effects of wood creosote in humans after ingestion. Beechwood creosote is lethal to animals, although the oral doses required to produce death are relatively high (300-525 mg/kg) (Miyazato et al. 1981). Oral dosing with 740 mg/kg/day of coal tar sacrificed 10 of 16 treated rats within 4 days of the initial dose, but no mortality was observed when rats were treated for only 2 days with the same dose, or for 5 days with 370 mg/kg/day (Hackett et al. 1984; Springer et al. 1986a). Ingestion of coal tar creosote can be fatal to both humans and animals. In the case reported by Bowman et al. (1984), death following ingestion of creosote (form and quantity not specified) was attributed to multi-organ failure. Death has been reported to occur in adults and children 14-36 hours after the ingestion of about 7 g or l-2 g creosote, respectively (Lewin 1929). The oral LD_{50} for coal tar creosote is reported as 433 mg/kg in mice and 725 mg/kg in rats (RTECS 1994). Another study reported an acute oral LD_{50} of 1,700 mg/kg in rats (Pfitzer et al. 1965). The reasons for this discrepancy in LD_{50} values are not known. Based on these data, coal tar creosote can be classified as mildly to moderately toxic. Death is preceded by signs of central nervous system intoxication following acute oral exposure in both humans and animals. Given the relatively high oral doses required to cause death following acute ingestion in both humans and animals, individuals living in areas surrounding hazardous waste sites contaminated with creosote may not be at high risk for death due to acute ingestion of creosote.

No information was available on the lethal effects of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following dermal exposure in humans. The dermal LD_{50} in rabbits has been estimated to be greater than 7,950 mg/kg (Pfitzer et al. 1965). Additional reports of mortality in animals after dermal exposure to coal tar or coal tar pitch volatiles were found (Bonser and Manch 1932; Deelman 1962). Wallcave et al. (1971) observed decreased survival time in mice dermally exposed to coal tar pitch for >31 weeks. Similar results were observed by Niemeier et al. (1988) for pigmented and nonpigmented mice exposed dermally to asphalt and coal tar pitch for more than 1 year. Thus, prolonged dermal exposure to coal tar products may cause increased mortality due to other effects, especially cancer. However, exposure of persons to coal tar and coal tar products at levels found in hazardous waste sites is unlikely to cause increased mortality.

Systemic Effects.

Respiratory Effects. Data from industrial health surveys of employees in wood preservative plants in which coal tar creosote and coal tar were the main treatments used, and in coal tar plants, indicate respiratory effects including reduced lung function (TOMA 1978, 1979); however, some limitations in the study design and data collection have been identified. Data from studies of inhabitants of log homes that were built with pentachlorophenol-treated logs suggest that inhalation exposure to fumes from treated logs may be significant (Hemandex and Stressman-Sundy 1980). Similar exposure may result from coal tar creosote-treated logs (Cammer 1982). However, residents living on soil contaminated with coal tar creosote showed no increase in the incidence of bronchitis (ATSDR 1994). Ptitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for 1 day. The rats exhibited dyspnea and slight nasal irritation. A significant increase in lung weight, histiocytosis of lung tissue, and lesions of the olfactory epithelium have been reported for rats exposed to coal tar aerosol for up to 13 weeks (Springer et al. 1982, 1986b, 1987). Lung damage was observed in rats and guinea pigs exposed to coal tar or asphalt vapors for up to 2 years (Hueper and Payne 1960).

No adverse respiratory effects attributable directly to wood creosote have been reported for humans following ingestion, Beechwood creosote is known to increase respiratory secretions, from which it derives part of it pharmaceutical value as an expectorant (Stevens et al. 1943). A slightly higher incidence of bronchitis or thickening of the tracheal mucous membrane was observed in mice fed beechwood creosote for 52 weeks (Miyazato et al. 1984a). This effect was considered secondary to irritation resulting from long-term inhalation exposure to volatile (but unidentified) components of creosote in the feed.

No toxic respiratory effects have been reported following oral coal tar product exposure in humans. Only one study has reported toxic respiratory effects for animals orally exposed to coal tar, and the effects were minor. Mice fed up to 344 mg/kg/day coal tar for 94 days showed no adverse effects on the lung, but mice fed similar doses of coal tar for 2 years showed a significant decrease in lung weight (Culp et al. 1998). The airborne component chemicals in coal tar products have not been well defined, and differ depending on the composition of the particular product. However, based on the results discussed above, it is possible that some components of beechwood creosote which are common to coal tar creosote could be irritating to the respiratory tract.

No toxic respiratory effects have been reported following dermal exposure to wood creosote, or coal tar products in either humans or animals. Data from industrial health surveys of employees in wood preservative plants in which coal tar creosote and coal tar were the main treatments used, and in coal tar plants indicate respiratory effects, including reduced lung function were present (TOMA 1978, 1979); however, the studies have some limitations with regard to design and data collection. How much of this respiratory toxicity occurred because of dermal exposure is not known. No increase in the incidence of bronchitis was noted in a population living on an abandoned creosote factory site, despite evidence indicating the soil and water were contaminated with creosote (ATSDR 1994).

Based on data in the literature, respiratory effects are likely to occur after inhalation exposure to coal tar products, but are unlikely after oral exposure. Beechwood creosote may cause respiratory effects after oral exposure. However, evaluation of people living near a coal tar creosote contaminated hazardous waste site indicates that respiratory effects are not easily detectable.

Cardiovascular Effects. No reports of adverse cardiovascular effects in humans or animals were found after inhalation, oral, or dermal exposure to wood creosote.

Reports of cardiovascular effects of coal tar products are scarce. An increase in mortality due to atherosclerosis was associated with cumulative inhalation exposure to tar from pot emissions in the aluminum industry (Ronneberg 1995b). An increase in diastolic blood pressure in employees exposed to coal tar creosote in a wood preservation plant has been reported (TOMA 1978). Rats exposed to high-boiling coal liquid (heavy distillate, HD) administered by inhalation (700 mg/m^3, for 6 hours/day, 5 days/week for 6 consecutive weeks) exhibited a 20% increase in arterial blood pressure (Sasser et al. 1989). Heart rate was also elevated in the HD-treated animals. The causal relationship, however, between HD and the elevation of blood pressure and heart rate is not clear since physiological

disturbances of other systems, whose activity influence pressure and rate parameters (e.g., pulmonary and renal systems) might have produced the observed changes in cardiovascular activity.

A report was found in the older literature that described the case of a woman who experienced hypertension attributed to oral coal tar creosote exposure by "self-medication" for chronic bronchitis (Robinson 1938). Cardiovascular collapse has also been reported to occur following the ingestion of lethal doses of coal tar creosote in humans (Lewin 1929). Creosote has been reported to cause an increase in blood pressure in rabbit intestines after intravenous injection (Kasai 1908). Some of these cases are anecdotal and occur in isolated instances. There is often a lack of dose and concentration data, and the possibility of confounding factors limits the usefulness of these findings. Furthermore, adverse creosote-induced cardiovascular effects have not been reported consistently in animals. Thus, it is not likely that the cardiovascular system is a major target organ of toxicity from coal tar product exposure.

Gastrointestinal Effects. No gastrointestinal effects have been observed in humans or animals after inhalation or dermal exposure to wood creosote or coal tar products.

Ulceration of the oropharynx and petechial hemorrhages over the gastrointestinal serosal surfaces were noted at autopsy in the case of a 70-year-old man who died following the ingestion of "industrial" (coal tar) creosote (Bowman et al. 1984). This acute tissue damage was attributed to a corrosive action of phenol (a component of creosote) via its ability to denature and precipitate proteins. Animals that died following the administration of single gavage doses of coal tar creosote in an acute range-finding study (doses ranged from 2.52 to 5.00 mg/kg) exhibited hyperemia and distention of the stomach upon necropsy. Similarly, rabbits that died following single dermal applications of undiluted coal tar creosote exhibited hyperemia of the intestines (Pfitzer et al. 1965). Creosote has been reported to cause peristaltic movements in rabbit intestine after either intravenous injection or direct application to intestinal tissue, most likely by direct action on the musculature (Kasai 1908).

No adverse gastrointestinal effects have been reported in humans or animals after oral exposure to wood creosote. Wood creosote is known to have antidiarrheal effects, from which it derives part of its pharmaceutical value (Ataka et al. 1996; Greenwood-VanMeerveld et al. 1999; Ogata et al. 1993, 1999). Orally administered wood creosote produced a significant reduction in colonic mobility in mice (Ogata et al. 1999). An *in situ* loop of the small intestines of female Wistar rats was filled with 3 mL of 5% (w/w) gum arabic in saline mixed with various concentrations of creosote. One hour later, the volume of the injected fluid remaining in the intestinal loop was measured to determine the net amount of fluid absorbed

by the intestinal epithelium. In the *in situ* intestinal loop experiment, the amount of intestinal fluid decreased to 48% of controls after administration of 53 mg/kg creosote, demonstrating that creosote increased net absorption of the fluid from the intestine with this dose (Ogata et al. 1993). The effect was unclear with a dose of 213 mg/kg creosote. The amount of Na^+ and Cl^- in the intestinal loop also decreased to 55 and 53%, respectively, of controls, with a dose of 53 mg/kg, indicating that the net fluid absorption was accompanied by an almost parallel absorption of salts.

A similar decrease in fluid volume within *in situ* ligated sections of rabbit jejunum was observed in a study of the effects of wood creosote on *Escherichia coli (E. coli)* heat labile enterotoxin-induced diarrhea (Ataka et al. 1996). Wood creosote induced a dose-dependent decrease in enterotoxin-induced intestinal fluid volume. This study demonstrates that wood creosote reduces the net secretion of intestinal fluid, but does not show whether this effect is due to increased absorption or decreased secretion, However, *in vitro* experiments by Greenwood-VanMeerveld et al. (1999) have shown that addition of beechwood creosote to rat jejunal tissue produces a decrease in transmural potential difference. This decrease is likely to be associated with an increase in the absorption of water and electrolytes, and may be due to inhibition of acetylcholide-induced secretion of chloride ions.

The toxicological significance of these changes is not known. Given that gastrointestinal lesions due to coal tar creosote were observed in only one isolated instance in humans, and the fact that only mild creosote-induced gastrointestinal effects of unknown toxicological significance have been reported in animals, it is likely that the gastrointestinal system is a target organ of toxicity only after the ingestion of relatively high doses of creosote.

Hematological Effects. No reports of adverse hematological effects in humans and animals after inhalation exposure to wood creosote were found in the literature. In one report of human oral exposure to chaparral, hematological parameters were normal (Alderman et al. 1994), whereas in another report, prothrombin time was increased (Gordon et al. 1995). Various hematological and clinical chemistry parameters have been observed to be altered by dietary exposure to beechwood creosote in rats and mice (Miyazato et al. 198 1, 1984a, 1984b). The only effect considered to be treatment-related by the authors was an increase in serum cholesterol in both rats and mice.

Although some industrial reports of coal tar product exposure indicate changes in hematological parameters after inhalation or dermal exposure (TOMA 1978, 1979), the results are not clear. Clinical reports of dermal exposure to coal tar indicate no effect on hematological parameters (Gilmour et al.

1993). Rats exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks had decreased red and white blood cell counts and hemoglobin concentration and increased reticulocytes (Springer et al. 1986b). Red blood cell counts, hemoglobin concentration, and the volume of packed red cells were also significantly decreased in mice exposed to 690 mg/m^3 coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but other hematologic parameters such as erythrocyte, leukocyte, and reticulocyte counts were unaffected by exposure (Springer et al. 1987). However, the toxicological significance of these changes are not known, particularly with regard to individuals exposed to coal tar creosote in areas surrounding hazardous waste sites.

Hepatic Effects. Observations made in animals suggest that coal tar creosote and other coal tar products have the potential to induce adverse effects in the liver. No reports of adverse hepatic effects in humans or animals after inhalation exposure to wood creosote were found in the literature. Acute toxic hepatitis has been attributed to ingestion of an herbal nutritional supplement product derived from the leaves of the creosote bush commonly known as chaparral (Alderman et al. 1994; Clark and Reed 1992; Gordon et al. 1995). This herbal remedy is considered by the FDA as having the potential to cause acute, toxic hepatitis (Nightingale 1993). Dietary exposure to beechwood creosote induces changes suggestive of liver injury in rats and mice (increased relative liver weights and increased liver enzymes). However, no treatment-related changes were observed at histological evaluation (Miyazato et al. 1981, 1984a, 1984b).

No adverse hepatic effects were reported after inhalation or dermal exposure of humans to coal tar products. Kock et al. (1994) reported death of 7 of 20 black rhinoceroses which had been held in creosote-treated holding pens. The animals which died had uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. Serum levels of aspartate transaminase (AST) and bilirubin were also elevated. A significant increase in relative liver weight was reported for pregnant rats and mice exposed dermally to 500 or 1,500 mg/kg/day coal tar for 5 days (Zangar et al. 1989). Relative liver weights were also significantly increased in rats and mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Subtle changes in liver histology were also noted for males and females exposed to 690 mg/m^3 compared with controls. These included a slight increase in cytoplasmic basophilia, slightly more variability in hepatocellular size, the presence of hepatomegalocytes, increased variability in nuclear size and minimal loss of cording and lobular pattern. Minimal scattered focal necrosis was also observed in liver tissue of some exposed animals, but not in controls.

Degeneration and necrosis of hepatocytes were observed at autopsy in the case of ingestion of coal tar creosote reported by Bowman et al. (1984). Given the advanced age of this man, the possibility of confounding factors, and the lack of comparison data, it is not possible to definitively attribute these effects to coal tar creosote ingestion. Experimental feeding of powdered clay pigeon targets containing an unspecified amount of coal tar pitch (15-30 g daily of powdered material for up to 15 days) caused death in eight of nine pigs (Davis and Libke 1968). Twenty-four to 48 hours prior to death, a decrease in hemoglobin, packed blood cell volume, and blood sugar concentration was noted. Autopsy revealed centrilobular hepatic necrosis and hemorrhage of the liver. Feeding of mice with 0.3% coal tar for 2 years produced a significant increase (40%) in liver weight compared with controls (Culp et al. 1998). The toxicological significance of these changes with regard to individuals exposed to coal tar creosote and other coal tar products in areas surrounding hazardous waste sites is not known.

Renal Effects. Observations made in both humans and animals suggest that wood creosote has the potential to induce adverse effects in the kidney. However, it is less clear if this is also the case for coal tar and coal tar products. After ingestion of chaparral, kidney failure has been observed (Gordon et al. 1995). Male rats chronically fed beechwood creosote in the diet exhibited an exacerbation of the spontaneously occurring chronic nephrosis normally seen in aging male rats (Miyazato et al. 1984b).

Prior to death, the patient described by Bowman et al. (1984) became acidotic and anuric after ingestion of coal tar creosote, indicating kidney failure. Acute renal tubular necrosis was revealed at autopsy. However, the acute tubular necrosis may have been due to vascular insufficiency rather than a direct toxic effect on the kidney. Oral administration of coal tar to rats and mice has produced either no adverse effects (Hackett et al. 1984; Weyand et al. 1994) or a decrease in kidney weight without histological changes (Culp et al. 1998). A significant increase in relative kidney weight was observed for pregnant rats and mice dermally exposed to 500 or 1,500 mg/kg/day coal tar for 5 days (Zangar et al. 1989).

Endocrine Effects. No reports of endocrine effects in humans after inhalation or dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles were found in the literature. No adverse effects of inhalation or dermal exposure to coal tar on the adrenal, pancreas, parathyroid, pituitary, prostate, or thyroid glands were reported for rats or mice after acute or intermediate inhalation or dermal exposure to coal tar (Springer et al. 1982, 1986b, 1987; Zangar et al. 1989).

No adverse endocrine effects in humans were reported after oral exposure to wood creosote, coal tar creosote, coal tar, or coal tar pitch. No adverse effects of oral exposure were observed in rats or mice

after ingestion of beechwood creosote for up to 3 months, although male rats exhibited an increase in relative adrenal weight after ingesting 313 mg/kg/day for 96 weeks (Miyazato et al. 1981, 1984a, 1984b). Adrenal weights were significantly increased in pregnant rats gavaged with up to 90 mg/kg/day coal tar on gestational days 12-16 (Hackett et al. 1984). No adverse effects were reported for adrenal weight in female mice orally exposed to coal tar creosote in DMSO during gestation (Iyer et al. 1993), or for histopathological evaluation of salivary glands, pancreas, thymus, para-thyroid, or adrenal glands in male and female mice given coal tar orally for 94 days (Weyand et al. 1994).

Based on information found in the literature, adverse endocrine effects seem unlikely in persons exposed to wood creosote, coal tar creosote, or other coal tar products at levels found in hazardous waste sites.

Dermal Effects. No reports of adverse dermal effects in humans or animals after inhalation exposure to wood creosote were found in the literature. Pruritus, most likely secondary to liver and kidney toxicity, was observed in a woman who had ingested chaparral (Alderman et al. 1994). Skin irritation has been reported for humans after dermal contact with the creosote bush (Leonforte 1986; Smith 1937). Irritation of periapical tissue has also been reported in dogs after exposure to beechwood creosote (Attalla 1968). Burns, irritation, and benign lesions of the skin (e.g., squamous papillomas) are the most frequent manifestations of coal tar product toxicity in humans in industrial or other situations where both inhalation (vapor) and dermal exposure occur (Bolt and Golka 1993; Haldin-Davis 1935; Jonas 1943; NIOSH 1982; Schwartz 1942; Shambaugh 1935; TOMA 1978, 1979). These effects also include mild-to-severe erythema, intense burning, itching, and subsequent pigmentation followed by desquamation, and have also been observed in animals (Bonser and Manch 1932; Kligman and Kligman 1994; Ptitzer et al. 1965; Schweikert and Schnyder 1972a, 1972b; Wallcave et al. 1971; Wrench and Britten 1975). Involvement of connective tissue is often seen. Coal tar products are also capable of inducing phototoxicity of the skin, so exposure to sun or UV light exacerbates the irritant effects (Diette et al. 1983; Emmett 1986; NIOSH 1981a, 1982). This has important implications for individuals living in areas surrounding hazardous waste sites who may come in contact with creosote-contaminated soils, as illustrated by the study conducted by ATSDR (1994). Accordingly, dermal effects, including rashes, itching, and burning, may be of concern to these populations.

Ocular Effects. No reports of adverse ocular effects in humans or animals after exposure to wood creosote were found. Eye irritation, including burning, redness, swelling, and watering have been noted after exposure to coal tar products and their volatile components (Birdwood 1938; Emmett 1986; Jonas

1943; NIOSH 1980a, 1981a, 1982; Pfitzer et al. 1965). Conjunctivitis of the eyes is a frequent manifestation of coal tar creosote toxicity following exposure to coal tar product volatiles, and direct dermal exposure in both humans and animals (Emmett 1986; Jonas 1943; Pfitzer et al. 1965). Thus, ocular irritation may be of concern to people coming in contact with soil or water contaminated with coal tar creosote or other coal tar products.

Body Weight Effects. No reports of adverse body weight changes in humans or animals after inhalation, oral, or dermal exposure to wood creosote or in humans after exposure to coal tar products were found in the literature. Rats, mice and rabbits, but not monkeys, exhibited a decrease in body weight after inhalation exposure to coal tar aerosol (MacEwen et al. 1977; Springer et al. 1986b, 1987). Weight loss was also noted in rats and mice after oral exposure to creosote or coal tar (Culp and Beland 1994; Culp et al. 1996a; Hackett et al. 1984; Iyer et al. 1993; Miyazato et al. 1981; Weyand et al. 1991, 1994), and after dermal exposure to coal tar (Deelman 1962; Zangar et al. 1989). However, it seems unlikely that weight loss would be a prominent adverse effect in people living near a hazardous waste site containing coal tar products.

Other Systemic Effects. Serum chemistry parameters were determined after oral exposure of rats or mice to beechwood creosote for up to 96 weeks (rats) or 52 weeks (mice) (Miyazato et al. 1981, 1984a, 1984b). Increases in serum cholesterol were noted in male and female rats after 3 months of exposure, and in rats after 96 weeks of exposure (Miyazato et al. 1981, 1984b). The significance of these changes is not clear. Food consumption has been shown to decrease during administration of coal tar in the feed to mice (Culp and Beland 1994). This may indicate a palatability problem, due to the taste of the coal tar.

Immunological and Lymphoreticular Effects. No adverse immunologic effects have been reported in humans following exposure to beechwood or coal tar creosote. Several cases of acute allergic dermatitis have been reported following contact with creosote bush resin (Leonforte 1986; Smith 1937). Creosote bush resin differs from creosote extracted from coal and wood tar, but all contain phenolic derivatives. It is not known whether these derivatives are the allergens in creosote bush resin. Contact dermatitis has also been reported after short-term dermal contact with coal tar (Cusano et al. 1992).

Inhalation exposure of rats and mice to high doses of coal tar has produced some toxic effects in the form of weight and morphological changes to the lymphoreticular tissues, but no information regarding associated functional changes in the immune system have been reported. Inhalation of 660 mg/m^3 coal tar aerosol for 5 days by pregnant rats produced a significant increase in spleen weight and a significant

decrease in thymus weight (Springer et al. 1982). Inhalation exposure of rats to 690 mg/m^3 coal tar aerosol for 13 weeks produced significant atrophy of the thymus, a decrease in megekaryocytes in the spleen, and a hypocellular bone marrow with a marked decrease in the number of megakaryocytes (Springer et al. 1986b). Similar decreases in thymus weight, but no histologic changes were observed for mice exposed to 690 mg/m^3 coal tar aerosol for 13 weeks (Springer et al. 1987).

There are very little data regarding the immunological or lymphoreticular effects of oral or dermal exposure to creosote. A significant decrease in thymus weight was recorded for pregnant rats gavaged on gestational days 12-16 with 90 mg/kg/day coal tar (Hackett et al. 1984). However, mice fed up to 462 mg/kg/day coal tar for 3 months showed no adverse gross or histopathological effects for the spleen or thymus (Weyand et al. 1994). Miyazato et al. (1981) observed an increase in relative spleen weight in male and female rats orally exposed to beechwood creosote, although the changes were not strictly doserelated. Dermal exposure of pregnant rats and mice to 500 or 1,500 mg/kg/day coal tar on gestational days 11-l5 resulted in a significant decrease in thymus weight of rats, a significant increase in relative spleen weight of mice, and no change in relative adrenal gland weight for either species (Zangar et al. 1989).

Humans are unlikely to experience immunologic effects from exposure to creosote in waste sites. The relevance of the results of animal studies to individuals who live in areas surrounding hazardous waste sites, and who will most likely be chronically exposed to low doses of coal tar creosote, is illustrated by a report of a population living on an abandoned creosote factory site (ATSDR 1994). Increased incidence of dermatitis and other skin complaints were associated with contact with creosote-contaminated soil and water. However, these effects primarily resulted from dermal irritation.

Neurological Effects. Adverse neurologic effects have been reported in both humans and animals following the acute ingestion of high doses of beechwood or coal tar creosote, or dermal exposure to coal tar creosote (Alderman et al. 1994; Cribb 1968; Gordon et al. 1995; Hanlon 1938; Miyazato et al. 1981; NIOSH 1980b). Such effects include salivation, vomiting, respiratory distress, thready pulse, vertigo, headache, loss of pupillary reflexes, hypothermia, cyanosis, muscle twitching, and convulsions. These observations suggest that creosote may be a general central nervous system stimulant following acute high-level exposure. However, the possibility exists that some of the effects observed in animals that licked treated utility poles may have been due to ingestion of pentachlorophenol. Pentachlorophenol, like creosote, is an oil-borne wood preservative with extensive use in the public utility industry for treatment of utility poles. The neurotoxic effects observed in cattle that licked treated utility poles are more

compatible with the metabolic effects (i.e., uncoupling of oxidative phosphorylation) associated with pentachlorophenol. For more information on the effects of pentachlorophenol, please refer to the ATSDR *Toxicological Profile for Pentachlorophenol* (ATSDR 1999). Thus, it is not possible to determine conclusively whether creosote is toxic to the central nervous system of animals, based on this report. However, no information was found to suggest that chronic low-level exposure to creosote by individuals in areas surrounding hazardous waste sites would result in neurotoxicity.

Reproductive Effects. Creosotes and coal tar products do not seem to be potent reproductive toxins. No adverse effects on sperm characteristics were reported in male workers exposed to coal tar pitch volatiles in an industrial setting (Ward 1988). In addition, no adverse reproductive outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (ATSDR 1994). A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

Miyazato et al. (1981) reported that oral exposure of rats to beechwood creosote in the diet for 3 months increased relative testes weight with no accompanying histological changes, but produced no changes in ovary weights. No changes in testis or ovary weight was observed for mice exposed to beechwood creosote for up to 96 weeks (Miyazato et al. 198 1, 1984a, 1984b). Beechwood creosote has been reported to cause contraction of the uterus in rabbits after intravenous injection (Kasai 1908).

Relative ovary weights were significantly decreased in rats and mice exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Testis weight in rats exposed to 140 and 690 mg/m^3 coal tar was significantly increased relative to controls, while testis weight in male mice exposed to 690 mg/m^3 coal tar was decreased relative to controls, but the difference was not significant. Examination of ovarian sections showed a decrease in the amount of luteal tissue in animals exposed to 690 mg/m^3 coal tar.

A significant decrease in number of live fetuses/litter and the number of resorptions was observed in female rats gavaged with 370 mg/kg/day coal tar on gestational days 12-16, but no significant difference in the number of live births was observed in female rats gavaged with 740 mg/kg/day coal tar on gestational days 12-14 (Hackett et al. 1984; Springer et al. 1986a). No adverse effects on reproductive indices were reported by Iyer et al. (1993) after oral exposure of mice to coal tar creosote in DMSO on

gestation days 5-9. Some evidence of maternal toxicity in the form of reduced body weight gain and changes in organ weights was observed for animals treated with coal tar (Hackett et al. 1984; Iyer et al. 1993; Springer et al. 1986a). A similar lack of effect on reproductive organs was observed by Weyand et al. (1994) after oral exposure of mice to coal tar for 185 days.

Dermal exposure of rats and mice to 500 or 1,500 mg/kg coal tar on gestational days 11-15 resulted in significant decreases in uterine weight (Zangar et al. 1989). Slight maternal toxicity in the form of significantly increased weights of the liver, kidney, and spleen were observed for treated mice. Rats showed more maternal toxicity than mice with a significant decrease in extragestational body weight as well as significant changes in the relative weights of maternal liver, kidney, and thymus for treated animals compared with controls. Prenatal mortality was significantly increased in all exposed rat fetuses and high dose mice fetuses compared to controls. Early resorptions (occurred before dosing) were similar in all groups, but middle resorptions (which corresponded to the dosing period) were significantly increased in exposed rats and high dose mice. Late resorptions were also significantly increased in exposed rats.

Developmental Effects. No reports of adverse developmental effects on humans or animals after exposure to wood creosote or on humans after exposure to coal tar were found in the literature. However a series of studies by Springer and coworkers (Hackett et al. 1984; Springer et a1.1982, 1986a; Zangar et al. 1989) have demonstrated serious developmental toxicity for rats and mice exposed to coal tar.

Treatment of pregnant rats with coal tar by all routes of exposure produces reduced growth (reduced crown-rump length and delayed ossification) of the offspring, and an increase in the incidence of cleft palates and small lungs (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). Dermal exposure of pregnant mice to coal tar produces an increase in the incidence of cleft palates dilated ureters and renal pelvic cavitation (Zangar et al. 1989). However, some evidence of maternal toxicity in the form of reduced body weight gain and changes in organ weights was observed for animals treated with coal tar (Hackett et al. 1984; Iyer et al. 1993; Springer et al. 1986a; Zangar et al. 1989). Zangar et al. (1989) carried out a comparison of the doses (method not stated) producing significant developmental effects in rats (Hackett et al. 1984; Springer et al. 1982; Zangar et al. 1989) for exposures to the same coal tar mixture, during the same gestational period, and at doses producing approximately equal maternal toxicity. They suggest that inhalation is the most effective route for developmental toxicity, followed by the oral and dermal routes in that order, with doses of 60, 180, and 500 mg coal tar/kg body weight resulting in adverse effects to the fetus by each of the three routes respectively. However, they

also noted that inhalation dosimetry is more difficult to calculate accurately due to unknown contributions from the oral and dermal routes.

Other studies of developmental toxicity of coal tar creosote have given mixed results suggesting that suggests that species differences in susceptibility to the developmental toxicity of coal tar creosote may exist. A decrease in mean body weight was observed in mouse fetuses born to dams exposed to coal tar creosote in DMSO during gestation (Iyer et al. 1993). Although the decrease (12%) was not significant when compared to control fetal body weight, this effect, in conjunction with a nonsignificant increase in the incidence of skeletal variations, suggest that coal tar creosote may have had an adverse effect on development. An *in vivo* developmental study in animals reported that dermal exposure to creosotetreated wood produced fetotoxic effects in pregnant sows (Schipper 1961). Oral exposure may also have occurred. This study was severely limited by lack of exposure data, unequal duration of exposure between treated and untreated groups, and the lack of statistical analysis of the results.

The developmental effects of coal tar were also assayed in a chick embryotoxicity screening test (CHEST) (Mayura et al. 1999). Coal tar dissolved in corn oil and 0.5% DMSO was injected into the yolks of 4-day-old chicken eggs. Eggs were monitored for embryo mortality and maintained up to the 18th day of incubation, at which time the embryos were examined for mortality, gross malformations, liver lesions, edema, and other abnormalities. Coal tar samples produced a dose-dependant increase in embryo mortality. Doses greater than 0.5 mg/kg coal tar produced 100% mortality, 0.25mg/kg produced 55% mortality, 0.125 mg/kg produced 20% mortality, and 0.0625 mg/kg produced 5% mortality. The main exposure-related abnormalities noted were liver lesions, discoloration of the liver, and edema.

In an *in vitro* study designed to identify developmentally toxic components of beechwood and coal tar creosote, beechwood creosote and coal tar creosote were fractionated by size exclusion chromatography and individual fractions were tested for developmental toxicity using a short-term rodent embryo culture assay (Okaygun 1988). On gestational day 10, Sprague Dawley rat embryos were explanted and cultured for 24 hours with individual fractions from beechwood and coal tar creosote dissolved in DMSO. Average crown-rump length of the viable embryos was measured. Mortality, somite number, yolk sac circulation, heart beat, and limb bud development were observed and noted. All fractions were tested in the presence of rat hepatic microsomal activation. Embryos cultured with only DMSO in the presence and absence of microsomal activation exhibited a crown-rump length of 50 reticle units. Embryos exposed to fractions of beechwood creosote had average crown-rump lengths of 32-46 reticle units.

