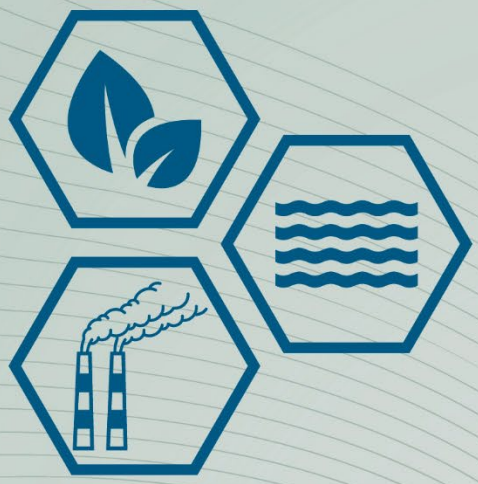

Toxicological Profile for Creosote

July 2024

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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FOREWORD

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

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(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, intermediate, and chronic health effects; and

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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

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VERSION HISTORY

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

CONTENTS

LIST OF FIGURES

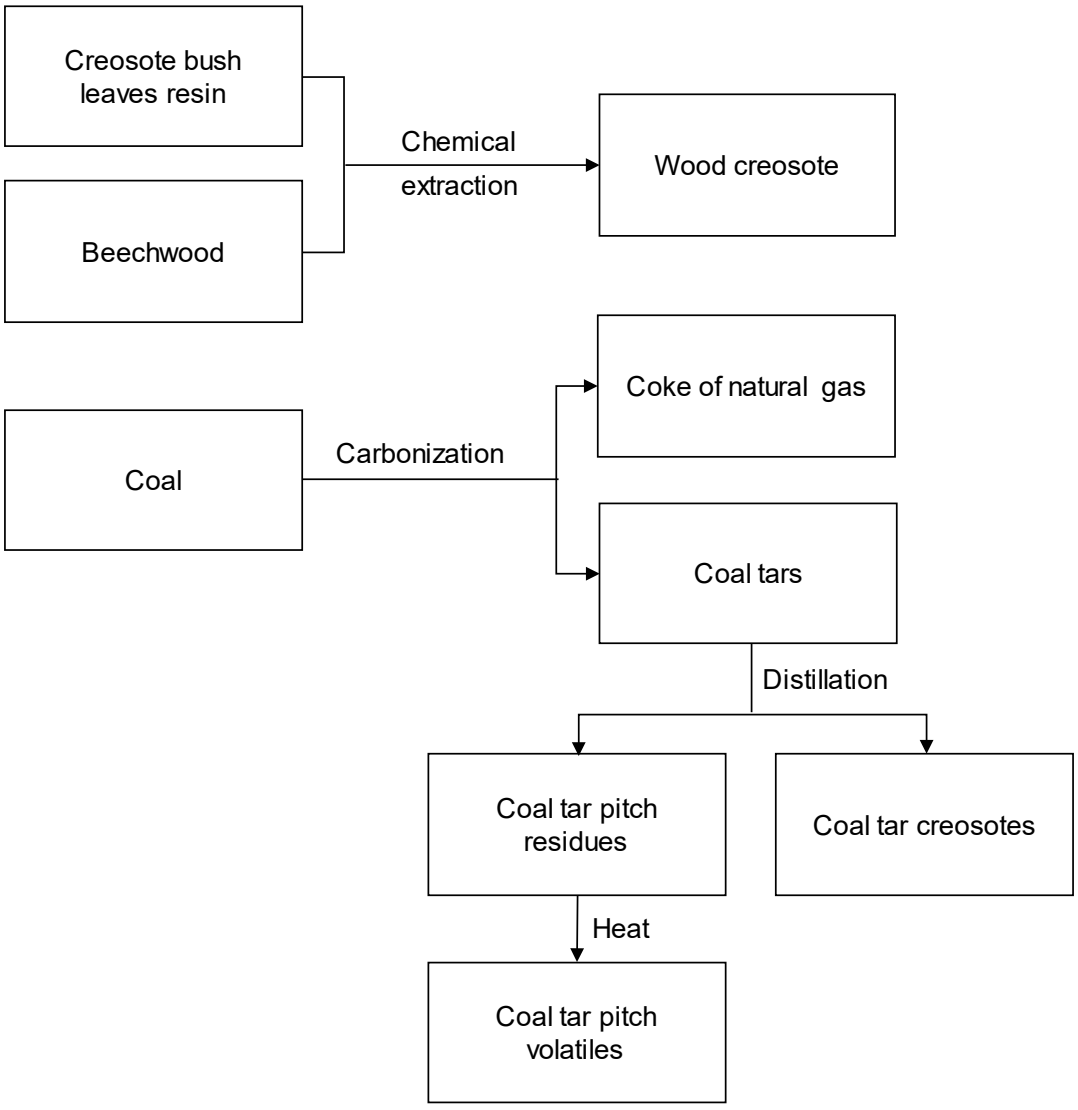
LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Creosote is the name used for a variety of products: wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles; this profile addresses these substances. Creosote compounds are complex mixtures of hundreds, if not thousands, of individual chemical components. For this profile, the substances were broadly divided into two categories: wood creosotes and coal tar products, which are very different complex mixtures that can vary greatly, even within the broad categories. Figure 1-1 shows how these substances are produced.

Figure 1-1. Origin of Wood Creosotes and Coal Tar Products



1. RELEVANCE TO PUBLIC HEALTH

Wood Creosotes. Wood creosote is derived from fractional distillation of either beechwood (*Fagus*, a type of deciduous tree) or the resin from leaves of the creosote bush (*Larrea tridentata*). Wood creosote consists mainly of phenol, cresols, guaiacols, and xylenols. It generally appears as a colorless or pale yellowish liquid and has a 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.

Coal Tar Products. Coal tar products refers to a broad category that includes coal tar, coal tar creosote, coal tar pitch, and coal tar pitch volatiles. Coal tars are byproducts of the carbonization of coal to produce coke and/or natural gas. Coal tar creosotes are distillation products of coal tar, while coal tar pitch is a residue produced during the distillation of coal tar. Coal tar pitch volatiles are compounds given off from coal tar pitch when it is heated. Coal tar 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., coal tar creosote), is not consistent, and 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 pyrolysis. Usually, coal tars are viscous liquids or semisolids that are black or dark brown with a naphthalene-like odor. Coal tars are complex combinations of polycyclic aromatic hydrocarbons (PAHs), phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. PAH composition of coal tars is variable. Analyses of PAHs in four coal tar samples revealed 2- to 20-fold differences in concentration of selected PAHs among the samples. For example, benzo[a]pyrene ranged from nondetectable levels to 1.7, 3.9, and 6.4 g/kg of coal tar. By comparison, coal tar creosotes have an oily liquid consistency and range in color from yellowish-dark green to brown. The coal tar creosotes consist of PAHs and PAH derivatives. At least 75% of the coal tar creosote mixture is PAHs. Coal tar pitch is a shiny, dark brown-to-black residue that contains PAHs and their methyl and polymethyl derivatives, as well as heteronuclear compounds. There are also over-the-counter medications and shampoos containing low-dose solutions of coal tar to treat certain skin conditions like dandruff, eczema, and seborrheic dermatitis. In the past, wood creosote was used as a disinfectant, laxative, and cough treatment, but is rarely used in these ways today in the United States.

Coal tar creosote has been used as a wood preservative pesticide in the United States for over 100 years. It is used as a fungicide, insecticide, and sporicide for above-ground and below-ground wood protection treatments, as well as for treating wood in marine environments. It is a restricted use pesticide, meaning that it is not available for purchase by the general public in the United States and may only be used by

certified pesticide applicators (EPA 2008, 2015). Since coal tar creosote is not available to the public, most exposures occur for workers employed handling or treating creosote-protected wood products. Dermal and inhalation are the most likely routes of occupational exposures.

People residing near wood treatment facilities or other facilities that produce or use coal tar and coal tar creosote may have exposure to the chemicals in these complex mixtures, particularly PAHs. Inhalation of air, dermal contact with contaminated environmental media (e.g., soil or water), and possibly ingestion of contaminated groundwater are possible exposure routes. PAHs from creosote may also be accumulated in fish and other aquatic species which may be another exposure route for humans. The public may also be exposed via dermal or inhalation routes to PAHs from the use of coal tar-based driveway sealants. There are also over-the-counter medications containing low-dose solutions of coal tar to treat certain skin conditions.

Most environmental releases of coal tar creosote arise from effluents in wood treatment facilities or accidental spills. Since these are complex mixtures of many chemicals, the environmental fate and transport is different for different components in the mixture. In general, many of the chemicals tend to adsorb to soil and sediment, which act as an environmental sink. Some components are volatile and may evaporate into air from water or soil where they can be degraded by atmospheric oxidation reactions or direct photolysis. Biodegradation tends to occur slowly for many of the components of coal tar creosote especially the high molecular weight PAHs. Components of wood creosote tend to be more volatile and less persistent than the components of coal tar and coal tar creosote.

1.2 SUMMARY OF HEALTH EFFECTS

The health effects of creosote and creosote compounds have been evaluated in observational occupational and population-based epidemiological studies, case reports, clinical trials, and experimental animal studies. Exposure to wood creosotes occurs mainly through intentional ingestion or dermal application of pharmaceutical products. Coal tar product exposure can occur through inhalation of coal tar aerosols or through dermal contact from industrial uses or from therapeutic applications. Associated health effects are discussed in terms of two major categories: coal tar products (coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles) and wood creosotes.

Coal Tar Products. Exposures to coal tar and coal tar products may take place in industrial and non-industrial settings and can occur through inhalation, oral, and dermal routes of exposure. Information

regarding the adverse human health effects of coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles is available from occupational surveys and retrospective health studies. Unfortunately, the usefulness of many of the occupational studies is hampered by incomplete characterization of worker exposure and the difficulty in ascribing adverse effects to a particular exposure route. Additional health effects information is available from the use of coal tar products in the medical treatment of psoriasis patients. Data are also available from animal studies, although the results are not always consistent across species or sex. The available information suggests that adverse respiratory and developmental effects and increased carcinogenicity risk are the most important health concerns related to exposure to coal tar and coal tar products.

Respiratory effects (coal tar products). Coal tar aerosols and volatiles have been linked to adverse respiratory effects. Occupational exposure studies evaluating respiratory effects have been conducted in wood processing and wood preservative workers, electrode manufacturing workers, and aluminum industry workers. An industrial health survey conducted in wood treatment plants reported reduced lung function in 17% of the employees examined, while workers in coal tar plants reported pulmonary deficits in 33% of the workers surveyed (Koppers Company 1979, 1981). Long-term residents near a wood treatment plant reported a significant increase in the prevalence of diagnosed bronchitis and asthma by history, while residents of an area that had been built on land formerly occupied by a coal tar creosote wood treatment facility also showed an increased risk of chronic bronchitis (ATSDR 1994; Dahlgren et al. 2004). Most studies evaluating respiratory effects in animals have focused on changes in lung weight, although a few animal studies have shown histopathological changes following inhalation exposure, including lesions of the olfactory epithelium and lungs (EPA 1995c, 1995d; Springer et al. 1982, 1986b, 1987).

Developmental effects (coal tar products). There are no reports of adverse developmental outcomes in humans exposed to coal tar and coal tar products. Women treated with coal tar for psoriasis or dermatitis did not exhibit an increase in spontaneous abortions or congenital disorders in their offspring (Franssen et al. 1999). There were no differences in the number of pregnancies; live, premature, and still births; or spontaneous abortions among women who resided in a housing development built on contaminated land formerly occupied by a coal tar creosote wood treatment plant (ATSDR 1994). On the other hand, multiple animal studies have shown that exposure to coal tar during pregnancy may have adverse effects on the fetus. Increased post-implantation loss and whole litter resorptions, decreased fetal body and lung weight, and increased incidences of malformations including hydrocephaly, dilated ventricles, and cleft palate have been observed in studies evaluating oral and dermal exposure (EPA 1995a, 1995b; Hackett et

al. 1984; Springer et al. 1986a; Zangar et al. 1989). In many of these animal studies, it is not possible to exclude the potential role of maternal toxicity in the development of adverse fetal effects, but the evidence suggests that fetal effects may result from maternal exposure to coal tar products.

Wood Creosotes. Exposure to wood creosotes appears to be confined to ingestion of plant extracts and dermal contact with the plants. Most of the toxicity data for oral exposure to wood creosotes come from reports of individuals who ingested plant extracts such as chaparral, an herbal extract prepared by grinding leaves of the creosote bush, or "seirogan," a Japanese folk remedy made with wood creosote that is typically taken for stomachaches. Information on adverse health effects associated with wood creosote is very limited. Isolated reports suggest that repeated exposure to chaparral is associated with adverse renal and/or liver effects; however, because of the limited amount of data, it is not possible to attribute the findings to ingestion of chaparral tea. Although the distribution of cancer cases in Japan coincided with "seirogan" production areas, an association between cancer incidence in Japan and the use of "seirogan" cannot be made with the available data. Animal studies evaluating cancer endpoints following oral exposure to wood creosotes have not identified a tumorigenic response. The available data suggest that hepatic effects are the main adverse outcomes that result from exposure to wood creosotes.

Hepatic effects (wood creosotes). Acute toxic hepatitis has been attributed to continued ingestion of chaparral. Case reports of intermediate-duration ingestion of chaparral have described patients with a variety of hepatic effects including jaundice (Alderman et al. 1994; CDC 1992; Gordon et al. 1995; Katz and Saibil 1990). Elevated liver enzymes have been observed, which often return to normal levels 3–6 weeks after exposure to chaparral was discontinued, and biopsies have revealed acute inflammation and other cellular changes (Alderman et al. 1994; CDC 1992; Gordon et al. 1995; Katz and Saibil 1990). In one severe case, the patient's liver biopsy showed severe acute hepatitis with areas of lobular collapse and nodular regeneration, mixed portal inflammation, and marked bile ductular proliferation (Gordon et al. 1995). In animal oral exposure studies, increased liver-to-body weight ratios and serum cholesterol have been observed (Miyazato et al. 1984a, 1984b), but the lack of associated changes in histopathology and lack of dose-response makes the toxicological significance of these changes questionable.