Coal tar exposure produces developmental toxicity in rats and mice. However, the developmental risk to humans of exposure to coal tar is less clear. No adverse developmental outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (ATSDR 1994). A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999). The doses which produced developmental toxicity in animals were relatively high and are unlikely to be attained through environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans from coal tar exposure cannot be discounted.

Genotoxic Effects. The genotoxic potential of coal tar creosote has been investigated using *in vitro* assays of the toxic materials themselves (Agurell and Stensman 1992; Baranski et al. 1992; Bos et al. 1984a, 1984b, 1985, 1987; Donnelly et al. 1993, 1996; Genevois et al. 1998; Kesik and Janik-Spiechawicz 1997; Leadon et al. 1995; Machado et al. 1993; Mayura et al. 1999; Mitchell and Tajiri 1978; Reddy et al, 1997; Simmon and Shepherd 1978; U.S. Department of Energy 1994) and of urine from exposed animals and people (Bos et al. 1984a, 1984c; Chadwick et al. 1995; De Meo et al. 1987; Gabbani et al. 1999; Mielzynska and Snit 1992). In addition, chromosomal aberrations in peripheral lymphocytes and DNA adduct formation have been examined after *in vivo* exposure to coal tar products (Bender et al. 1988; Culp and Beland 1994; Culp et al. 1996a; Ericson et al. 1998, 1999; Genevois et al. 1996; Godschalk et al. 1998; Goldstein et al. 1998; Hughes et al. 1993; Lewtas et al. 1997; Pavanello and Levis 1992, 1994; Phillips and Alldrick 1994; Randerath et al. 1996; Sarto et al. 1989; Schoket et al. 1990; Weyand and Wu 1995; Weyand et al. 1991, 1994; Wu et al. 1998; Yadav and Seth 1998; Zhang et al. 1990). Results of these studies are summarized in Tables 2-4 (*in vivo*) and 2-5 (*in vitro*). The available genotoxicity data indicate that creosote is an indirect mutagen (i.e., requiring the presence of an exogenous mammalian metabolic system) and induces gene mutation in bacteria and mouse lymphoma cells, The mutagenicity of creosote observed in the conventional *S. typhimurium* assay is at least partially contributed to by the PAHs such as B[a]P and benzanthracene (Bos et al. 1984b). Bos et al. (1987) identified fluoranthene as one of the major volatile components of creosote responsible for the genotoxicity observed in *S. typhimurium* strains.

Condensed fumes from coal tar pitch and roofing and paving asphalt were tested for mutagenic activity in a modified Ames test using *S. typhimurium* TA98 (Machado et al. 1993). Benzo[a]pyrene was detected in all samples, and averaged 18,100 ppm for whole coal tar pitch, compared to <6 ppm for whole asphalt.

Table 2-4. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo*

Species (test system)	End point	Results	Reference
	CREOSOTE		
Mammalian systems: Rat/liver	DNA adducts	+	Chadwick et al. 1995
Mouse/lung, forestomach, spleen	DNA adducts	+	Weyand et al. 1991
	COAL TAR		
Non-mammalian systems: Perch/liver	DNA adducts	+	Ericson et al. 1998, 1999
Mammalian systems: Human/lymphocytes	Chromosomal aberrations/Sister chromatid exchange	+	Sarto et al. 1989
Human/lymphocytes	Sister chromatid exchange	+	Wu et al. 1998
Human/lymphocytes	Chromosomal aberrations/Sister chromatid exchange	+	Yadav and Seth 1998
Human/skin	DNA adducts	–	Schoket et al. 1990
Human/skin	DNA adducts	+	Zhang et al. 1990
Human/skin, blood cells	DNA adducts	+	Godschalk et al. 1998
Human/lymphocytes	DNA adducts	–	Pavanello and Levis 1992
Human/lymphocytes	DNA adducts	+	Pavanello and Levis 1994
Human/blood	DNA adducts	+	Santella et al. 1995
Rat/liver, lung, forestomach	DNA adducts	+	Culp and Beland 1994

Table 2-4. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo (continued)*

Species (test system)	End point	Results	Reference
	COAL TAR (cont'd)		
Mammalian systems *(cont'd)*:			
Rat/lymphocytes, lung, skin	DNA adducts	+	Genevois et al. 1996
Rat/lung, liver, forestomach	DNA adducts	+	Goldstein et al. 1998
Mouse/forestomach, small intestine	DNA adducts	+	Goldstein et al. 1998
Mouse/forestomach, small intestine	DNA adducts	+	Culp et al. 1996a
Mouse/lung, forestomach	DNA adducts	+	Weyand and Wu 1995
Mouse/lung, forestomach	DNA adducts	+	Weyand et al. 1994
Mouse/skin, lung, liver, kidney heart	DNA adducts	+	Randerath et al. 1996
Mouse/skin	DNA adducts	+	Hughes et al. 1993
Mouse/skin	DNA adducts	+	Phillips and Alldrick 1994
Mouse/skin	DNA synthesis	+	Walter et al. 1978
	COAL TAR PITCH VOLATILES		
Mammalian systems:			
Human blood cells	Chromosomal aberrations	+	Bender et al. 1988
Human/white blood cells	DNA adducts	+	Lewtas et al. 1997
Rat/lung	DNA adducts	+	Lewtas et al. 1997

+ = positive results; – = negative results

Table 2-5. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Calf thymus DNA	DNA adducts	+	No data	Reddy et al. 1997
Salmon testes DNA	DNA adducts	+	–	Genevois et al. 1998
Prokaryotic organisms:				
Salmonella typhimurium (histidine auxotrophs)	Gene mutation	+	–	Simmon and Shepherd 1978[a]
S. typhimurium	Gene mutation	+	+	Agurell and Stensman 1992
S. typhimurium	Gene mutation	+	–	Baranski et al. 1992
S. typhimurium	Gene mutation	+	–	Bos et al. 1983, 1984b, 1984c, 1985, 1987
S. typhimurium	Gene mutation	+	–	Donnelly et al. 1993, 1996
S. typhimurium	Gene mutation	+	+	Kesik and Janik-Spiechowicz 1997
S. typhimurium	Gene mutation	+	–	Mayura et al. 1999
S. typhimurium	Gene mutation			Machado et al. 1993
S. typhimurium (taped-plate assay; vapor exposure)	Gene mutation	+	–	Bos et al. 1985, 1987
Escherichia coli WP2 (TK=/–), (tryptophan auxotroph)	Gene mutation	–	–	Simmon and Shepherd 1978[a]
Mammalian cells:				
Human mammary epithelial cells	DNA adducts	No data	+	Leadon et al. 1995
Mouse lymphoma cells	Gene mutation	+	–	Mitchell and Tajiri 1978
V79	Gene mutation	–	–	U.S. Department of Energy 1994
V79	Sister chromatid exchange	+	+	U.S. Department of Energy 1994

Table 2-5. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro (continued)*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Mammalian cells *(cont'd)*:				
V79	Micronucleus	+	+	U.S. Department of Energy 1994
Mammalian body fluids:				
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	–	No data	Bos et al. 1984a
S. typhimurium (human urine sample; coal tar treatment)	Gene mutation	+	No data	Clonfero et al. 1990
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	+	No data	De Meo et al. 1987
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	+	No data	Gabbani et al. 1999
S. typhimurium (human urine sample; coal tar treatment)	Gene mutation	+	No data	Granella and Clonfero 1992
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	+	No data	Mielzynska and Snit 1992
S. typhimurium (human urine sample; coal tar treatment)	Gene mutation	+	No data	Sarto et al. 1989
S. typhimurium (rat urine sample)	Gene mutation	+	No data	Bos et al. 1984a
S. typhimurium (rat urine sample)	Gene mutation	+	No data	Chadwick et al. 1995

[a]*S. typhimurium* strains TA1537, TA98, and TA100 showed increases in frameshift mutation; strain TA1535 and *E. coli* straub WP2 showed no increase in base-pair substitutions.

+ = positive results; – = negative results

Fume condensates from coal tar pitch contained 250-480 ppm compared to 0.1-2.8 ppm for asphalt. The coal tar pitch fume condensates were strongly mutagenic, and mutagenicity was correlated with PAH content of the samples. The temperature at which the fumes were collected was also positively correlated with mutagenicity and PAH content. The asphalt fume condensates were also mutagenic, but 100-fold less so than the coal tar pitch fume condensates. Mutagenicity did not correlate as well with PAH content as it did for the coal tar pitch fume condensates.

In a wood-preserving factory, spot samples collected from the contaminated surfaces including that of creosote-treated wood showed mutagenic activity in *S. typhimurium* strains TA98, TA1537, TA1538 and TAl00 in the presence of microsomal activation (Bos et al. 1984a, 1984c). Despite the contamination of the work area, no increase in mutagenic activity was detected in the urine samples of workers who inhaled creosote vapors and possibly had skin contact with the residual surface creosote. This negative mutagenic response was probably a result of a low level of creosote exposure or the fact that the components present in the workers' urine were not mutagenic (Bos et al. 1984a, 1984c). Coal tar creosote (type Pl[1]) was mutagenic in the mouse lymphoma assay (Mitchell and Tajiri 1978). A dose-related increase in the number of forward mutations was observed in L5178Y mouse lymphoma cells following metabolic activation. Simmon and Shepherd (1978) found that creosote (type Pl) produced a mutagenic dose-response and a doubling above background mutation rate in S. typhimurium strains TA1537, TA98, and TA100. *S. typhimurium* strain TA1535 and *E. coli* WP2 strain did not demonstrate a positive response with metabolic activation. These results indicate that the genetic mode of action of creosote in *S. typhimurium* is by frameshift mutation. The mutagenic potential of several fractions of creosote (type Pl) has been examined in bacterial strains TA98 and TA1537 (Bos et al. 1984b). The mutagenicity of creosote was found to be associated at least partially with PAHs (B[a]P and benzanthracene) which were detected in concentrations of 0.18 and 1.l%, respectively (Bos et al. 1983, 1984b). Both compounds, although mutagenic in a conventional Ames assay, showed no activity in a *S. typhimurium* taped-plate assay (Bos et al. 1985). When creosote samples were further tested for the presence of "volatile mutagens," vapors escaping from creosote increased the number of revertants per plate in the presence of exogenous mammalian metabolic activation system (S9 mix) (Bos et al. 1985). Results of the study suggest that the volatile components of creosote may also contribute to the genotoxic risk from occupational exposure to creosote. Creosote has been shown to contain mutagens which are volatile at

[1]Creosote is classifies according to a set of standards regarding physical property specifications for creosote that must be met for certain uses of creosote. These specifications are presented in Table 3-4. Type P1/P13 creosote is straight creosote distillate and is used in ground contact, land, fresh and marine water applications. Type P2 creosote is used by the railroad industry in the treatment of railroad crossties.

37 ºC (Bos et al. 1987). These were present in the distillation fraction having the highest boiling range (>360 ºC). Upon further HPLC and UV spectroscopic analysis of the fraction and mutagenicity tests, the mutagenic response observed was correlated with the presence of fluoranthene (5.2%) in the creosote samples. The commercially available fluoranthene also tested positive in the taped-plate assay.

The genotoxic risk associated with dermal exposure to coal tars has been addressed in human subjects. Sarto et al. (1989) examined the mutagenicity of urine samples collected before and during the coal tar therapy of male, nonsmoking subjects treated for psoriasis with topical applications of pure coal tar or 4% coal tar-containing ointment. In addition, peripheral blood lymphocytes collected before, during, and after coal tar application were assayed for sister chromatid exchanges and chromosomal aberrations. The results suggest that urinary mutagen levels, as well as the frequency of chromosomal aberrations and sister chromatid exchange in lymphocytes, were related to the levels of exposure to coal tar, thus demonstrating that both the pure coal tar and the 4% coal tar ointment were genotoxic mixtures. Similar findings of mutagenicity of urine collected from psoriatic patients treated with coal tar were reported in other studies (Clonfero et al. 1990; Gabbani et a1.1999; Granella and Clonfero 1992).

The mutagenic activity of urine samples taken from workers briefly exposed to coal tar creosote vapors in a wood preserving factory was investigated (Bos and Jongeneelen 1988; Bos et al. 1984a, 1984c). Of the three workers tested, two moved wood in and out of the wood impregnating cylinder and one operated the cylinder. No mutagenic activity was detected in 10-day urine samples of workers. All had the potential for brief inhalation exposure to coal tar creosote. Frequency and level of exposure were not given. Furthermore, the possibility of dermal exposure by contact with residual surface coal tar creosote cannot be excluded. The absence of mutagens in the urine samples tested by *S. typhimurium* assay was attributed by the authors to a relatively low level of exposure, improper timing for urine sample collection, and the insensitivity of the assay. The data are not sufficient to draw a conclusion regarding the genotoxic potential of inhaled coal tar creosote vapors in humans, but they do suggest that extrapolation of mutagenicity tests on a single component (e.g., PAHs) may not predict the action of the mixture.

The mutagenicity of the urine from 31 control workers and 19 workers exposed to coke oven emissions in a steel mill was tested using *S. typhimurium* strains TA98 or TA 100 and S9 liver microsomal fractions (De Meo et al. 1987). Direct-acting mutagens were also assayed in urine using the SOS spot test and *E. coli* PQ37. Workers exposed to coke oven emissions had significantly higher urine mutagenicity than nonexposed workers. Urinary mutagenicity increased during the working period. This effect was due to pro-mutagen exposure, since no direct-acting mutagens were detected. Environmental levels of

benzo[a]pyrene ranged from 0.01 to 0.6 mg/m^3, but no correlation between exposure and urine mutagenicity was found (Table 2-5). Pretreatment of male Fischer 344 rats with orally administered coal tar creosote resulted in urinary excretion of mutagenic metabolites as measured by the Ames assay (Chadwick et al. 1995).

Genotoxic effects of dermal exposure to creosote and coal tar have also been investigated in animals. Bos et al. (1984c) administered 250 mg/kg creosote dissolved in olive oil to the close-shaven skin of male Wistar rats; control rats received olive oil. Urine samples were collected for 24 hours. Mutagenicity of the urine was determined using the *S. typhimurium* strains TA98 and TAl 00 with S9 or B-glucoronidase activation, or both. Rats treated with creosote on the close-shaven skin produced urinary mutagens which resulted in about 70% of the number of revertant colonies found after intraperitoneal treatment with the same dose. A combination of activating systems produced the highest number of revertants.

The available genotoxicity data suggest that creosote has a potential to induce gene mutation in humans exposed via inhalation, and perhaps other routes as well (particularly by the dermal route) at hazardous waste sites. However, much of the data from *in vitro* studies discussed above describes the mutagenic activity of selected PAHs. It is not yet known how the various PAHs contained in the coal tar creosote mixture interact, and what the effects of these possible interactions are on the ultimate genotoxic expression of the mixture. There are no definitive genotoxicity data on humans at present.

Cancer. Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer (Cookson 1924; Goulden and Stallard 1933; Henry 1946, 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935). These papers reported a similar disease etiology for different groups of workers exposed to creosote that included the development of dermatoses, such as squamous papillomas, that progressed to carcinoma, usually squamous-cell carcinoma. Cancer of the scrotum in chimney sweeps has also been associated with prolonged exposure to coal tar creosote. The latency period for the development of dermatoses, such as squamous papillomas, was usually 20-25 years (Cookson 1924; Henry 1946, 1947; O'Donovan 1920). Worker exposure in the past was much greater than it now is because of less sophisticated industrial practices used in the past, the lack of knowledge concerning occupational hygiene, and the current recognition of the dangers of excessive exposure to the health of workers. Other factors that should be considered when extrapolating the findings of this older literature to present conditions are the role of exposure to UV radiation in the form of sunshine in these workers (UV radiation is now known to be a major cause of skin cancer), the composition of the creosote products, and

other health factors that differ in Great Britain prior to 1940 and the present. Although these earlier studies lack crucial information concerning specific exposures and did not consider other risk factors for the development of skin cancer, when taken as a group, and in view of the presence of carcinogenic PAHs, they present convincing evidence of a relationship between chronic creosote exposure and the development of skin carcinoma in humans, especially if exposure to sunlight can be established. More recent studies, also suggest that prolonged human exposure to coal tar creosote and other coal tar products may cause cancer of the skin and other organs (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Dusich et al. 1980; Finkelstein 1989; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Liu et al. 1997; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockett and Arena 1983; Riinneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; Spinelli et al. 1991; Stern et al. 1980; Tremblay et al. 1995).

On the other hand, several studies are available which have found no association between exposure to creosote or other coal tar products and cancer in humans (Blair et al. 1993; CEOH 1997; Kromhout et al. 1992; Kunze et al. 1992; Lindelof and Sigurgeirsson 1993; Maugham et al. 1980; Pittelkow et al. 1981; Schildt et al, 1999; Swaen and Slangen 1997; TOMA 1980, 1982; Wright et al. 1985). No increased incidence of nonmelanoma skin cancer was observed in 426 patients 25 years after they had undergone 4 years of coal tar medicinal therapy in combination with UV light for the treatment of atopic dermatitis and neurodermatitis (Maugham et al. 1980). This study is limited in that follow up occurred in only 72% of the patients, and there was no discussion of recall bias or of the effects of mobility (i.e., relocation of the study participants) on the results. In a 25-year retrospective study of 280 psoriatic patients treated with crude coal tar in combination with UV radiation at the Mayo clinic, it was found that the incidence of skin cancer in these patients was not significantly increased above the expected incidence for the general population (Pittelkow et al. 1981). Chemical and biological analysis of coal-tar-based therapeutic agents and industrial coal tar indicated that the therapeutic agents and the industrial materials were similar (Wright et al. 1985). The authors suggest that the lack of carcinogenic effects after therapeutic exposure may be due to solvents and surfactants present in the preparations which may alter deposition and absorption by the skin. Reducing the contact with the therapeutic agents by regular washing may also be a factor (Wright et al. 1985).

Another study reported that there was no increase in the risk of skin, bladder, or lung cancer in wood treatment plant workers (TOMA 1980). Limitations in this study include: the study population was small; the study population was comprised of 46.5% blacks who experience a very low incidence of skin cancer

as compared to whites, thus biasing the results; the exposure and follow up periods did not allow a long enough latency period for tumor development; and there was no verification provided that those studied were actually exposed to creosote or coal tar. However, it is possible that because black people are less sensitive to UV light-induced cancer, their prominence in this study might help to isolate the effects of creosote alone from those of UV light or UV light plus creosote in future studies.

A large body of evidence exists indicating that coal tar creosote and several of its fractions are carcinogenic when applied to the skin of laboratory animals and can act as a tumor initiating and promoting agent (Bonser and Manch 1932; Boutwell and Bosch 1958; Cabot et al. 1940; Deelman 1962; Emmett et al. 1981; Hueper and Payne 1960; Kligman and Kligman 1994; Lijinsky et al. 1957; Mahlum 1983; Niemeier et al. 1988; Poe1 and Kammer 1957; Sal1 and Shear 1940; Springer et al. 1989; Wallcave et al. 1971; Watson and Mellanby 1930). Many of the early studies that reported that coal tar creosote is carcinogenic when dermally applied to rodent skin are limited in that they lack appropriate negative control data, the dose of creosote and the chemical composition of the fractions studied were not quantified, and no other tissues were examined. The results from later studies that include appropriate control groups are consistent with the findings of the earlier studies.

Experiments in mice have shown a significant increase in lung tumors in mice fed coal tar for 260 days and liver, lung, and forestomach hemangiosarcomas, histiocytic sarcomas, and sarcomas in mice fed coal tar for 2 years (Culp et al. 1998; Goldstein et al. 1998; Weyand et al. 1995). However, the relevance of these experiments to human exposure is unclear as the insoluble nature of coal tar makes it unlikely that humans will be exposed to it via drinking water.

IARC (1985) has classified creosote as a Group 2A, probable human carcinogen, based on limited human evidence and sufficient animal evidence of carcinogenicity. EPA has classified creosote as a Group B1 probable human carcinogen, based on sufficient evidence from animal studies and limited evidence from human studies (EPA 1988a; IRIS 1995). Thus, based on the human and animal data summarized above, it is possible that individuals who chronically come in skin contact with creosote may be at an elevated risk for developing skin cancer, particularly when exposure to other carcinogenic substances occurs, as is a likely scenario in areas surrounding hazardous waste sites.

2.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disrupters. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife.

Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al.1993; Hoe1 et al.1992).

No studies were located regarding endocrine disruption in humans after exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. An excess of breast cancer cases in St. Louis Park, Minnesota, was tentatively associated with coal tar contamination of the water supply (Dean et al. 1988). However, in a subsequent analysis of these data, the Minnesota Department of Health (1985) concluded that this study did not provide adequate evidence to associate breast-cancer with coal tar creosote-contaminated water (for a detailed discussion of these data see Section 2.2.2.8 Cancer). No adverse effects on sperm characteristics were reported in male workers exposed to coal tar pitch volatiles in an industrial setting (Ward 1988). In addition, no adverse reproductive outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (ATSDR 1994). A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

There is evidence from some animal studies that exposure to coal tar has adverse effects on reproductive success, but these effects are likely to be due to fetotoxicity rather than maternal endocrine disruption, and other studies have found no adverse effects. A significant decrease in number of live fetuses/litter and the number of resorptions was observed in female rats gavaged with 370 mg/kg/day coal tar on gestational days 12-16, but no significant difference in the number of live births was observed in female rats gavaged with 740 mg/kg/day coal tar on gestational days 12-14 (Hackett et al. 1984; Springer et al. 1986a). Dermal exposure of rats and mice to 500 or 1,500 mg/kg coal tar on gestational days 11-15 resulted in significant increases in prenatal mortality in all exposed rat fetuses and high dose mice fetuses compared to controls (Zangar et al. 1989). Early resorptions (occurred before dosing) were similar in all groups, but middle resorptions (which corresponded to the dosing period) were significantly increased in exposed rats and high dose mice. Late resorptions were also significantly increased in exposed rats. No adverse effects on reproductive indices were reported by Iyer et al. (1993) after oral exposure of mice to coal tar creosote in DMSO on gestation days 5-9. A similar lack of effect on reproductive organs was observed by Weyand et al. (1994) after oral exposure of mice to coal tar for 185 days.

There have been some reports of adverse effects of creosote on the reproductive organs of animals, but these are largely confined to changes in organ weight and several other studies have found no effect. Miyazato et al. (1981) reported that oral exposure of rats to beechwood creosote in the diet for 3 months increased relative weight of the testis. However, there were no accompanying histological changes in the testis and no changes in ovary weights. No change in testis or ovary weight was observed for mice exposed to beechwood creosote for up to 96 weeks (Miyazato et al. 1981, 1984a, 1984b). Relative ovary weights were significantly decreased in rats and mice exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Testis weight in rats exposed to 140 and 690 mg/m^3 coal tar was significantly increased relative to controls, while testis weight in male mice exposed to 690 mg/m^3 coal tar was decreased relative to controls, but the difference was not significant. Examination of ovarian sections showed a decrease in the amount of luteal tissue in animals exposed to 690 mg/m^3 coal tar. Dermal exposure of rats and mice to 500 or 1,500 mg/kg coal tar on gestational days 11-15 resulted in significant decreases in uterine weight (Zangar et al. 1989).

Adverse effects in other endocrine organs are limited to a few reports of weight changes in the adrenal glands. Oral exposure of male rats to 313 mg/kg/day beechwood creosote for 96 weeks produced a significant increase in the relative weight of the adrenal glands of male rats (Miyazato et al. 1984b). An increase in adrenal weight was also observed in rats gavaged on gestational days 12-16 with

90 mg/kg/day coal tar (Hackett et al. 1984). However, other studies of coal tar and beechwood creosote have shown no effect on the adrenal glands (Iyer et al. 1993; Miyazato et al. 1981; Springer et al. 1986b, 1987; Weyand et al. 1994; Zangar et al. 1989).

No *in vitro* studies were located regarding endocrine disruption of creosote. There is some evidence that certain PAHs, (e.g., benzo[a]pyrene) may act as endocrine disruptors (ATSDR 1995), but it is not clear whether these compounds have similar effects when incorporated into a complex mixture such as coal tar creosote. For more information on the health effects of these compounds, the reader can refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995).

2.7 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are

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

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

The effects of creosote have not been thoroughly studied in children, but they would likely experience the same health effects seen in adults exposed to creosote. No information was located pertaining to adverse health effects in children or young animals from beechwood or bush creosote and only one study was located which examined effects of exposure to coal tar creosote (ATSDR 1994). This was a survey of inhabitants of a housing development that had been built on part of an abandoned creosote wood treatment plant. In this study, increased incidence of skin rashes compared to unexposed controls was the only health effect reported in children (less than 11 years of age) exposed to coal tar creosote. The incidence of rashes in different age groups varied, but did not show any definite trend.

Data from studies of adult humans occupationally exposed to coal tar creosote indicate that cancer is likely to be the most severe adverse effect of coal tar exposure, although there is also evidence of skin and eye irritation (see Sections 2.2 and 2.5 for more details). Studies of animals after inhalation, oral, or dermal exposure to coal tar creosote confirm cancer as a likely outcome of coal tar exposure and suggest

that there may also be adverse effects to the lungs, liver, spleen, thymus, skin, and eyes (see Sections 2.2 and 2.5 for more details). However, the concentrations of coal tar used in animal studies are higher than could be expected from proximity to a hazardous waste site and so it is not clear how relevant some of these systemic effects are to children. Children exposed to creosote will probably have a longer potential latency period and may therefore be at greater risk of developing cancer from these substances.

There are very few data on human exposure to wood or bush creosote. Case reports of people who have drunk chaparral tea indicate kidney damage as a likely outcome (Gordon et al. 1995), while ingestion of beechwood creosote exacerbates chronic nephrosis in rats (Miyazato et al. 1984b). Dermal exposure to either the creosote bush or beechwood creosote may cause skin irritation (Attalla 1968; Leonforte 1986; Smith 1937). These studies suggest that dermal contact with creosote from toxic waste sites could cause skin irritation, but there is a low probability of kidney damage because the insolubility of wood creosote makes contamination of water supplies by toxic waste sites unlikely to occur and doses from ingestion of contaminated soil are likely to be low.

No reports of adverse developmental effects on humans or animals after exposure to wood creosote or on humans after exposure to coal tar were found in the literature. No adverse developmental outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (ATSDR 1994). A retrospective study of dermal exposure to coal tar found no increased risk of birth defects associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

A series of studies by Springer and coworkers (Hackett et al. 1984; Springer et a1.1982, 1986a; Zangar et al. 1989) have demonstrated serious developmental toxicity for rats and mice exposed to coal tar. However, some evidence of maternal toxicity in the form of reduced body weight gain and changes in organ weights was also observed for animals treated with doses of coal tar producing developmental toxicity (Hackett et al. 1984; Iyer et al. 1993; Springer et al. 1986a). Treatment of pregnant rats with coal tar by all routes of exposure produces reduced growth (reduced crown-rump length and delayed ossification) of the offspring, and an increase in the incidence of cleft palates and small lungs (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). Dermal exposure of pregnant mice to coal tar produces an increase in the incidence of cleft palates dilated ureters and renal pelvic cavitation (Zangar et al. 1989). Zangar et al. (1989) carried out a comparison (method not stated) of the doses producing significant developmental effects in rats (Hackett et al. 1984; Springer et al. 1982; Zangar et al. 1989) for

exposures to the same coal tar mixture, during the same gestational period, and at doses producing approximately equal maternal toxicity, via the three routes of exposure. They found that administration of doses of 500, 180, and 60 mg/kg/day by the dermal, oral, and inhalation routes respectively, resulted in adverse effects to the fetus (Zangar et al. 1989). This suggests that inhalation may be the most effective route for developmental toxicity, followed by the oral and dermal routes in that order. However, the authors noted that inhalation dosimetry is more difficult to calculate accurately due to unknown contributions from the oral and dermal routes.

Adverse perinatal effects of coal tar creosote were reported for a study in pigs (Schipper 1961). Farrowing sows housed in cages treated with coal tar creosote had an increase in the number of stillborn piglets compared to control animals farrowing in untreated cages. The surviving piglets were dehydrated, with rough skins and severe diarrhea. Weight gain of the surviving piglets was reduced until the animals were 5-6 weeks old. One-week-old pigs were reported to have a greater tolerance to creosote than newborn animals, suggesting that more mature animals may be less sensitive to some of the effects of coal tar. However, the results of this study are severely limited by lack of exposure data, unequal duration of exposure between treated and untreated groups, and the lack of statistical analysis of the results.

Adverse developmental effects due to coal tar were also seen in a chick embryotoxicity screening test (CHEST) (Mayura et al. 1999). Injection of coal tar (dissolved in corn oil and 0.5% DMSO) into the yolks of 4-day-old chicken eggs produced a dose-dependant increase in embryo mortality. Doses greater than 0.5 mg/kg coal tar produced 100% mortality, 0.25 mg/kg produced 55% mortality, 0.125 mg/kg produced 20% mortality, and 0.0625 mg/kg produced 5% mortality. The main exposure-related abnormalities noted were liver lesions, discoloration of the liver, and edema.

Coal tar exposure produces developmental toxicity in rats and mice, and may also do so in pigs. However, the developmental risk to humans of exposure to coal tar is less clear. The doses which produced developmental toxicity in animals were relatively high and are unlikely to be attained through environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans from coal tar exposure cannot be discounted.

Creosotes and coal tar products do not appear to be reproductive toxins in humans. A study of women exposed to coal tar creosote at a housing development that had been built on part of an abandoned

creosote wood treatment plant found that although the number of women reporting difficulty in becoming pregnant was significantly increased for the first year of the study; by the second year, the rates among exposed women were comparable with those of the controls and that rates of stillbirth, low weight birth, or spontaneous abortions were similar to those of unexposed populations (ATSDR 1994). A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

Evidence from some animal studies suggests that exposure to coal tar may produce some reproductive toxicity. However, not all studies have found reproductive effects, and the dose level and the time during gestation at which it is received may be important factors. A significant decrease in number of live fetuses/litter and the number of resorptions was observed in female rats gavaged with 370 mg/kg/day coal tar on gestational days 12-16, but no significant difference in the number of live births was observed in female rats gavaged with 740 mg/kg/day coal tar on gestational days 12-14 (Hackett et al. 1984; Springer et al. 1986a). Increased prenatal mortality was found in rats and mice dermally exposed to 500 or 1,500 mg/kg/day coal tar on gestational days 11-15 (Zangar et al. 1989). In contrast, Iyer et al. (1993) reported that mice exposed to 400 mg/kg/day creosote in DMSO on gestational days 5-9 showed minimal maternal toxicity (a significant decrease in maternal weight gain), but no significant differences in fetal survival, gender ratio or the incidence of major malformations.