Cancer. Studies of workers exposed to coal tar in various industrial environments have found increased cancer risk involving several tissues including the respiratory tract, skin, lung, pancreas, kidney, scrotum, prostate, rectum, bladder, and central nervous system (see Section 2.19). These adverse effects have not been observed in patients undergoing coal tar therapy. Although exposure from inhalation is likely a major factor, significant dermal exposure and possibly oral exposure may also occur in industrial settings,

making the ability to distinguish between routes of exposure difficult. Animal studies have demonstrated the carcinogenic potential of coal tar products through primarily dermal exposure but also following inhalation and oral exposure and have identified cancers of the lungs, liver, forestomach, and skin. In addition, numerous studies provide consistent evidence that exposure to coal tar is genotoxic. Studies evaluating wood creosotes have not identified similar effects in rodents.

The Department of Health and Human Services (HHS) has classified coal tars, coal-tar pitches, and coke-oven emissions to be human carcinogens based on sufficient evidence of carcinogenicity from studies in humans (NTP 2021). The U.S. Environmental Protection Agency (EPA) concluded that coke oven emissions (coal tar pitch volatiles) are a human carcinogen (Group A) based on sufficient evidence in humans and animals (IRIS 1989) and that creosote is a probable human carcinogen (Group B1) based on limited evidence in humans and sufficient evidence in animals (IRIS 1988). The International Agency for Research on Cancer (IARC) classified creosotes as probably carcinogenic to humans (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals (IARC 2010). In addition, IARC (2012a) classified the carcinogenicity of creosote compounds for specific occupational settings and cancer types. Coke production is carcinogenic to humans (Group 1) based on sufficient evidence in humans for the carcinogenicity of coke production (cancer of the lung) and sufficient evidence in experimental animals for the carcinogenicity of samples of tar taken from coke ovens. Coal gasification is carcinogenic to humans (Group 1) based on sufficient evidence in humans (cancer of the lung) and sufficient evidence in experimental animals for the carcinogenicity of samples of tar taken from coke ovens. Coal gasification is carcinogenic to humans (Group 1) based on sufficient evidence in humans (cancer of the lung) and sufficient evidence in experimental animals for the carcinogenicity of coal tars from gasworks and manufactured gas plant (MGP) residues. Aluminum production is carcinogenic to humans (Group 1) based on sufficient evidence in humans (cancers of bladder and lung) and sufficient evidence in experimental animals for the carcinogenicity of airborne particulate polynuclear organic matter from aluminum-production plants. Coal tar distillation is carcinogenic to humans (Group 1) based on sufficient evidence in humans (cancer of the skin) and sufficient evidence in experimental animals for the carcinogenicity of coal tars. Exposure to coal tar pitch in roofers and pavers is carcinogenic to humans (Group 1) based on sufficient evidence in humans (cancers of the lung and bladder) and sufficient evidence in experimental animals for the carcinogenicity of coal tar pitch (IARC 2012a).

1.3 MINIMAL RISK LEVELS (MRLs)

MRLs for creosote compounds have not been derived. Coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles and wood creosotes are extremely complex mixtures containing numerous compounds; furthermore, the compositions of the mixtures are not consistent. Even within a class of creosote compounds, the chemical mixtures vary such that adverse effects profiles and potency may vary within a class of creosote compounds. This is demonstrated by inconsistent results observed in studies evaluating the same class of compounds; a single lowest-observed-adverse-effect level (LOAEL) value may not be representative for a class of compounds. Thus, derivation of an MRL based on single study or group of studies may not be protective for other exposures. The database for creosote compounds was not considered adequate for derivation of inhalation or oral MRLs for any exposure duration (Tables 1-1 and 1-2).

Table 1-1. Minimal Risk Levels (MRLs) for Coal Tar Products[a]

No MRLs were derived for any exposure route or duration for coal tar products.

[a]See Appendix A for additional information.

Table 1-2. Minimal Risk Levels (MRLs) for Wood Creosotes[a]

No MRLs were derived for any exposure route or duration for wood creosotes.

[a]See Appendix A for additional information.

CHAPTER 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. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figures 2-1 and 2-2 provide an overview of the database of studies in humans or experimental animals included in this chapter of the profile for coal tar products and wood creosotes, respectively. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to creosote, but may not be inclusive of the entire body of literature.

For the purposes of this profile, studies have been divided into two categories: coal tar products and wood creosotes. Animal inhalation studies for coal tar products are presented in Table 2-1 and Figure 2-3; animal oral studies for coal tar products are presented in Table 2-2 and Figure 2-4; animal oral studies for wood creosotes are presented in Table 2-3 and Figure 2-5; and animal dermal studies for coal tar products are presented in Table 2-4.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses or concentrations (levels of exposure) used in the studies. Effects have been classified into “less serious LOAELs” or “serious LOAELs

(SLOAELs)." "Serious" effects (SLOAELs) 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 scientific judgment may be required in establishing whether an endpoint 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 endpoints. 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 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 the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of creosote are indicated in Tables 2-1, 2-2, and 2-4 and Figures 2-2 and 2-3.

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

This profile addresses the toxicological and toxicokinetics database for several creosote mixtures: wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. These mixtures are composed of many individual compounds of varying physical and chemical characteristics and differ from each other with respect to their composition. For chemical mixtures, note that interpretation of NOAELs and LOAELs may have some limitations if exposure is based on only one chemical of the mixture.

Coal tars are byproducts 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 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. 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 (AWPA 1988). 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; Rønneberg 1995; Rønneberg and Andersen 1995). Coal tar creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants (EPA 1981a, 1984).

Wood creosote is the general term for creosote derived from either beechwood (*Fagus*, referred to as beechwood creosote) or the resin from leaves of the creosote bush (*Larrea*, referred to as creosote bush resin). Wood creosote is a colorless or pale yellowish liquid and has a characteristic smoky odor and burnt taste. Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol. It had therapeutic applications in the past as a disinfectant, laxative, and stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States. Creosote bush resin consists of phenolic (e.g., flavonoids and nordihydroguaiaretic acid), neutral (e.g., waxes), basic (e.g., alkaloids), and acidic (e.g., phenolic acids) compounds. 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).

Although wood creosote and coal tar creosote have some components in common, such as phenols, the differences in composition are pronounced enough to assume with reasonable certainty that they will have different toxicological properties. As such, for the purposes of this profile, the creosote mixtures have been grouped into coal tar products (coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles) and wood creosotes (creosote bush and beechwood creosote). Another factor to consider when evaluating health effect data for creosote mixtures is that the composition of a particular creosote mixture, although referred to by specific name (e.g., wood creosote or coal tar creosote), is not consistent because 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 pyrolysis. Thus, studies cannot be directly compared due to the variable composition of test materials. Throughout this profile, every attempt is made to specify the characteristics of the creosote, coal tar, coal tar pitch, or coal tar pitch volatiles under discussion, and to indicate which health 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 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. Evaluation and interpretation of the toxicology of

the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive, or other interactions) and how they influence the overall toxicity of 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 1995, 2008a, 2008b).

Pharmaceutical Uses. Coal tar creosote, beechwood creosote, and creosote bush are all used medicinally in different applications. Coal tar is used therapeutically for psoriasis and other skin conditions, with some therapies following cutaneous application of coal tar-based ointment with exposure to ultraviolet (UV) irradiation (i.e., Goeckerman regimen). Most of the toxicity data for oral exposure to wood creosotes comes from reports of individuals who ingested plant extracts such as chaparral, an herbal extract prepared by grinding leaves of the creosote bush, or "seirogan," a Japanese folk remedy made with wood creosote that is typically taken for stomachaches. Beechwood creosote is used as a "gastric sedative," a gastrointestinal antiseptic, and an antidiarrheal agent, or as an expectorant/cough suppressant based on its presumed ability to increase the flow of respiratory fluids. These pharmaceutical substances contain additional chemicals and vary in composition, making it difficult to determine if effects are related specifically to creosote, other chemicals, or the combination. Some of these studies are discussed below, but the results are often complicated by exposure to additional chemicals or UV radiation. Due to this, studies specifically examining therapeutic uses such as "seirogan" and the Goeckerman regimen are not reviewed in this profile.

Human Studies. Most of the available literature on human exposure to creosote products comes from individual case reports or studies evaluating occupational exposure. Case reports have focused primarily on oral and dermal uses, while most occupational studies are primarily evaluating inhalation exposure. In some cases, dermal and oral exposures are likely to contribute to the total exposure. Unless otherwise specified, occupational studies are assumed to be chronic-duration exposure scenarios. Occupations that are considered important for creosote exposure evaluation include creosote workers, wood preservers, aluminum workers, roofers, and pavers. Studies on occupational exposures have primarily focused on cancer and mortality, while a few have looked at respiratory, cardiovascular, and neurological diseases. Unfortunately, the usefulness of the available occupational studies is confounded by co-exposures to numerous other possibly carcinogenic compounds, incomplete characterization of worker exposure, and identifying the specific chemical exposure as coal tar products are complex mixtures that vary in composition and component concentrations. When occupational exposures are measured, exposure information is not collected uniformly and often relies on specific components of the coal tar mixture, for example benzo[a]pyrene, which is itself a carcinogen. Due to the complex nature of the coal tar and

creosote compounds and concurrent occupational exposures, most of the available occupational studies are presented qualitatively without discussion of exposure concentrations. However, if exposure concentrations are reported, they are included in the discussion. In addition, these studies are categorized by occupation type, given that different occupations likely have exposure to different compounds of creosote and can be more readily compared within occupation than across occupations.

Animal Studies. Information is more readily available for animal exposure to wood creosote and coal tar creosote compounds by inhalation, oral, and dermal exposure for acute, intermediate, and chronic durations. A wide variety of outcomes have been examined for each exposure route, including several studies evaluating the carcinogenic effects of these compounds in animals. Most of the available animal studies have examined the general toxicity of creosote and creosote compounds, and measured health effects are limited to body and organ weights changes. In the absence of data on histopathological changes, it is difficult to determine if changes in organ weights are toxicologically significant. Similarly, decreased body weights are often observed following exposure to creosote compounds, but in most cases, these changes are accompanied by decreased food or water intake, particularly when exposure is by the oral route. These results are further confounded by the lack of a known target organ system for the creosote compounds. Therefore, for the purposes of identifying adverse effects, organ weight changes in the absence of corresponding histopathology or functional changes, or body weight changes that are accompanied by changes in food or water intake are not considered adverse.

Overview of Health Effects. Although a target system has not been specifically identified for the creosote compounds, studies in laboratory animals have identified several common health effects following exposure by any route. Human studies, while not sufficient to determine exposures, do qualitatively support some of the effects observed in animals. The outcomes examined in human and animal studies of coal tar products and wood creosotes are presented in Figures 2-1 and 2-2, respectively. Mixed results are often reported at similar exposure concentrations and between the species and sexes, which could be the result of differences in the composition of the test material. Some effects have been observed more consistently, and these data are summarized below:

- **Respiratory effects (coal tar products).** Increased bronchitis and asthma have been reported by residents living near coal tar sources, while decreased respiratory function has been observed in workers exposed to creosote products. Animal studies evaluating exposure to coal tar aerosols have identified changes in lung weight and histopathological lesions in the nasal cavities and lungs of rodents.

- **Neurological effects (coal tar products and wood creosotes).** Neurological effects have been reported following inhalation, oral, and dermal exposure to creosote compounds. Case reports of individuals and survey studies suggest that neurotoxicity (e.g., dizziness, altered vision, headache) may be an early sign of toxic exposure to creosote. In laboratory animals, clinical signs of neurological effects have been reported (listlessness, decreased activity, prostration).

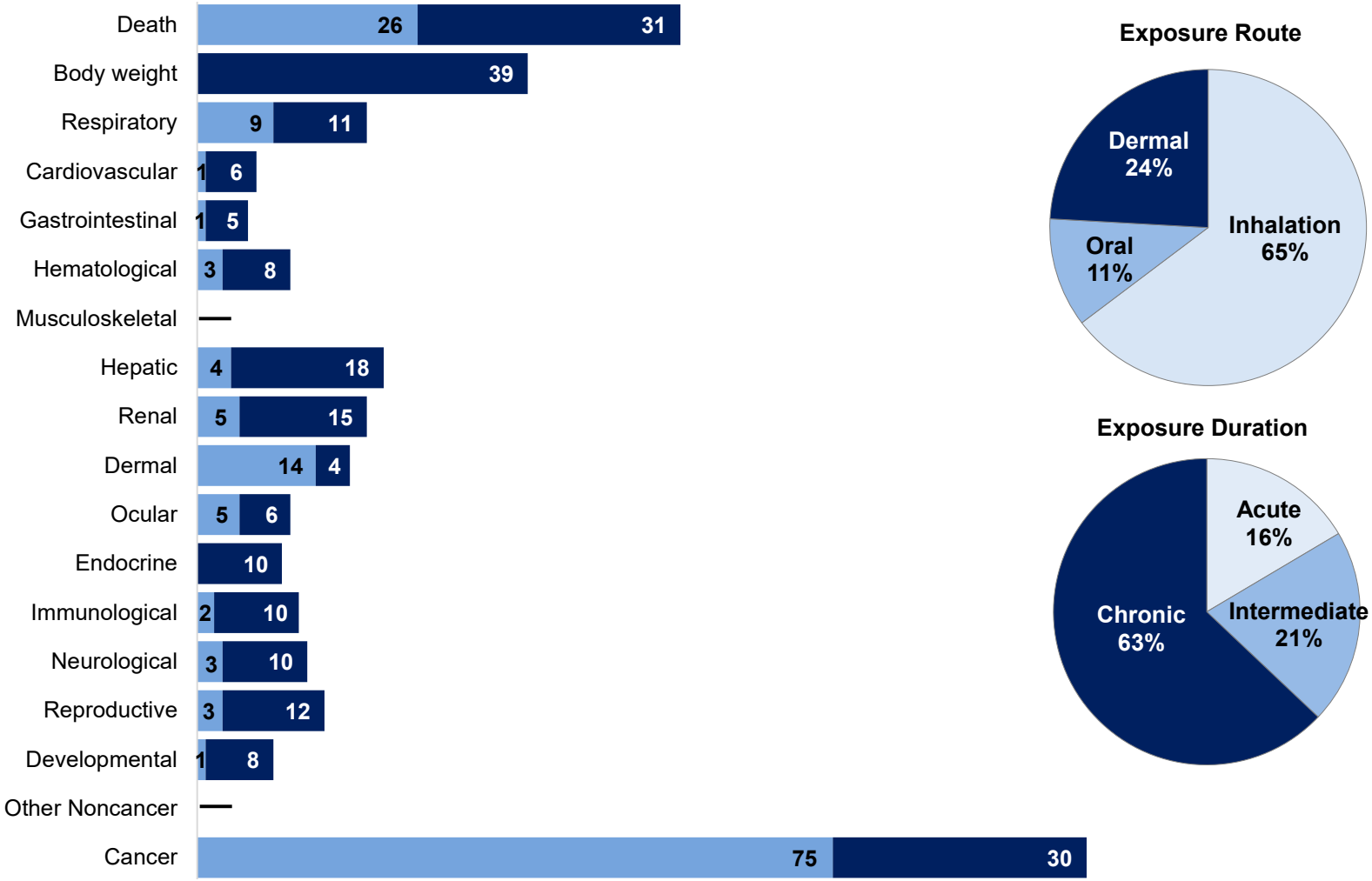
- **Hepatic effects (wood creosotes).** Human case reports of intermediate-duration exposure to wood creosotes have identified the potential of hepatic effects including jaundice and changes in liver enzymes and histopathology. Animal studies have shown mixed results on the hepatic effects of creosote, but several studies have shown changes in liver weight, serum chemistry, and histopathology following exposure.