Data suggest that the PAHs found in coal tar creosote produce developmental and reproductive toxicity and that children may be more susceptible to the adverse effects of these compounds, but it is not clear whether PAHs which form part of the complex mixture of coal tar creosote will have the same effects as PAHs studied alone. For more information on the health effects of these compounds, the reader can refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995).

Coal tar is composed of hydrocarbons which are lipophilic substances and are therefore likely to distribute to lipid-rich tissues including breast milk and the placenta. For instance, PAHs and their metabolites are known to cross the placenta (ATSDR 1995) and are likely to be excreted in breast milk although this has not been assessed. A study of the distribution of intratracheally administered radioactive benzo[a]pyrene mixed with a benzene extract of coal fly ash in pregnant rats found that a small proportion of the radioactivity was distributed to the fetal lung and liver and to the placenta (respectively 1.9, 1.4, and 4% of the amount in maternal lung). Lipophilic components of creosote are

likely to be stored in maternal fat deposits and could be mobilized during lactation with possible exposure of the neonate, but this has not been studied.

The pharmacokinetics of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes. Information on individual components is not adequate to define the properties of the whole mixture and for this reason no PBPK models have been developed for creosote. Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase). Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual which will again affect the relative toxicity of particular components of creosote for old or young individuals. For instance, several cytochrome P450 isozymes are known to be absent or expressed at very low levels in the developing human fetus while glucuronyl transferases and sulphotransferases do not reach adult levels until l-3 years of age (Leeder and Kearns 1997).

There is no information as to possible transgenerational effects of creosote in humans or animals. Creosote and its metabolites may reach the germ cells and PAHs are known to form DNA adducts which could theoretically produce damage to germ cells, but this question has not been studied. No method is currently available to measure the complete wood, or coal tar creosote mixture, or other coal tar products in human tissues or fluids. However, phenols and the individual PAH components can be measured in the urine of exposed individuals including children. PAH-DNA adducts can also be measured in body tissues or blood following exposure to creosote. However, because PAHs are ubiquitous in the environment, detection of PAH metabolites or DNA adducts in the body tissues or fluids is not specific for exposure to creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source.

2.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to creosote are discussed in Section 2.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by creosote are discussed in Section 2.8.2.

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

the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.10 “Populations That Are Unusually Susceptible”.

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Creosote

No method is currently available to measure the parent wood creosote mixtures. However, phenols can be measured in the urine after exposure to wood creosote (Ogata et al. 1995). Male volunteers were given 133 mg of wood creosote in a capsule, followed by 200 mL water. Urine samples were collected at various time intervals. Phenol, guaiacol, *p*-cresol, and cresol were detected in the urine.

No method is currently available to measure the parent creosote mixture and other coal tar products in human tissues or fluids. However, individual components of the mixture can be measured. Urinary naphthols have been shown to be accurate biomarkers of naphthalene exposure during tar distillation or impregnation of wood with coal tar creosote (Bieniek 1997; Heikkilä et al. 1997). PAH components of the creosote mixture and their metabolites can also be measured in the urine of exposed individuals (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Bowman et al. 1997; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Elovaara et al. 1995; Grimmer et al. 1997; Hansen et al. 1993; Heikkilä et al. 1995; Jongeneelen et al. 1985, 1988; Malkin et al. 1996; Ny et al. 1993; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995; Viau et al. 1995; Weston et al. 1994). For example, Jongeneelen et al. (1985) found a metabolite of coal tar creosote, 1-hydroxypyrene, in concentrations of l-40 µg/g creatinine in urine samples taken from workers who handled approximately 2,400 g creosote/day. 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 urine metabolites could be detected following exposure to low levels of creosote. However, in another study, workers asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Jongeneelen et al. 1988). In these workers, occupational exposure appeared to be related to the amount of 1-hydroxypyrene in the urine. The identification of 1-hydroxypyrene 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 creosote has been detected following both short-and long-term exposure. However, because PAHs are ubiquitous in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source.

PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote that contains PAHs (Culp and Beland 1994; Pavanello and Levis 1994; Schoket et al. 1990; Zhang et al. 1990). These PAH-DNA adducts are not specific for coal tar creosote, and the adducts measured could have been from exposure to other sources of PAHs.

2.8.2 Biomarkers Used to Characterize Effects Caused by Creosote

The available genotoxicity data derived by *in vitro* techniques indicate that coal tar products such as coal tar creosote and coal tar pitch are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system) and induce gene mutation in bacteria and mouse lymphoma cells, The mutagenicity of creosote and coal tar pitch observed in the conventional *S. typhimurium* assay is at least partially contributed to by the PAHs such as B[a]P and benzanthracene. However, because these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote have been negative, or have been positive in instances where exposure to other mutagens may have occurred, these changes cannot be considered specific biomarkers of effects caused by creosote, nor is it possible to determine whether the genotoxic effects result from either acute or chronic exposure to either low or high levels of coal tar creosote because all of the data were from in vitro studies. The same can be said for determination of chromosomal aberrations in peripheral lymphocytes from exposed humans (Bender et al. 1988; Sarto et al. 1989). Furthermore, because the mutagenicity of coal tar creosote is at least partially due to its PAH components, exposure to PAHs from other sources could produce the same results. Coal tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact. Therefore, burns and irritation of the skin and eyes are the most frequent manifestations of coal tar creosote toxicity following acute dermal exposure to high levels. However, damage to the skin is not specific to creosote, and can be seen with other corrosive or photosensitizing agents. No other biomarkers (specific or otherwise) have been identified following exposure to coal tar creosote.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.9 INTERACTIONS WITH OTHER CHEMICALS

The primary interactions known to occur between coal tar creosote and other substances involve the induction of cancer. Coal tar creosote is a complex mixture of organic substances consisting predominantly of liquid and solid aromatic hydrocarbons. Several of these components of coal tar creosote are known animal.carcinogens as well as cocarcinogens, initiators, promoters, potentiator, or inhibitors of carcinogenesis. Pretreatment of male Fischer 344 rats with orally administered coal tar creosote resulted in urinary excretion of mutagenic metabolites of creosote, and increased the bioactivation of orally administered 2,6-DNT to mutagenic metabolites, as measured in the Ames assay (Chadwick et al. 1995). As discussed in Section 2.2.3.8, coal tar creosote and several of its fractions are carcinogenic when applied to the skin of mice. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment, and can enhance and accelerate tumor induction by B[a]P. Thus, the risk of cancer following dermal exposure to creosote is likely to be enhanced when concurrent exposure to other potential co-carcinogens, tumor promoters, initiators, and potentiators occurs. Due to the ubiquitous nature of PAHs and other carcinogenic substances in the environment, particularly at hazardous waste sites, the likelihood that these types of synergistic interactions with creosote will occur could be important in assessing potential hazards.

Another effect of coal tar creosote exposure that could be affected by interaction with other chemicals is photosensitivity. Certain pharmaceutical agents (e.g., tetracycline) that, in and of themselves, cause photosensitivity may be synergistic with coal tar creosote or coal tar.

Pentachlorophenol and arsenical compounds are also used in wood preserving. For this reason, it is likely that they will be found with creosote at hazardous waste sites. However, there is no information available on the potential interactions of creosote with pentachlorophenol or arsenical compounds.

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to creosote than will most persons exposed to the same level of creosote in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of creosote, or compromised function of organs affected by creosote. Populations who are at greater risk due to their unusually high exposure to creosote are discussed in Section 5.7, Populations With Potentially High Exposures.

Data indicate that the some populations may be at increased risk of developing skin cancer following prolonged dermal exposure to industrial grade coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. The results of earlier occupational studies (Henry 1946, 1947), case reports (Cookson 1924; Lenson 1956; O'Donovan 1920), and experimental animal studies (Boutwell and Bosch 1958; Poe1 and Kammer 1957; Roe et al. 1958) indicate that the general population may be at risk of developing skin cancer following prolonged dermal exposure to coal tar creosote. This risk may be increased for people with skin damaged from excessive sun exposure, disease, or exposure to other substances that potentiate the carcinogenic effect of coal tar creosote (Cabot et al. 1940; Lenson 1956; Lijinsky et al. 1957; Sal1 and Shear 1940; TOMA 1978, 1979).

There is some limited evidence, based on animal studies and the known health effects of the PAH constituents of coal tar creosote, that additional subsections of the population may be susceptible to the toxic effects of creosote. These include people with pre-existing respiratory, kidney or liver disease. People with deficient immune systems may also be at high risk of developing adverse health effects due to exposure to carcinogens, such as PAHs (Stjernsward 1966, 1969; Szakal and Hanna 1972). Another potentially susceptible group are those individuals with the genetic trait of inducible AHH, one of the mixed function oxidases. When this enzyme is induced, the rate at which aryl compounds, such as PAHs, are biotransformed into toxic intermediates is increased, rendering these individuals at higher risk. 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, 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). These percentages were estimated from the population frequency of genetically controlled AHH induction (Calabrese 1978). Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase) enzymes. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. These enzymes are also known to have age-dependant expression and susceptibility may therefore vary with the age of the individual. However, no studies were located which addressed differential susceptibility of children to the effects of creosote. A detailed discussion of children's susceptibility can be found in Section 2.7.

Coal tar exposure produces developmental toxicity in rats and mice, and may also do so in pigs. However, the developmental risk to humans of exposure to coal tar is less clear. The doses which

produced developmental toxicity in animals were relatively high and are unlikely to be attained through environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans from coal tar exposure cannot be discounted and the human fetus may be another susceptible population,

2.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to creosote. 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 creosote. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to creosote:

Ellenhorn MJ, ed. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. New York, NY: Elsevier Publishing.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders.

Viccellio P, ed. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippencott-Raven.

2.11.1 Reducing Peak Absorption Following Exposure

Human exposure to creosotes and coal tar ,mixtures generally means an exposure to a combination of large molecular toxins (including PAHs) and more immediately chemically reactive phenolic chemicals. The phenolic components act as direct caustic agents to skin, to mucosa, and to cornea, causing burns and scarring. The tars are photosensitizers and potential DNA-combining agents with different and latent clinical consequences, including cancer. Exposure to these may compounds occur via ingestion and direct liquid application. Since the ingredients have a range of boiling points, vapor inhalation is much more likely for the lower molecular weight creosols than for tars and heavier oils. Creosol vapors are considered caustic and directly injurious to respiratory mucosa. Although relatively nonvolatile, tar absorption following inhalation exposure to mists can occur through mucocilliary trapping and transport followed by gastrointestinal absorption.

The suggested emergency management of direct cutaneous exposure to creosote is prompt and comprehensive decontamination (Haddad et al. 1998). Treatment commonly includes removal of all contaminated clothing and washing of the skin, hair, and nails with large volumes of soapy water. It is recommended that those administering the treatment wear rubber gloves for their own protection. In order to reduce dermal irritation from creosote-contaminated soil and water, limited exposure, through the wearing of protective clothing, and immediate washing of exposed skin were the recommendations of the Texas Department of Health to residents of a housing development built on an abandoned creosote factory site (ATSDR 1994).

The treatment to manage exposure from ingestion also focuses on the acute effects of the phenolic and PAH components. Phenolic compounds cause corrosive esophageal burns and there may also be a risk of causing pneumonitis in the patient by aspiration of PAHs in coal tar derivatives, so emesis is contraindicated as a means of elimination (ATSDR 1995; Haddad et al. 1998). Activated charcoal has been used as a treatment to reduce absorption of hydrocarbons such as PAHs, however, its efficacy is not documented by clinical studies and it could potentially interfere with endoscopic examination of the gastrointestinal tract (Viccellio et al. 1998). Gastric lavage with olive oil avoids the dangers of additional esophageal damage while eliminating the phenols from continued mucosal contact and may be the preferred method of removing creosote, particularly if a substantial amount has been ingested (Haddad et al. 1998; Viccellio et al. 1998).

The treatment for contaminated eyes commonly includes irrigation with copious amounts of room temperature water, or saline if available, for at least 15 minutes. If irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, it is recommended that an ophthalmologic examination be performed. Phenol burns are alkaline in nature, and thus more corrosive than organic acids in damaging cornea1 tissue and delaying recovery.

Should an inhalation exposure occur, treatment commonly includes moving the exposed individual to fresh air and monitoring for respiratory distress. Injuries to the lungs are more likely when there is severe upper respiratory irritation and persistent cough. Emergency airway support and 100% humidified supplemental oxygen with assisted ventilation may be needed.

2.11.2 Reducing Body Burden

Most of the damage relating to the phenolic components in creosote and coal tar is immediate and requires no specific chronic management. It is recommended that mucosal surfaces be evaluated for possible scarring (especially the esophagus or cornea) if exposure was directly injurious. As with other ingested or inhaled PAHs (e.g., from combustion products like cigarette smoke), there are no documented means to enhance elimination of coal tars.

With regard to the possible absorption of the PAH component of coal tar creosote or other coal tar products, there are no known ways of reducing the body burden of PAHs. Data from acute-duration studies in animals indicate that PAHs are rapidly metabolized and eliminated in the urine and feces within days. No data are available to describe possible bioaccumulation after chronic exposure. Since PAHs are lipid soluble, however, it is possible that some accumulation could occur in the tissue fat.

2.11.3 Interfering with the Mechanism of Action for Toxic Effects

Coal tars produce photosensitivity and photoreactive dermatitis when applied to the skin (Hathaway et al. 1991) even in areas not usually exposed to direct sunlight (e.g., beneath the chin). It is recommended that patients be cautioned about sun exposure and the need for appropriate clothing several days after exposure, to prevent accelerated sunburning. These agents are physically heavy oils and are known to be both irritating and comedogenic (Amdur et al. 1991), so physical sun barriers are preferred to chemical sun screens or oils.

Phenols can produce a “lightening” effect on cutaneous coloration (TOMES 1994) with depigmentation and vitiligo. This is seen most commonly with repeated cutaneous application, but can also follow cutaneous burns. Sun exposure magnifies the evidence of this process and should be avoided. Most patients with chemical vitiligo recover with normal skin color returning after several months.

2.12 ADEQUACY OF THE DATABASE

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

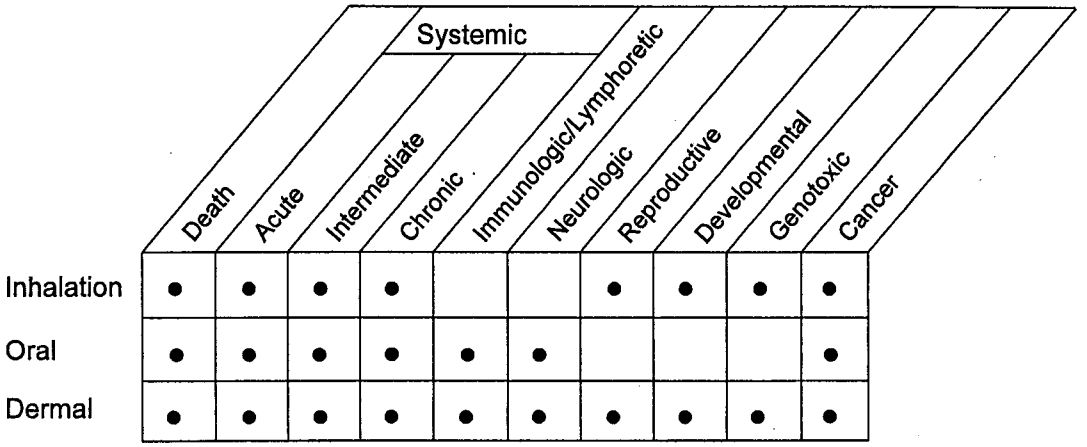
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

2.12.1 Existing Information on Health Effects of Creosote

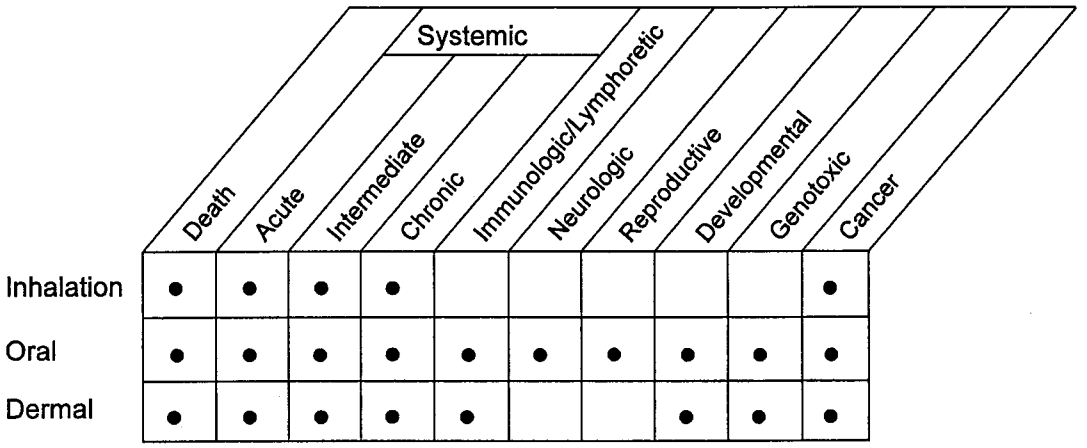
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to creosote are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of creosote. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The, dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989c), 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 database for the health effects of both wood creosote and coal tar products in experimental animals is inadequate, and consists primarily of acute lethality studies or old animal studies that would be considered inadequate by current standards. The systemic effects of ingested creosote have only been well described for beechwood creosote, although some studies exist for coal tar products. Little information is available on the effects of coal tar creosote following inhalation exposure. However, dermal exposure to coal tar creosote and other coal tar products has been shown in numerous studies to induce skin and lung tumors in mice. Since coal tar creosote is a complex mixture consisting primarily of PAHs, the toxic effects of coal tar creosote may be inferred from available information on these constituents. However, given the fact that many of these constituents are known cocarcinogens, initiators, promoters, and potentiators of carcinogenesis, the possibility for the occurrence of synergistic interactions in creosote cannot be ruled out. Thus, information on the toxicity of the various components of coal tar creosote cannot take the place of sound data on the toxic effects of the creosote mixture itself. This can also be assumed to be true for the other coal tar products. An additional factor to be considered when

Figure 2-5. Existing Information on Health Effects of Wood Creosote, Coal Tar Creosote, and Other Coal Tar Products



Human



Animal

● Existing Studies

reviewing the database for creosote is the effect of weathering. When creosote is released into the environment, weathering produces rapid changes in chemical composition (see Section 5.3). Thus, although data on toxic effects of unweathered creosote would be useful for individuals who are occupationally exposed to creosote, it is not clear how useful such data will be for individuals undergoing environmental exposure to weathered creosote.

2.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available on the effects of acute-duration exposures to creosotes and coal tar products in humans and animals (oral and dermal). However, there are few well conducted animal or human studies describing health effects following inhalation exposure. The type of information available includes primarily LD_{50} values and data on acute toxicity in animals (coal tar products and beechwood creosote), and acute toxicity following accidental or intentional ingestion or dermal exposure in humans (coal tar creosote and other coal tar products). Coal tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact, such as the skin and eyes. Acute ingestion of coal tar creosote appears to affect primarily the kidney and liver. Thus, the toxic effects of coal tar creosote on the skin following single-dose dermal exposure in humans are well characterized, but little else is known regarding the systemic effects of this form of creosote in either humans or animals. The available information is insufficient to derive either an acute oral or inhalation MRL for coal tar creosote or other coal tar products because human reports that identified target organs lacked exposure information, and no short-term animal studies exist that describe effects other than death or developmental defects. Identification of target organs from short-term animal studies following oral and dermal exposure would be useful in assessing the risk associated with the acute ingestion of or skin contact with coal tar creosote-contaminated water or soils by humans. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it is impossible to predict effects following exposure by one route based on effects observed following exposure by another route.

Intermediate-Duration Exposure. Information is available on the effects of intermediate-duration dermal exposures to coal tar creosote in humans and the effects of intermediate-duration exposures to beechwood creosote (oral) and coal tar creosote (oral and dermal) in animals. However, there are few well-conducted animal studies describing the health effects of inhalation exposure to coal tar creosote,

coal tar, coal tar pitch, or coal tar pitch volatiles. The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal tar creosote describe dermal, hepatic, renal, hematological, and respiratory end points. Little or no in depth information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either an intermediate oral or inhalation MRL for coal tar creosote or other coal tar products because no intermediate-duration human or animal studies exist that describe adverse effects other than on the skin. Given the widespread use of coal tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of intermediate-duration exposures to coal tar creosote and other coal tar products by the oral and dermal routes (by conducting 90-day intermediate toxicity studies) would be useful to identify target organs in animals in order to assess the risk associated with the intermediate-duration ingestion of, or skin contact with, coal tar creosote-contaminated water or soils by humans. Since coal tar products give off volatile components, studies of inhalation exposure to these compounds would also be useful. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Chronic-Duration Exposure and Cancer. Some information is available on the effects of chronic-duration dermal exposures to coal tar creosote and other coal tar products in humans and the effects of chronic-duration exposures to beechwood creosote (oral) and coal tar creosote (dermal) in animals. However, there are few well-conducted animal studies describing the health effects of chronic oral or inhalation exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal tar creosote describe dermal, but very rarely other systemic effects. Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either a chronic oral or inhalation MRL for coal tar creosote because no chronic-duration human or animal studies exist that describe effects other than on the skin. Given the widespread use of coal tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic

effects of chronic-duration exposures to coal tar creosote by the oral and dermal routes would be useful to identify target organs in animals in order to assess the risk associated with the chronic-duration ingestion of, or skin contact with, coal tar creosote-contaminated water or soils by humans. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer. More recent cancer epidemiological studies and surveys of the literature help to fill in data gaps, but are retrospective, and often fail to provide exact information concerning exposure. Several skin painting studies have been conducted in animals using coal tar creosote and its various fractions. Although many of these studies would be considered inadequate by current standards, the results nevertheless indicate that coal tar creosote and its constituents can induce skin tumors as well as act as tumor initiators and promoters. Carcinogenicity studies conducted with beechwood creosote by the oral route, found no evidence of cancer in mice. However, oral cancer bioassays with coal tar in mice found a significant incidence of liver, lung, and forestomach tumors. More information on the carcinogenic potential of chronically ingested coal tar creosote (e.g., an oral bioassay in rats) would be useful. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure.

However, since creosote appears to cause route-of-entry adverse effects (e.g., skin tumors following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Genotoxicity. The genotoxic potential of coal tar creosote has been investigated almost exclusively using *in vitro* assays and animal tissues although some evaluations of chromosomal aberrations in peripheral lymphocytes and DNA adducts in skin and other tissues have been conducted. The limited genotoxicity tests that have been conducted on urine obtained from humans exposed to creosote had varied results. The available data indicate that creosote is an indirect mutagen and induces gene mutation in bacteria and mouse lymphoma cells. However, a substantial database exists on the genotoxic effects of the PAHs found in the creosote mixture. More *in vivo* assays using human tissues with coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, or specific components of these mixtures, would be useful to more completely characterize the genotoxic potential of these mixtures.

Reproductive Toxicity. Little information on the reproductive effects of coal tar creosote in humans or animals is available. One epidemiological study in humans indicates no reproductive hazard from exposure through environmental contamination and another indicated no increased risk of spontaneous abortion from the use of coal tar as a dermal treatment for psoriasis during pregnancy. However, animal studies have shown that exposure to coal tar causes increased resorptions, decreased ovary weights (with a loss of luteal tissue), and increased testis weights in mice and rats. An increase in relative testis weight was also observed in rats administered beechwood creosote in the diet for 3 months. There were no accompanying gross or histopathological lesions of the testes in these animals, so the toxicological significance of this change is not known. Given the widespread potential for exposure to coal tar creosote, and industrial exposure to other coal tar products, and the indication from animal studies that creosote may be a reproductive toxicant, multi-generation reproductive toxicity studies should be conducted by the oral and dermal routes of exposure. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since coal tar has been shown to produce reproductive toxicity in animals by the oral, dermal, and inhalation routes, it appears that reproductive toxicity may not be route-dependent.

Developmental Toxicity. Information on the developmental effects of creosote in humans was not found. A series of studies by Springer and coworkers (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989) have demonstrated serious developmental toxicity for rats and mice exposed to coal tar by all routes. Given the widespread potential for exposure to coal tar creosote, and industrial exposure to other coal tar products, and the animal data mentioned above, additional oral and dermal developmental toxicity studies in animals would be useful. to assess the potential risk for creosote-induced adverse developmental effects. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since coal tar has been shown to produce developmental toxicity in animals by the oral, dermal, and inhalation routes, it appears that developmental toxicity may not be route-dependent.

Immunotoxicity. The only available information on the immunological effects of creosote in humans describes the occurrence of acute allergic dermatitis following exposure to creosote bush resin and coal tar. Animal studies have provided evidence of weight and morphological changes to the lymphoreticular tissues following exposure to coal tar, but no information regarding associated changes in the immune system have been reported. The relevance of these findings to exposure to human creosote exposure is not known. However, these data are suggestive of possible immunotoxicity and more information on the immunologic effects of coal tar creosote would be useful. Preliminary information on the potential for

creosote to induce immunotoxic effects may be obtained from go-day dermal studies that examine effects on lymphoid tissue and blood components. If adverse effects on these parameters are observed, then a full battery of immunotoxic tests may be warranted to further characterize the potential immunotoxicity of creosote administered by the dermal route. Immunotoxicity studies of coal tar creosote by inhalation and oral exposure, and of wood creosote, coal tar and coal tar pitch exposure by inhalation, oral and dermal routes would fill the data needs for these compounds.

Neurotoxicity. Available information about possible neurotoxic effects of creosote is very limited, but some signs of neurological involvement in humans and animals (rats and mice) following short-term, high-level, oral exposure to creosote (both beechwood and coal tar) have been described. These effects were generally excitatory in nature (e.g., convulsions). No reliable data are available on the short-term neurotoxic effects of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile exposure by the inhalation, oral, or dermal routes, or long-term neurotoxic effects of low-level exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles by the inhalation, oral, or dermal routes in humans or animals. Reports of individuals exposed to creosote suggest that neurotoxicity (e.g., dizziness, altered vision, etc.) may be an early sign of toxic exposure to creosote. Short-term and long-term neurotoxicity studies in animals, using sensitive functional and neuropathological tests, and exposure by the inhalation, oral and dermal routes would be useful in determining if coal tar creosote is a neurotoxic agent.

Epidemiological and Human Dosimetry Studies. Few controlled epidemiological studies have been conducted in humans on the effects of exposure to coal tar creosote. In particular, epidemiological studies of workers in creosote treatment plants would be useful to more fully assess the risk of inhalation and dermal exposure to coal tar creosote. Most of the available information on the effects of coal tar creosote in humans comes from cases of acute poisoning following the accidental or intentional exposure to coal tar creosote and from occupational exposures in the wood-preserving and construction industries. Limitations inherent in these studies include unquantified exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow up periods, and brief exposure periods. Despite their inadequacies, studies in humans suggest that coal tar creosote is a dermal irritant and a carcinogen following dermal exposure. Only one well-conducted epidemiological study of people living in close proximity to a coal tar creosote-contaminated area was found in the literature. Additional well-controlled epidemiological studies of people with documented exposure to creosote, living in close proximity to areas where coal tar creosote has been detected in

surface and groundwater, or near hazardous waste sites, and of people occupationally exposed to creosote could add to and clarify the existing database on creosote-induced human health effects. Particular effects to be examined include cancer (of the skin and other organs) and other adverse skin effects.

Biomarkers of Exposure and Effect.

Exposure. No method is currently available to measure the parent creosote mixture in human tissues or fluids. However, the PAH components of the creosote mixture and their metabolites (e.g., l-hydroxy-pyrene) can be measured in the urine of exposed individuals following relatively high-level exposures of acute and chronic duration. 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 creosote has been detected. 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 creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote containing PAHs. Again, these PAH-DNA adducts are not specific for coal tar creosote, and the adducts measured could have been from exposure to other sources of PAHs. Therefore, a biomarker of exposure specific to creosote would be useful to monitor exposure to this mixture.

Effect. The formation of benzo[a]pyrene-DNA adducts has been demonstrated and may also serve as a biomarker of PAH-induced carcinogenicity. However, these adducts are not specific for coal tar creosote exposure, as exposure to benzo[a]pyrene from sources other than coal tar creosote can occur. Studies to identify and measure effects more diagnostic of coal tar creosote-specific injury would be useful. Also, increasing the sensitivity of these tests would be valuable in evaluating the health status of individuals who have been exposed to low levels of creosote.

Absorption, Distribution, Metabolism, and Excretion. Studies monitoring the pharmacokinetics of the coal tar creosote mixture are limited. Much of the information regarding the disposition of creosote is based on indirect evidence or the pharmacokinetic information available on a single class of components of creosote, the PAHs.

Absorption of creosote occurs following all routes of exposure. The presence of creosote components in tissues and the presence of metabolites in urine were evidence of its absorption. However, no studies are available that quantify the extent and rate of creosote absorption. Studies in humans regarding the

distribution of creosote are not available and little information is available for animals. Its distribution is based on assumptions derived from studies that monitored the distribution of PAHs, components of creosote.

The metabolism of creosote has not been extensively studied, but preliminary results indicate that hydroxylation of the major PAH components is a principal degradation pathway in both humans and animals following all routes of exposure. 1-Hydroxypyrene is one metabolite that has been identified, but there were no studies available regarding the identification of other metabolites. Elucidation of additional biotransformation pathways and products is also important in examining potential toxic effects of creosote. Also, no studies were located regarding the rate or extent of creosote metabolism.

Studies regarding the excretion of creosote by humans or animals were not available. It is known that PAHs and their metabolites are primarily excreted in the bile and the feces. However, direct excretion studies with creosote would be more useful. Information is available regarding the disposition of creosote's individual components, but no information is available regarding how these components interact to affect the overall disposition.

In summary, no data are available regarding the toxicokinetics of the creosote mixture and all information must currently be inferred from what is known about the PAH components of creosote. Interactions between the components of the creosote mixture could occur that could alter the rate and extent of absorption, distribution, metabolism, and excretion of creosote from what might be predicted based on what is known about the individual PAH components. Therefore, more information on the toxicokinetics of the creosote mixture itself would be useful to predict possible target organs of toxicity as well as allow for extrapolation of toxic effects across routes of exposure.

Comparative Toxicokinetics. The available information indicates that the absorption, distribution, metabolism, and excretion of creosote is qualitatively similar in humans and rodents. This general conclusion was primarily based on evidence derived from studies on the individual PAH components of creosote. Recent papers have described specific kinetic aspects of individual components of the coal tar products. Little work has been done to address this topic for wood creosote. Detailed pharmacokinetic studies in humans and animals specific to the creosote mixture would provide a better indication of species differences and indicate whether the ability to extrapolate across species may be possible in the future.

Methods for Reducing Toxic Effects. Current methods for reducing toxic effects focus on reducing peak absorption after exposure. Recommendations are primarily based on methods devised for phenolic compounds, and it is not certain how appropriate these are for all forms of creosote, particularly those derived from coal tar. There is currently no method for reducing body burden of creosote once it has been absorbed or of interfering with its toxic effects. Treatment is generally supportive of respiratory and cardiovascular functions. Clinical information as to the efficacy of currently recommended practices such as gastric lavage would be a useful addition to the database for these chemicals.

Children's Susceptibility. Studies addressing the effects of creosote in children are limited to a single survey of health effects among residents of a housing development that had been built on a creosote waste site (ATSDR 1994). Other human studies are predominantly of occupationally exposed adults. Studies of effects in young animals are also limited, but include several developmental studies that demonstrate fetotoxicity and developmental defects in mice and rats due to coal tar exposure (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No data are available to determine whether children vary from adults either in the health effects they are likely to experience from creosote exposure, or in their relative susceptibility to these effects. Epidemiological studies of environmentally exposed populations (if such a population could be located), which include children might help to clarify the types of health effects observed in children after creosote exposure. A small retrospective study of women exposed to coal tar (as a treatment for psoriasis) during pregnancy found no increased incidence of abortion or birth defects (Franssen et al. 1999). Expanding this study to include a larger number of individuals and data as to the stage of pregnancy during which the women were exposed, could provide information as to whether the developmental defects observed in animals are also of concern for humans. Animal studies which compare the effects of creosote exposure on animals of different ages would provide information on the comparative susceptibility of young and adult individuals.

The pharmacokinetics of creosote have not been defined because of the chemical complexity of these mixtures. Information on individual components is not sufficient to define the properties of the mixture and for this reason no PBPK models have been proposed for creosote. Individual components of creosote are metabolized by several different enzyme systems including phase I and phase II enzymes. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity

of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual which will again affect the relative toxicity of particular components of creosote for old or young individuals. However, the interactions taking place when creosote components are metabolized are likely to be extremely complex so that information on age-related activity of any particular enzyme will probably not be very informative as to differential toxicity of the mixture.

Child health data needs relating to exposure are discussed in 5.8.1 Identification of Data Needs: Exposures of Children.

2.12.3 Ongoing Studies

Creosote is currently subject to an EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration standard and data call-in, and the Creosote Council II is currently conducting a research program that includes testing in intermediate inhalation, intermediate dermal, developmental, and reproductive toxicity. Specific studies currently listed (FEDRIP 2000) include CYP1A1 as a biomarker of exposure and susceptibility to creosote, the effect of wood creosote on diarrhea in rats, and modifiers of PAH carcinogenesis; the list does not currently include any health effects research for wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical synonyms and identification numbers for wood creosote, coal tar creosote, and coal tar are listed in Tables 3-1 through 3-3. Coal tar pitch is similar in composition to coal tar creosote and is not presented separately. Coal tar pitch volatiles are compounds given off from coal tar pitch when it is heated. The volatile component is not shown separately because it varies with the composition of the pitch. Creosotes and coal tars are complex mixtures of variable composition containing primarily condensed aromatic ring compounds (coal-derived substances) or phenols (wood creosote). Therefore, it is not possible to represent these materials with a single chemical formula and structure. The sources, chemical properties, and composition of coal tar creosote, coal tar pitch, and coal tar justify treating these materials as a whole. Wood creosote is discussed separately because it is different in nature, use, and risk.

Information regarding the chemical identity of wood creosote, coal tar creosote, and coal tar is located in Tables 3-l through 3-3.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Wood creosote, coal tar creosote, coal tar, and coal tar pitch differ from each other with respect to their composition. Descriptions of each mixture are presented below.

3.2.1 Wood Creosote

Wood creosotes are derived from beechwood (referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (Larrea, referred to herein as creosote bush resin). Beechwood creosote consists mainly of phenol, cresols, guaiacols, and xylenols. It is a colorless or pale yellowish liquid, and it has a characteristic smoky odor and burnt taste (Miyazato et al. 1981). It had therapeutic applications in the past as a disinfectant, laxative, and a stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States. Beechwood creosote is obtained from fractional distillation (200-220 ºC at atmospheric pressure) of beechwood or related plants. The mixture has only recently been characterized to any significant extent (Ogata and Baba 1989). Phenol, *p*-cresol, and guaiacols (guaiacol and 4-methylguaiacol) comprise the bulk of beechwood creosote. Xylenols, other methylated

Table 3-1. Chemical Identity of Wood Creosote

Characteristic	Information	Reference
Chemical name	Wood creosote	Merck 1989
Synonym(s)	Beechwood creosote, creosote, creasote	Merck 1989
Registered trade name(s)	Not applicable	
Chemical formula	Not applicable	
Chemical structure[a]	Not applicable	
Identification numbers:		Windholz 1983
CAS registry	8021-39-4	Merck 1989
NIOSH RTECS	G05870000	HSDB 2000
EPA hazardous waste	U051	HSDB 2000
OHM/TADS	No data	
DOT/UN/NA/IMCO	UN 2810; IMO 6.1	HSDB 2000
HSDB	1979	HSDB 2000

[a]Wood creosote is a mixture composed primarily of phenolic compounds.

CAS = Chemical Abstracts Services; 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; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Chemical Identity of Coal Tar Creosote

Characteristic	Information	Reference
Chemical name	Coal tar creosote	American Wood Preserver's Association 1988
Synonym(s)	Creosote, creosote oil, dead oil, brick oil, coal tar oil, creosote P1, heavy oil, liquid pitch oil, wash oil, creosotum, cresylic creosote, naphthalene oil, tar oil, AWPA #1, Preserv-o-sote	HSDB 2000
Registered trade name(s)	Sakresote 100	HSDB 2000
Chemical formula	Not applicable	
Chemical structure[a]	Not applicable	
Identification numbers:		
CAS registry	8001-58-9	Merck 1989; Weiss 1986
NIOSH RTECS	GF9615000	HSDB 2000
EPA hazardous waste	U051	HSDB 2000
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN 1136/1137; IMO 3.2/3.3	HSDB 2000
HSDB	6299	HSDB 2000
NCI	No data	

[a]Coal tar creosote is a mixed compound composed primarily of polycyclic aromatic hydrocarbons including phenanthrene, acenaphthene, fluorene, anthracene, and pyridine.

CAS = Chemical Abstracts Services; 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; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-3. Chemical Identity of Coal Tar

Characteristic	Information	Reference
Chemical name	Coal tar	Merck 1989
Synonym(s)	Crude coal tar, pixalbol, tar	HSDB 2000
Registered trade name(s)	Psorigel, Clinitar	Merck 1989
Chemical formula	Not applicable	
Chemical structure[a]	Not applicable	
Identification numbers:		
CAS registry	8007-45-2	HSDB 2000
NIOSH RTECS	No data	
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO	UN 1999; IMO 3.2/3.3	HSDB 2000
HSDB	5050	HSDB 2000
NCI	No data	

[a]Coal tar is a mixed compound composed primarily of polycyclic aromatic hydrocarbons including phenanthrene, acenaphthene, fluorene, anthracene, and pyridine.

CAS = Chemical Abstracts Services; 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; RTECS = Registry of Toxic Effects of Chemical Substances

guaiacols, and trimethylphenols account for virtually all of the remaining phenolics in the material. Since beechwood creosote is obtained from different sources using nonstandardized procedures, its composition may vary to some degree. For the sample analyzed by Ogata and Baba (1989), more than two-thirds of the more than 20 compounds identified (Table 3-4) were represented by just four components (phenol, p-cresol, guaiacol, and 4-methylguaiacol). Selected chemical and physical properties of wood creosote are shown in Table 3-5.

Creosote bush resin consists of phenolics (e.g., flavonoids and nordihydroguaiaretic acid), neutrals (e.g., waxes), basics (e.g., alkaloids), and acidics (e.g., phenolic acids). The phenolic portion comprises 83-91% of the total resin. Nordihydroguaiaretic acid accounts for 5-10% of the dry weight of the leaves (Leonforte 1986). No other relevant chemical/physical data are available for creosote bush resin; the substance is therefore not addressed further in this profile.

3.2.2 Coal Tar Creosote, Coal Tar, and Coal Tar Pitch

These three substances are very similar mixtures obtained from the distillation of coal tars. The physical and chemical properties of each are similar, although limited data are available for coal tar, and coal tar pitch. Chemical Abstracts Service Numbers (CAS #) are associated with coal tar creosote (8001-58-9), coal tar pitch (67996-93-2), and coal tar (8007-45-2). Literature searches for coal tar pitch produce data identical to that obtained for coal tar creosote. A distinction between these materials is provided in the following discussion.

Coal tars are by-products of the carbonization of coal to produce coke and/or natural gas. Physically, they are usually viscous liquids or semi-solids that are black or dark brown with a naphthalene-like odor. The coal tars are complex combinations of polycyclic aromatic hydrocarbons, phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. By comparison, coal tar creosotes are distillation products of coal tar. They have an oily liquid consistency and range in color from yellowish-dark green to brown. The coal tar creosotes consist of aromatic hydrocarbons, anthracene, naphthalene, and phenanthrene derivatives. At least 75% of the coal tar creosote mixture is polycyclic aromatic hydrocarbons (PAHs). Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. The pitch is a shiny, dark brown to black residue which contains polycyclic aromatic hydrocarbons and their methyl and polymethyl derivatives, as well as heteronuclear compounds (American Wood Preserver's Association 1988). Coal tar creosote is defined by the latter organization as:

Table 3-4. Identity of Major Components of Wood Creosote[a]

Compound	Relative peak area, (percent total peak area)
phenol	14.45
methylhydroxycyclopentenone	0.23
o-cresol	3.22
dimethylhydroxycyclopentenone	0.50
p-cresol	13.60
guaiacol	23.76
2,6-xylenol	1.04
3,4-xylenol	0.70
6-methylguaiacol	0.31
3,5-xylenol	2.94
2,4-xylenol	2.80
2,5-xylenol	0.68
unknown	1.31
2,3-xylenol	0.70
3-methylguaiacol	1.85
5-methylguaiacol	1.29
4-methylguaiacol	19.01
2,4,6-trimethylphenol	0.40
2,3,6-trimethylphenol	0.48
4-ethylguaiacol	6.36
4-ethyl-5-methylguaiacol	0.21
4-propylguaiacol	0.45

[a]As identified by gas chromatography/mass spectrometry (Ogata and Baba 1989); composition of wood creosotes may vary from source to source.

Table 3-5. Physical and Chemical Properties of Wood Creosote

Property	Information	Reference
Molecular weight	Not applicable	
Color	Yellowish to colorless	Merck 1989
Physical state	Liquid	Weiss 1986
Melting point	No data	
Boiling point	≈203 °C	Merck 1989
Specific gravity at 25 °C	1.08	Merck 1989
Odor	Characteristic smokey odor	Merck 1989
Taste	Caustic, burning taste	Merck 1989
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water	150–200 parts	Merck 1989
Organic solvent(s)	Miscible with alcohol, ether, fixed or volatile oils	Merck 1989
Partition coefficients:	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	74 °C (closed cup)	Clayton and Clayton 1981
Flammability limits in air	No data	
Explosive limits	No data	
Other	The major components of wood creosote (phenols) are susceptible to oxidative degradation when exposed to air (oxygen), particularly if the material is basic (high pH).	Not applicable

> A distillate derived from coal tar. As used in the wood preserving industry, creosote denotes a distillate of coal tar produced by the high temperature carbonization of bituminous coal. Coal tar creosote consists principally of liquid and solid aromatic hydrocarbons and contains some tar acids and tar bases; it is heavier than water and has a continuous boiling range beginning at about 200 ºC.

Coal tar creosote is now commonly defined by function, and refers to "the fractions or blends of fractions specifically used for timber preservation" (IARC 1987). Coal tar creosote is referred to as "creosote" by the U.S. EPA. The substance is a complex mixture typically composed of approximately 85% PAHs and 2-17% phenolics (Bedient et al. 1984). The composition of the mixture may also vary across lots and across manufacturers. Properties of coal tar creosote are shown in Table 3-7.

Coal tar pitch is the tar distillation residue produced during coking operations (NIOSH 1977). The grade of pitch thus produced is dependent on distillation conditions, including time and temperature. The fraction consists primarily of condensed ring aromatics, including 2-6 ring systems, with minor amounts of phenolic compounds and aromatic nitrogen bases. The number of constituents in coal tar pitch is estimated to be in the thousands (HSDB 2000). A list of the components comprising the PAH fraction of coal tar pitch is shown in Table 3-6. Properties for this substance are similar or identical to those shown in Table 3-7 for coal tar creosote.

Coal tar itself is produced by the carbonization, or coking of coal. Coal tar is defined by Hawley (1977) as:

> A black, viscous liquid (or semi-solid), naphthalene-like odor, sharp burning taste; obtained by the destructive distillation of bituminous coal, as in coke ovens; 1 ton of coal yields 8.8 gallons of coal tar, Combustible. Specific gravity 1.18-l .23 (66/60 ºF). Soluble in ether, benzene, carbon disultide, chloroform; partially soluble in alcohol, acetone, methanol, and benzene; only slightly soluble in water.

The composition of the coal tar mixture is dependent on the sources and preparation parameters of the creosote, and as a result the creosote components are rarely consistent in their type and concentration. An example of the composition variability among creosote samples was recently presented by Weyand et al. (1991). In that study, the concentrations of several PAHs were analyzed in four coal tars. All of the PAHs identified exhibited 2-fold to nearly 20-fold differences in concentration among the four samples. Benzo[a]pyrene, a component whose individual toxicity has been examined extensively, ranged from nondetectable levels (detection limit 0.3 g/kg) to 1.7, 6.4, and 3.9 g/kg of coal tar.

Table 3-6. Identity of PAH Components of Coal Tar Pitch[a]

Peak No.	Compound[b]	Peak No.	Compound[b]
1	naphthalene	31	acridine
2	benzo(b)thiophene	32	phenanthridine
3	quinoline	33	carbazole
4	2-methylnaphthalene	34	methylphenanthrene, - anthracene
5	1-methylnaphthalene	35	methylphenanthrene, - anthracene
6	biphenyl	36	methylphenanthrene, - anthracene
7	2-ethylnaphthalene	37	4H-cyclopenta(def)phenanthrene
8	dimethylnaphthalene	38	methylphenanthrene, - anthracene
9	dimethylnaphthalene	39	methylphenanthrene, - anthracene
10	dimethylnaphthalene	40	methylcarbazole
11	methylbiphenyl	41	methylcarbazole
12	acenaphthene	42	2-phenylnaphthalene
13	naphthonitrile or azaacenaphthylene	43	dihydropyrene or isomer
14	dibenzofuran	44	fluoranthene
15	fluorene	45	azafluoranthene, -pyrene
16	methylacenaphthene	46	phenanthro(4,5-bcd)thiophene
17	methylacenaphthene	47	azafluoranthene, -pyrene
18	methylacenaphthene	48	pyrene
19	methyldibenzofuran	49	benzonaphthofuran
20	methyldibenzofuran	50	benzacenaphthene or isomer
21	9,10-dihydroanthracene	51	benzacenaphthene or isomer
22	9,10-dihydrophenanthrene	52	benzonaphthofuran
23	methylfluorene	53	benzonaphthofuran
24	methylfluorene	54	benzo(lmn)phenanthridine
25	methylfluorene	55	benzo(kl)xanthene
26	methylfluorene	56	methylfluoranthene, - pyrene
27	1,2,3,4-tetrahydroanthracene	57	4H-benzo(def)carbazole
28	dibenzo(bd)thiophene	58	azafluoranthene, -pyrene
29	phenanthrene	59	benzo(a)fluorene
30	anthracene	60	methylfluoranthene, -pyrene

Table 3-6. Identity of PAH Components of Coal Tar Pitch[a] *(continued)*

Peak No.	Compound[b]	Peak No.	Compound[b]
61	benzo(a)fluorene	91	7H-benzo(c)carbazole
62	benzo(c)fluorene or isomer	92	methylbenz(a)anthracene or isomer
63	methylbenzacenaphthene or isomer	93	tetramethylfluoranthene or isomer
64	methylbenzonaphthofuran or isomer	94	5H-benzo(b)carbazole
65	methylpyrene or isomer	95	methylbenzophenanthridine or isomer
66	methylpyrene or isomer	96	dimethylbenzo(cdf)carbazole
67	methylbenzonaphthofuran or isomer	97	methylchrysene or isomer
68	methylbenzonaphthofuran or isomer	98	methylchrysene or isomer
69	methylazapyrene or isomer	99	methylbenz(a)anthracene or isomer
70	methylbenzonaphthofuran or isomer	100	dimethylbenz(a)anthracene or isomer
71	methylbenzofluorene	101	methylbenz(a)anthracene or isomer
72	dihydrochrysene or isomer	102	dimethylbenz(a)anthracene or isomer
73	dimethylfluoranthene, -pyrene	103	11H-benz(bc)aceanthrylene or isomer
74	trimethylfluoranthene, - pyrene	104	methylbenz(a)anthracene or isomer
75	dimethylfluoranthene, -pyrene	105	4H-cyclopenta(def)chrysene or isomer
76	benzo(b)naphtho(2,1-d)thiophene	106	methylbenz(a)anthracene or isomer
77	benzo(c)phenanthrene	107	binaphthalene or isomer
78	benzo(ghi)fluoranthene	108	4H-cyclopenta(def)triphenylene or isomer
79	dimethylbenzonaphthofuran	109	dimethylbenz(a)anthracene or isomer
80	benzo(b)naphtho(1,2-d)thiophene	110	methylbenz(a)anthracene or isomer
81	dibenzoquinoline or isomer	111	binaphthalene or isomer
82	tetrahydrochrysene or isomer	112	dimethylbenz(a)anthracene or isomer
83	benzo(a)naphtho(2,3-d)thiophene	113	methylbenz(a)anthracene or isomer
84	benz(a)anthracene	114	binaphthalene or isomer
85	chrysene	115	phenylphenanthrene or isomer
86	11H-benzo(a)carbazole	116	dihydrobenzofluoranthene or isomer
87	naphthacene	117	dimethylchrysene or isomer
88	methylbenzonaphthothiophene	118	dibenzophenanthridine or isomer
89	methylbenz(a)anthracene or isomer	119	biquinoline
90	tetramethylfluoranthene or isomer	120	biquinoline

Table 3-6. Identity of PAH Components of Coal Tar Pitch[a] *(continued)*

Peak No.	Compound[b]	Peak No.	Compound[b]
121	benzo(j)fluoranthene	151	methylbenzopyrene or isomer
122	dihydrobenzofluoranthene or isomer	152	methylbenzopyrene or isomer
123	benzo(b)fluoranthene	153	11H-cyclopenta(ghi)perylene or isomer
124	dihydrobenzofluoranthene or isomer	154	methylbenzopyrene or isomer
125	benzo(k)fluoranthene	155	dimethylbenzopyrene or isomer
126	dibenzonaphthofuran or isomer	156	methylbenzopyrene or isomer
127	dihydrobenzofluoranthene or isomer	157	methylbenzopyrene or isomer
128	dimethylchrysene or isomer	158	dimethylbenzopyrene or isomer
129	azabenzopyrene or isomer	159	11H-indeno(2,1,7-cde)pyrene or isomer
130	dibenzonaphthofuran or isomer	160	dimethylbenzopyrene or isomer
131	benzophenanthrothiophene	161	dinaphthothiophene
132	azabenzopyrene or isomer	162	dimethylbenzopyrene or isomer
133	benzo(e)pyrene	163	dibenzophenanthridine or isomer
134	dibenzonaphthofuran or isomer	164	dibenzonaphthothiophene
135	benzo(a)pyrene	165	dimethylbenzopyrene or isomer
136	dibenzonaphthofuran or isomer	166	dibenzocarbazole
137	perylene	167	dimethylbenzopyrene or isomer
138	dibenzonaphthofuran or isomer	168	dibenzo(bg)phenanthrene or isomer
139	methylbenzofluoranthene or isomer	169	benzo(g)chrysene or isomer
140	methylbenzofluoranthene or isomer	170	dinaphthothiophene
141	azabenzopyrene or isomer	171	dimethylbenzofluoranthene or isomer
142	4H-naphtho(1,2,3,4-def)carbazole or isomer	172	dibenzoacridine or isomer
143	methylbenzofluoranthene or isomer	173	dinaphthothiophene
144	dibenzofluorene or isomer	174	dinaphthothiophene
145	dihydroindenopyrene or isomer	175	benzo(c)chrysene or isomer
146	dibenzofluorene or isomer	176	dibenzocarbazole
147	dibenzofluorene or isomer	177	dimethylbenzofluoranthene or isomer
148	methylbenzopyrene or isomer	178	dibenz(aj)anthracene
149	dibenzo(cg)phenanthrene or isomer	179	indenopyrene or isomer
150	dimethyldibenzonaphthofuran or isomer	180	dimethyldibenzonaphthofuran

Table 3-6. Identity of PAH Components of Coal Tar Pitch[a] *(continued)*

Peak No.	Compound[b]	Peak No.	Compound[b]
181	methyldibenzophenanthrene, -anthracene	191	dimethyldibenzonaphthofuran
182	indenopyrene or isomer	192	picene
183	methylbenzophenanthrothiophene	193	dimethylbenzopyrene or isomer
184	dibenz(ac)anthracene	194	dimethyldibenzonaphthofuran
185	methyldibenzophenanthrene, -anthracene	195	benzo(ghi)perylene
186	dimethylbenzofluoranthene or isomer	196	benzo(a)naphthacene or pentacene
187	dibenz(ah)anthracene	197	dimethyldibenzonaphthofuran
188	trimethylbenzofluoranthene or isomer	198	anthanthrene
189	dimethyldibenzophenanthrene, -anthracene	199	methyl indenopyrene or isomer
190	benzo(b)chrysene		

[a]As reported by Guillén et al. 1992; compounds presented in elution order.
[b]Tentative identification by gas chromatography/mass spectrometry.

Table 3-7. Physical and Chemical Properties of Coal Tar Creosote

Property	Information	Reference
Molecular weight	Not applicable	
Color	Translucent brown to black; oily liquid; yellowish to dark green-brown	Merck 1989
Physical state	Liquid	Weiss 1986
Melting point	No data	
Boiling point	194–400 °C	Clayton and Clayton 1981
Specific gravity	1.07–1.08	Clayton and Clayton 1981
Odor	Aromatic smokey smell Characteristic sharp odor	DOT 1985 Merck 1989
Odor threshold:		
Water	No data	
Air	No data	
Taste	Burning, caustic taste	Clayton and Clayton 1981
Solubility:		
Water	Slightly soluble	Clayton and Clayton 1981
Organic solvent(s)	Miscible with alcohol, ether, fixed or volatile oils	Clayton and Clayton 1981
Partition coefficients:	1.0 (log K_{ow})	HSDB 2000
Vapor pressure	No data	
Autoignition temperature	335 °C	Merck 1996
Flashpoint	74 °C	Merck 1989
Flammability limits in air	No data	
Explosive limits	No data	

Limited chemical/physical data exist for coal tar. Table 3-8 summarizes the current information. Because of the variability in feedstock and manufacturing processes, presentation of exact values for various properties presented in Tables 3-7 and 3-8 is not possible.

Table 3-8. Physical and Chemical Properties of Coal Tar

Property	Information	Reference
Molecular weight	Not applicable	
Color	Almost black, thick liquid, or semisolid	Merck 1989
Physical state	Semisolid	Weiss 1986
Melting point	No data	
Boiling point	No data	
Specific gravity	1.18–1.23	Hawley 1981
Odor	Naphthalene-like	Osol 1980
Odor threshold:		
Water	No data	
Air	No data	
Taste	Sharp, burning taste	Osol 1980
Solubility:		
Water	Slightly soluble	Merck 1989
Organic solvent(s)	Mostly dissolves in benzene; partially dissolves in alcohol, ether, chloroform, acetone, and petroleum ether	Merck 1989
Partition coefficients	No data	
Vapor pressure	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Explosive limits	No data	

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

4.1 PRODUCTION

Wood creosote, coal tar creosote, coal tar, and coal tar pitch differ from each other in composition. Wood creosotes (CAS Registry number 8021-39-4) are derived from beechwood (referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (Larrea, referred to herein as creosote bush resin). Beechwood creosote is not commercially produced in the United States (HSDB 2000).

Coal tars are by-products of the carbonization of coal to produce coke and/or natural gas. By comparison, coal tar creosotes are distillation products of coal tar. Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. Coal tar pitch volatiles are compounds given off by coal tar pitch when it is heated, and thus vary with the composition of the coal tar pitch (see Table 3-6). The volatile component of coal tar has not been addressed separately from coal tar pitch in this section.

Because coal tar is a by-product of steel manufacturing, domestic production of coal tar products may vary depending on demand for steel (USITC 1987). Coal tar production in the United States was 168.6 million gallons in 1986 (USITC 1987) and 188.5 million gallons in 1987 (USITC 1988). In 1992, 7.03×10^8 kg (1.55×10^9 pounds) of crnde coal tar was produced (USITC 1994). Creosote has been produced commercially in the United States since 1917 (IARC 1985). Creosote production falls into two categories: distillate (100% creosote), and creosote in coal tar solution. Distillate production in 1986 was 46.8 million gallons; creosote in coal tar solution was 3 1.6 million gallons (USITC 1987). Distillate production in 1987 was 47.3 million gallons. Production of creosote in coal tar solution in 1987 was not disclosed, but solution sales in 1987 were 34.3 million gallons (USITC 1988). Distillate production in 1992 was 2.41×10^8 kg (5.32×10^8 pounds); creosote in coal tar solution was 1.10×10^8kg (2.43×10^9 pounds) (USITC 1994). The U.S. International Trade Commission classifies pitch of tar as hard (melting point ≥161 ºF), medium (melting point 110-160 ºF), or soft (melting point 80-109 ºF) (USITC 1994). Production of hard pitch in 1987 was 4.93×10^5 tons. Soft pitch production data for 1987 were not disclosed, but 6.52×10^5 tons were sold (USITC 1988). Production of hard pitch was 6.08×10^8 kg (1.34×10^9 pounds) in 1992. Production and sales figures for medium and soft pitch were not disclosed for 1992 (USITC 1994).

Table 4-1 lists the facilities in each state that manufacture or process coal tar creosote, the intended use, and the range of maximum amounts of creosote that are stored on site. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI) (TRI97 2000). Only certain types of facilities are legally required to report; therefore, this is not an exhaustive list.

4.2 IMPORT/EXPORT

Available figures on imports and exports (NTDB 1994) are based on millions of gallons of all forms of creosote. Figures from the period 1984-1987 show fluctuations in the range of l-10 million gallons of creosote products in both import and export levels. Recent data pertaining to the import or export of creosote (NTDB 1995) are presented in Table 4-2. The categories used by the National Trade Data Bank do not directly correspond to the four categories described in Section 4.1.

4.3 USE

Coal tar creosote has been used as a wood preservative pesticide in the United States for over 100 years. Wood preservation accounts for over 97% of current coal tar creosote production (Santodonato et al. 1985). Coal tar creosote is applied to wood by commercial pressure treatment or by home and farm dipping or brushing, although this latter use is not significant since creosote now has restricted use as a wood preservative pesticide (EPA 1986b). Coal tar creosote is a wood preservative and water-proofing agent for log homes, railroad ties, telephone poles, marine pilings, and fence posts. In addition, coal tar creosote prevents animal and vegetable growth on concrete marine pilings, and is a component of roofing pitch, fuel oil, and lamp black, and a lubricant for die molds (Cammer 1982; HSDB 2000). Other uses include animal and bird repellent, insecticide, animal dip, fungicide, and a pharmaceutical agent for the treatment of psoriasis (IARC 1985). Coal tar is registered as a pesticide active ingredient with the U.S. EPA and in 1998 was being evaluated for re-registration (HSDB 2000). The leaves of the creosote bush are ground to produce an herbal nutritional supplement for use as an antioxidant or free radical scavenger to retard aging and to treat a variety of skin conditions including acne. The supplement is claimed, in nonscientific publications, to have antiamoebic, antifungal, and antiviral properties. Suggested uses include oral applications for colds, influenza, diarrhea, urinary tract infections, and topical applications for dandruff (Katz and Saibil 1990).