- **Developmental effects (coal tar products).** Although few studies have examined the potential for creosote to cause developmental effects in humans, several animal studies using coal tar products have identified fetal effects following inhalation, dermal, or oral exposure. Increases in mid and late resorptions and early fetal mortality have been observed along with decreases in fetal weight and lung weight/size.

- **Cancer (coal tar products).** The carcinogenic effect of creosote has been well established in animals with supporting observational associations from occupational studies. In animals, tumors appear to be the primary result from coal tar exposure by inhalation, oral, or dermal routes, typically at the site of exposure, although distal tumors have also been observed. Inhalation and dermal studies have identified neoplastic effects in the lungs and skin, while oral studies have shown additional carcinogenic effects in the liver and gastrointestinal system. In addition, numerous studies provide consistent evidence that exposure to coal tar is genotoxic.

Figure 2-1. Overview of the Number of Studies Examining Creosote (Coal Tar Products) Health Effects*

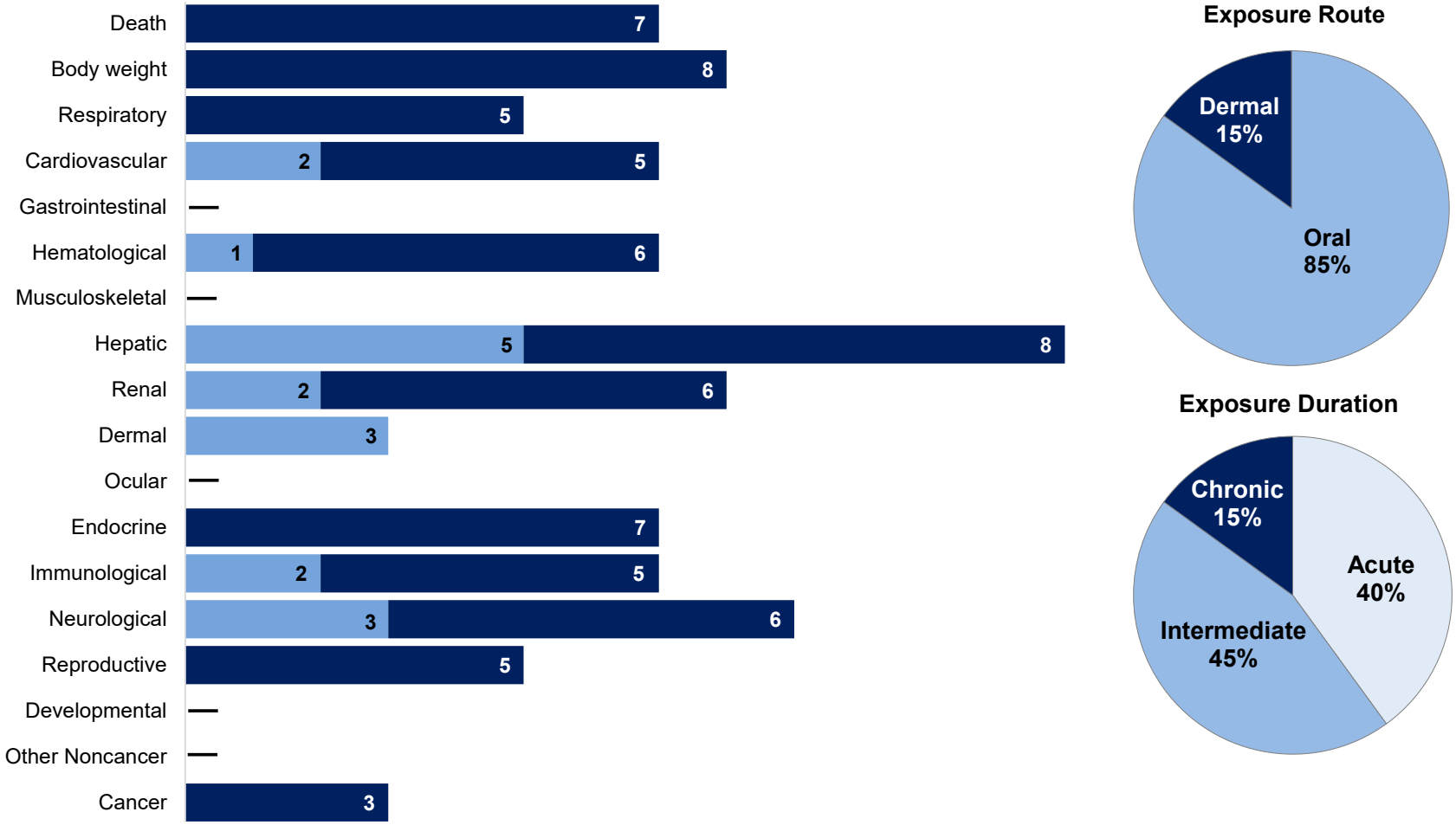
Most studies examined the potential cancer, death, and body weight effects of creosote.
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 136 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-2. Overview of the Number of Studies Examining Creosote (Wood Creosotes) Health Effects*

Most studies examined the potential hepatic, renal, and neurological effects of creosote.
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 16 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
EPA 1994									
1	Rat (CD) 5 M, 5 F	4 hours	600, 5,000	LE, CS, BW	Neuro		600		Decreased activity
P1/P13 creosote									
EPA 1994									
2	Rat (CD) 5 M, 5 F	4 hours	600, 5,300	LE, CS, BW	Neuro		600		Decreased activity
P2 creosote									
Springer et al. 1982									
3	Rat (CD) 23–25 F	5 days GDs 12–16 6 hours/day	0, 17, 84, 660	BW, OW, GN, HP, DX	Bd wt	84	660		Decreased body weight (11%)
					Resp	660			
					Hepatic	660			
					Renal	660			
					Endocr	660			
					Immuno	660			
					Develop	84		660	Increased resorptions, decreased crown-rump length, decreased fetal weight, decreased fetal lung size, reduced ossification
Heavy distillate									

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
EPA 1995c									
4	Rat (CD) 20 M, 20 F	13 weeks 5 days/week 6 hours/day	0, 4.7, 48, 102	LE, CS, BW, FI, BI, HE, GN, HP, OP, BC	Bd wt	102			
					Resp		4.7		Chronic inflammation, epithelial hyperplasia, squamous metaplasia in the nasal cavity, and alveolar macrophages with granular pigments in the lungs
					Hemato	48	102		Decreased hemoglobin, decreased hematocrit, decreased erythrocytes, increased reticulocytes
					Hepatic	102			
					Renal	102			
					Ocular	102			
P2 creosote									
EPA 1995d									
5	Rat (CD) 20 M, 20 F	13 weeks 5 days/week 6 hours/day	0, 5.4, 49, 106	LE, CS, BW, FI, BI, HE, GN, HP, OP, BC	Bd wt	106			
					Resp	5.4	49		Chronic inflammation, epithelial hyperplasia, squamous metaplasia in the nasal cavity, and alveolar macrophages with granular pigments in the lungs
					Hemato	49 F 106 M	106 F		Decreased hemoglobin, decreased erythrocytes, increased reticulocytes
					Hepatic	106			
					Ocular	106			
P1/P13 creosote									

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Heinrich et al. 1994a, 1994b									
6	Rat (Wistar) 72 F	10 months 5 days/week 17 hours/day	0, 1.1, 2.6	LE, CS, HP	Cancer			1.1	CEL: Lung tumors (squamous cell carcinomas)
Coal tar pitch									
Sasser et al. 1989									
7	Rat (Fischer-344) 48 M	6 weeks 5 days/week 6 hours/day	0, 700	LE, CS, BW	Bd wt		700		Decreased body weight (17%)
					Cardio		700		Elevated heart rate and blood pressure
Heavy distillate									
Springer et al. 1986b									
8	Rat (Fischer-344) 10 M, 10 F	5 weeks 5 days/week 6 hours/day	0, 30, 140, 690	LE, BW, OW, GN, HP	Bd wt	140	690 F	690 M	LOAEL: Decreased body weight (14%) SLOAEL: Decreased body weight (27%)
					Resp		30		Histiocytosis of the lung
					Cardio	690			
					Gastro	690 F			Epithelial hyperplasia and chronic inflammation of the cecum
						140 M	690 M		
					Hemato	30	140		Decreased red blood cells, hemoglobin, and volume of packed red cells; increased reticulocytes; decreased number of megakaryocytes in the spleen
					Hepatic	140	690		Increased relative liver weight; hepatic lesions and focal necrosis; increased serum cholesterol

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	690 F			Increased relative kidney weight, pelvic epithelial hyperplasia
						140 M	690 M		
					Endocr	690			
					Immuno	140	690		Decreased relative thymus weight, thymus atrophy
					Neuro	690			
					Repro	140 F	690 F		Decreased luteal tissue in the ovary
						690 M			
Heavy distillate									
Springer et al. 1986b									
9	Rat (Fischer-344) 22 M, 22 F	13 weeks 5 days/week 6 hours/day	0, 30, 140, 690	LE, BW, OW, GN, HP	Bd wt	30	140		Decreased body weight (10%)
					Resp		30		Histiocytosis of the lung
					Cardio	690			
					Gastro	140	690		Epithelial hyperplasia, ulcers, and chronic inflammation of the cecum
					Hemato	140	690		Decreased red blood cells, decreased hemoglobin, decreased volume of packed red cells, increased reticulocytes, decreased megakaryocytes in the spleen and bone marrow
					Hepatic	140	690		Increased relative liver weight, hepatic lesions and focal necrosis, increased serum cholesterol and triglycerides
					Renal	140 F	690 F		Increased relative kidney weight, pelvic epithelial hyperplasia, and pigmentation of cortical tubules
						30 M	140 M		

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	690			
					Immuno	140	690		Decreased relative thymus weight; thymus atrophy
					Neuro	690			
					Repro	140 F	690 F		Decreased relative weight, decreased luteal tissue in the ovary
						690 M			
Heavy distillate									
MacEwen et al. 1977									
10	Mouse CAF1- JAX 43–225 F	90 days	0, 0.2, 2, 10	CS, HP	Cancer			10	CEL: Skin tumors (type not specified)
Coke oven coal tar									
MacEwen et al. 1977									
11	Mouse ICR CF-1 55–225 F	90 days	0, 0.2, 2, 10	CS, HP	Cancer			2	CEL: Skin tumors (type not specified)
Coke oven coal tar									
Springer et al. 1987									
12	Mouse (CD-1) 60 M, 60 F	13 weeks 5 days/week 6 hours/day	29, 140, 690	BW, OW, BC, GN, HP	Bd wt	690			
					Resp	140	690		Olfactory epithelial atrophy
					Cardio	690			
					Gastro	690			
					Hemato	140	690		Decreased red blood cells, decreased hemoglobin, decreased reticulocytes, decreased volume of packed red cells
					Hepatic	140	690		Increased relative liver weight, hepatic lesions, and necrosis

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	690			
					Endocr	690			
					Immuno	690			
					Neuro	690			
					Repro	140 F 690 M	690 F		Decreased ovary weight, decreased luteal tissue
Heavy distillate									
MacEwen et al. 1977									
13	Rabbit (New Zealand) 18 F	9 months 5 days/week 6 hours/day	0, 10	LE, CS, BW	Bd wt			10	Decreased body weight (30%)
Coke oven coal tar									
CHRONIC EXPOSURE									
MacEwen et al. 1977									
14	Monkey (*Macaca mulatta*) 5 M, 9 F	18 months 5 days/week 6 hours/day	0, 10	CS, BW	Bd wt	10			
Coke oven coal tar									
Heinrich et al. 1994a, 1994b									
15	Rat (Wistar) 72 F	20 months 5 days/week 17 hours/day	0, 1.1, 2.6	LE, CS, HP	Cancer			1.1	CEL: Lung tumors (squamous cell carcinomas)
Coal tar pitch									