Beechwood creosote and its compounds calcium creosotate, creosote carbonate, and creosote valerate were used in the past as antiseptics and expectorants (Merck 1989). Treatments for leprosy (Samson and

Table 4-1. Facilities that Manufacture or Process Creosote

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
AL	8	10,000-9,999,999	1, 4, 6, 9
AR	2	100,000-9,999,999	1, 3, 8, 9
AZ	1	100,000-999,999	9
CA	2	10,000-999,999	9
CO	1	10,000,000-49,999,999	9
CT	1	100,000-999,999	9
FL	1	100,000-999,999	9
GA	3	10,000-999,999	2, 4, 8, 12
IL	3	1,000,000-9,999,999	1, 4, 9
IN	3	100,000-9,999,999	1, 3, 9
KS	1	10,000-99,999	9
KY	3	100,000-999,999	8, 9
LA	5	100,000-49,999,999	9
MI	1	1,000,000-9,999,999	8
MO	1	1,000,000-9,999,999	9
MS	8	10,000-9,999,999	2, 3, 9
NJ	1	100,000-999,999	9
NY	1	100,000-999,999	9
OH	2	10,000,000-49,999,999	1, 4
OK	1	1,000,000-9,999,999	2, 3, 9
OR	3	100,000-9,999,999	8
PA	7	0-999,999	1, 4, 8, 9, 13
SC	1	1,000,000-9,999,999	9
SD	1	100,000-999,999	2, 3, 9
TN	1	1,000,000-9,999,999	1, 3, 9
TX	4	100,000-9,999,999	1, 4, 9, 12
UT	1	1,000,000-9,999,999	1, 5

Table 4-1. Facilities that Manufacture or Process Creosote *(continued)*

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
VA	3	100,000-9,999,999	8, 9
WA	1	100,000-999,999	12
WI	2	100,000-999,999	9
WV	4	1,000-9,999,999	1, 3, 8, 9, 12

Source: TRI97 2000

[a]Post office state abbreviations used
[b]Range represents maximum amounts on site reported by facilities in each state
[c]Activities/Uses:

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

Table 4-2. Import/Export Volumes for Creosote

Tariff Category	Imports/ Exports	1991	1992	1993	1994	1995
Creosote oils	Exports (1000kg)	3,978	8,027	9,158	14,900	6,838
	Imports (1000 L)	NR	17,584	22,674	17,994	9,466
Other oils and products of coal tar distillation	Exports (1000kg)	10,842	0	0	0	0
	Imports (1000 L)	NR	10,690	40,475	219,424	12,643
Pitch from coal and other mineral tars	Exports (1000kg)	39,592	76,586	91,659	103,034	43,740
	Imports (1000 L)	NR	6,226	115,688	77,791	50,315

Source: National Trade Data Bank (NTDB 1995)

NR = not reported

Limkako 1923), pneumonia (McKinlay 1933), and tuberculosis (Fellows 1939a) also involved ingestion of beechwood creosote. Beechwood creosote is rarely used in the United States for medicinal purposes today.

The major use of coal tar pitch is as the binder for aluminum smelting electrodes. Pitch is also used in roofing, surface coatings, and for pitch coke production. Pipe-coating enamels made from pitch are used to protect buried oil, gas, and water pipes from corrosion (IARC 1985).

4.4 DISPOSAL

Seventy-seven large handlers of coal tar creosote report that 97% (1,040,420 pounds) of the creosote released to the environment from their facilities is through air emissions (TRI97 2000). Treatment of creosote sludge generated from coal tar creosote production includes fixing, solidifying, and covering with clay. In the past, settling lagoons were used in treatment. However, they are no longer being used, and those which were used are now being remediated. “Disposal in place” requires groundwater monitoring for a 30-year period (Ball et al. 1985). Four Resource Conservation and Recovery Act (RCRA) hazardous wastes are listed due, in part, to their creosote content (40 CFR 261.31 and 261.32 [EPA 1981a, 1981b]). These are:

- Waste waters, process residuals, preservative dripage, and spent formulations from wood preserving processes generated at plants that use creosote formulations
- Bottom sediment sludge from the treatment of waste waters from wood preserving processes
- Waste water treatment sludges generated in the production of creosote
- Off-specification creosote (does not meet desired chemical composition).

Due to RCRA Land Disposal Restrictions, creosote can no longer be disposed in hazardous waste landfills unless it meets EPA specified treatment standards (EPA 1990c). No technology- or concentration-based standards for the three RCRA hazardous wastes containing creosote specify creosote as a constituent for monitoring treatment performance (40 CFR 268.43 [EPA 1988b]). Industrially used creosote-treated wood can be burned in an industrial incinerator or boiler (EPA 1986b). Treated wood used in the home or farm should be buried or disposed with household garbage; it should not be incinerated (American Wood Preserver’s Association 1988). The potential for many types of hazardous pollutants to be included with creosote wastes seriously diminishes the potential for recycling or re-use.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Creosote has been identified in at least 59 of the 1,591 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for creosote is not known. The frequency of these sites can be seen in Figure 5-l. Of these sites, all 59 are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown).

Coal tar creosote is a complex commercial mixture of some 300 organic constituents. The most common forms are derived from coal tar distillation, yielding coal tar creosote in temperature ranges between 210 and 280 ºC. Coal tar and coal tar pitch share many of the polycyclic aromatic hydrocarbons (PAHs) components of coal tar creosote. For the coal tar derivatives, the composition of the mixture varies from batch to batch depending on the coking process used. Creosote consists primarily of PAHs and, therefore, the fate of many of the components of the mixture is similar to that of PAHs.

Coal tar creosote has been widely used as a wood-treatment pesticide since the turn of the century. As a result of this widespread and long-term use, workers in the wood-preserving industry have been exposed to coal tar creosote for many years. Human exposure to coal tar creosote can occur by inhalation or direct dermal contact. Studies have indicated that dermal exposure to creosote used in wood treatment or in coking oven processes contributed more significantly to the total body burden than respiratory exposures (Klingner and McCorkle 1994; Malkin et al. 1996; Van Rooij et al. 1993b). In other industries, such as rubber processing, occupational exposure to coal tar pitch volatiles may lead to excessive respiratory exposure to PAHs, including benzo[a]pyrene (Rogaczewska and Ligocka 1994). Individuals working in wood-preserving facilities are one of the largest exposed groups. Exposure may also occur during handling and installation of treated wood products in structures such as bridges, piers, retaining walls, cross ties, and fencing; as a result of burning treated scrap wood; and through contact with contaminated media at hazardous waste sites. The general public is unlikely to experience any significant exposure to liquid creosote through the direct use of wood preservative products because EPA canceled all nonwood uses of the material and restricted use of coal tar creosote products to certified applicators in January 1986 (EPA 1986b; R.U.P. 1994).

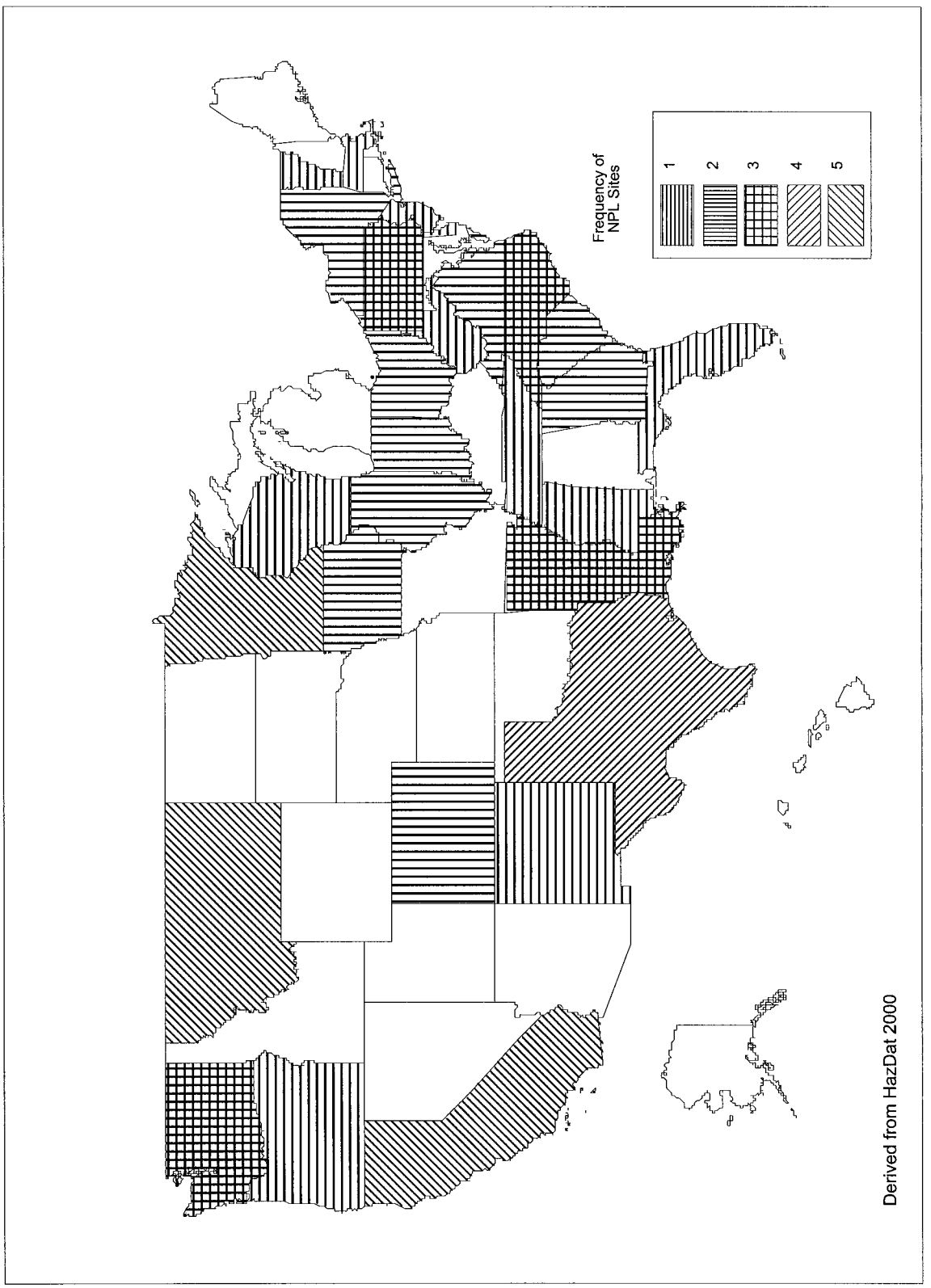


Figure 5-1. Frequency of NPL Sites with Creosote Contamination

Children are exposed to creosote via the same routes that adults are, and small children are more likely than adults to be in close contact with yard dirt or playground dirt, lawns, and indoor (carpet) dust, all of which may be contaminated with creosote residues. Because of a tendency to put their unwashed hands and foreign objects into their mouths, and to chew on objects, children may be exposed to creosote through oral ingestion of the chemical. Dermal exposure may occur through contact with treated wood used for utility poles, bridges, fences, and railroad crossties. Children may be exposed by playing near pools of discarded creosote or by playing at abandoned hazardous waste sites.

Pharmaceutical creosote preparations are derived from the processing of such woody plants as beechwood (von Burg and Stout 1992). Wood creosote (beechwood creosote) is a yellow, transparent liquid with a characteristic smoky odor, obtained by fractional distillation of wood tar. It is composed primarily of phenol, phenols, cresols, guaiacols, xylenols, and small amounts of alkyl-2-hydroxy-2-cyclopentenl-ones. It has been used as an expectorant, a “gastric sedative,” a gastrointestinal antiseptic, and particularly as an antidiarrheal agent (Ogata et al. 1993).

Creosote has been identified in at least 59 of the 1,591 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 2000). However, the number of sites evaluated for creosote is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Biotransformation by microbes is the primary process by which creosote constituents are degraded in soils, surface waters, and groundwater. The mixture is relatively stable and persistent in the environment; half-life data are not available.

5.2 RELEASES TO THE ENVIRONMENT

There are no known natural sources of the creosote mixture (IARC 1973). However, several of the PAH constituents of the mixture are known to have natural sources; the reader is referred to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995) and the ATSDR *Toxicological Profile for Cresols* (ATSDR 1992) for additional information on natural sources, releases, and levels of PAHs and cresols associated with creosote production, use, and disposal.

Creosote has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 59 of the 1,591 EPA NPL hazardous waste sites (HazDat 2000).

According to the U.S. Department of Agriculture (USDA), the major source of creosote released to the environment is waste water effluents from wood treatment facilities (USDA 1980). Companies that preserve wood with coal tar creosote may treat their aqueous wastes in on-site biological treatment plants or release the waste water into a municipal water treatment system (EPA 1975, 1978). According to the Toxics Release Inventory (TRI), coal tar creosote manufacturing and processing facilities listed for 1997 (TR197 2000) report that the major portion of creosote released to the environment is released to the air. Table 5-l lists releases to the environment in 1997 from facilities that manufacture or process coal tar creosote. Only certain types of facilities are legally required to report; this is not an exhaustive list.

Coal tar creosote components may also be slowly released from the surface of treated wood products by oil exudation, leaching by rain water, or volatilization. Losses of creosote from impregnated wood are dependent on the kind of coal used to produce the coal tar, the kind of coke oven used to make the coal tar, and the conditions under which the wood is used (Leach and Weinert 1976).

Treatment of waste waters from wood-preserving processes that use creosote and/or pentachlorophenol produces bottom sediment sludge. EPA defines these as K00l sludges (EPA 1980); in the early 1990s approximately 1,000 metric tons per year of K001 sludges were produced from active wood-preserving facilities (Davis et al. 1993). At that time, 55 wood-preserving facilities had been identified as NPL sites primarily because of contamination with K00l sludge (Davis et al. 1993).

Creosote-containing materials are also encountered at abandoned dump sites or abandoned facilities where creosote was produced or used in significant amounts. In addition to wood-preserving facilities, coal tar creosote was a by-product of the production of so-called town gas, an illuminating gas made from coal (Arvin and Flyvbjerg 1992; EPA 1987b; Flyvbjerg et al. 1993). Around the turn of the century, virtually every large community in the United States had such a manufactured gas facility (EPA 1987b). From 1816-l 947, >11 billion gallons of coal tar was generated at manufactured gas plants in the United States (Lee et al. 1992). The total number of town-gas sites may have approached 11,000. Several hundred of the larger sites have been evaluated for the NPL. Coke-producing facilities also generate coal tar wastes, including cresol emissions to the atmosphere (Grosjean 1991).

At older production facilities or places where wastes have been disposed off-site, the creosote materials are often mixed with other chemicals. For instance, pentachlorophenol (PCP) is commonly encountered at NPL sites involved with wood-preserving operations along with such metals as copper, chromium, and arsenic (Davis et al. 1993; Kuehl et al. 1990; Mueller et al. 1989, 1991). At many of these sites, PAHs

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

		Total reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
AL	8	168030	182	11000	0	179212	204	62440
AR	2	29363	1060	1625	0	32048	93	31772
AZ	1	6805	0	0	0	6805	0	870
CA	2	3038	49	0	0	3087	0	6061
CO	1	5803	0	0	0	5803	103	0
CT	1	1000	0	0	0	1000	0	0
FL	1	500	0	0	0	500	0	0
GA	3	2350	5	0	0	2355	0	12100
IL	3	42866	1781	0	0	44647	2445	11376
IN	3	7742	3052	15000	0	25794	1211	0
KS	1	250	0	0	0	250	0	0
KY	3	130857	43	0	0	130900	34	4550
LA	5	116116	191	0	0	116307	1602	7799
MI	1	6596	0	0	0	6596	0	0
MO	1	5525	565	0	0	6090	2812	2162
MS	8	48505	1126	0	0	49631	797	41246
NJ	1	1840	0	0	0	1840	1400	3700

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Creosote (*continued*)

		Total reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
NY	1	40	0	0	0	40	5	1454
OH	2	83116	0	0	0	83116	0	0
OK	1	0	3	0	0	3	0	0
OR	3	21688	5	250	0	21943	58	5805
PA	7	28509	6	0	0	28515	8	3063
SC	1	13020	0	0	0	13020	3684	15562
SD	1	15900	0	0	0	15900	0	21100
TN	1	500	0	0	0	500	0	0
TX	4	144833	123	0	0	144956	149	39265
UT	1	2972	0	0	0	2972	0	0
VA	3	19098	0	0	0	19098	10	446
WA	1	255	255	55	0	565	0	0
WI	2	43471	0	0	0	43471	0	413
WV	4	53450	6	0	0	53456	0	17829
Totals	**77**	**1004038**	**8452**	**27930**	**0**	**1040420**	**14615**	**289013**

Source: TRI97 2000

[a]Data in TRI are maximum amounts released by each facility
[b]Post office state abbreviations used
[c]The sum of fugitive and stack releases are included in releases to air by a given facility
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells

POTW = publicly owned treatment works

from combustion sources other than coal tar may have been introduced. The wastes from old town-gas sites may contain benzene, toluene, ethylenebenzene, or xylenes, and sometimes cyanides (Arvin and Flyvbjerg 1992; EPA 1987b; Flyvbjerg et al. 1993).

No major sources of wood creosote releases to the environment have been reported.

5.2.1 Air

Atmospheric releases of creosote from wood-preserving plants are not well defined. Coal tar creosote constituents such as naphthalene, acenaphthalene, acenaphthene, phenanthrene, and fluorene have been detected in emissions at a pressure treatment facility that treated logs for use as utility poles and marine pilings (Engineering Science 1986). Releases may occur at several points in the treatment process, such as when cylinder doors are opened after a treatment cycle, or when creosote is transferred from the heater to the cylinder at the beginning of the impregnation process. Atmospheric releases vary from plant to plant, depending on the process design, and are considered to be significantly smaller than releases to surface water in aqueous effluents (Henningsson 1983). It should be noted, however, that the more volatile PAHs may be less toxic (and especially less carcinogenic) than the less volatile PAHs.

On a hot, sunny day evaporation of creosote from the surface of treated wood may release coal tar creosote constituents to the atmosphere. Only the volatile creosote components such as acenaphthene ant naphthalene will volatilize; the heavier fractions will remain on the wood (USDA 1980). Volatilization may also be greater during warmer months when ambient temperatures are higher. Gevao and Jones (1998) observed greater volatilization of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene from creosote-treated wood at 30 ºC than at 4 ºC.

In a terrestrial microcosm study, release of ^{14}C-labeled creosote components to the atmosphere from treated wood accounted for 1.0% of total acenaphthene and 1.4% of phenanthrene, whereas 93.5 and 95% of these components, respectively, were retained in the wood (Gile et al. 1982).

Other potential sources of atmospheric releases include incineration of scrap wood treated with the mixture and re-entrainment of dust and soils contaminated with components of the mixture in the vicinity of hazardous waste sites. Creosote has been detected in air samples collected at 2 of the 59 current or former NPL sites where creosote has been identified in some environmental medium (HazDat 2000).

According to TRI97 (TRI97 2000), an estimated total of 1,004,038 pounds of coal tar creosote, amounting to 96.5% of the total environmental release, was discharged to air from manufacturing and processing facilities in the United States in 1997. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No sources of wood creosote releases to the atmosphere have been reported.

5.2.2 Water

The major source of creosote released into surface waters and groundwater is waste water effluents from wood-preserving facilities (USDA 1980). In previous years, waste water generated from wood treatment facilities was often discharged to unlined evaporation/settling lagoons where a sludge was formed. Water-soluble creosote components then percolated through the soil to reach the groundwater table. Waste waters may include process water generated from steam conditioning of the wood; preservative formulation recovery and regeneration water; water used to wash excess preservative from the surface of the wood; condensate from drying kilns used to dry preserved or surface-protected wood; water that accumulates in door and retort sumps; and rain falling on or in the immediate vicinity of the treating cylinder and work tank area. Groundwater contamination from creosote waste waters and sludge stored in unlined surface water impoundments at a wood treatment facility has been reported in Pensacola, Florida (Baedecker et al. 1988; Elder and Dresler 1988; Goerlitz et al. 1985). Similar contamination problems have been reported in Conroe, Texas (Borden 1986), and St. Louis Park, Minnesota (Hickock et al. 1982).

Given the very viscous nature of coal tar creosote or creosote-containing wastes, significant migration into groundwater supplies is seldom encountered unless the soils are extremely porous. For instance, a very sandy substrate at the American Creosote Works NPL site at Pensacola, Florida, allowed a significant plume of wood-preserving wastes to enter the groundwater (Goerlitz et al. 1985). In most instances, the main concern over creosote materials entering well water is that minute quantities (ng/L) of coal tar components produce extremely objectionable tastes and odors (Arvin and Flyvbjerg 1992).

In addition to discharges or migration into groundwater from disposal sites, coal tar creosote has often been introduced to receiving waters as the result of spills while transporting coal tar materials on barges or during loading and unloading accidents around docks or navigation facilities. Well documented examples include a spill near Slidell, Louisiana, on the Bayou Bonfouca (DeLeon et al. 1988). During the

years 1986-1991, 1,400 incidents of chemical and petroleum spills into the Newark Bay were documented; among these were spills of 53,000 gallons of liquid asphalt and 75 gallons of creosote (Gunster et al. 1993).

Water-soluble creosote constituents (e.g., phenols) may be released to surface water or groundwater by leaching from the surface of creosote-contaminated soils at hazardous waste sites or from treated wood products, such as marine pilings, coming into contact with water. For example, some studies have shown that creosote is lost to a greater extent from marine timber than from timber placed in fresh water as a result of wood cell contraction caused by the high concentration of salts in sea water (Henningsson 1983). Creosote has been detected in groundwater samples collected at 25 of the 59 NPL sites and in surface water samples collected at 9 of the 59 sites where creosote has been identified in some medium (HazDat 2000).

According to TRI97 (2000), an estimated total of 8,452 pounds of coal tar creosote, amounting to 0.8% of the total environmental release, was discharged to water from manufacturing and processing facilities in the United States in 1997. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No sources of wood creosote releases to water have been reported.

5.2.3 Soil

Coal tar creosote may be released to soils at wood treatment facilities as a result of bleeding of the product from treated timber in stockyard and storage areas. Rain water may also wash the soluble components directly from the surface of treated timber and into the soil (Henningsson 1983). Localized, but severe, contamination of soils is often encountered on the grounds of older (often abandoned) wood-preserving or town-gas facilities (Davis et al. 1993; EPA 1987b).

There is also a potential for release of creosote to soil from hazardous waste sites. Creosote has been detected in soil samples collected at 33 of the 59 NPL sites and in sediment samples collected at 6 of the 59 NPL sites where creosote has been identified in some medium (HazDat 2000).

According to TR197 (2000), an estimated total of 27,930 pounds of creosote, amounting to 2.6% of the total environmental release, was discharged to land from manufacturing and processing facilities in the

United States in 1997. The TRI data (Table 5-l) should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No sources of wood creosote releases to soil have been reported.

5.3 ENVIRONMENTAL FATE

As with other chemical mixtures, the fate and transport processes affecting creosote can be extremely complex. Creosote components may partition to the air, water, soil, or biota depending on their physical and chemical properties. Compounds initially released to the atmosphere may undergo atmospheric deposition and reach surface water directly or through runoff carrying soil-bound compounds (Stangroom et al. 1998). For coal tar creosote materials encountered in old production facilities or waste disposal sites, materials contained in the top several feet of soil will have become “weathered,” with virtually all the phenolic and heterocyclic fractions having volatilized, oxidized, or biodegraded (von Burg and Stout 1992). The lighter fractions of the PAH materials will also have degraded. The remaining weathered creosote will show limited ability to move off-site. Johnston et al. (1993) studied the PAH composition of coal-tar-containing samples collected at a number of coal gasworks sites in Australia. Most of these sites were abandoned nearly a century ago. The samples were taken from areas where the coal tar components would have undergone environmental modification to varying degrees since deposition, They concluded that aqueous partitioning and volatilization are probably the main processes that control environmental modification of coal tar at gasworks sites.

Newly produced creosote, or materials from a spill or a more recent disposal site, may pose more serious toxicity concerns. A complicating factor in interpreting the available literature is that creosote alone may not by the only source of toxicity. Especially at NPL or other waste disposal sites, such chemicals as pentachlorophenol (PCP) or heavy metals may be involved. Without an extensive battery of chemical analyses, perhaps combined with bioassay tests, making even semi-quantitative judgements on toxicity issues can be problematic. Much of the remedial work conducted under the Superfund program has simply aimed to reduce the volume of wastes at NPL sites with creosote contamination. A large percentage reduction by total weight does not always translate into a corresponding reduction in toxicity (Brooks et al. 1998; Hyiityainen and Oikari 1999b; Mueller et al. 1991).

5.3.1 Transport and Partitioning

Coal tar creosote constituents released to surface waters will differentially partition to the water column or to sediments depending on their water solubility and sorptive properties. For example, PAHs, the major constituents of creosote, generally tend to sorb strongly to soil and sediment particulates, and often have low aqueous solubilities and mobility (Hickock et al. 1982). Many components in the PAH fraction, particularly the higher molecular weight (HMW) PAHs, will remain in a virtually stationary tar-like mass at the place where they were deposited. Nitrogenous bases present in creosote waste water (e.g., aniline, toluidines, and xylidines) are relatively soluble, mobile, and persistent in groundwater (Pereira et al. 1983). However, behavior at a given site is also dependent on site-specific characteristics. For example, PAHs, phenol, and heterocyclic components of creosote wood treatment process wastes were found to migrate en masse in groundwater through a contaminated sand and gravel aquifer in Pensacola, Florida; sorption of these different classes of organic constituents in the low organic carbon (<0. 1%) aquifer materials was not important (Pereira and Rostad 1986). In an investigation of coal-tar contaminated surface sediments, PAHs were observed to have moved 400 meters in groundwater from buried subsurface coal tar; persistence of the PAHs, naphthalene in particular, was partially attributed to anoxic conditions (Madsen et al. 1993, 1996). Additionally, sediment-bound creosote components may be released over time. In a laboratory study of creosote-contaminated sediment and natural lake water, Hyotyainen and Oikari (1999b) found that creosote-derived 4- to 6-ring PAHs released from the sediment during incubation were toxic to water fleas (*Daphnia magna*) and to the photoluminescent bacteria *Vibrio fischeri*.

In an investigation of the partitioning of PAHs from coal tar wastes at manufactured gas plant sites into groundwater, partitioning of the various fractions of the complex mixture was observed to be inversely related to solubility, with the more soluble compounds partitioning to water more readily (Lee et al. 1992). Although coal tar is a complex mixture of compounds with varying physical and chemical properties, data analyzed with regard to a partitioning model indicated that ideal behavior was observed for the individual compounds and that the model was useful in estimating concentrations in groundwater.

In an investigation of the extent of creosote contamination at four wood-preservative plants with process water surface impoundments, unspecified creosote components were found to have moved 20-60 feet vertically from the impoundments to the water table and up to 500 feet horizontally from the sources (Ball 1987).

In a 50-day microcosm study of the aquifer materials of the Libby, Montana, Superfund site, 59% of radiolabeled phenanthrene was bound to the soil, while only 2.2% was volatilized (Mohammed et al. 1998).

In a terrestrial microcosm study, 2.7% of radiolabeled phenanthrene and 4.3% of radiolabeled acenaphthene were found in soil samples taken in a lo-cm zone around creosote-treated posts, whereas concentrations of the compounds that remained in the posts were 95 and 93.5% of the amounts applied, respectively, after 2.5 months (Gile et al. 1982).

In an investigation of the release of creosote from treated wood into fresh water and sea water, naphthalene, phenanthrene, acenaphthene, dibenzofuran, fluorene, and 2-methylnaphthalene were found to be the major components that migrated into water (Ingram et al. 1982). The rate of migration was found to increase significantly with increasing temperature within the range of 20-40 ºC; slower migration occurred from aged than from freshly treated pilings. In a microcosm study of the leaching of PAHs from cresote-impregnated pilings into aquatic environments, the aqueous concentration of PAHs increased with the number of pilings used (Bestari et al. 1998). These authors calculated a rate loss of creosote from the wood pilings into the water of approximately 50 $\mu g/cm^2$/day (273 mg/piling/day). Creosote was observed to be removed from the water rapidly after 7 days, and was close to background concentrations (0.8-6.7 µg/L) by 84 days; losses were attributed to photolysis and microbial degradation, while sorption to sediment was not significant.

In an investigation of the volatilization of PAHs from creosote-treated wood, desorption of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene was directly related to concentration and was greater at 30 ºC than at 4 ºC (Gevao and Jones 1998). The authors reported desorption half-lives of 0.7-31 years at 4 ºC and 0.3-l year at 30 ºC for fluoranthene and acenaphthene, respectively. It is also possible to have volatilization from surface soil to the atmosphere. Coal tar constituents have Henry's law constant ranging from 0.11 to $8.65x10^{-8}$ atm m^3/mo1e and vapor pressures of $1.2x10^{-8}$ to 95 mmHg (Swann et al. 1983), indicating that some newly leached compounds may rapidly volatilize from both moist and dry soil before binding to soil can occur.

Limited uptake of some creosote constituents has been detected in plants exposed to creosote-treated wood in nearby soil. Only 0.04% of applied acenaphthene and 0.1% of phenanthrene partitioned to plant tissue in one study (Gile et al. 1982). While systemic uptake may be minimal, such coal tar creosote

components as PAHs can adsorb to plant roots or surfaces. This seems a common way that vegetables or other produce for human consumption can pick up trace amounts of creosote materials (ATSDR 1995).

Animals such as voles, crickets, snails, pill bugs, and worms have exhibited the capacity to assimilate radiolabeled creosote components in terrestrial microcosm studies. Creosote components were found to accumulate to the greatest extent in the vole, with bioconcentration factors (BCFs) of 12-31. The ^{14}C mass balance content of the animals was 1.2% of applied acenaphthene and 0.8% of applied phenanthrene versus 4.3 and 2.7%, respectively, in soils (Gile et al. 1982). In addition, mussels taken from creosote-treated pilings have been found to contain significantly more benzo[a]pyrene, a creosote constituent, than those growing elsewhere (Dunn and Stich 1976). Accumulation of creosote-derived PAHs has been reported in benthic organisms in Pensacola Bay (Elder and Dresler 1988; Rostad and Pereira 1987). Fluoranthene, pyrene, benzo[a]pyrene, anthracene, chrysene, and phenanthrene were detected in higher concentrations in tissues of snails *(Thais haemastoma)* and oysters *(Crassostrea virginica)* taken from offshore sites near an onshore wood-treatment plant compared with those from control sites. Experimental and estimated log K_{ow} values for many of the main constituents of coal tar are 1.22-5.22 (HSDB 2000; Meylan and Howard 1995). Based on these values, BCFs of 5-5,500 have been estimated and are consistent with reported experimental BCFs of 2-9,200 for fish and aquatic organisms, indicating that bioaccumulation may be important in the fate of some components of coal tar (Kobayashi et al. 1979; Linder et al. 1985).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Little information was found in the available literature concerning the transformation of wood or coal tar creosote components in the atmosphere. Some volatile coal tar constituents may undergo oxidation by vapor phase reaction with photochemically produced hydroxyl radicals, with calculated half-lives of 2 hours to 10 days based on experimental and estimated rate constants of $1.12\text{-}103 \times 10^{12}$ cm/molecules-second at 25 ºC and using an average atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3 (Atkinson 1989; Meylan and Howard 1993). Rates may be slowed since some components will exist as particulate matter in the atmosphere (Eisenreich et al. 1981). Additionally, some components of coal tar may undergo nighttime reactions with nitrate radicals (Atkinson et al. 1987). Based on an experimental rate constant of 3.8×10^{-12} cm/molecules-second for phenol, and an atmospheric nitrate radical

concentration of $2x10^8$ molecules/cm^3, a half-life of 15 minutes can be calculated for the compound (Atkinson 1989).