Table 2-1. Levels of Significant Exposure to Creosote (Coal Tar Products) – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
MacEwen et al. 1977									
16	Rat (Sprague-Dawley) 40 M, 40 F	18 months 5 days/week 6 hours/day	0, 10	CS, BW, HP	Bd wt		10		Decreased body weight (11% males, 14% females)
					Cancer			10	CEL: Lung tumors (squamous cell carcinomas)
Coke oven coal tar									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; F = female(s); Cardio = cardiovascular; CAS = Chemical Abstracts Service; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; OP = ophthalmology; OW = organ weight; P1/P13 = CAS Registry Number 8001-58-9, coal tar creosote; P2 = CAS Registry Number 65996-92-1, coal tar distillate; Repro = reproductive; Resp = respiratory; SLOAEL = serious LOAEL

Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Acute (≤14 days)

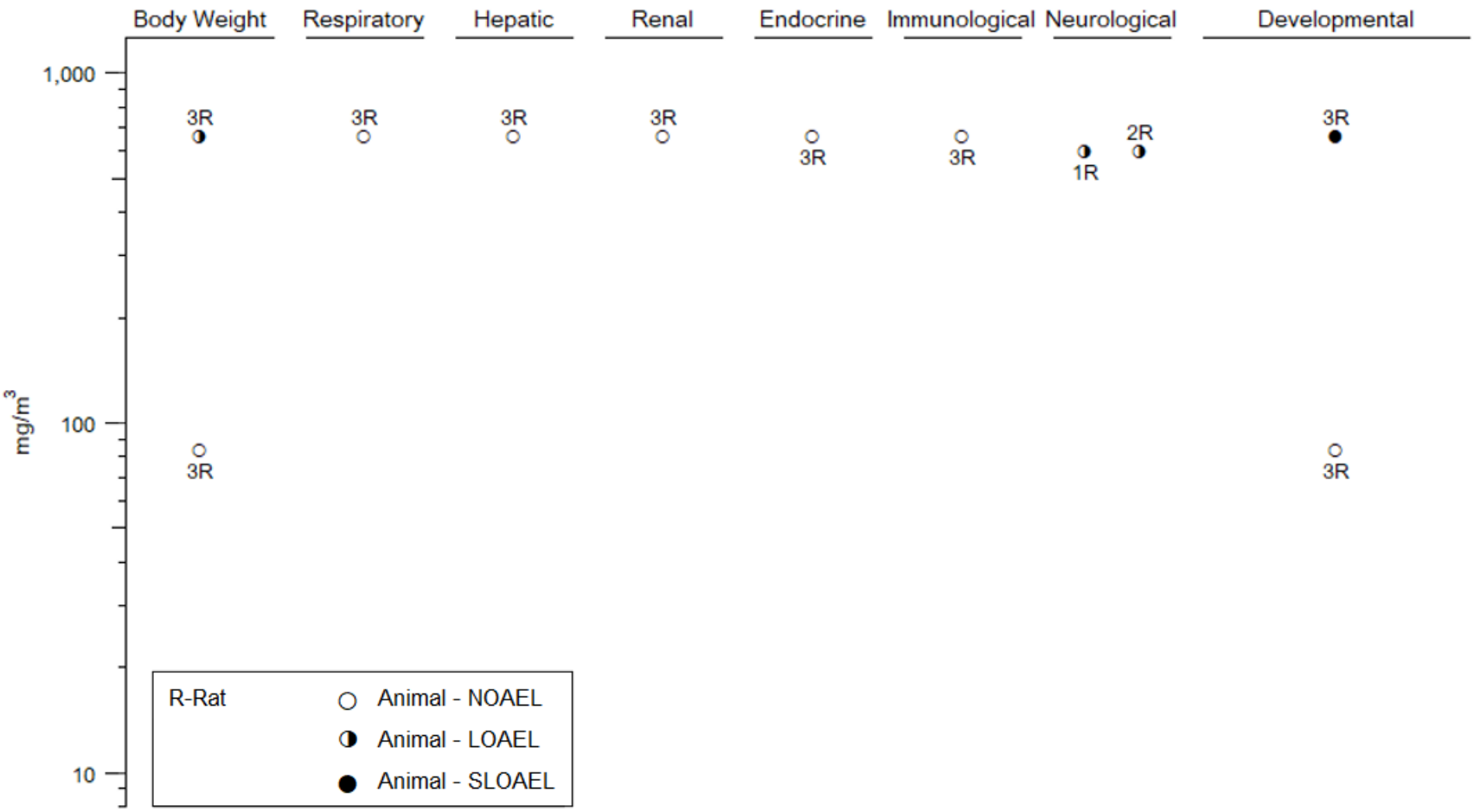


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

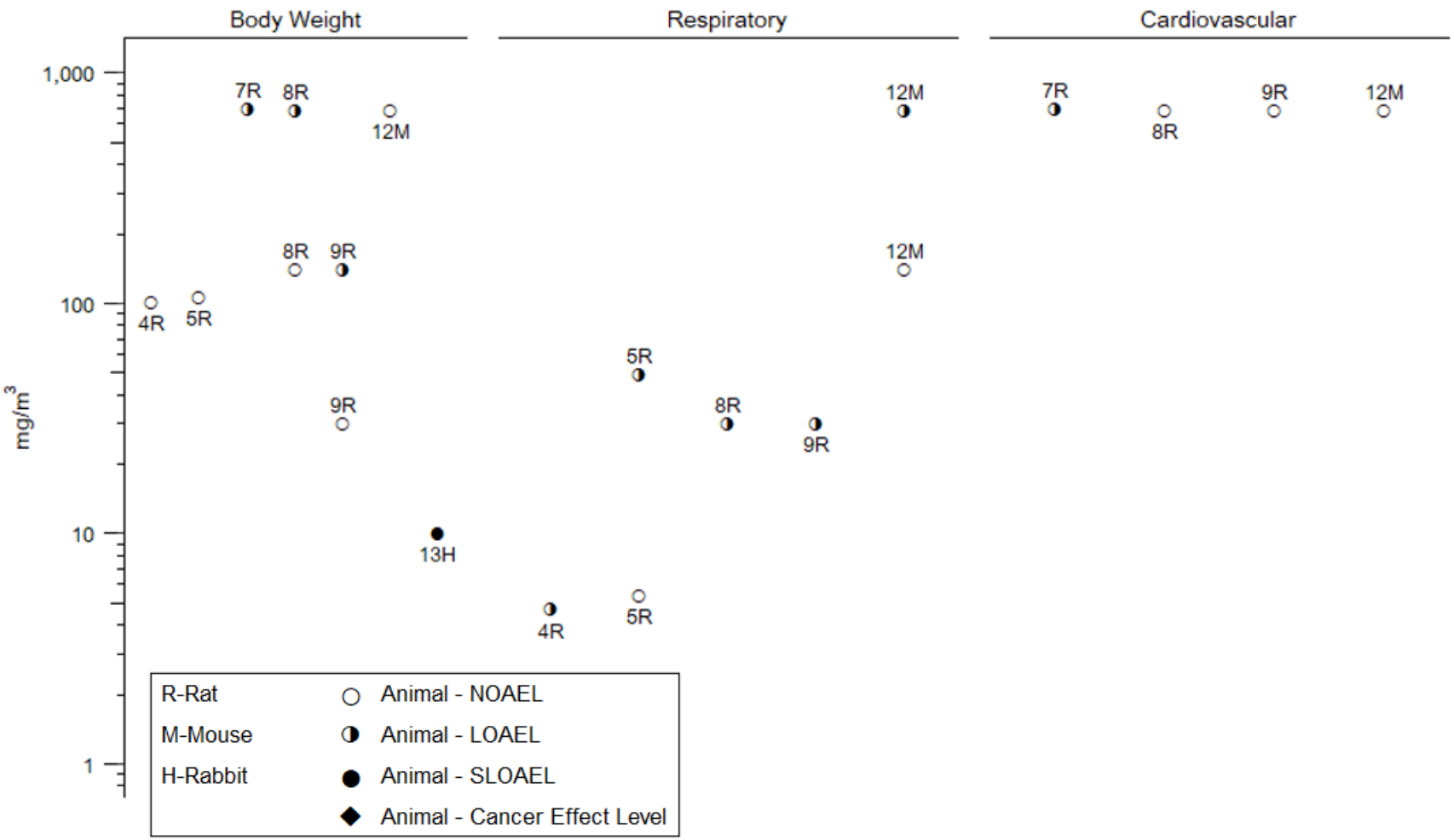


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

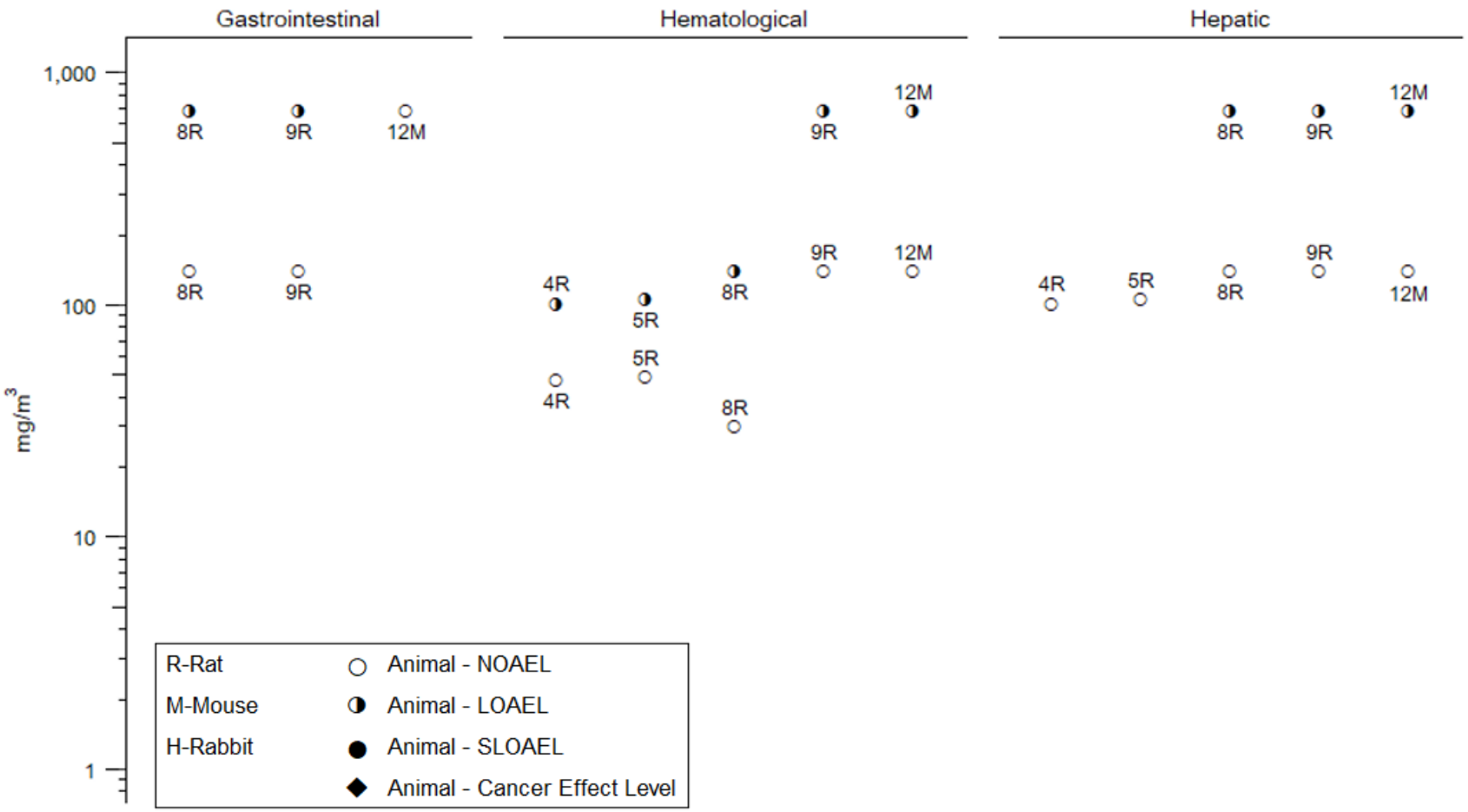


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

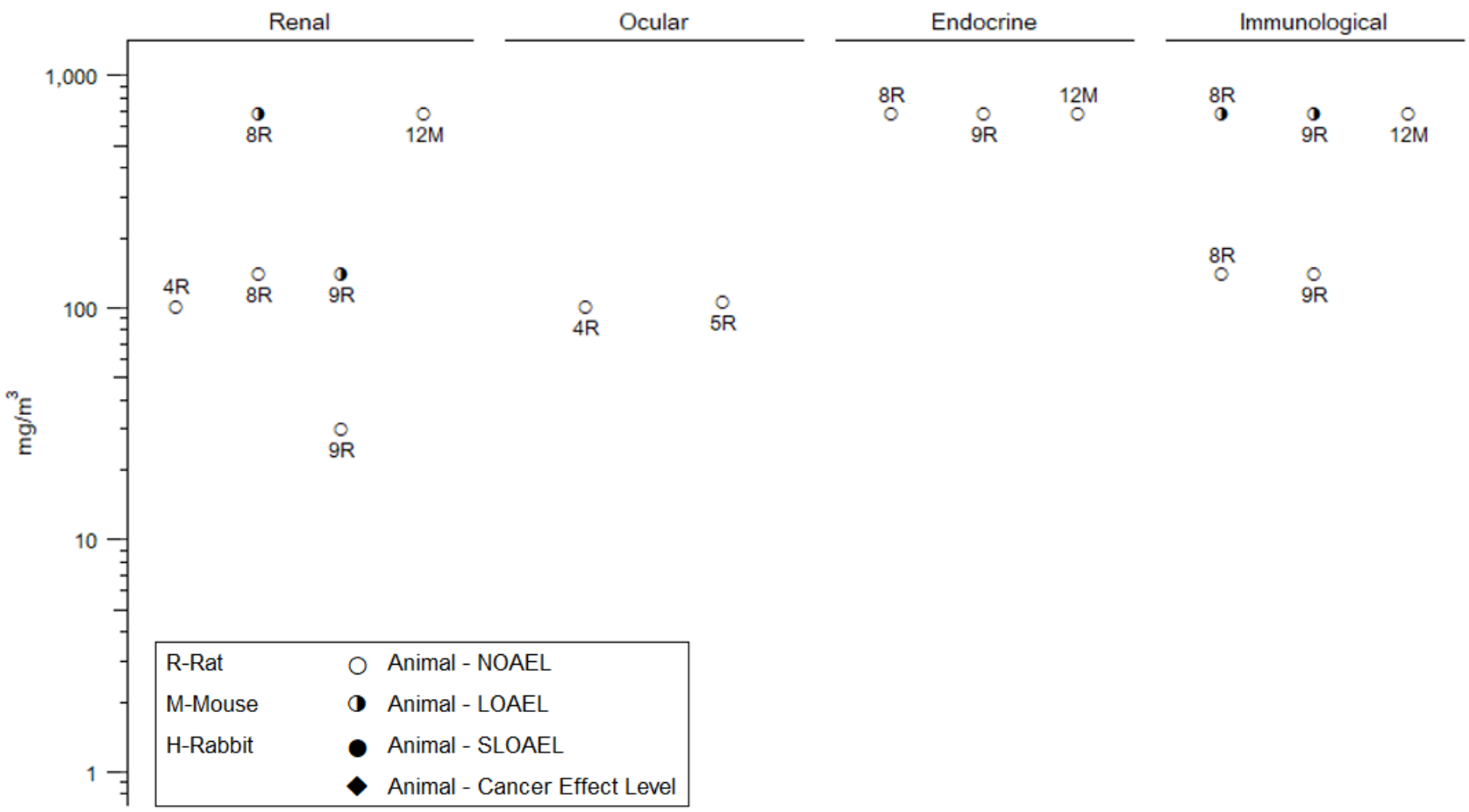


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

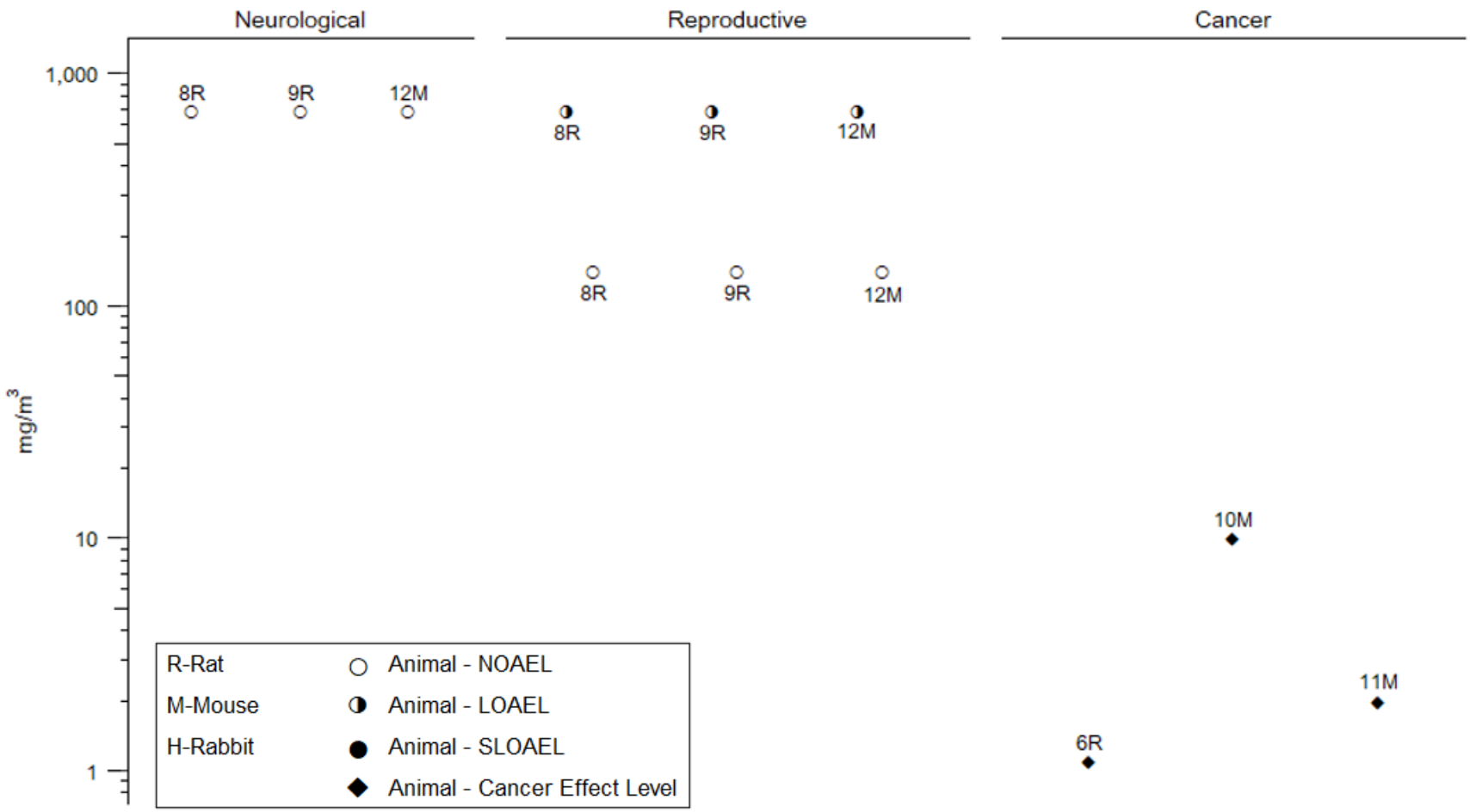


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Chronic (≥365 days)

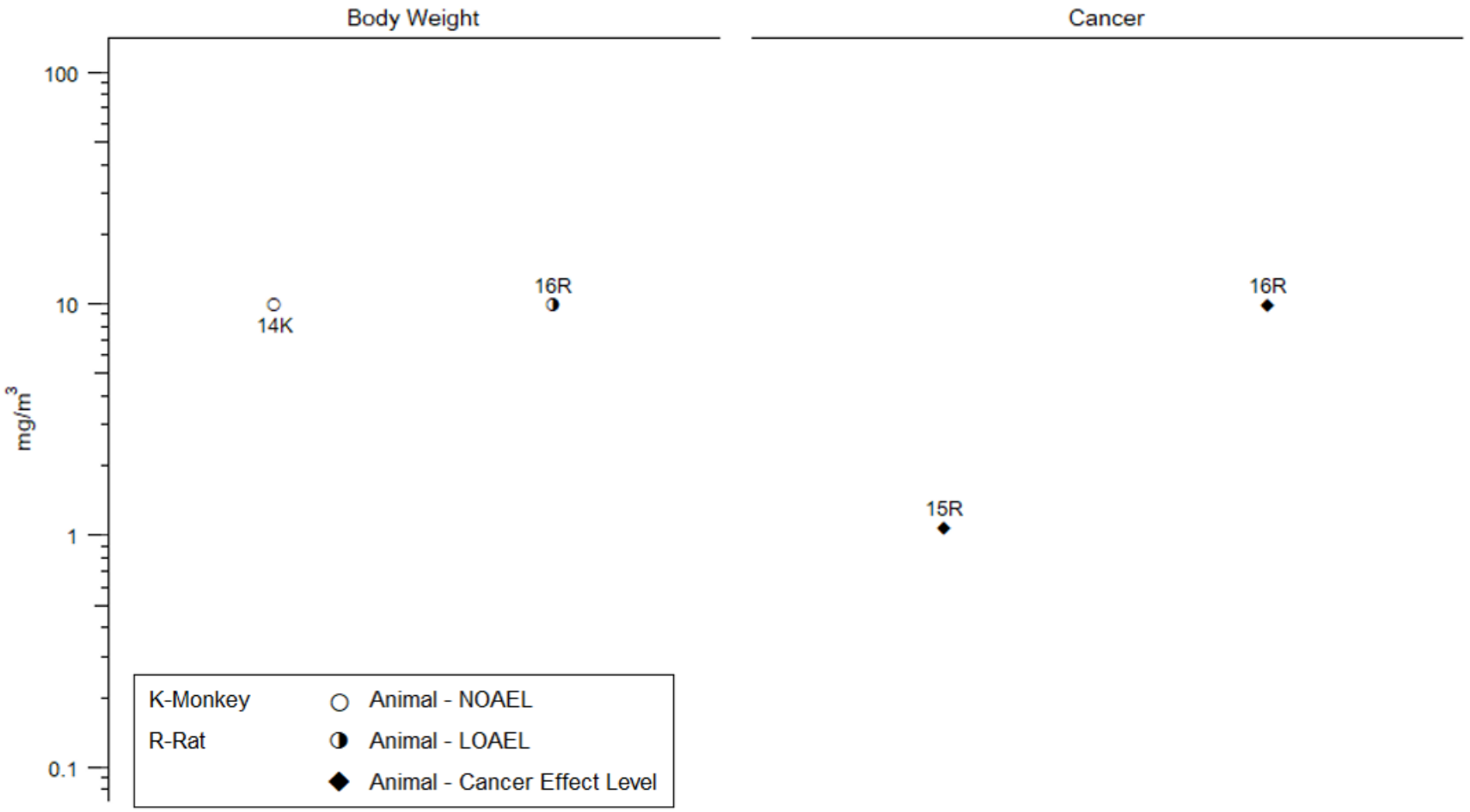


Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
EPA 1994									
1	Rat (CD) 5 M, 5 F	1 time (GO)	1,500, 2,000, 2,500, 3,000, 4,000	LE, CS, BW, GN	Death			1,893 F	LD_{50}
								2,451 M	LD_{50}
					Bd wt	4,000			
					Renal		2,500		Distended bladder
					Neuro		1,500		Decreased activity
P1/P13 creosote									
EPA 1994									
2	Rat (CD) 5 M, 5 F	1 time (GO)	1,000, 1,500, 2,000, 2,300, 3,500	LE, CS, BW	Death			1,993 F	LD_{50}
								2,524 M	LD_{50}
					Bd wt	3,500			
					Renal	2,300	3,500		Distended bladder
					Neuro		1,000		Decreased activity
P2 creosote									
EPA 1995a									
3	Rat (CD) 30 F	10 days GDs 6–15 1 time/day (GO)	0, 25, 50, 175	LE, CS, BW, DX	Bd wt	50	175		Decreased body weight gain (16%)
					Develop	50		175	Increased post-implantation loss and whole litter resorptions
P1/P13 creosote									
EPA 1995b									
4	Rat (CD) 30 F	10 days GDs 6–15 1 time/day (GO)	0, 25, 75, 225	LE, CS, BW, DX	Bd wt	75		225	Decreased body weight gain (24%)
					Develop	75		225	Increased post-implantation loss and whole litter resorptions
P2 creosote									

Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hackett et al. 1984									
5	Rat (CD) 16–36 F	5 days GDs 12–16 1 time/day (G)	0, 90, 140, 180, 370, 740	LE, BW, GN, OW, HP, RX, DX	Death			740	Increased mortality (63%)
					Bd wt			90	Decreased extragestational (e.g., weight gain minus the weight of the gravid uterus) body weight gain (93%)
					Hepatic	370			
					Renal	370			
					Endocr	370			
					Immuno	370			
					Repro	370			
					Develop		90	370	LOAEL: Decreased absolute fetal lung weight (15%), decreased fetal body weight (9%) SLOAEL: Increased incidence of fetal malformations (cleft palate, syndactyly/ectrodactyly, and missing toenails on hind feet)
Heavy distillate									
Springer et al. 1986a									
6	Rat (Sprague-Dawley) 26 F	3 days GDs 12–14 1 time/day (G)	0, 740	LE, BW, DX	Bd wt			740	SLOAEL: Decreased gestational weight gain (19%), decreased extragestational (40%) body weight gain
					Develop			740	Increased fetal mortality (54%), decreased fetal body weight (14–40%)
Coal liquid									

Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Fielden et al. 2000									
7	Mouse (mature ICR) 4–7 F	4 days 1 time/day (GO)	0, 10, 50, 100	BW, OW, RX	Bd wt	100			
					Hepatic	100			
					Repro	100			
Coal tar creosote									
Fielden et al. 2000									
8	Mouse (immature ICR) 4–7 F	4 days 1 time/day (GO)	0, 10, 50, 100	BW, OW, RX	Bd wt	100			
					Hepatic	100			
					Repro	100			
Coal tar creosote									
Fielden et al. 2000									
9	Mouse (mature DBA/2) 4–7 F	4 days 1 time/day (GO)	0, 10, 50, 100	BW, OW, RX	Bd wt	100			
					Hepatic	100			
					Repro	100			
Coal tar creosote									
Fielden et al. 2000									
10	Mouse (immature DBA/2) 4–7 F	4 days 1 time/day (GO)	0, 10, 50, 100	BW, OW, RX	Bd wt	100			
					Hepatic	100			
					Repro	100			
Coal tar creosote									

Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Iyer et al. 1993									
11	Mouse (ICR) 20–29 F	5 days GDs 5–9 1 time/day (G)	0, 400	BW, OW, RX, DX	Bd wt	400			
					Resp	400			
					Hepatic	400			
					Renal	400			
					Endocr	400			
					Develop		400		Decreased fetal weight (12%)
Petroleum creosote									
INTERMEDIATE EXPOSURE									
Culp and Beland 1994									
12	Mouse (B6C3F1) 8 M	28 days (F)	0, 263, 568, 968, 1,639, 3,128	BW, FI	Bd wt	3,128			
Coal tar									
Weyand et al. 1991									
13	Mouse 5 M	15 days (F)	0, 659, 1,871, 3,125, 1,250	CS, BW	Bd wt	3,125			
Manufactured gas plant residue									
Weyand et al. 1994									
14	Mouse (B6C3F1) 12 M, 12 F	185 days (F)	M: 0, 51, 251, 462; F: 0, 42, 196, 344	LE, CS, BW, HP, BC, GN	Bd wt	344 F 462 M			
					Resp	344 F 462 M			
					Cardio	344 F 462 M			

Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Gastro	344 F			
						462 M			
					Hemato	344 F			
						462 M			
					Hepatic	344 F			
						462 M			
					Renal	344 F			
						462 M			
					Endocr	344 F			
						462 M			
					Immuno	344 F			
						462 M			
					Repro	344 F			
						462 M			
Manufactured gas plant residue									
Weyand et al. 1994									
15	Mouse (B6C3F1) 12 M, 12 F	94 days (F)	M: 0, 51, 251, 462; F: 0, 42, 196, 344	LE, CS, BW, HP, BC, GN	Bd wt	344 F			
						462 M			
					Resp	344 F			
						462 M			
					Cardio	344 F			
						462 M			
					Gastro	344 F			
						462 M			
					Hemato	344 F			
						462 M			

Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	344 F			
						462 M			
					Renal	344 F			
						462 M			
					Endocr	344 F			
						462 M			
					Immuno	344 F			
						462 M			
					Repro	344 F			
						462 M			
Manufactured gas plant residue									
Weyand et al. 1995									
16	Mouse A/J 30 F	260 days (F)	0, 100, 236	BW, FI, GN, HP	Bd wt	236			
					Cancer			100	CEL: Lung tumors (pulmonary adenomas)
Manufactured gas plant residue									
CHRONIC EXPOSURE									
Culp et al. 1996, 1998									
17	Mouse (B6C3F1) 48 F	2 years (F)	0, 40, 120, 346	LE, BW, GN, HP, OW	Death			346	Increased early mortality (85%)
					Bd wt	346			
					Resp	346			
					Hepatic	120	346		Increased absolute liver weight (40%)
					Renal	346			
					Cancer			120	CEL: Lung tumors (alveolar/ bronchiolar adenomas)
Manufactured gas plant residue									

Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Culp et al. 1996, 1998									
18	Mouse (B6C3F1) 48 F	2 years (F)	0, 12, 33, 117, 333, 739, 1,300	LE, BW, GN, HP, OW	Death			333	Increased early mortality (79%)
					Bd wt	1,300			
					Resp	1,300			
					Hepatic	117	333		Increased absolute liver weight (40%)
					Renal	1,300			
					Cancer			333	CEL: Lung tumors (alveolar/bronchiolar adenomas/ carcinomas), liver tumors (hepatocellular adenomas/ carcinomas), forestomach tumors (papillomas/carcinomas), hemangiosarcomas

Manufactured gas plant residue

[a]The number corresponds to entries in Figure 2-4; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-4. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; F = female(s); Cardio = cardiovascular; CAS = Chemical Abstracts Service; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; (GO) = gavage in oil; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; OW = organ weight; P1/P13 = CAS Registry Number 8001-58-9, coal tar creosote; P2 = CAS Registry Number 65996-92-1, coal tar distillate; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level

Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Acute (≤14 days)

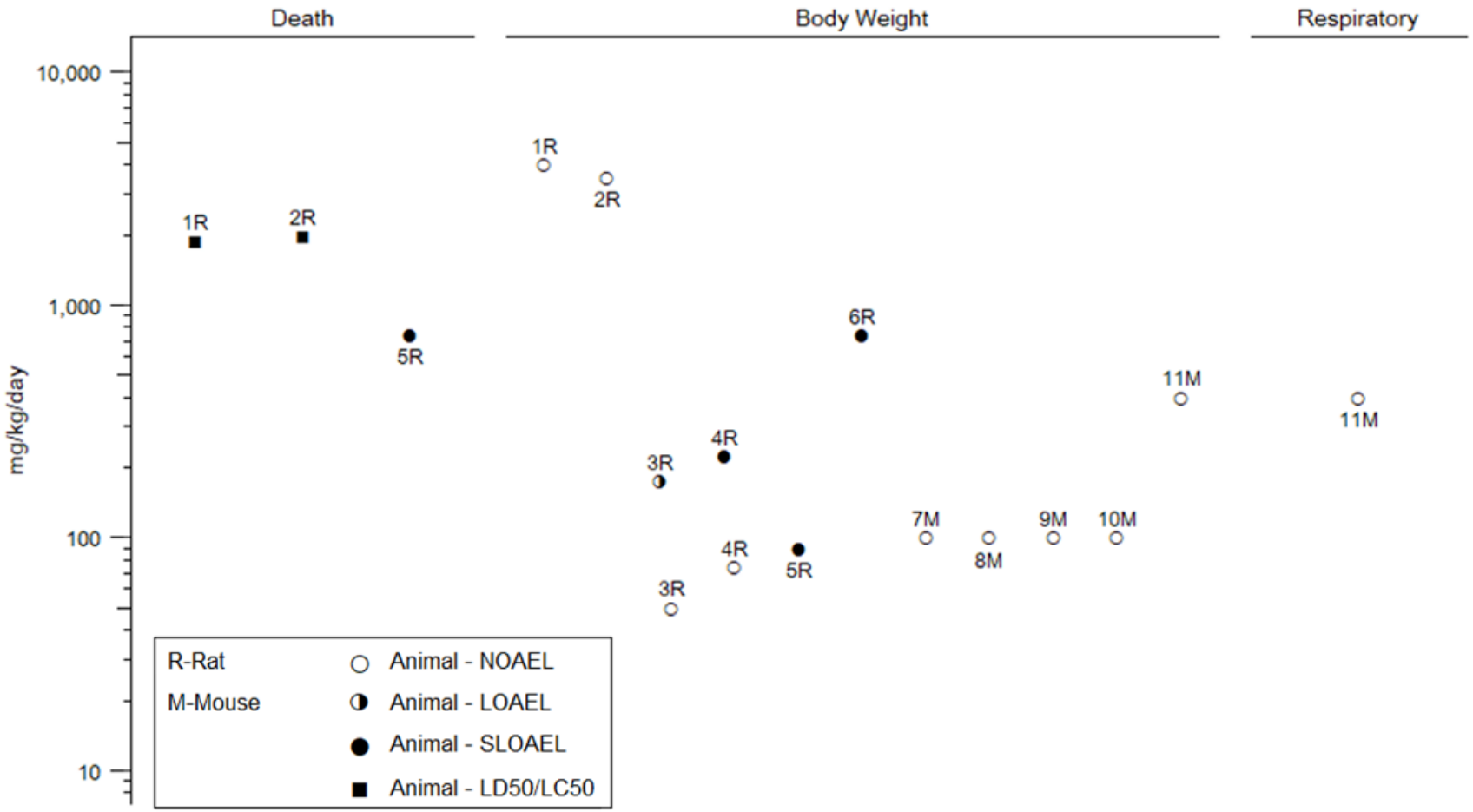


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Acute (≤14 days)

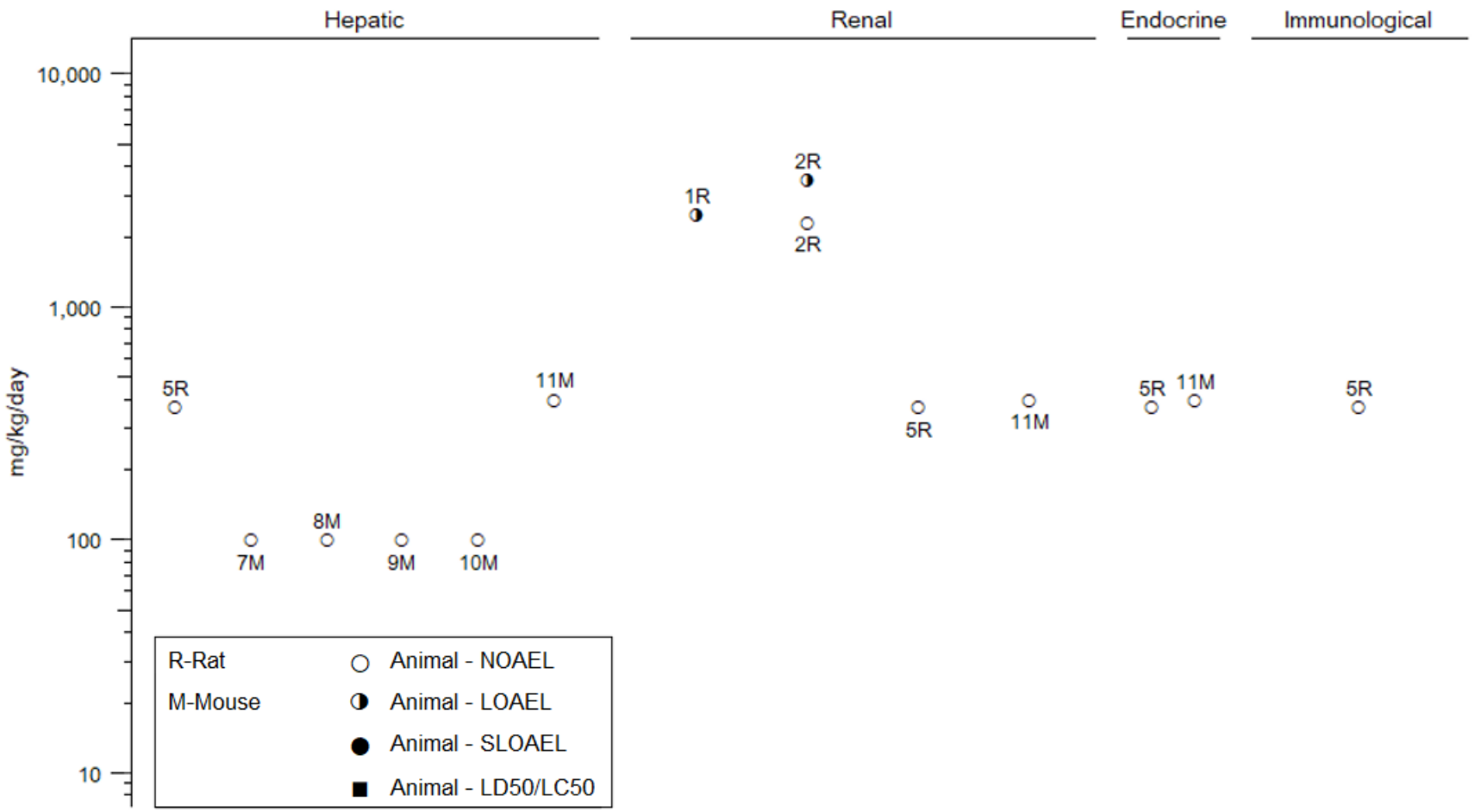


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Acute (≤14 days)

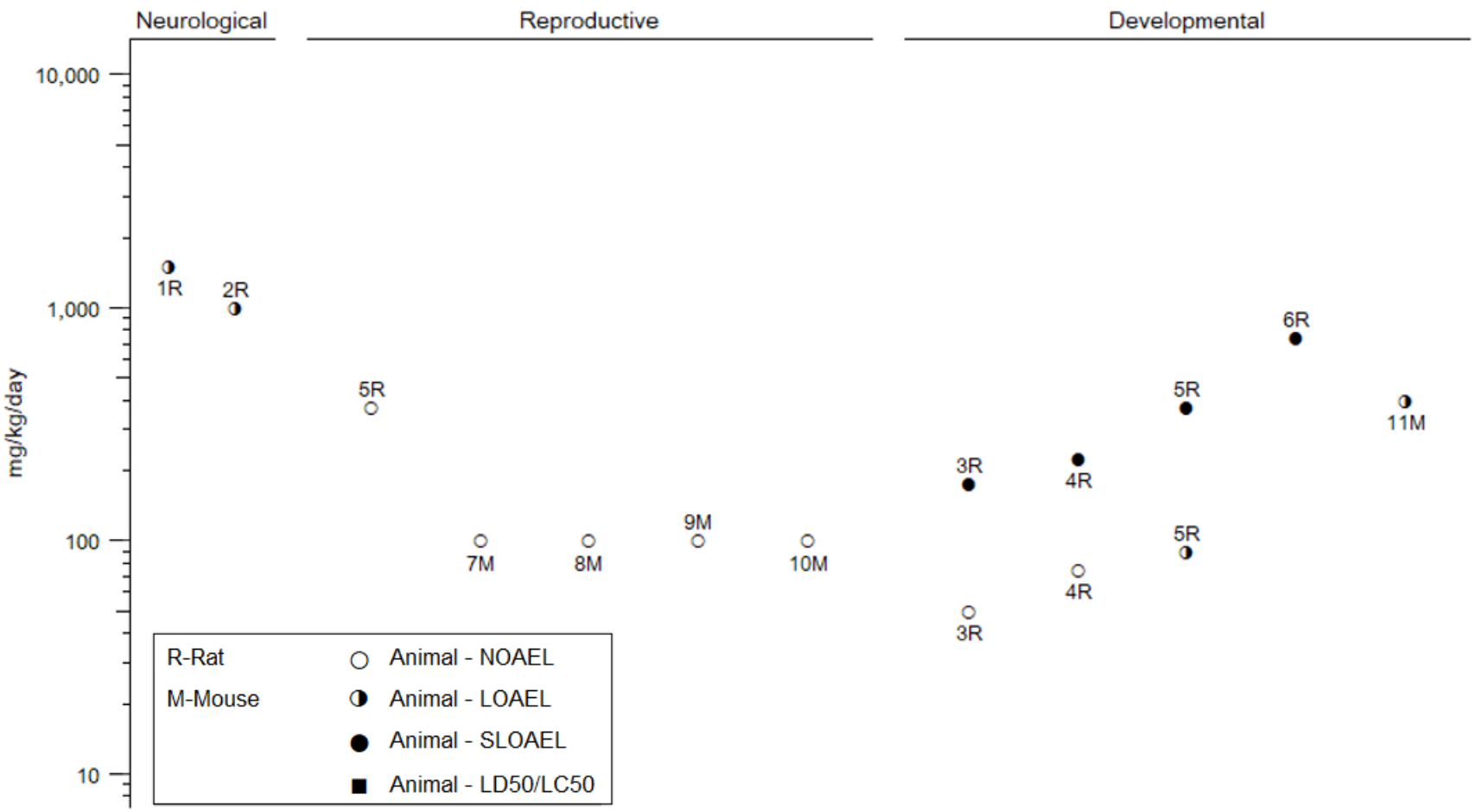


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Intermediate (15–364 days)