Among the more volatile constituents of creosote are the cresols in its phenolic fraction. These materials comprise only about 1% of the creosote by weight, but it is the cresol components that give creosote its distinctive odor and its resin-like properties. The more generally recognized source categories related to coal tar production or products containing creosote include coal tar distillation facilities or coke ovens, but another source may come from chemical transformation in the air around urban centers (Grosjean 1991).

The air of many urban areas shows appreciable levels of volatile organic compounds (VOCs) such as toluene. A major source is often nonstationary sources such as automobiles since toluene is an octane booster in nonleaded gasolines. Toluene can react with hydroxyl radicals to form the same types of cresols found in the phenols portion of creosote. Although other reaction pathways can lead to the rapid degradation of these cresols, appreciable transient build-ups of cresol vapors are possible. Degradation products include a variety of nitrocresols, aliphatic carbonyls, and ketoacids. These degradation products can become part of other atmospheric reactions in the air of typical urban areas. These transient cresol concentrations could amount to l0-13% of the toluene levels. This cresol source is worth further study in urban areas showing exceptionally high levels of VOCs in the ambient air (Grosjean 1991).

5.3.2.2 Water

Coal tar constituents present in surface waters may be degraded by direct and indirect photolysis. Estimated aqueous photolysis half-lives of 8.4, 71, and 21 hours have been reported for phenanthrene, naphthalene and fluoranthene, respectively (Zepp and Schlotzhauer 1979). Other coal tar constituents which may undergo aqueous photolysis are acenaphthalene, anthracene, benzene, quinoline, phenol, cresol, and carbazide. In a microcosm study, PAHs leached from creosote-impregnated wood pilings were degraded in aquatic environments by photolysis and microbial degradation, while sorption to sediment was not significant (Bestari et al. 1998). Photolysis in water is not expected to be a major route of the environmental fate of creosote constituents, particularly for the less soluble compounds.
Coal tar creosote components are degraded in aquatic environments mainly by microfaunal metabolism (Borthwick and Patrick 1982; Ingram et al. 1982). Microorganisms may act on the creosote-treated wood itself or on creosote components that have leached from the treated wood. Quinoline, the major tar base

in creosote, has been reported to be degraded in surface water and groundwater by bacteria of the genus Pseudomonas (Bennett et al. 1985). Biotransformation of the phenolic components of creosote apparently also occurs under anaerobic conditions in contaminated groundwater (Ehrlich et al. 1983; Goerlitz et al. 1985). Adaptation of soil microorganisms to PAH contaminants in groundwater originating from creosote treatment plant wastes has also been reported (Wilson et al. 1986).

Work on NPL sites has helped identify numerous bacteria and fungi that can biodegrade creosote materials. In addition to *Pseudomonas*, bacteria in the genus *Alcaligenes* can degrade phenolic compounds under aerobic conditions (Mueller et al. 1989). So long as the groundwater is not completely anoxic, numerous soil microorganisms can degrade creosote materials. Work at NPL sites suggests that up to 90% of the creosote degradation is associated with biologically mediated processes. Although this can lead to an appreciable reduction in the quantity of the creosote materials, it is the phenolic and lower molecular weight (LMW) PAHs that are degraded while the HMW PAHs that have been shown to resist biological attack may persist. In a study of biodegradation of creosote-contaminated groundwater from the American Creosote Superfund Site, Mueller et al. (1991) observed a toxic and teratogenic response of inland silverside (*Merida beryllina*) embryos to the biotreated water at both 10 and 100% concentrations. They attributed the response to the cumulative effects of carcinogenic HMW PAHs that remained after 14 days of incubation. The higher levels of biodegradation observed for the LMW PAHs was attributed to their greater aqueous solubility and consequent greater bioavailability.

Much less is known about biodegradation processes under more anoxic conditions, which would be typical of groundwater and vadose zone waters. Work on town-gas sites in Europe has demonstrated that where nitrate levels are high, or where nitrate is supplied to groundwater, various facultative bacteria can degrade coal tar components using the nitrate or nitrite as an electron acceptor (Flyvbjerg et al. 1993). In general, however, biodegradation under anoxic conditions appears to proceed very slowly. Even when supplied with ample quantities of such electron acceptors as nitrates, half-lives in excess of 20 days were observed in laboratory microcosms for the anoxic biodegradation of dimethylphenol components in creosote, and cresol components showed little indication of significant disappearance unless the experiments were continued in excess of 90 days (Arvin and Flyvbjerg 1992).

Creosote components have been detected in surface water samples taken near a wood-treatment facility that ceased operation 30 years earlier (Black 1982). The creosote, which appeared to have permeated the sandy surface soils down to an impervious clay layer, was entering the river via seepages and springs. Weathering processes produced only minor constitutive changes in the creosote with relative losses of the

lower molecular weight components. These changes probably reflected the greater volatility and solubilities of the 2-3 carbon ring PAHs.

5.3.2.3 Sediment and Soil

Coal tar creosote components are slowly released from treated wood products by oil exudation, rain water leaching, and by volatilization of the lighter fractions (Henningsson 1983). USDA (1980) reported that the major components of creosote were not detected in soil samples taken to a depth of 6 inches within 2-24 inches from treated poles, presumably as a result of biotransformation of mobilized components by soil microorganisms. Creosote components released to soils in waste water effluents have been found to be biotransformed by soil microbes under aerobic conditions (Middleton 1984). Bacteria of the genus *Pseudomonas* isolated from a creosote-contaminated waste site have been reported to degrade creosote-derived quinoline (Bennett et al. 1985). Acclimation to creosote phenolic constituents by soil microorganisms has also been demonstrated (Smith et al. 1985).

Where the coal tar creosote is in well-oxygenated conditions, lignin degrading fungi like the white rot fungus *Phanerochaete sordida* can remove much of the PAH fraction (Davis et al. 1993). This fungus can also biodegrade PCP, which has often become mixed with the wastes found at creosote production or disposal sites.

Many of the same bacteria and fungi capable of biodegrading creosote components in aqueous systems can be found in soils. Especially where the creosote is close to the surface and under aerobic conditions, the vast majority of the phenolics can be consumed in less than a year (von Burg and Stout 1992). The majority of the lighter fractions of the PAH components (from 53 to 75% by weight) can be biodegraded within 2 months (there was no significant depletion of heavier fractions with 5-ring or higher PAHs) (Davis et al. 1993).

While biodegradation of PAHs in soil may be enhanced using bioremediation procedures, not all techniques are equally effective at reducing toxicity. In a study of PAH-contaminated soil from the Reilly Tar Superfund Site in St. Louis Park, Minnesota, although total EPA priority pollutant PAH concentrations were decreased 48-74% following treatment with one of four bioremediation technologies, following two of the four techniques, toxic (mutagenic) compounds were still present (Brooks et al. 1998). None of the four techniques tested was successful at removing the 5- and 6-ring HMW PAHs.

However, persistence of the PAHs, naphthalene in particular, has been observed in seep sediments where groundwater contaminated from buried subsurface coal tar emerged at the base of a hill; persistence of the LMW PAH naphthalene was attributed mainly to anoxic conditions (Madsen et al. 1993, 1996).

For sediments, much of the literature involves biologically oriented tests to identify hotspots with pronounced degrees of toxicity to aquatic and marine species. For instance, bioassays using benthic amphipods and highly creosote-contaminated sediments from Eagle Harbor in Washington's Puget Sound showed several toxic hotspots with acute toxicity to the infaunal marine amphipod *Rhepoxynius abronius* (Swartz et al. 1989). The authors suggest similar causal factors may underlie the common pattern of hepatic lesions and neoplasms observed in English sole from Eagle Harbor. As with bioremediation, natural attenuation of creosote-contaminated sediment may continue to present risks to aquatic organisms as sediment-bound creosote constituents may be released over time. In a laboratory study using contaminated sediment and natural lake water, Hyiityainen and Oikari (1999b) found that creosote-derived 4- to 6-ring PAHs released from the sediment during incubation were toxic to water fleas *(D. magna*) and to the photoluminescent bacteria *V. fischeri*.

Work at coal tar creosote-contaminated sites on the Elizabeth River in Virginia, indicates a strong positive correlation between exposure to the creosote-contaminated sediments and the incidence of hepatic neoplasms on a resident forage fish, the mummichog (*Fundulus heteroclitus*) (Vogelbein et al. 1990). Similar cancer epizootics in fishes are found at other major harbor sites (e.g., the lower Hudson River, Boston Harbor, and Los Angeles harbor) showing creosote or PAH-laden sediments. Such findings have been proposed (Vogelbein et al. 1990) as indicators of serious toxic concerns in coastal and estuarine environments that may have human health implications if bioaccumulation can be documented.

5.3.2.4 Other Media

Very little information was found in the available literature on the transformation or degradation of coal tar creosote or wood creosote in animals or plants. Eisler (1987) found that many aquatic organisms are able to rapidly metabolize and eliminate PAHs, the major constituents of the commercial mixture.

Transport and transformation of creosote in the environment may affect the coal tar creosote constituents in treated wood. The USDA reported that the relative levels of 18 major creosote residues in treated marine pilings did not change following 9.5 years of service; of the originally applied creosote, 93% was

retained on the wood (HSDB 2000). Both creosote and total PAHs decreased during the in-service period.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to creosote depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on creosote levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

No information was found in the available literature regarding ambient atmospheric concentrations of wood or coal tar creosote-derived components (i.e., PAHs) in the United States (HSDB 2000). Workplace air concentration data are discussed in Section 5.5. Data on ambient atmospheric concentrations of PAHs derived from other sources can be found in the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995).

5.4.2 Water

No information was found in the available literature regarding ambient water concentrations of wood or coal tar creosote-derived components (i.e., PAHs) in the United States (HSDB 2000). However, in a microcosm study, Bestari et al. (1998) reported that measured background concentrations of 16 monitored creosote-derived PAHs in the microcosm water ranged from nondetectable to 1.5 µg/L which was comparable to background estimates for a variety of natural water sources.

Results from 2 years of groundwater sampling at an abandoned wood treatment facility in Conroe, Texas, where coal tar creosote had been used for about 20 years, showed that monitoring wells were contaminated with levels of up to 3,490 µg/L naphthalene, 1,263 µg/L methylnaphthalene, 425 µg/L dibenzofuran, and 302 µg/L fluorene. The contaminants had apparently migrated through the clay and sand soils on the site from three waste pits. A plume of groundwater contamination by organics at trace levels was found to extend up to 300 feet from the waste pit locations (Bedient et al. 1984).

At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), creosote-derived naphthalene, acenaphthene, fluorene, pyrene, and phenanthrene were measured in groundwater at levels ranging from nondetectable to 10^5 ppb (ATSDR 1994). Surface water at the site had no detectable levels of the acid and base/neutral compounds which were monitored.

5.4.3 Sediment and Soil

PAH contamination of soil has been found at the site of a wood-preservation facility that operated in Slidell, Louisiana, from 1892 to 1970, when a fire destroyed the plant facilities. It is believed that environmental releases of creosote occurred throughout the plant's operating history and as the result of the 1970 fire, when creosote was released from storage tanks and flowed over the ground and into adjacent water bodies. Waste creosote and debris have accumulated in eight areas at the site. The deposits are up to 2 feet thick and have contaminated underlying soils (based on visual inspection) to as much as 1 foot below the surface. PAH concentrations show a rapid decrease with increasing depth, ranging from 15,680 mg/kg (ppm) at the surface to 1 mg/kg (ppm) within 9 feet. PAH concentrations as high as 2,488 mg/kg also have been measured in the soils matrix of the shallow aquifer (Acharya and Ives 1994).

Several PAH constituents of creosote were detected in soil samples taken at an abandoned wood treatment facility in Conroe, Texas, at depths of up to 25 feet. Maximum concentrations of the compounds were detected in samples collected at the 0.7-l .8-foot depth. Maximum concentration levels were 3.7 mg/kg for naphthalene, 3.4 mg/kg for methylnaphthalene, 3.8 mg/kg for dibenzofuran, 4.2 mg/kg for fluorene, and 2.2 mg/kg for anthracene. An investigation of vertical variations in contaminant concentrations in the soil zone above the water table revealed that, in general, >90% of the organics were removed within the first 5 feet at the location studied. Organics can be degraded by microbes, adsorbed onto soil, or altered by interactions with soil humus (Bedient et al. 1984).

At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), creosote-derived pyrene, fluoranthene, phenanthrene, and anthracene (base/neutral compounds) were measured in surface and subsurface soils at levels ranging from nondetectable to 1,000 ppm (ATSDR 1994).

In sediment samples from a creek adjacent to the Koppers Company, Inc. NPL site, creosote-derived base/neutral compounds were detected at concentrations up to 100 ppm; one creosote-derived base/neutral compound was detected in downstream sediment at a maximum of 1 ppm (ATSDR 1994). Creosote-derived base/neutral compounds were also detected in the sediment of the drainage ditch at the site, at levels ranging from l-100 ppm.

Coal tar creosote-derived phenanthrene, 1,2-benzanthracene, and benzo[a]pyrene have been detected in river sediments at concentrations of up to 231, 62, and 16 mg/kg (wet basis), respectively, directly downstream from the site of a former wood treatment facility. At 4,000 meters from the source, these levels decreased to 0.35, 1.02, and 0.40 mg/kg (wet basis), respectively (Black 1982). Creosote-derived PAHs were also detected in the sediments of Pensacola Bay and a drainage stream in the vicinity of a former wood treatment facility near Pensacola, Florida. PAH concentrations ranged from 200 µg/g for naphthalene to 140 mg/kg for anthracene in stream sediments; concentrations in Pensacola Bay ranged from 75 µg/kg for benzanthracene to 190 µg/kg for fluoranthene (Elder and Dresler 1988).

PAH concentrations have been determined in sediment cores collected from the Arthur Kill, Hackensack River, and Passaic River in northern New Jersey. These rivers are in industrialized areas near former creosote wood-preserving facilities that operated through the 1960s and 1970s. Temporal distributions were determined in each core based on the activities of the radionuclides ^{210}Pb and ^{137}Cs. Sediments at depths corresponding to the years 1978 and 1964 contained total PAHs at concentrations of 1.71 mg/kg (ppm) for 1978, and not detected to 35.7 mg/kg for 1964 (Huntley et al. 1993). In a study of Eagle Harbor, an estuarine bay of the Puget Sound in which sediments were contaminated with creosote from a wood treatment facility, total PAHs were detected at concentrations as high as 6,461 mg/kg (Swartz et al. 1989).

In the vertical profile of sediments in a seep area at the base of a hill where PAHs emerged after being transported approximately 400 meters in groundwater from a buried subsurface coal tar source, naphthalene was detected at 2-45 ppm (Madsen et al. 1996).

5.4.4 Other Environmental Media

Since wood and coal tar creosotes are complex mixtures, techniques for relating apparent bioaccumulation or biomagnification in food chains to human health concerns are not well defined. Fish or shellfish directly exposed to coal tar creosote wastes will be tainted by offensive odors and tastes. Extracts of shellfish taken from the wharf of the biological station in St. Andrews and from Passamaquoddy Bay (both in New Brunswick, Canada) indicated contamination with creosote oil (Zitko 1975). Concentrations of creosote oil found were as follows:

Shellfish	Location	Concentration µg/g lipid
mussel	Biological Station	1,046
periwinkle	Biological Station	3,254
	Passamaquoddy Bay	459
whelk	Biological Station	354
	Passamaquoddy Bay	202
clam	Passamaquoddy Bay	459

The biological station's wharf had been periodically repaired using lumber treated with coal tar creosote; no other sources of coal tar creosote in the vicinity of the Passamaquoddy Bay sampling site were known. The author suggested that the differences in creosote oil concentration in periwinkles and whelks collected in the same localities may indicate that PAHs are not bioaccumulated. However, in an estuarine environment near a Pensacola, Florida, creosote-contaminated wood-preservation facility site, a native mollusc *(T. haemstoma)* and a nonnative mollusc *(C. virginica)* both exhibited bioaccumulation of fluorene, pyrene, and phenanthrene at up to 10 times greater than observed in controls (Elder and Dresler 1988). Lobsters maintained in commercial tidal compounds that were constructed with creosote-treated wood were found to contain high levels of several creosote constituents (EPA 1980). In the edible lobster meat, benzo[a]pyrene was present at up to 281 ng/g (ppb), chrysene was present at up to 303 ng/g, benzo[a]anthracene was present at up to 222 mg/g (ppm), benzo(b)fluoranthene was present at up to 261 ng/g, dibenzo(a,h)anthracene was present at up to 153 ng/g, and indeno(1,2,3-cd)pyrene was present at up to 137 ng/g.

Additionally, a study at a creosote spill near Lake Pontchartrain in Louisiana, provided some indications that biomagnification through food chains leading to humans can take place. This study documented the bioaccumulation of creosote-derived PAH fractions in the marsh clam *Rungia cuneata* (DeLeon et al. 1988). With total PAH levels in the ambient water ≤25 ppb, caged clams introduced to an area near a

major creosote spill showed tissue concentrations of benzopyrenes up to 600 ppb after 4 weeks of exposure. This clam is a major food item for crustaceans such as the blue crab that are part of commercial fisheries in the Lake Pontchartrain area.

Creosote-treated wood such as marine pilings may be left in the environment for many years. The USDA reported that residual creosote in marine pilings after 25, 40, and 59 years of service ranged from 280 to 380 kg/m^3 (HSDB 2000).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Potential sources of non-occupational human exposure to creosote include contact with creosote-treated wood products (e.g., railroad ties used for landscaping), incineration of creosote-treated scrap lumber, and contact with contaminated environmental media at hazardous waste sites (e.g., ingestion of contaminated groundwater). At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), a study by the Texas Department of Health found an increased incidence of skin rashes in residents who had dermal contact with soil at the site (ATSDR 1994).

Risk of exposure to creosote constituents through contact with contaminated groundwater will vary with the individual chemicals involved as well as with the mix of chemicals present at any one time and the environmental conditions. Physical and chemical properties of the compounds, including solubility and molecular weight, will affect distance which a contaminant plume may travel from the source, as well as its susceptibility to biodegradation or sorption (King and Barker 1999). The environment in which contamination occurs is also of importance since natural attenuation of chemical compounds may be dependent on whether oxidizing or reducing conditions are present. In an investigation of natural attenuation of contaminant plumes from an emplaced coal tar creosote source, King et al. (1999) observed greater and more rapid decreases in plume mass for some compounds, such as phenol, *m*-xylene, and carbazole, while the dibenzofuran plume mass and extent remained relatively constant, and the plume mass and travel distance from the source for naphthalene and I-methylnaphthalene increased throughout the 4-year study. Therefore, potential for exposure to creosote constituents present in groundwater will differ from location to location and over time.

Direct exposure of homeowners to wood treatment products containing creosote should be limited, since EPA has restricted the sale and use of such products to certified applicators. Industrial sources have noted

that there have been no reports or instances of health effects allegations in the last 20 years (ending in 1996), except for rare reports of skin irritation resulting from public contact with creosote-treated wood.

Another potential source of nonoccupational exposure is the therapeutic use of coal tar shampoos for anti-dandruff therapy, coal tar ointments for treatment of eczematous dermatitis, and mineral coal tar for the treatment of psoriasis. Adsorption of PAHs may occur through the skin, lungs, and gastrointestinal tract (Strickland et al. 1996). van Schooten et al. (1994) measured the urinary excretion of a specific PAH metabolite, 1-hydroxypyrene, to assess the internal dose of PAH after acute dermal application of coal tar shampoo. The shampoo selected for the experiment had a PAH concentration of 2,840 mg/kg, including pyrene (285 mg/kg) and benzopyrene (56 mg/kg). In other brands, the concentrations were at least 100 times lower. A single use of the coal tar shampoo resulted in increased 1-hydroxypyrene excretion in all participants. The mean increase of totally excreted 1-hydroxypyrene on day 1 was 10 times the pre-experiment background values. On day 2, the mean increase was 5 times. Interindividual variation was considerable, with a variation in the first day increase of between 3 and 20 times. The 1-hydroxypyrene values observed in coke oven workers are similar to the values obtained on day 1 after a single treatment with coal tar shampoo (0.4-8.3 μmol/mol creatinine) (van Schooten et al. 1994). However, exposure levels determined using the 1-hydroxypyrene biomarker may be affected by the time of measurement following exposure (Viau and Viskočil 1995). Viau and Viskočil observed maximum excretions of 1-hydroxypyrene in urine a few hours after exposure to pyrene in a coal tar-based shampoo or following dermal contact with either creosote or pyrene.

Occupational exposure to PAHs and other constituents of creosote may occur in several industries where workers are exposed to coal tar creosote, coal tar, coal tar pitch volatiles, or products containing creosote. Such occupations include jobs in the wood preserving industry, railroad work (installation and removal of crossties), treated lumber installation work involving structures such as fences or bridges, electric utility work involving treated poles, coke oven work, jobs in the rubber industry or tire plants, road paving work, roofing work, chimney cleaning, aluminum smelting work, iron foundry work, steel plant work, and site remediation work involving creosote-contaminated environmental media.

Individuals working in the wood-preserving industry comprise the largest portion of the population potentially exposed to coal tar creosote. Workers employed at creosote pressure-treatment facilities may be exposed by direct dermal contact or by inhalation of volatilized components. Potential exposure to coal tar creosote in these plants is minimized by the use of closed systems for receiving, transferring, mixing, storing, and applying the mixture to wood products. Similarly, dermal exposure from the

handling of freshly treated wood is minimized by the use of highly mechanized processes. Exposure via inhalation, however, is more likely to occur. For example, worker exposure may be significant during opening of treatment cylinder doors and cylinder cleaning operations (EPA 1981b). Inhalation and dermal exposure are also more likely in plants using nonpressure treatment methods such as thermal and dip treatments in open tanks. An estimated 100 workers were involved in commercial thermal and dip treatment operations in the late 1970s. Some of these workers experienced consistently high inhalation exposures (USDA 1980). Other historical nonpressure treatment exposures included an estimated 50,000 individuals (e.g., homeowners, farmers, landscapers) who applied creosote in noncommercial brush, dip, spray, and soak treatments (EPA 1981a). Dermal contact and inhalation may have resulted in exposure to high concentrations of creosote components for these individuals, but the exposures were usually of intermittent frequency (USDA 1980). However, designation of creosote products as restricted use pesticides by EPA in 1986 has probably decreased the number of individuals potentially exposed in these nonpressure wood treatment applications (EPA 1986b).

In 1996, there were 25,000 workers employed in 75-100 domestic wood treatment plants using coal tar creosote. As a result of the use of engineering controls and personal protective equipment (e.g., respiratory protection and impervious gloves) required in the 1986 settlement of the EPA Special Review process,[2] airborne exposures to creosote components in the workplace are generally below the OSHA permissible exposure limit (PEL) of 0.2 mg benzene soluble particulates per m^3 air (Rivers 1990).

However, prior to the consistent use of these controls by industry, workers were potentially exposed to higher airborne concentrations of creosote constituents. For example, the concentrations of creosote (i.e., coal tar pitch volatiles) components in 3- to 8-hour personal air samples, taken over a 2-day period at a railroad tie treatment facility in Somerville, Texas, were found to range from 0.003 to 1.211 mg/m^3 (NIOSH 1980b). Another industrial hygiene survey of worker exposure to creosote at a wood-treatment facility in Tacoma, Washington, showed coal tar pitch volatiles in personal air samples ranging from <0.0004 to 0.112 mg/m^3 (NIOSH 198 lb). The higher concentrations were found at the end of the treatment process when the cylinder was opened. NIOSH investigated creosote exposure among dock builders in Brooklyn, New York, in 1980. Employees were reported to have substantial direct skin

[2]A Special Review of a currently registered pesticide may be initiated by EPA when validated data indicate that certain types of toxicity (e.g., carcinogenicity, developmental toxicity, acute effects) exist for humans or for non-target plant or animal species. A formal process exists for notifying registrants and other interested parties, requesting further data regarding the pesticide in question, analyzing and reporting risks and benefits, and requesting public review. The final regulatory decision may be implemented over a period of time or it may be imposed immediately as an emergency action based solely on the EPA's finding of immediate danger to human health or the environment.

contact with creosote. Breathing zone concentrations of the cyclohexane extractable fraction of the coal tar pitch volatiles ranged from 0 to 0.059 mg/m^3 of air (NIOSH 1981a). Comprehensive studies of worker exposure to creosote in wood treatment plants have been conducted by Koppers Company, alone and in conjunction with NIOSH (Markel et al. 1977; SRI 1993). Data from these studies indicated that, on the average, employee exposure to particulate polycyclic organic materials (PPOM) was within the permissible level of 0.2 mg/m^3 recommended by NIOSH for coal tar pitch volatiles. The only components that could be reliably measured in the vapor-phase fractions collected were naphthalene, methylnaphthalene, and acenaphthene. The concentrations of these chemicals ranged from 0.54 to 2.0 mg/m^3. Fluorene and phenanthrene-anthracene were detected in trace quantities, but were not quantifiable. Benzene-soluble particulates (PPOM) ranged from 0.02 to 0.10 mg/m^3. The World Health Organization reported that air concentrations of creosote-derived PAHs were 0.05-650 µg/m^3 at a wood treatment plant where railway sleepers were treated with creosote; the main creosote constituents detected were naphthalene, fluorene, and phenanthrene (HSDB 2000). At a second plant, where a coal tar solution was used to treat railway sleepers and telephone poles, PAHs were detected in the air at 0.004-l1 mg/m^3 (HSDB 2000).

A gravimetric analytical method has been used in most of these workplace monitoring studies. This method involves the collection of airborne particulates on glass fiber filters and subsequent extraction by solvents, such as benzene or cyclohexane. The extracted fraction of the particulate matter is determined by weighing. As a result of two significant shortcomings of this method, the inability to identify constituents of the airborne particulates and to sample vapor phase components, EPA (1981a) concluded that definitive information was not available on the identity of airborne components of creosote in workplace atmospheres. EPA (1981a) also stated that quantitative estimates of dermal exposures were not available for treatment plant workers. Quantitative inhalation or dermal exposure data for workers applying creosote in nonpressure treatment scenarios and for downstream workers who install, handle, or contact treated wood products were also unavailable. An industrial hygiene survey of wood treatment facilities conducted in Finland revealed that vapor phase components were an important source of worker exposure. Vapors were collected on XAD-2 resin (recovery 82-102%) and analyzed by gas chromatography (GC). PAHs were collected on glass fiber filters and analyzed with high-pressure liquid chromatography (HPLC) using a fluorescence detector. Most of the airborne contaminants in worker breathing zones were in the vapor phase, with naphthalene the main component, averaging 52% of the total concentration; the proportion of particulate PAHs to total concentration of vapors was <0.5-3.7%. The major components in the vapors have acute toxicity potential but are not as tumorigenic or mutagenic as the less volatile PAHs (Heikkila et al. 1987). A recent study by Becker et al. (1999) demonstrated the

feasibility of quantifying thiaarenes (sulfur-containing polycyclic aromatic hydrocarbons). Using GC with atomic emission detection, these authors measured thiaarene concentrations of 0.4-19.0 μg/m^3 in the personal air space of workers at an aluminum reduction plant who were exposed to coal tar pitch volatiles.

Exposure to coal tar creosote may also occur during installation of treated poles, during inspection and maintenance operations, and through casual contact (USDA 1980). One of the major end point uses of creosote is treatment of railroad cross ties. Since cross ties are installed mechanically by railroad companies, workers generally have minimal dermal exposure in this process. Exposure via inhalation, however, is considered to be moderate and consistent during this type of installation procedure. In other situations, cross ties may be installed manually, in which case, there is consistent moderate to high exposure via skin contact as well as by inhalation. The amount of exposure via skin contact ranges from low to high depending on whether workers wear protective clothing. Skin contact is considered minimal for railroad personnel who inspect ties in use, as well as for the general public who may have casual contact with creosote-treated cross ties. In instances where crossties are used for landscaping purposes, contractors involved in the sale and installation of freshly treated ties experience consistent moderate inhalation exposure and minimal to occasionally high dermal exposure.

Installation of treated lumber and timbers in structures such as bridges, piers, retaining walls, fences, and barns involves a significant amount of manual contact. Likewise, the installation of switch ties, cross planks, crossarms, block flooring, and fence posts is usually done manually. In these situations, human exposure via inhalation is considered moderate while exposure via skin contact may vary from minimal to high depending on the type of protective equipment used (USDA 1980).

Exposure of individuals installing treated fence posts, lumber and timbers via inhalation of creosote volatiles (e.g., acenaphthene and naphthalene) can also occur when freshly treated materials are handled under calm, hot, sunny conditions (USDA 1980). Exposure may be even greater during warmer months when ambient temperatures are higher. Acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene were observed to undergo more volatilization from creosote-treated wood at 30 ºC than at 4 ºC (Gevao and Jones 1998).

The risk of direct dermal contact is particularly high for workers installing treated poles. Activities such as attaching fittings often preclude the use of protective gloves, and as a result of creosote bleeding from the treated poles, the potential for dermal contact of workers performing maintenance operations persists for years after installation (Henningsson 1983).

Individuals employed in industries that manufacture and process creosote or products containing creosote may be exposed to the highest concentrations of this compound. The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 241 workers employed at 3 facilities were potentially exposed to creosote in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

Rubber processing workers at a tire plant in Poland who were occupationally exposed to coal tar pitch volatiles were found to have been exposed to excessive (>0.2 mg/m^3) levels of PAHs, including benzo[a]pyrene (Rogaczewska and Ligocka 1994). Measurements of benzo[a]pyrene were generally in the range of <4-142 ng/m^3, but were as high as 3,470-6,060 ng/m^3 for workers who weighed the raw materials.

In an investigation of the effect of decreased dermal exposure to creosote on the internal dose of PAHs in workers at a creosote wood impregnation plant, the use of Tyvek coveralls worn beneath outer work-clothes decreased the internal dose of pyrene (Van Rooij et al. 1993b). Workers not wearing the overalls had total pyrene skin contamination of 47-15 10 µg/day and had urinary levels of 1-hydroxypyrene of 6.6 µg. For dermally protected workers, dermal pyrene contamination was approximately 35% less than that of the unprotected workers and urinary levels of 1-hydroxypyrene were 3.2 µg. The low level of efficacy was attributed to uncovered skin areas (face, wrists, ankles). Volatile pyrene in the breathingzone air was measured at 0.3-3.0 $µg/m^3$. The authors determined that for creosote workers, the level of dermal exposure to PAHs is the main determinant of the internal exposure dose; 15 times more pyrene was absorbed through dermal uptake than through respiratory uptake. Data from earlier studies indicate that the daily skin contamination with pyrene was higher for creosote workers (median of 350 µg) compared with that measured for coke oven workers (70 µg) and road pavers (117 µg); for aluminum workers, a pyrene level of 395 µg was measured (Van Rooij et al. 1993b).

Previously, the only information on biological indicators of exposure to coal tar found in the available literature involved a study of 1-hydroxypyrene in the urine of a creosote wood-treatment plant worker (Jongeneelen et al. 1985). The pyrene metabolite, 1-hydroxypyrene, is now more commonly used as a biological indicator to assess total PAH exposure in several industries as well as for nonoccupational uses of coal-tar based products (Malkin et al. 1996; Strickland et al. 1996). Elovaara et al. (1995) studied inhalation and dermal exposure to naphthalene and 10 large PAHs in creosote impregnation plant workers. Air concentrations of the compounds were measured and compared with measurements of

urinary 1-hydroxypyrene. Urinary concentrations, due to high dermal exposures were high (16-120 µmol/mol creatine) even in the morning, were lower in postshift measurements (19-85 µmol/mol creatine) and then were highest in the evening (27-122 µmol/mol creatine), indicating that time of sampling is important. The authors concluded that the biomarker was useful in determining exposure to 3- to 6-ring PAHs, but not to naphthalene volatiles.

Jongeneelen (1992) related urinary concentrations of 1-hydroxypyrene for coke oven workers exposed to fumes containing PAHs to measured levels of coal tar pitch volatiles in order to equate the biological indicator data with lung cancer relative risk levels determined using epidemiological data obtained from U.S. and European coke plants. A urinary concentration of 2.3 µmol/mol creatine was equated with the threshold limit value (TLV) (ACGIH) of 0.2 mg/m^3 for coal tar pitch volatiles, and consequently with the relative risk for lung cancer of approximately 1.3 for a group of exposed workers. Although an empirical relationship between the biomarker 1-hydroxypyrene and relative cancer risk in an exposed group may be determined, because creosote constituents vary from source to source, and because the carcinogenic PAH fraction and the routes of exposure will also vary, the health risks related to exposure to coal tar creosote versus coal tar pitch volatiles versus coal tar will differ between exposed groups such as creosote and coke oven workers (Viau et al. 1995). Viau et al. (1995) did conclude, however, that PAHs from background environmental contamination and from smoking could be excluded from consideration of urinary excretion of 1-hydroxypyrene within a certain group of workers.

Coal-handling workers at a coke oven who were exposed to coal-tar sludge (67% coal tar) through dermal contact had increased urinary 1-hydroxypyrene concentrations following work shifts (Malkin et al. 1996). Urinary concentrations of the biomarker increased from a preshift mean of 1.00 µmol/mol creatine to a postshift level of 1.7 µmol/mol creatine. The increases were attributed to dermal exposure, as exposure to volatile pyrene was determined to be minimal.

A review paper of studies using the concentration in urine of 1-hydroxypyrene as a biomarker of PAH exposure included levels reported in various studies (Strickland et al. 1996). The respective pre- and postshift urinary excretion levels of 1-hydroxypyrene for coke oven workers were 0.89 and 2.47 µmol/mol creatine; for asphalt pavers, respective levels were 1.35 and 1.76 µmol/mol creatine.

Other biomarkers used to determine exposure to the creosote include urinary concentrations of 1-naphthol, 2-naphthol, and 1-pyrenol. Naphthalene is the main volatile present in creosote vapors. For workers exposed to creosote volatiles during tar distillation, Bieniek (1997) measured volatile

concentrations of 0.77 mg/m^3 for naphthalene, 0.016 mg/m^3 for 1-naphthol, and 0.012 mg/m^3 for 2-naphthol; corresponding urinary concentrations of 693.1 and 264.4 µmol/mol creatine were measured for l- and 2-naphthol, respectively.

For workers exposed to creosote by chiseling coal tar pitch layer or by handling creosote-impregnated wood, exposure to total PAHs and 4- to 6-ring PAHs was 50 times higher for the worker exposed to the coal tar pitch layer while exposure to volatile naphthalene was >6 times higher for the wood handlers (Heikkilä et al. 1995). Total PAHs and 4- to 6-ring PAHs were measured at 440 and 290 µg/m^3, respectively, in the work area of the chiseler. Urinary concentrations of 1-pyrenol were 24 times higher for the chiseler compared with the wood handlers: Volatile naphthalene was measured at 1,000 µg/m^3 in the work area of the wood handlers and 160 µg/m^3 in the work area of the chiseler. Urinary concentrations of 1-naphthol were 15-20 times higher for the wood handlers as compared with the chiseler.

Workers in a creosote railroad tie impregnation plant exposed to 1.5 mg/m^3 naphthalene, 5.9 µg/m^3 particulate PAH, and 1.4 µg/m^3 4- to 6-ring PAHs were measured for the urinary biomarker 1-naphthol (Heikkilä et al. 1997). Postshift urinary concentrations were a mean of 20.5 µmol/L; urinary concentrations in occupationally nonexposed male smokers were below the detection limit of 0.07 µmol/L. The authors concluded that 1-naphthol was a good biomarker for determining exposure to volatile naphthalene from creosote, but was not a good indicator of inhalation or dermal exposure to PAHs from creosote.

Polycyclic aromatic hydrocarbons are capable of forming adducts with DNA in cells. Exposure to PAHs from creosote were measured in the personal work areas of coke oven workers in the Czech Republic (Lewtas et al. 1997). Measured levels of DNA adducts in white blood cells of a nonoccupationally exposed population were well correlated with the low to moderate environmental exposures. The DNA adducts of the coke oven workers who were exposed to carcinogenic PAHs at levels of <5->200,000 ng/m^3 (<0.005->200 µg/m^3) did not correlate well with the exposure levels. These authors concluded that various mechanisms were responsible for the lower DNA-binding potency at the higher exposure levels, precluding the use of a linear model for dose-response extrapolation in risk assessment.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 2.7 Children's Susceptibility.

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

Children are exposed to creosote via the same routes that adults are, including inhalation of contaminated air, ingestion of groundwater used as a source of drinking water, and dermal contact with contaminated soil or products treated with coal tar creosote. Additionally, small children are more likely than adults to be in close contact with yard dirt or playground dirt, lawns, and indoor (carpet) dust. Creosote residues bound to soil or dust particles in carpets or on bare floors may present an exposure route for infants and toddlers through dermal contact and oral ingestion. Children are known to participate in frequent hand-to-mouth activity and to have a tendency to put foreign objects into their mouths. As a result of this behavior, children may ingest creosote present in soil and dust or through direct transfer of the chemical from their skin to their mouths. Children are lower to the ground than adults and something which may exist at arm or hand level for an adult may be at mouth level for a child. Because of behavior such as putting their mouths on objects or chewing on objects, children may be exposed to coal tar creosote through oral ingestion of the chemical through chewing on treated wood, such as fences, bridge, or pier railings. Adsorption of PAHs may occur through the skin, lungs, and gastrointestinal tract. However, exposure to certain levels of creosote constituents does not mean that the compounds will be bioavailable at those levels. No U.S. data were found on exposure or body burden measurements made on children.

Coal tar creosote is widely used for the preservation and water-proofing of wood which is used for utility poles, railroad ties, log homes, fence posts, barns, bridges, piers, and marine pilings. Creosote is also used in roofing and road paving; is used and/or produced in coke oven operations, and in the aluminum, iron, and steel industries; and is used therapeutically in coal-tar based shampoos, as a treatment for

psoriasis and eczema, and as a treatment for intestinal ailments. Prior to its designation as a Restricted Use Pesticide in 1986, it was available for home and farm use.

Children are likely to play in or near areas where adults would be less likely to venture, such as areas with no trespassing signs, in creeks, on the ground, in the dirt, in ditches near where utility poles are present, and on or near railroad tracks. Additionally, children are likely to collect and bring home found pieces of wood for use in building clubhouses or treehouses. Because coal tar creosote is used to preserve utility poles and railroad ties, playing near utility (telephone or electrical) poles and near or on railroad tracks may pose a risk of exposure to children. Children are subject to inhalation exposure, which may be of increased risk during warmer months when volatilization of PAHs may be higher. Gevao and Jones (1998) observed greater volatilization of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene from creosote-treated wood at 30 ºC than at 4 ºC. However, if the creosote constituents have leached downward from the treated wood and are present in the soil surrounding the utility poles or railroad tracks, volatilization from the soil surface is not as likely, as the majority of the coal tar creosote would be bound to the soil particles. In that case, and in the case of direct contact with treated poles or railroad ties, children are more likely to be exposed dermally and through oral ingestion which may occur when they put unwashed hands in their mouths. No U.S. data were found documenting significant exposure to children through such means as ingested soil or dust particles.

Children may be exposed to coal tar creosote when playing near abandoned hazardous waste sites or if their parents are occupationally exposed to creosote-contaminated soil through involvement with site remediation or clean-up procedures and bring soil-bound contamination into the home on work clothes or footwear, despite preventative procedures which may be in place at the work site. Creosote constituents have been measured in the surface soil at levels as high as 15,680 ppm (PAHs) at the site of an old wood preservation facility in Slidell, Louisiana, that was destroyed by fire (Acharya and Ives 1994). At an abandoned wood treatment facility in Conroe, Texas, PAH constituents of creosote have been detected in the 0.7- to l.8-foot soil depth at maximum concentrations of 3.7 ppm for naphthalene, 3.4 ppm for methylnaphthalene, 3.8 ppm for dibenzofuran, 4.2 ppm for fluorene, and 2.2 ppm for anthracene (Bendient et al. 1984). At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), creosote-derived pyrene, fluoranthene, phenanthrene, and anthracene (base/neutral compounds) were measured in surface and subsurface soils at levels ranging from nondetectable to 1,000 ppm (ATSDR 1994).

Although biodegradation of creosote in soil, on treated wood, in waste water effluent, and in aquatic environments has been observed, the process may only serve to reduce the total amount of creosote present. While the phenolic and LMW PAHs are degraded, the HMW PAHs that have been shown to resist biological attack may persist. Thus, it is possible that children exposed to the creosote constituents remaining in soil or other media following some biodegradation may be exposed to the more toxic components of creosote. However, the presence of creosote components in soil does not mean that the soil-bound compounds will be bioavailable if ingested. In a study of PAHs and their metabolites in the blood, feces, and urine of rats, the authors observed that rats that were orally exposed to contaminated soils showed significantly higher excretion of unchanged 1-OH-pyrene and benzo[a]pyrene in feces, and significantly lower excretion of 1–OH-pyrene in both feces and urine, than did rats that were dosed with the pure compounds, indicating that the ingested soil-bound compounds were less available in the body for metabolism (van Schooten et al. 1997). Similar results were observed in a study of mice that ingested soil-bound coal tar (Koganti et al. 1998). In that study, the bioavailability of PAHs from soil-bound coal tar was estimated to be 9-75% less (based on 1-OH-pyrene excreted in urine) than that observed in mice dosed with an organic extract of the soil; estimates of PAH bioavailability based on chemical-DNA adduct formation ranged from nondetectable to 76%. Other authors have observed differences in bioavailability of soil-bound creosote constituents between types of soil. Goon et al. (1991) observed higher oral bioavailability of soil-bound benzo[a]pyrene with sand soil versus clay soil. The clay fraction of soil is more chemically and physically reactive than the sand fraction, allowing for greater adsorption. In the same study, the authors also observed, however, that the oral bioavailability of the compounds in soil remained at a similar level for the first 30 days following contamination, but decreased by 6 months following the initial contamination.

Children may be exposed to creosote constituents brought into the home by parents or other household members who are occupationally exposed. Creosote residues may be present on clothing items and shoes of workers employed in industries where creosote-derived products are used or produced, and utility company workers who are in contact with treated wood. Exposure to children may occur through dermal contact with contaminated items. Because children are likely to be in close contact with carpet or floors, transfer of contaminated dirt from work shoes to carpeting provides a means of exposure. Respiratory exposure from contact with occupationally exposed workers is not likely to be significant.

A potential source of exposure in infants is the presence of creosote constituents in breast milk. The hydrocarbons found in coal tar creosote are lipophilic substances and, as such, may potentially be found in breast milk, although this has not been assessed. No data were found in the available literature on the

presence of creosote constituents in breast milk. It has been determined that creosote-derived PAHs may cross the placenta (ATSDR 1993a). For more information on the health effects of PAHs, the reader is referred to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (ATSDR 1995).

Data were not available in the literature on the weight-adjusted intake of creosote by children. In one documented case, creosote fumes caused methemoglobinemia in an infant, leading to temporary hypoxia and cyanosis (Dean et al. 1992).

Data were not available in the literature on the dietary exposure of creosote to children. Based on the bioaccumulation of creosote constituents in fish and other aquatic organisms, and the potential for uptake or contamination in plant food sources, dietary exposure is theoretically possible, but is unlikely to be significant. An exception to this may be in residential areas such as that built on the old Koppers Company, Inc. site. Homegrown produce grown in contaminated soils may provide a significant source of exposure to children. The drinking of chaparral tea may result in oral exposure to wood creosote. Case reports of people who have drunk chapparal tea indicate kidney damage as a likely outcome (Gordon et al. 1995).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals living in the vicinity of hazardous waste sites and abandoned wood-treatment plants contaminated with coal tar creosote may experience higher levels of exposure than the rest of the general population. These environmental exposures generally are at a lower dose but of longer duration than the occupational exposures.

Individuals who apply coal tar creosote directly to wood, including farmers, carpenters, and homeowners who come in contact with creosote-treated wood products, are believed to be exposed to the highest levels of creosote components via inhalation and dermal contact. It has been estimated that historically about 4,000 workers may have been routinely exposed and up to 50,000 people may have been intermittently exposed to coal tar creosote through its application as a preservative to wood products (USDA 1980). The size of this population may have decreased since EPA restricted the use of creosote to certified applicators.

Other individuals who are potentially exposed to coal tar creosote, coal tar, coal tar pitch volatiles, or products containing creosote include coke oven workers, rubber industry or tire plant workers, road

paving workers, roofers, chimney cleaners, aluminum smelting workers, iron foundry workers, steel plant workers, and site remediation workers who are involved with creosote-contaminated soils or water. Whether from bioaccumulation or from direct exposure, fish and shellfish may accumulate creosote constituents at concentrations high enough to prompt public health officials to issue consumption advisories. As of September 1994, creosote was involved in the two fish consumption advisories listed below (EPA 1995):

State	Waterbody	Geographic Extent
Louisiana	Bayou Bonfouca	7 miles
Oregon	Willamette River	1,000 foot radius from McCormack and Baxter wood treatment site

5.8 ADEQUACY OF THE DATABASE

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

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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. Limited physical property data, such as boiling point and density (see Table 3-2), are available for the coal tar creosote mixture. Additional physical and chemical property data, such as water solubility, vapor pressure, K_{oc}, and Henry's law constant values would be useful in order to predict the partitioning and transformation of coal tar creosote components in air, water,

and soil. These values are currently not available because their determination is complicated by the fact that creosote is a mixture of variable composition. However, data on vapor pressure, water solubility, etc., are available for individual components of creosote, and these can be used to estimate the behavior of creosote.

Production, Import/Export, Use, Release, and Disposal. Manufacturing methods are well described in the literature. Production figures are limited because of the confidential nature of this business information. Uses of creosote, both coal tar and beechwood, are well described. Since the use of coal tar creosote as a wood preservative has been restricted, the potential of the population to be exposed is greatly diminished. The major releases of creosote resulting from treatment processes at wood-preserving plants are known, but the levels are not well quantified. Current production, release, and disposal information would assist in identifying the levels of creosote present in the environment and, thus, populations potentially exposed as a result of these processes. Creosote sludge from production processes can be treated and disposed on-site with proper groundwater monitoring. Creosote can no longer be disposed in hazardous waste landfills unless treated to EPA specified standards. Creosote-treated wood used in industrial applications can be burned in an industrial incinerator or boiler; however, treated wood used in domestic or farm applications should be buried rather than incinerated.

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1997, became available in 1999. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The limited information available regarding transport and partitioning of creosote components among environmental compartments indicates mobility of water soluble PAHs, phenol, and heterocyclic constituents of the mixture in water; sorption of PAH components in soils; and bioconcentration of creosote-derived PAHs by terrestrial and aquatic organisms. In an examination of the partitioning of coal tar-derived PAHs into groundwater and the usefulness of a computer model to simulate such, Lee et al. (1992) found that theoretically “ideal” behavior was observed for the individual compounds and that the model was useful in estimating concentrations in groundwater. This finding indicates that, although coal tar is a complex mixture of compounds with varying physical and chemical properties, the fate of the individual compounds may be modeled as if they were present as single contaminants. Additional studies on the behavior of the transport of the individual components of

creosote when present as a mixture may be necessary. Biotransformation appears to be the most important degradation process in soils and aquatic environments. Additional data on the transport of volatile creosote components in the atmosphere and the partitioning of creosote released to surface waters and soils would be useful. Quantitative data on the rates of biotransformation in soils, surface water, and groundwater under aerobic and anaerobic conditions would also be useful. Data on the degradation rates or relative persistence of the HMW PAHs would be particularly useful since these components of creosote are among the more toxic fraction, and are less soluble and less readily degraded than the LMW PAHs. The importance of other transformation processes, such as photolysis, photooxidation, and hydrolysis, in relation to biotransformation and rates of transport between media, should also be defined. These data would be useful to help define potential pathways of human exposure and to estimate ambient concentrations of creosote components in environmental media.

Bioavailability from Environmental Media. Very limited information was found in the available literature regarding the uptake of creosote components by living organisms from contaminated water and soil at hazardous waste sites. Studies have been done with persistent constituents (e.g., PAHs) which show that plant uptake from soils is limited, whereas bioconcentration in aquatic organisms from contaminated surface waters has been demonstrated. Data from human and animal studies indicate that creosote components are absorbed following ingestion or inhalation, or after dermal contact with the mixture. Additional data on the bioavailability of creosote components following ingestion or inhalation of creosote-contaminated soils would be helpful. Of particular importance are data on the bioavailability of the HMW PAHs that may persist in soil and are resistant to many bioremediation techniques.

Food Chain Bioaccumulation. Very limited information was found in the available literature regarding the biomagnification of creosote-derived compounds among food chain trophic levels. Many aquatic organisms are able to rapidly metabolize and eliminate PAHs, the major constituents of the commercial mixture (Eisler 1987). However, the marsh clam *Rungia cuneata*, which is a major food item for crustaceans such as the bluecrab that are part of commercial fisheries, showed tissue concentrations of benzopyrenes up to 600 ppb after 4 weeks of exposure to creosote after a major spill; total PAH levels in the ambient water were ≤25 ppb (DeLeon et al. 1988). Additional studies are needed to determine whether this bioaccumulation indeed moves up the trophic chain to pose human exposure concerns. Also, vegetables and other produce grown in or around deposits of creosote wastes may uptake or be contaminated by creosote constituents through adsorption to roots or surfaces. Since these materials will be hard to remove through washing or other food preparation processes, consumption of these may

provide a route for exposure. Additional data are needed on the ability of agricultural plants to uptake creosote constituents.

EPA (1993) has issued Fish Sampling and Analysis Guidance that provides an overview of the issues involved in considering fish consumption advisories for PAHs. Since PAHs may be derived from creosote or other sources such as the combustion of petroleum products, state-issued advisories for PAHs should also be examined to see if creosote-derived sources are at issue.

Exposure Levels in Environmental Media. Limited information is available regarding ambient concentrations of creosote-derived PAHs in soils and no data are available regarding atmospheric concentrations of creosote components. Very limited information is available on concentrations of component compounds in surface waters and sediments, including those receiving wood treatment plant effluents. Data are still lacking for contaminated media in the vicinity of hazardous waste sites. These data would be useful to estimate the exposure of populations coming into contact with components of the mixture through inhalation of contaminated air, consumption of contaminated surface water or groundwater, or direct dermal contact with environmental media.

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

Exposure Levels in Humans. A population exists that is potentially exposed to creosote through contact with contaminated media at hazardous waste sites and with treated wood products. A second potentially exposed workforce population exists at wood treatment facilities and in other industries in which creosote-derived products are produced or used. Currently, no information exists that demonstrates tissue levels of any components of the mixture in these populations. Although exposure is now estimated in occupationally exposed workers using urinary concentrations of biomarkers, such as 1-hydroxypyrene, actual exposure levels are harder to determine. Estimates of human exposure to creosote constituents, or body burdens of creosote components, are complicated by the lack of information on exposure to creosote constituents and levels of creosote-derived components in the environment. Collecting information on tissue levels of creosote components in humans would be necessary to examine the relationship between levels of creosote-derived compounds in the environment, human tissue levels, and subsequent

development of health effects. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Data on the exposure levels and body burden measurements of creosote constituents in children are needed to determine the risks associated with exposure. Because small children are likely to engage in hand-to-mouth activity (with unwashed hands) and to be in close contact with dirt, lawns, and indoor (carpet) dust, and because creosote residues bound to soil or dust particles in carpets or on bare floors, may present an exposure route for infants and toddlers through dermal contact and oral ingestion, bioavailability from soil data are necessary. Bioavailability data are also necessary to determine the amount of contaminant that children may be exposed to through dermal contact with treated wood, such as may occur when children play on railroad tracks. Data on the bioavailability of creosote constituents from treated wood are also necessary because through behaviors such as putting their mouths on objects or chewing on objects, children may be exposed to creosote through oral ingestion of the chemical through chewing on treated wood, such as fences, bridge, or pier railings.

Data are also necessary on whether children are different from adults in their weight-adjusted intake of creosote compounds. Creosote compounds may be present in dietary sources such as fish or food grown in or near contaminated soils. While data on the oral bioavailability of some soil-bound components of creosote are available, it is necessary to determine the exposure contribution of such sources to children and to determine the contribution to body burden in children.

Data are necessary on the number of children (<18 years of age) who may be occupationally exposed to creosote and on the levels of exposure they may experience. It is possible that some workers in industries such as tire plants or those involved in roofing or road paving may be exposed to creosote in their daily tasks. Information on this is may be important in assessing whether occupational exposure in children is similar to the levels observed for all occupationally exposed workers.

Child health data needs relating to susceptibility are discussed in 2.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for creosote were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance 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.

5.8.2 Ongoing Studies

A search of federally funded research in progress (FEDRIP 2000) revealed several studies that are discussed in this section. Creosote is currently subject to a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration standard and data call-in by EPA. In addition, the Creosote Council II is planning to conduct a research program that includes testing for worker exposure and protection.

Remedial investigation/feasibility studies being conducted at the 59 NPL sites where creosote has been found and at the numerous creosote-contaminated Resource Conservation and Recovery Act (RCRA) corrective action sites should provide data on concentrations of the mixture in contaminated media in the vicinity of hazardous waste sites. For example, creosote constituents have been found in surface water impoundments and soil samples taken near wood treatment facility sites in Colorado, Louisiana, Texas, and Montana.

The Cornell University Superfund Basic Research and Educational Pilot Program was recently (1992) established with the aim to conduct research on the bioavailability and impact of hazardous substances in health and ecological risk, specifically as related to exposure, neurological, and immunological effects; and the remediation of sites containing polychlorinated biphenyls (PCBs), PAHs, and heavy metals. Relevant areas of study include biodegradation of NAPL, kinetic controls on environmental fate in soil and aquifers, sequestration in soil and its effects on bioavailability, and microscale parameters modeling macroscale fate in soil. A current study concerns the determination of factors leading to the persistence of creosote-derived PAHs (naphthalene and phenanthrene) in fresh water sediments at a field site.

The USDA is sponsoring a study by researchers at Purdue University on the interaction of organic chemicals, including coal tar, with soils. Researchers are investigating and modeling the abiotic processes controlling the mobility and bioavailability of organic compounds in soil. They will be determining the adsorption of and release rates of PAHs from a coal tar/soil waste matrix.

The U.S. Geological Survey is investigating the fate and transport of immiscible contaminants, including coal tar and creosote wastes, in subsurface groundwater. Models will be developed to simulate and

predict the migration of slightly soluble, highly volatile immiscible contaminants in the field. These models will eventually aid in the design of control and abatement techniques.

Researchers at Brown University are conducting a study funded by OSTI to determine the vapor pressures and heats of vaporization of heavy, primary coal tars. The researchers are attempting to provide needed physical property data by means of direct measurements of the vapor pressures of coal tar fractions. They are also attempting to determine vapor pressures using well-established techniques and modifications of those techniques.

Data from field and laboratory studies of creosote-contaminated groundwater are being analyzed by the U.S. Geological Survey to determine the transformation pathways of selected organic compounds, assess the relative importance of physical, chemical, biochemical, and microbial processes in the transformation of these compounds under ambient conditions, and study relevant biotransformation processes occurring in the subsurface groundwater.

The U.S. Geological Survey is sponsoring a study to examine the interactions between the organic constituents of contaminants, including creosote, and to develop a modular, multiphase, and compositional model of volatile organic transport and biodegradation for variably saturated media (unsaturated zone and groundwater). The model will be applied to estimate rates of movement and biodegradation at selected field sites.

The National Science Foundation is sponsoring a study by Rutgers University researchers on the multisubstrate biodegradation kinetics of PAHs from creosote, coal tar, and diesel fuel. The relative biodegradabilities and substrate interactions of PAHs in sole and multi-substrate systems will be determined and related to dissolution kinetics processes governing bioavailability. An integrated mathematical model of the behavior of PAHs in NAPL-contaminated soils will be developed and validated.

The National Science Foundation is sponsoring a study of the biodegradation of coal tar-derived 4- and 5-ring PAHs. The re-use of treatment sites and the potential for groundwater contamination by leachate from treatment sites will be addressed. Treated residue and treatment leachate will both be tested for mutagenic properties to determine whether toxicity has also been decreased.

Researchers at Carnegie-Mellon University, in a study sponsored by Department of Energy, are investigating the physicochemical and biochemical solubilization and mineralization of coal tar-derived PAHs. The study will address the rate-controlling processes for microbial degradation of the PAHs in both the environment and in waste water treatment processes; the kinetics of solute solubilization and rates of mineralization will be determined. The possible synergistic interactions between PAH-degrading bacteria and biosurfactant/emulsifier-producing bacteria will also be investigated. The results of the research should be applicable to both remediation of coal-tar contaminated soils in the environment and treatment systems for coal conversion process effluents.

EPA is sponsoring a study to develop an in situ process that will enhance the rate and efficiency of the biodegradation of hydrophobic organic chemicals at military installations and Superfund sites. Research activities will focus on the identification of chemical or biological emulsifiers (surfactants) that will enhance the bioavailability of petrogenic waste (including creosote and coal tars), and thus enhance their biodegradation.

Researchers at Tienzyme, Inc. in State College, Pennsylvania, are investigating the use of surfactant- or surfactant/lipid-based formulations to enhance the removal of HMW PAHs from creosote- and tar-contaminated soils by bioremediation involving white-rot fungi.

The USDA is sponsoring several studies on creosote. Researchers at the University of Illinois are investigating the effects of accelerated aging on the rate of biodegradation of creosote-treated red oak ties by common oak decay fungi. The effects of natural weathering on the rate of biodegradation of creosote-treated ties selected from tracks located in the Midwest will be examined. Computer models will compare the rates of biodegradation results of naturally weathered ties and ties exposed to accelerated aging processes.

Researchers at Mississippi State University are conducting a study sponsored by the USDA to develop biological systems for bleaching pulp, to isolate and characterize the natural cultures of fungi and bacteria that are capable of modifying the structure of lignin, and to develop bioremediation systems that can be used to clean up contaminated groundwater and subsoil at wood-treatment sites.

Researchers at Mississippi State University are investigating the in situ bioremediation of creosote and PCP contaminated water in an attempt to develop a rapid biological technique for the cleanup of groundwater using oxygen, surfactants, cofactors, and micronutrients. Surfactants will be evaluated for

their abilities to enhance the bioremediation of wood-preserving process waste water containing high concentrations of PCP, PAHs, oil, and grease.

A study sponsored by the USDA is currently underway to acquire information on the biochemistry and physiology of xenobiotic degradation by wood-degrading fungi, to optimize the expression of fungal xenobiotic-degrading activity in contaminated media, and to develop technologies that are based on fungal xenobiotic-degrading abilities for remediation and/or treatment of contaminated media. A field treatability study to test the ability of three species of lignin-degrading fungi to deplete PCP and PAH components of creosote in contaminated soil is being conducted, as well as a field demonstration to assess the technical and economic feasibility of using lignin-degrading fungi to remediate soil contaminated with PCP and creosote.

Researchers at Louisiana State University are investigating the recycling of utility poles for use in engineered wood products. Creosote in the poles will be removed using organic extractants and steam, and the poles will be evaluated to determine their residual decay resistance and to determine the effect of residual creosote on the physical, mechanical, and gluing properties of the used utility poles. The study will include the reduction of the poles into smaller sized, defect-free wood materials for the production of engineered woods, as well as the determination of the effect of joint designs on the strength properties of the wood laminated composites made from the pieces of the poles.

Researchers at the University of Tasmania are currently assessing performance parameters of various types of solid fuel heaters and solid fuel burning appliances (heaters and stoves) when fueled with briquettes and briquette/wood mixes. Parameters being investigated include creosote formation and the effect of briquette use on creosote build-up in flues. Researchers are also comparing differences in the emissions of smoke and formation of creosote when softwoods and hardwoods are burned in wood heaters.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring creosote, its metabolites, and other biomarkers of exposure and effect to creosote. 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.

The analytical methods used to quantify creosote and related mixtures in biological and environmental samples are summarized below. As noted in Chapter 3, coal-derived mixtures (creosote, pitch, tar) are chemically very similar; the methods used for their analysis are directed to the primary components of these mixtures. In most cases uncovered through a search of the recent literature, the methods used for coal-derived mixtures are based on analysis of high-pressure liquid chromatography (HPLC) with ultraviolet (UV) absorbance detection to nondestructively separate these compounds for collection and characterization.

The high resolving power of capillary gas chromatography (GC) is required for the successful analysis of coal-derived materials, since these mixtures can contain hundreds of components with very similar chemical properties. Guillen et al. (1992) and Blanc0 et al. (1992) have demonstrated the full power of capillary GC using both mass spectrometry (MS) and flame ionization detection (FID) for analyzing coal tar. Specific applications for biological and environmental analyses are described below.