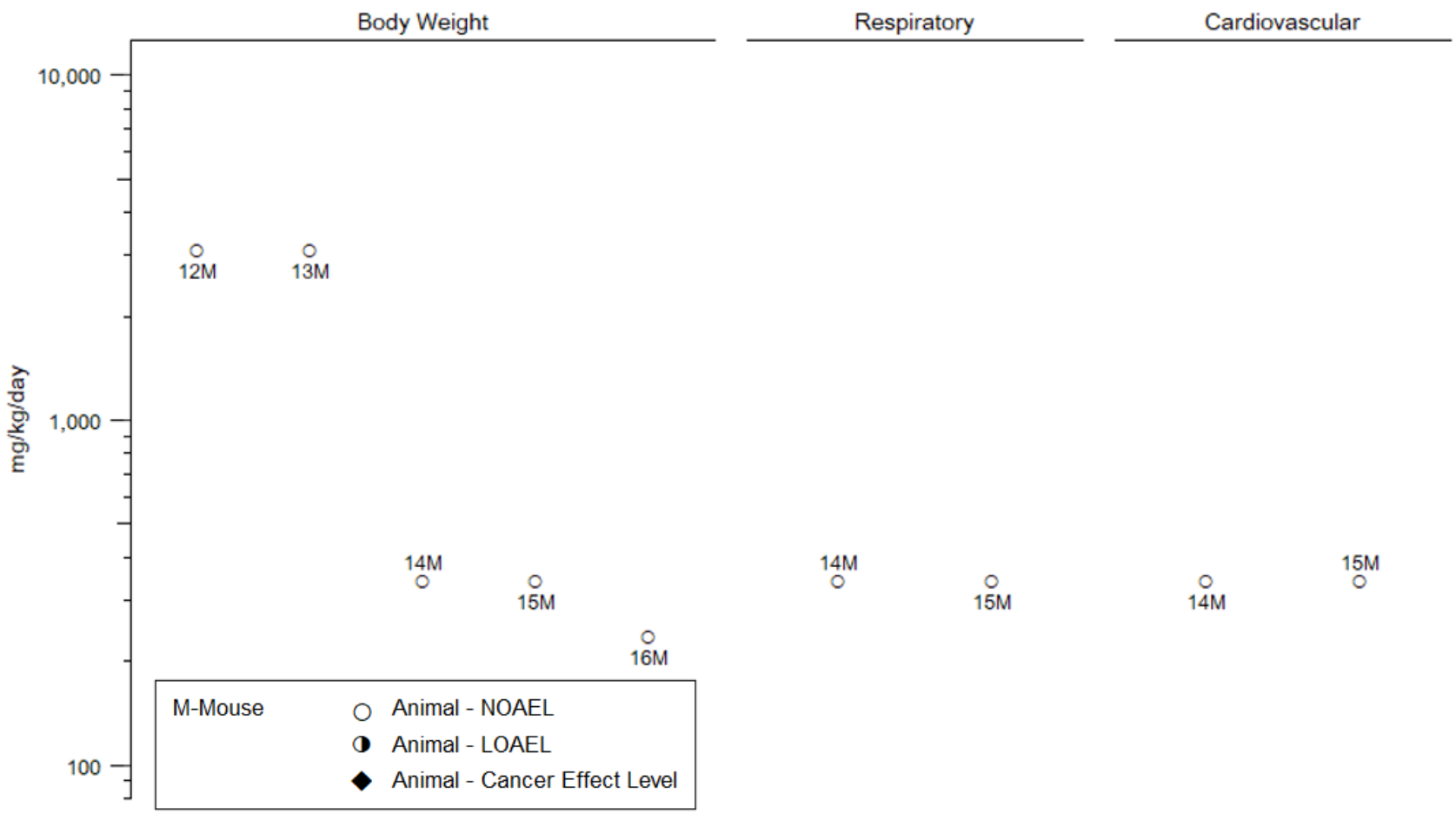


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Intermediate (15–364 days)

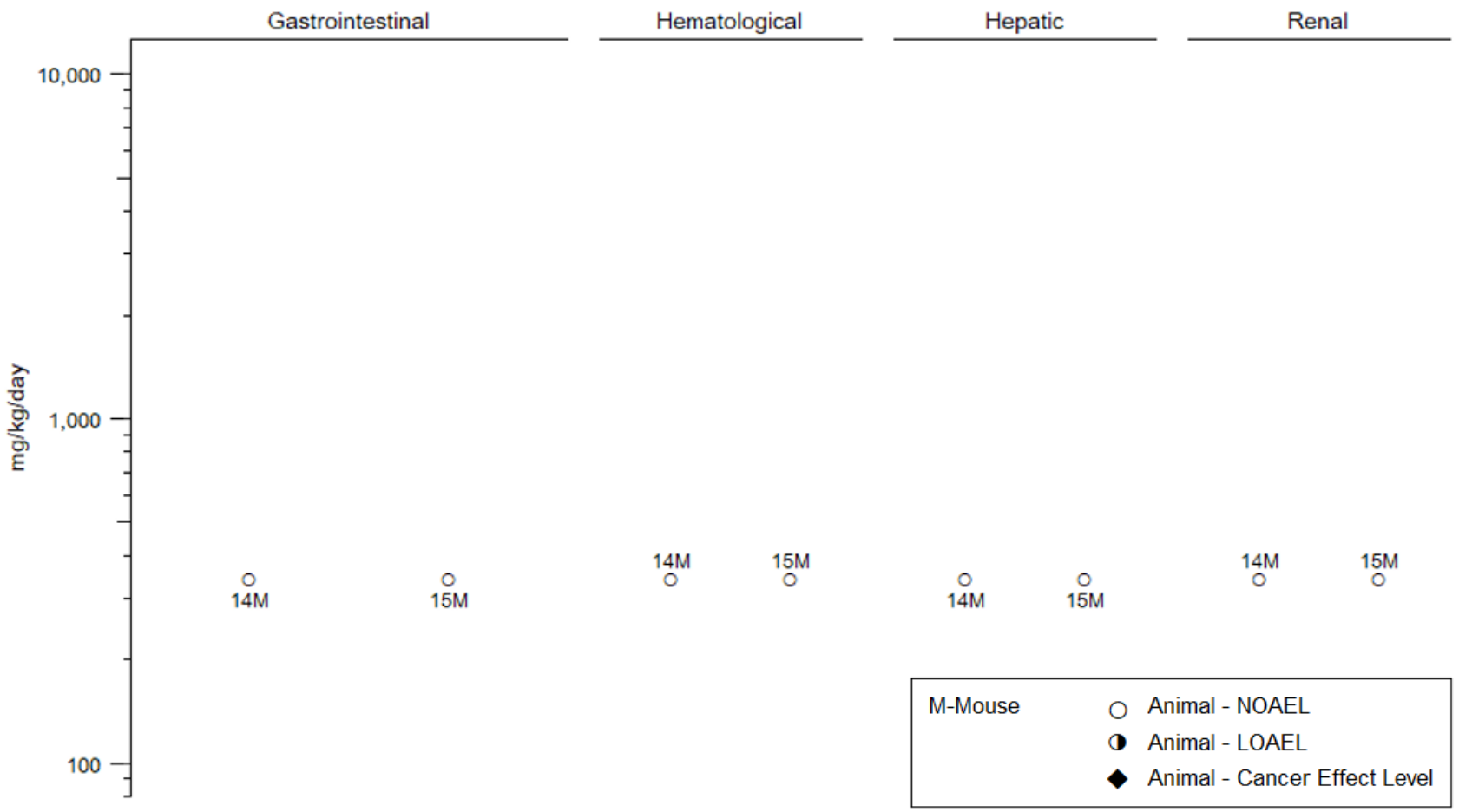


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Intermediate (15–364 days)

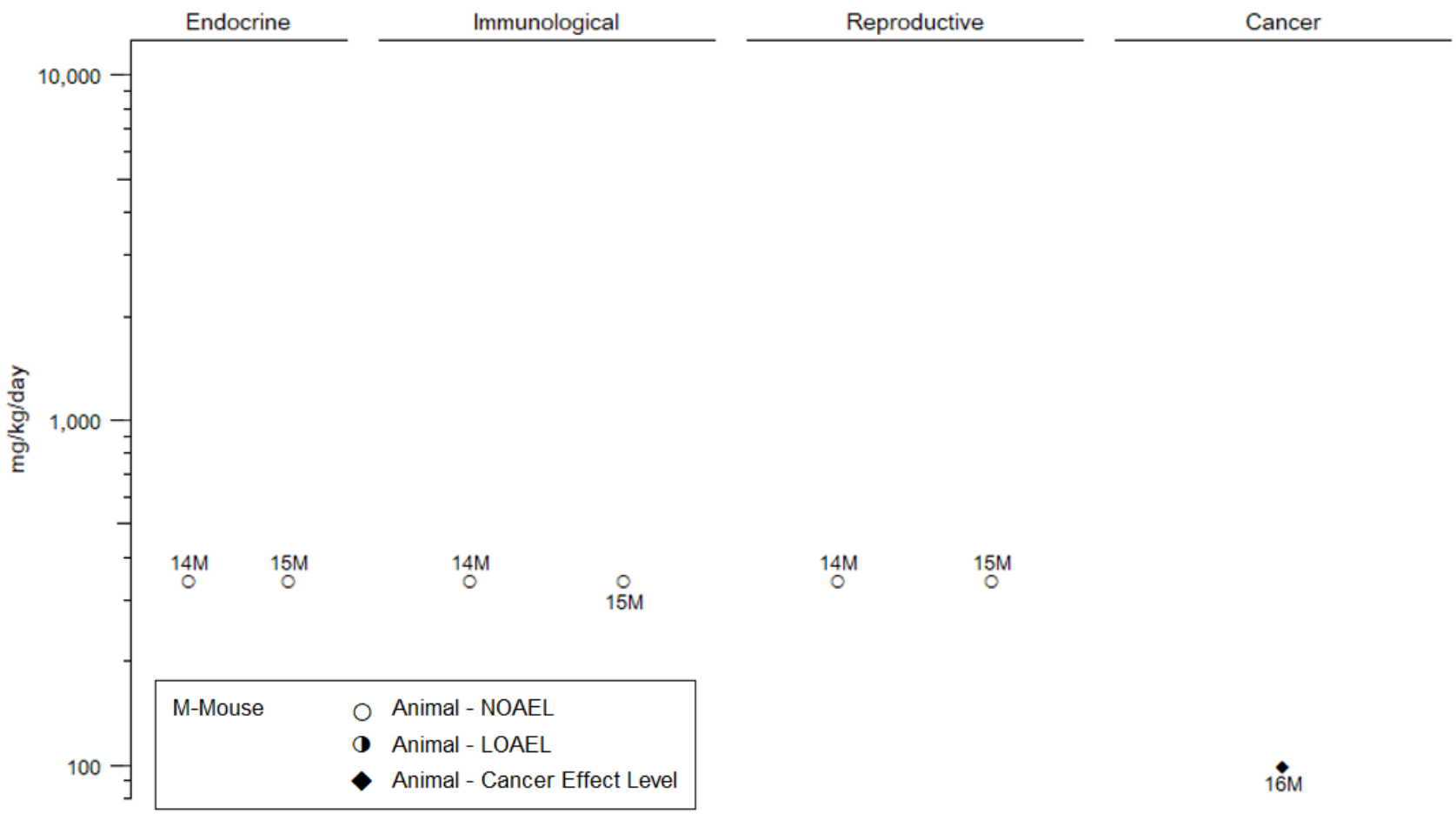


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Chronic (≥365 days)