6.1 BIOLOGICAL SAMPLES

The levels of creosote in biological materials can be estimated by measuring the PAH content in biological samples. Methods include GC/FID, GC/MS and HPLC. Synchronous luminescence spectroscopy (SLS), ^{32}P-postlabeling, and immunoassay techniques, i.e., enzyme linked immunosorbent assays (ELISA) and ultrasensitive enzyme radio immunoassay (USERIA), are methods currently being developed to detect and quantify ultratrace levels of PAH adducts bound covalently to macromolecules

(e.g., DNA). Table 6-l lists the available analytical methods for determining creosote/coal tar-derived PAH components in biological samples. GC/MS and HPLC have been employed to detect creosote-derived PAH complexes at ppt (pg/g) levels in human tissues, including adipose tissue, blood, and urine (Liao et al. 1988; Obana et al. 1981). The detection and quantification of trace levels of PAHs in biological tissues involves extensive and rigorous clean-up procedures including Florisil, silica, and alumina column chromatography (Liao et al. 1988; Obana et al. 1981).

There is considerable evidence, both *in vitro* and *in vivo*, that PAHs are enzymatically converted to highly reactive metabolites that bind covalently to macromolecules such as DNA, thereby causing carcinogenesis and mutagenesis in mammalian systems. Thus, benzo[a]pyrene (a procarcinogenic PAH and the most thoroughly studied one) is converted by specific cellular enzymes to the syn- and anti-isomers of 7β, 8δ-dihydroxy-(9δ, 10δ)-epoxy-7,8,9,10-tetrahydro-benzo[a]pyrene (B[a]PDE) and binds covalently to DNA, resulting in formation of the putative B[a]PDE-DNA adduct (Autrup and Seremet 1986; Harris et al. 1985; Haugen et al. 1986; Santella et al. 1995).

In an analysis of B[a]P and coal tar pitch volatiles in workplace air conducted by Ny et al. (1993), these researchers analyzed urine samples for the PAH biomarker 1-hydroxypyrene, and observed a high correlation between biomarker levels and PAH air levels. Analyses were also conducted by HPLC with fluorescence detection. Tolos et al. (1990) reported results of 1-hydroxypyrene urinalysis for aluminum reduction plant workers, and showed a strong positive correlation between the compound and 17 environmental PAHs. This work verified the choice by earlier researchers (Jongeneelen et al. 1988) of the pyrene metabolite as a useful marker of exposure to PAHs. Elovaara et al. (1995) also demonstrated the usefulness of 1-hydroxypyrene as a biomarker for exposure to naphthalene and 10 other PAHs for creosote impregnation plant workers. Particulate PAHs were Soxhlet extracted with cyclohexane and analyzed by HPLC with fluorescence detection.

The ELISA technique has been employed for detecting antibodies in serum bound to B[a]PDE-DNA adducts. The USERIA method involves measuring the immunological response of B[a]PDE-DNA in the presence of rabbit anti-serum, alkaline phosphatase enzyme, and radiolabeled para nitrophenyl phosphate (PNPP). The radioactivity of the hydrolyzed tritiated PNPP is measured by a scintillation counter. Both ELISA and USERIA methods have been employed to detect PAH-DNA adducts at lo-l5 mol levels in the blood and tissues of humans occupationally exposed to PAH (Amin et al. 1982; Harris et al. 1985; Haugen et al. 1986; Newman et al. 1988; Perera et al. 1988). The ^{32}P-postlabeling method involves a 5'-labeling of DNA adducts that have been digested with nuclease P_1 enzyme system to

Table 6-1. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Biological Samples

Form	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Coal tar creosote, Coal tar	Adipose tissues	Benzene/hexane extraction of adipose tissue; addition of Na_2SO_4; cleanup with Florisil column; elution of PAHs with 8% benzene in hexane, sample concentration	GC/MS	5–50 ng/g	52–95 recovery	Liao et al. 1988
Coal tar creosote	Liver homo-gentate	Extraction of homogenate with ethyl acetate; water removal (Na_2SO_4), concentration.	HPLC	No data	No data	Amin et al. 1982
		Saponification of minced tissue, extraction with hexane; clean up by solvent partition, concentration; purification by silica/alumina chromatography; concentration of eluent.	HPLC	0.006–0.46 ng/g	No data	Obana et al. 1981
Coal tar creosote	Blood	Separation of white cells; isolation of DNA by standard Rnase and phenol treatment.	ELISA	$1x10^{-15}$ mol BPDE per µg DNA	No data	Perera et al. 1988
Coal tar creosote, Coal tar		Isolation of PAH-DNA adduct from white cells; digestion of adduct with radiolabeled (^{32}P)ATP; radiolabeled adduct resolution by TLC/	^{32}P-postlabeling	$0.3x10^{-15}$ mol BPDE per µg DNA	No data	Phillips et al. 1988
Coal tar creosote		Separation of lymphocyte cells and isolation of BPDE-DNA adduct by standard treatments.	ELISA or USERIA and SLS	$0.006–0.23x10^{-15}$ mol BPDE per µg DNA	No data	Harris et al. 1985

Table 6-1. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Biological Samples *(continued)*

Form	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Coal tar creosote	Urine	Animal dosing with radiolabeled B[a]P; collection of urine, addition of MeOH; c-18 Sep-Pak column cleanup; elution with aqueous MeOH.	HPLC	$5x10^{-12}$ mol 7-BPDE-Gua per µg of labeled B[a]P	No data	Autrup and Seremet 1986
Coal tar creosote, Coal tar pitch Coal tar		Hydrolysis of conjugates enzymatically; isolation of 1-pyrenol using SPE column.	HPLC/FI	0.45 nmol/L	No data	Tolos et al. 1990
Coal tar creosote, Coal tar pitch		Hydrolysis of conjugates enzymatically; isolation of 1-pyrenol using SPE column	HPLC/FI	10 nmol/L	84–88	Ny et al. 1993

BPDE = benzo[a]pyrene diol epoxide; B[a]P = benzo[a]pyrene; DMSO = dimethyl sulfoxide; ELISA = enzyme linked immunosorbent assay; FI = fluorescence; Gua = guanine; GC/MS = gas chromatography/mass spectrometry; HPLC = high-performance liquid chromatography; $NADP^+$ = oxidized nicotinamide adenosine dinucleotide; SLS = synchronous luminescence spectroscopy; SPE = solid phase extraction; USERIA = ultra-sensitive enzyme radioimmunoassay

3'-mononucleotides. Adducts present in the digest that were resistant to nuclease P_1 were thus labeled with ^{32}P, while unmodified nucleotides were not. The digested DNA adducts are separated by thin-layer chromatography (TLC) and quantified by scintillation counting. A detection limit of $0.3x10^{-15}$ mol of PAH adduct per μg of DNA (less than one adduct in 10^7 nucleotides) has been achieved (Philips et al. 1988).

6.2 ENVIRONMENTAL SAMPLES

As with biological samples, the PAH component fraction is most often used as an indicator of creosote contamination of environmental media. For example, screening for total PAHs is often used at hazardous waste sites when creosote contamination is suspected. The PAH fraction (neutral) is used in these analyses because it is more persistent than the acidic or basic fractions, which tend to be more mobile and biodegradable. The methods used to measure total PAHs can also be used to detect the nitrogen, oxygen, and sulfur heterocyclic components of the mixture. Table 6-2 lists the available analytical methods for determining creosote/coal tar-derived PAH components in environmental samples.

The efficacy of supercritical fluid extraction was demonstrated to be a promising technique for coal tar pitch (Camel et al. 1993). Extraction procedures for coal tar pitch volatiles on air sampling filters have been compared by Hekmat et al. (1994). Methylene chloride was shown to be superior as an extracting solvent to cyclohexane. For coal tar pitch volatiles collected on poly(tetrafluoroethylene) filters or glass fiber filters and extracted with benzene, cyclohexane, or dichloromethane, Hekmat et al. (1994) found that the highest recoveries were achieved with collection on poly(tetrafluoroethylene) filters, desorption with dichloromethane, and analysis using spectrophotometry (UV quantitation). Cyclohexane was not found to be a suitable substitute for benzene. These authors also concluded that spectrophotometric methods were superior to gravimetric methods of measurement of coal tar pitch volatiles.

Hale and Aneiro (1997) reviewed recent progress made in improving analytical techniques for determining components of creosote in environmental media. The multiple extraction and purification steps required prior to chromatographic analysis is problematic in that compounds may be lost through volatilization or transformed through photodegradation. More efficient extraction procedures include supercritical fluid extraction, accelerated solvent, and microwave, and solid-phase extraction. Newer methods also include on-line purification and coupling of extraction and chromatography. These authors found that MS use has increased, especially since ion traps and mass selective detectors have become more available. Other increasingly common methods are HPLC with fluorescence and diode array UV;

Table 6-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Wooden sleepers (railroad crossties) in playground	Extraction of sample with ether; filtration through anhydrous sodium sulfate and evaporation of solvent; acid/base/neutral liquid-liquid partition	GC/MS	1–3 ng/sample	No data	Rotard and Mailahn 1987
Coal tar creosote	Dissolution of sample in cyclohexane and extraction with 90% ethanol; evaporation of extract to dryness; dissolution of residue in cyclohexane, extraction with nitromethane; evaporation of extract to dryness and dissolution of residue with small amount of benzene	GC	10 ppm	No data	Lijinsky et al. 1963
	Dissolution of sample in methylene chloride at a concentration of ≈10% (w/w).	GC	No data	No data	Nestler 1974a
River sediments	Digestion of wet sediment sample in boiling EtOH/KOH; extraction of hydrocarbons into cyclohexane; extract concentration and Florisil column cleanup; elution of PAH complex with 50% methylene chloride/hexane; concentration of sample.	HPLC	No data	No data	Black 1982
Contaminated groundwater	Filtration through prebaked glass-fiber filters to remove suspended sediments; cleanup with bonded-phase extraction column; elution of organics from column with acetonitrile followed by methylene chloride; water removal (Na_2SO_4); concentration by nitrogen blow-down.	GC/MS	50 µg/L	95 recovery	Rostad et al. 1984

Table 6-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater	pH to 12. Extraction with CH_2Cl_2. Drying and concentration of organic phase (containing neutral and bases). Adjustment of aqueous phase pH to 7 and extraction; then to pH 2 and extraction. Both extracts derivatized to TMS esters/ethers.	GC/FID	100 ppb	>90% for PAHs; ≈30–50% for phenols; ≈>70% for bases	Mueller et al. 1991
Impregnated wood (workplace)	Heating of sample at 60 °C in a chamber; cleanup with XAD-2 column; extraction with ether.	GC/MS	0.07 to 0.11 µg/L using ITMS (α, β, and sulfate)	116–128	Heikkilä et al. 1987
	Collection of heated sample on a prewashed (cyclohexane) glass fiber filter; extraction of sample with cyclohexane and evaporation to dryness; dissolution of residue in acetonitrile/water (85/15)	HPLC	8 ng/m^3	No data	
Creosote treated wood	Heating of sample in injection port of GC	GC	No data	No data	Lorenz and Gjovik 1972
Gas and particulate matter (workplace)	Pumping sample through a glass fiber filter-XAD-2 adsorbent sampling system; extraction with ether in ultrasonic bath; concentration of extract and dilution with acetonitrile	HPLC	0.005–2.5 mg/m^3	87–102 recovery	Andersson et al. 1983
Breathing zone air (workplace)	Pumping air through Teflon filters and sorbent tubes. Extraction of particulate and tubes with benzene. Concentration of extracts	GC	0.05 mg/sample	No data	Tolos et al. 1990
Breathing zone air (workplace)	No information	HPLC/FI	No data	No data	Rogaczewska and Ligocka 1991
Breathing zone air (workplace)	Pumping air through filters and XAD resin. Extraction of both with benzene. Concentration.	HPLC/UV-FI	No data	No data	Ny et al. 1993

Table 6-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Creosote	Dissolution in cyclohexane; washing with H_2SO_4; neutralization of acid fraction and extraction with cyclo-hexane; alumina column cleanup.	HPLC/UV or GC/MS	No data	No data	Galceran et al. 1994
Water and sediment	Extraction (Soxhlet for sediment only) of PAHs with methylene chloride	HPLC/spectro-fluorometric detection	No data	Water - 74.4 ± 7.8% to 103 ± 1.1%; Sediment - 71.3 ±2.9% to 105 ±3.1%	Bestari et al. 1998
Creosote-treated wood	Soxhlet extraction of PAHs with dichloromethane; concentration of extracts and cleanup on silica column eluted with hexane; drying with anhydrous sodium sulfate; extraction in series with hexane, hexane:DCM (60:40); elution with hexane:DCM (60:40)	GC/FID	No data	HMW PAHs - 104 ± 0.9% LMW PAHs - 84 ± 5%	Gevao and Jones 1998
Sediment pore water and elutriate	Drying with anhydrous sodium sulfate; Soxhlet extraction with acetone:hexane (59:41); concentration of extract; cleanup on silica column eluted in series with hexane and dichloromethane; concentration and redissolution in hexane	GC/FID	2–5 ng/g	No data	Hyötyläinen and Oikari 1999b
Coal tar pitch volatiles on glass filters	Soxhlet extraction with dichloromethane; cleanup on silica columns eluted with cyclohexane; concentration; HPLC separation using backflush	GC/S-selective AED	4 ng/m^3	Cleanup recoveries were estimated at 97-100%	Becker et al. 1999

FI = fluorescence; GC = gas chromatography; HPLC = high-performance liquid chromatography; MS = mass spectrometry; PAH = polycyclic aromatic hydrocarbon; UV = ultraviolet; FID = flame ionization detection; AED = atomic emission detection

and C-, S-, and N-selective GC detectors. The use of HPLC with fluorescence detection allows for a lower limit of detection for some PAHs than does GC/FID.

GC/FID or GC/MS are the most widely employed analytical techniques for the determination of coal-derived PAHs in contaminated groundwater, railroad cross ties, and impregnated wood (Gevao and Jones 1998; Heikkilä et al. 1987; King and Barker 1999; Lijinski et al. 1963; Lorenz and Gjovik 1972; Nestler 1974a; Rostad et al. 1984; Rotard and Mailahn 1987). GC/FID is one of the methods recommended by EPA for detection of PAHs in waste water and solid waste (EPA 1986c). GC/FID was utilized by Bieniek (1997) to determine the breathing-zone air concentration of naphthalene in a coking plant. Hyötyäinen and Oikari (1999b) utilized GC/FID to determine PAHs in sediment pore water and elutriates.

Heikkilä et al. (1987; 1997), employed GC/MS to determine creosote levels in workplace air from impregnated wood. Detection limits of $10x10^{-6}$ to $50x10^{-6}$ g of creosote per m^3 of sample and recoveries of 82 and 102% were achieved. Heikkilä and co-workers measured the components of PAHs with reverse-phase HPLC using fluorescence detection. A similar study was conducted by Heikkilä et al. (1995) for a worker exposed to coal tar pitch. For the detection of creosote vapors, naphthalene was used as an indicator since it constitutes about 18% by weight of total PAHs in creosote (Andersson et al. 1983; Heikkilä et al. 1987). Rotard and Mailahn (1987) used a modified sample extraction procedure to identify various components of creosote extracts in railroad cross ties. The procedure involved the separation of compounds by functional group using acid, base, and neutral conditions. Detected compounds included phenanthrene, anthracene, and naphthalene (neutral extractions), quinoline, and isoquinoline (basic extraction), cresols, and phenols (acidic extraction). Mohammed et al. (1998) used GC/MS to determine creosote-derived PAHs in aquifer materials. Recent literature has shown that GC with (sulfur selective) atomic emission detection (CG/AED) is successful in determining the thiaarene fraction of total PAHs in the atmosphere without prior separation of the thiaarenes from the PAHs (Becker et al. 1999).

Grimmer et al. (1997) developed a technique using GC/MS for simultaneously determining 25 urinary metabolites as a measure for exposure to individual PAHs. Samples are treated enzymatically with glucuronidase and arylsulfatase and extracted with benzene or toluene; the extract is then divided and one part is treated with diazomethane to convert phenols into methylethers and the other part is used to convert dihydrodiols into phenols. Following further purification, individual metabolites are determined using GC/MS. The detection limit for various compounds is approximately 0.01 ng. Inter-individual variation was significant. These authors determined that the correlation between inhaled PAHs to their urinary metabolites will vary with the individual, but appeared to be linear for an individual.

Rostad et al. (1984) developed a method for the isolation and detection of creosote in contaminated groundwater. This method involved passage of the sample through a small column containing a solid-bonded phase sorbent, which retained the organic compounds. The authors indicated that this method is simple, faster, and cheaper to perform than the acid/base/neutral extraction procedure. It effectively isolated all organic compounds from contaminated groundwater regardless of polarity, functional group, or water solubility in one step, thereby minimizing hazardous exposure to sample.

A study on the spatial and temporal distribution of PAHs from various sources (wood-preserving facilities, refineries, chemical manufacturers, etc.) was reported by Huntley et al. (1995). The concentrations of PAHs were shown to increase with sediment depth from analysis of core samples. Samples were analyzed using EPA Method 8310 (GC/MS).

HPLC with fluorescence detection has been used to identify coal-derived PAHs in river sediments (Black 1982). Andersson et al. (1983) employed an Amberlite XAD-2 adsorbent for isolating organic compounds from gas and particulate matter in a creosote impregnating plant. Good sample recoveries and detection limits were achieved. HPLC, with either fluorescence or UV detection, is an EPA-recommended method for the analysis of both solid and liquid hazardous waste (EPA 1986c). At present, HPLC cannot achieve the high resolution capability of capillary gas chromatography (GC). HPLC, however, does offer some advantages for the determination of coal-derived PAHs in environmental samples. HPLC offers a variety of stationary phases capable of providing unique selectivity for the separation of PAH components and/or isomers that are often difficult to separate by GC. In addition, UV absorption and fluorescence detection provide sensitive and selective detection of PAHs. Rogaczeska and Ligocka (1991) reported results of a study of occupational exposure to coal tar pitch volatiles, including benzo[a]pyrene (B[a]P), by measuring B[a]P in air using HPLC with fluorescence detection.

An acid partition and alumina column clean-up procedures were used to analyze for several acridines (HPLC/UV) in creosote by Galceran et al. (1994). HPLC with fluorescence detection was used for analysis of the PAH components from a coal tar sample (NIST SRM 1597) as reported in a review article by Wise et al. (1993). Since fluorescence detection affords more selectivity than UV absorbance detection, less clean-up is required for certain sample types. This study also showed the utility of a multi-dimensional approach to PAH analysis from complex samples. This methodology involves use of normal phase liquid chromatography (LC) to separate PAH fractions, which can then be analyzed by reverse phase LC with fluorescence. Coal tar pitch has also been analyzed using planar chromatography as an initial fractionation technique (Herod and Kandiyoti 1995). The resultant fractions were analyzed either

directly on the silica by MS, or were extracted from the silica for further fractionation using size exclusion chromatography. The approach yielded structural information not readily available from direct characterization of the original mixture.

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 creosote 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 creosote.

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. Wood creosote and coal-Derived tars are complex mixtures of organic compounds and no methods exist for measuring all components in biological media. Virtually all potential human and ecological exposure is limited to the coal-derived tars and not wood creosote (which is used medicinally). Sensitive methods exist for measuring components of the coal-derived mixtures. Most of these methods involve detection of PAHs, the predominant components of creosote, and their metabolites. These analytical methods can reliably detect trace levels of PAHs in human tissues and body fluids, making them sensitive enough to measure background levels in the population, as well as levels at which biological effects might occur. PAHs, however, are not unique to creosote exposure. Analytical methods currently exist which are sensitive and selective enough to measure possibly unique or unusual components of creosote, and are capable of yielding a unique “fingerprint” for the mixture. These would be useful in monitoring exposures that might occur in work environments and near hazardous waste sites where creosote has been detected.

Although these capabilities exist, they have not been applied except in the case of the pyrene biomarker discussed earlier.

The analytical methods for measuring PAHs and their metabolites in biological tissues and fluids are sensitive enough to measure levels at which health effects might occur, as well as background levels in the population. Methods also exist for measuring PAH-DNA adducts, and research efforts are underway to develop methods that will detect ultratrace levels of these adducts in biological media. The increased sensitivity may allow correlation between levels of these adducts and observed health effects of PAH exposure related to coal products. There is also a need for methods to quantitatively correlate monitored levels of various PAHs in biological tissues or fluids to toxic effects in humans. Methods dependent on monitoring PAHs, however, are not specific for coal-derived products exposure. Methods sensitive and selective enough to detect a unique component or group of components making up the mixture would allow a more accurate assessment of the health effects associated with exposure to monitored levels of creosote and tars. The use of 1-pyrenol as illustrated above is an example of such an approach. Additional methods, targeting the detection of unique components of coal tar, coal tar creosote, and coal tar pitch in biological samples, would facilitate detection of exposure to these mixtures.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Reliable and sensitive methods are available for measuring PAHs from creosote and tars in soil, water, air, and other environmental media. Exposure to such materials is most likely to occur in industrial settings where coal-derived tars are manufactured or used. Creosote-contaminated water and soil are a concern in areas near hazardous waste sites and other areas where creosote might be concentrated. The analytical methods available are accurate and sensitive enough to quantitatively detect PAHs in these and other environmental media, and are effective for estimating creosote levels in media known to be contaminated with this substance. There is a lack of sensitive and reliable methods for detecting and measuring degradation products in environmental media. Development of such methods would allow assessment of the possible health effects of exposure to creosote/tar metabolites and assist in determining the level of potential exposure to these products.

The minimal use of wood creosote for other than medicinal purposes probably argues against a pressing need for analytical methods for environmental monitoring of this substance. The rather short half-life of phenolic substances under most environmental conditions increases the difficulty of developing such assay methods.

6.3.2 Ongoing Studies

No ongoing studies concerning techniques for measuring And determining creosote in biological and environmental samples were reported.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding coal tars, coal tar pitch, and creosote in air, water, and other media are summarized in Table 7-l. ATSDR has derived no MRLs for any of the creosotes, in part because creosote is a mixture that can vary in chemical components and concentrations. No EPA reference concentration or reference dose exists for the compound.

The EPA has determined that creosote is a class B1 carcinogen (probable human carcinogen) (IRIS 2000). A potency factor was not provided in IRIS. IARC classifies creosote as Group 2A (probably carcinogenic to humans) and coal tars as Group 1 (carcinogenic to humans) (IARC 2000). The National Toxicology Program classifies coal tar (coke oven emissions, coal tar, coal tar pitch, and creosotes) as a known human carcinogen (NTP 1998).

Coal tar creosote is on the list of chemicals appearing in "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1987B). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to coal tar pitch volatiles to institute engineering controls and work practices to reduce employee exposure to, and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 0.2 mg/m^3. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1999a).

Table 7-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Cancer classification		IARC 2000
	Creosote	Group 2A[a]	
	Coal tar	Group 1[b]	
NATIONAL Regulations and Guidelines:			
a. Air:			
ACGIH	TWA—Coal tar pitch volatiles	0.2 mg/m^3	ACGIH 1999
NIOSH	REL—Coal tar pitch volatiles	0.1 mg/m^3	NIOSH 2000
OSHA	8-hour time weighted average—Coal tar pitch volatiles	0.2 mg/m^3	29 CFR 1910.1000 OSHA 1999a
	8-hour time weighted average for shipyard workers—Coal tar pitch volatiles	0.2 mg/m^3	29 CFR 1915.1000 OSHA 1999b
	8-hour time weighted average for construction workers—Coal tar pitch volatiles	0.2 mg/m^3	29 CFR 1926.55 OSHA 1999c
b. Water			
		No data	
c. Food			
FDA	Beechwood creosote Synthetic flavoring substance and adjuvants	Used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice	21 CFR 172.515 FDA 1999d
	Beechwood creosote, creosote, coal tar Over the counter expectorant drug product	Active Ingredient	21 CFR 310.545 FDA 1999b
	Coal tar Active ingredient for the control of dandruff seborrheic dermatitis, and psoriasis	0.5–5%	21 CFR 358.710 FDA 1999a

Table 7-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont'd)*			
	Creosote label warnings		21 CFR 369.20
	External use	Do not apply to large areas of the body	FDA 1999c
	Douche preparations	Do not use more often than twice weekly, unless directed by a physician	
	Authorized for use as a denaturant in denatured spirits	Yes	27 CFR 21.151 BATF 1999
d. other			
ACGIH	Cancer classification		ACGIH 1999
	Coal tar pitch volatiles	A1[c]	
EPA	RfD	No data	IRIS 2000
	RfC	No data	
	Cancer classification—creosote	B1[d]	
	Reportable quantity for creosote and coal tar regarded as a CERCLA hazardous substance by RCRA section 3001	1 pound	40 CFR 302.4 EPA 1999d
	Identification and Listing of creosote as a Hazardous Waste	Yes; U051	40 CFR 261.33 EPA 1999b
	Toxic Chemical Release Reporting—effective date for creosote	1/1/90	40 CFR 372.65 EPA 1999a
NTP	Cancer classification—Coal tar and coal tar aerosols	Known to be a human carcinogen	NTP 1998
STATE Regulations and Guidelines:		No data	

[a]Group 2A: Probably carcinogenic to humans
[b]Group 1: Carcinogenic to humans
[c]A1: Confirmed human carcinogen
[d]B1: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = comprehensive environmental response compensation and liability act; CFR = code of federal regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicological Program; OSHA = Occupational Safety and Health Administration; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average

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9. GLOSSARY

Absorption-The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption-The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)-Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model-A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers-Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Case-Control Study-A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report-Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series-Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously. Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study-A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study-A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs-Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship-The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Environmental Protection Agency (EPA) Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology-Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity-A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life-A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence-The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure--Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects-Functional changes in the immune response.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo-Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})-Acalculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects-Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)-An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)-A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity-State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality-Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen-A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy-The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{OW})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio (OR)-A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound-A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)-An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide-General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics-The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model-A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model-A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model-Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence--The number of cases of a disease or condition in a population at one point in time.

Prospective Study-A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1 * can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µ/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)-A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a lo-hour workday during a 40-hour workweek.

Reference Concentration (RfC)-An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RtD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study-A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk-The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor-An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)-The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (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)-An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic-The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)-A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic-Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly.found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance, During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1,2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 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 (15–364 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 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific 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.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 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**

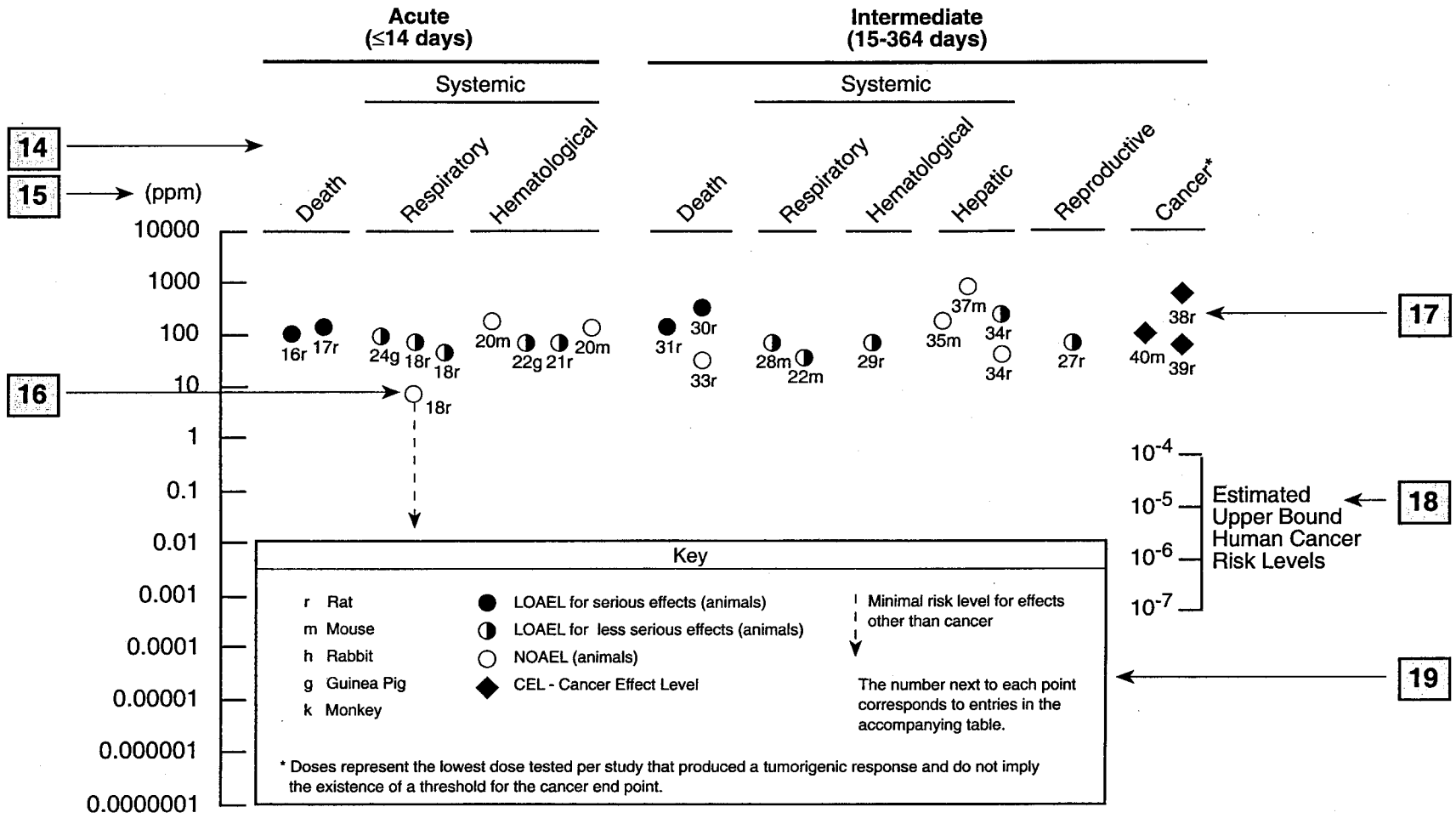
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC 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).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

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 end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this 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 end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the 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 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.9, “Interactions with Other Substances,” and 2.10, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive 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 C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
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
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
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
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
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
γ	gamma
δ	delta
µm	micrometer

µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result