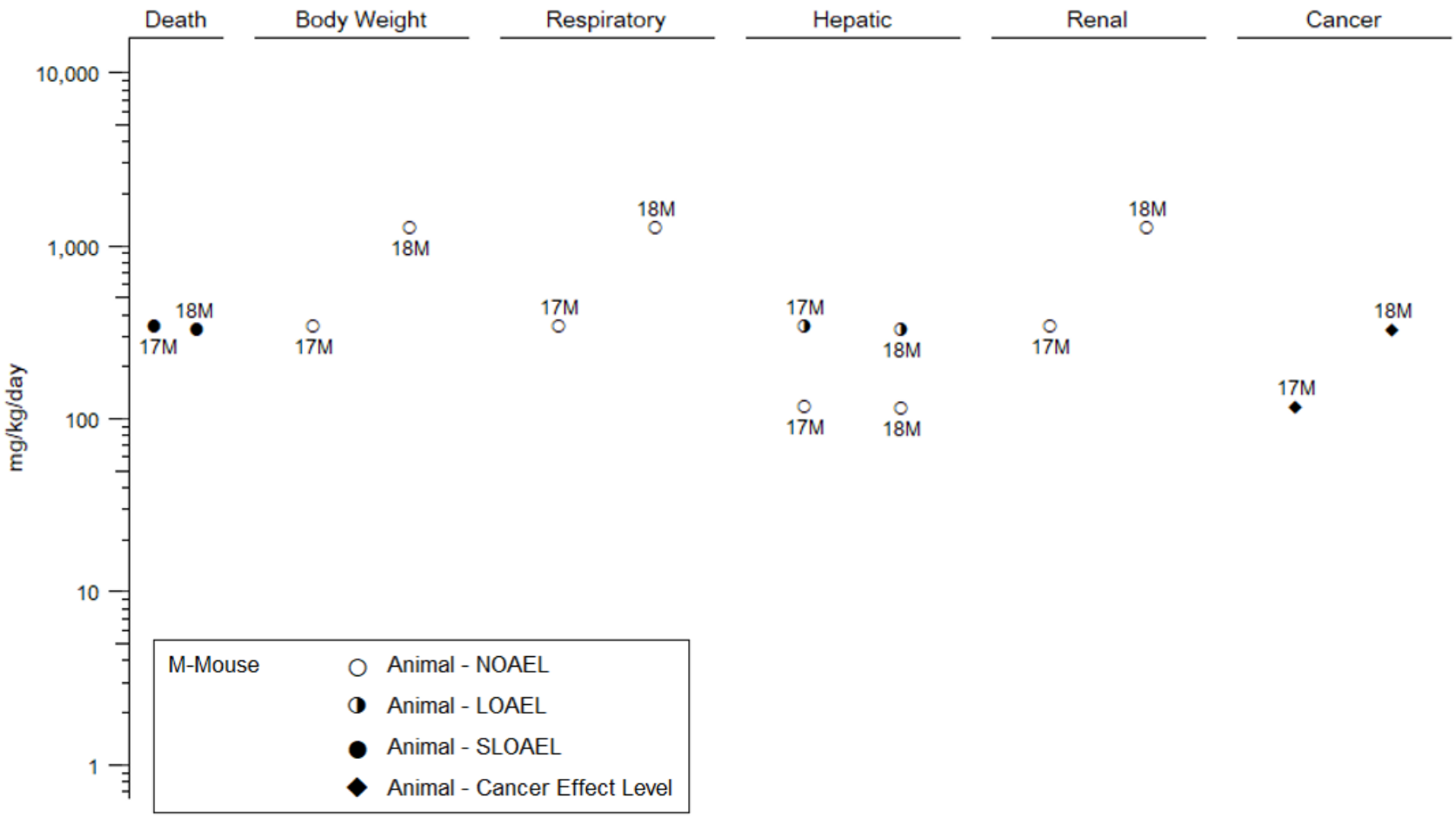


Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Miyazato et al. 1981									
1	Rat (Wistar) 10 M, 10 F	1 time (GW)	600, 700, 800, 900, 1,200, 1,100	LE, CS	Death			870 F 885 M	LD_{50}
Beechwood creosote									
Miyazato et al. 1981									
2	Mouse (ddY) 10 M, 10 F	1 time (GW)	313 (females only), 376, 451, 541, 650, 780, 936 (males only)	LE, CS	Death			433 F 525 M	LD_{50}
Beechwood creosote									
Takemori et al. 2020									
3	Mouse C57Bl/6J 4–6 M	3 days (NS)	0, 10	BW, BC	Bd wt Hepatic Endocr	10 10 10			
Wood creosote									
Takemori et al. 2020									
4	Mouse C57BL/6J db/db 4–6 M	3 days (NS)	0, 10	BW, BC	Bd wt Hepatic Endocr	10 10 10			
Wood creosote									

Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Miyazato et al. 1981									
5	Rat (Wistar) 12 M, 12 F	3 months (F)	M: 0, 163, 207, 532, 934; F: 0, 150, 210, 583, 832	LE, CS, BW, FI, HE, BC, GN, OW, RX	Bd wt	832 F			
						934 M			
					Resp	832 F			
						934 M			
					Cardio	832 F			
						934 M			
					Hemato	832 F			
						934 M			
					Hepatic	210 F	583 F		Increased serum cholesterol
						207 M	532 M		
					Renal	8,320 F			
						934 M			
					Endocr	832 F			
						934 M			
					Immuno	832 F			
						934 M			
					Neuro	934 F			
						934 M			
					Repro	832 F			
						934 M			

Beechwood creosote

Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Quynh et al. 2014									
6	Rat (Sprague-Dawley) 6 M	4 weeks 1 time/day (syringe)	0, 30, 70, 100	BW, FI, HE, BC	Bd wt	100			
					Hemato	100			
					Hepatic	100			
					Renal	100			
Korean beechwood creosote									
Miyazato et al. 1981									
7	Mouse (ddY) 12 M, 12 F	3 months (F)	M: 0, 120, 230, 465, 859, 1,207; F: 0, 134, 253, 584, 947, 1,336	LE, CS, BW, FI, HE, BC, GN, OW, RX	Bd wt	1,336 F			
						1,207 M			
					Resp	1,336 F			
						1,207 M			
					Cardio	1,336 F			
						1,207 M			
					Hemato	1,336 F			
						1,207 M			
					Hepatic	1,336 F			
						1,207 M			
					Renal	1,336 F			
						1,207 M			
					Endocr	1,336 F			
						1,207 M			
					Immuno	1,336 F			
						1,207 M			

Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	1,336 F			
						1,207 M			
					Repro	1,207 M			
Beechwood creosote									
CHRONIC EXPOSURE									
Kuge et al. 2001									
8	Rat (Sprague-Dawley) 60 M, 60 F	96–103 weeks 1 time/day (G)	0, 20, 50, 200	LE, CS, BW, HE, OP, GN, OW, HP	Death			200	Increased mortality (70% males, 67% females)
					Bd wt	50 F	200 F		Decreased terminal body weight (14%)
						200 M			
					Resp	50		200	Reddened lungs and edema
					Cardio	200			
					Hemato	200			
					Hepatic	200			
					Renal	200			
					Ocular	200			
					Endocr	200			
					Immuno	200			
					Repro	200			
Wood creosote									
Miyazato et al. 1984b									
9	Rat (Wistar) 51 M, 51 F	96 weeks (F)	M: 0, 143, 313; F: 0, 179, 394	LE, CS, BW, OW, FI, GN, HP, BC, BI	Bd wt	179 F	394 F		Decreased body weight (10%)
						313 M			
					Resp	394 F			
						313 M			

Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cardio	394 F			
						313 M			
					Hemato	394 F			
						313 M			
					Hepatic		179 F 143 M		Increased serum cholesterol in females; increased relative liver weight and serum cholesterol in males
					Renal		179 F 143 M		Increased relative kidney weight, increased BUN, nephrosis
					Endocr	394 F			
						313 M			
					Immuno	394 F			
						313 M			
					Neuro	394 F			
						313 M			
					Repro	394 F			
						313 M			
Beechwood creosote									
Miyazato et al. 1984a									
10	Mouse (ddY) 57 M, 57 F	52 weeks (F)	M: 0, 247, 474; F: 0, 297, 532	LE, CS, BW, OW, GN, BC, FI, HP, HE	Bd wt	532 F			
						474 M			
					Resp	532			
						474 M			
					Cardio	532 F			
						474 M			

Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hemato	532 F			
						474 M			
					Hepatic	532 F			
						474 M			
					Renal	532 F			
						474 M			
					Endocr	532 F			
						474 M			
					Immuno	532 F			
						474 M			
					Neuro	532 F			
						474 M			
					Repro	532 F			
						474 M			
Beechwood creosote									

[a]The number corresponds to entries in Figure 2-5; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-5. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; BUN = blood urea nitrogen; F = female(s); Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; (F) = feed; FI = food intake; (G) = gavage; GN = gross necropsy; (GW) = gavage in water; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious LOAEL

Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Acute (≤14 days)

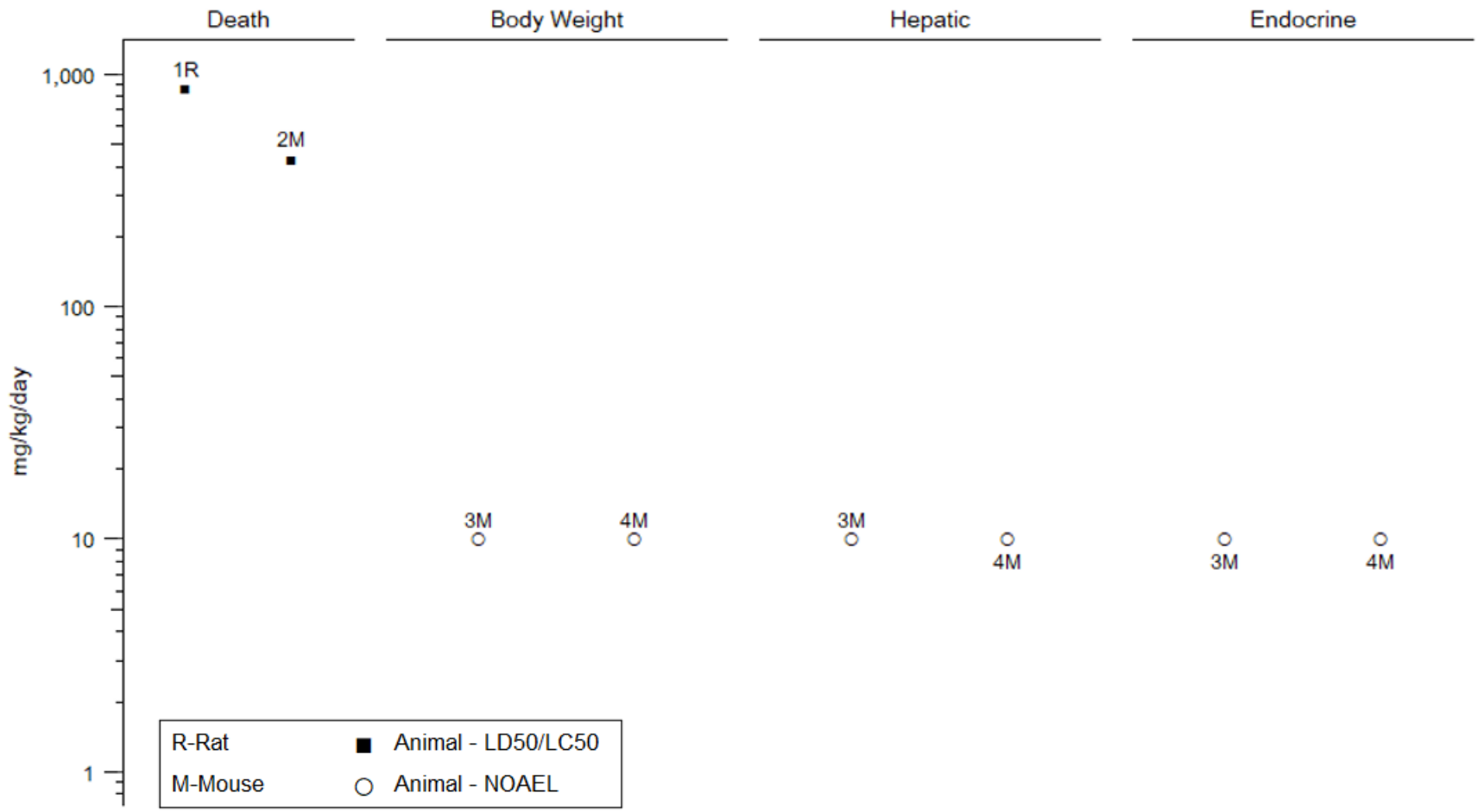


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Intermediate (15–364 days)

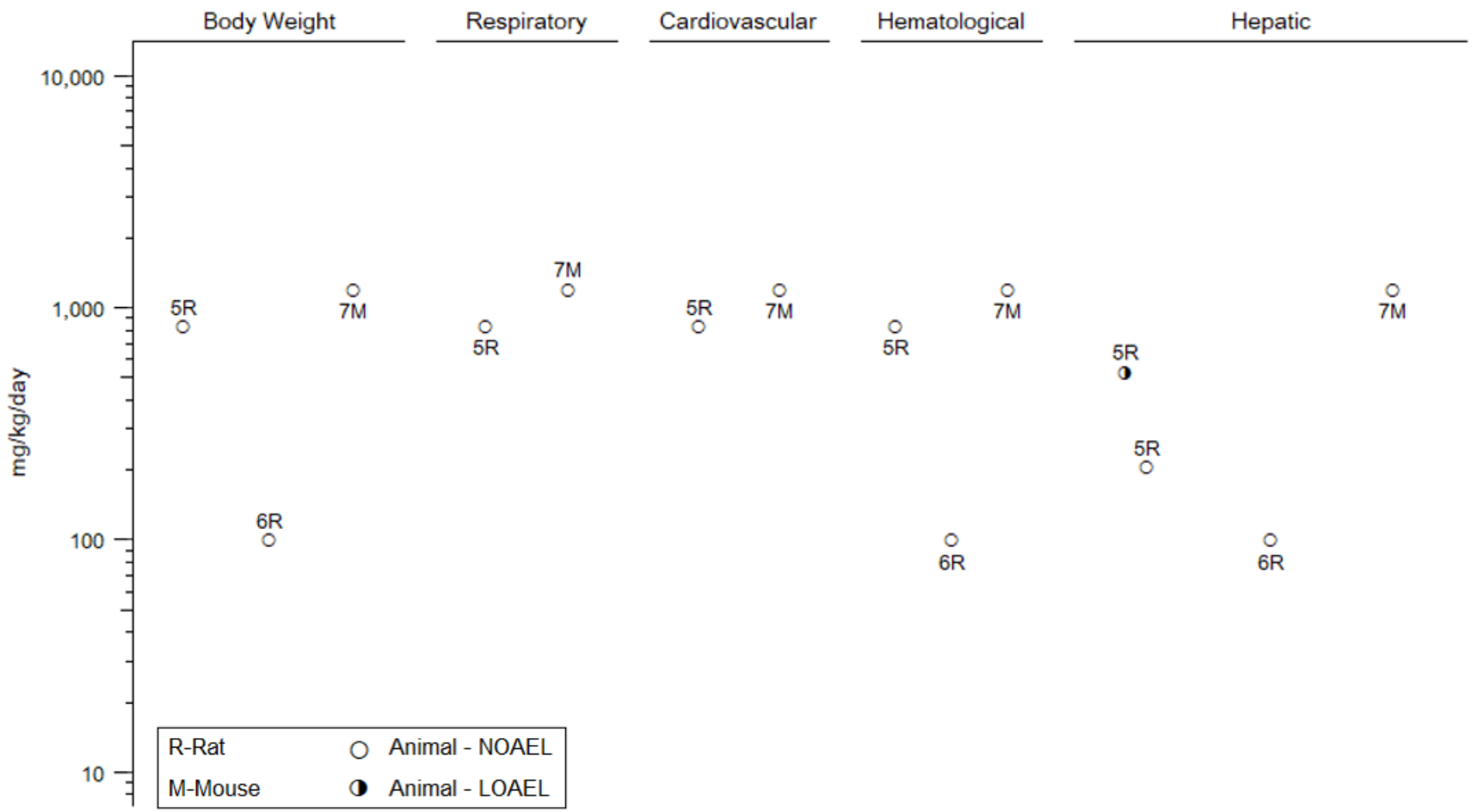


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Intermediate (15–364 days)

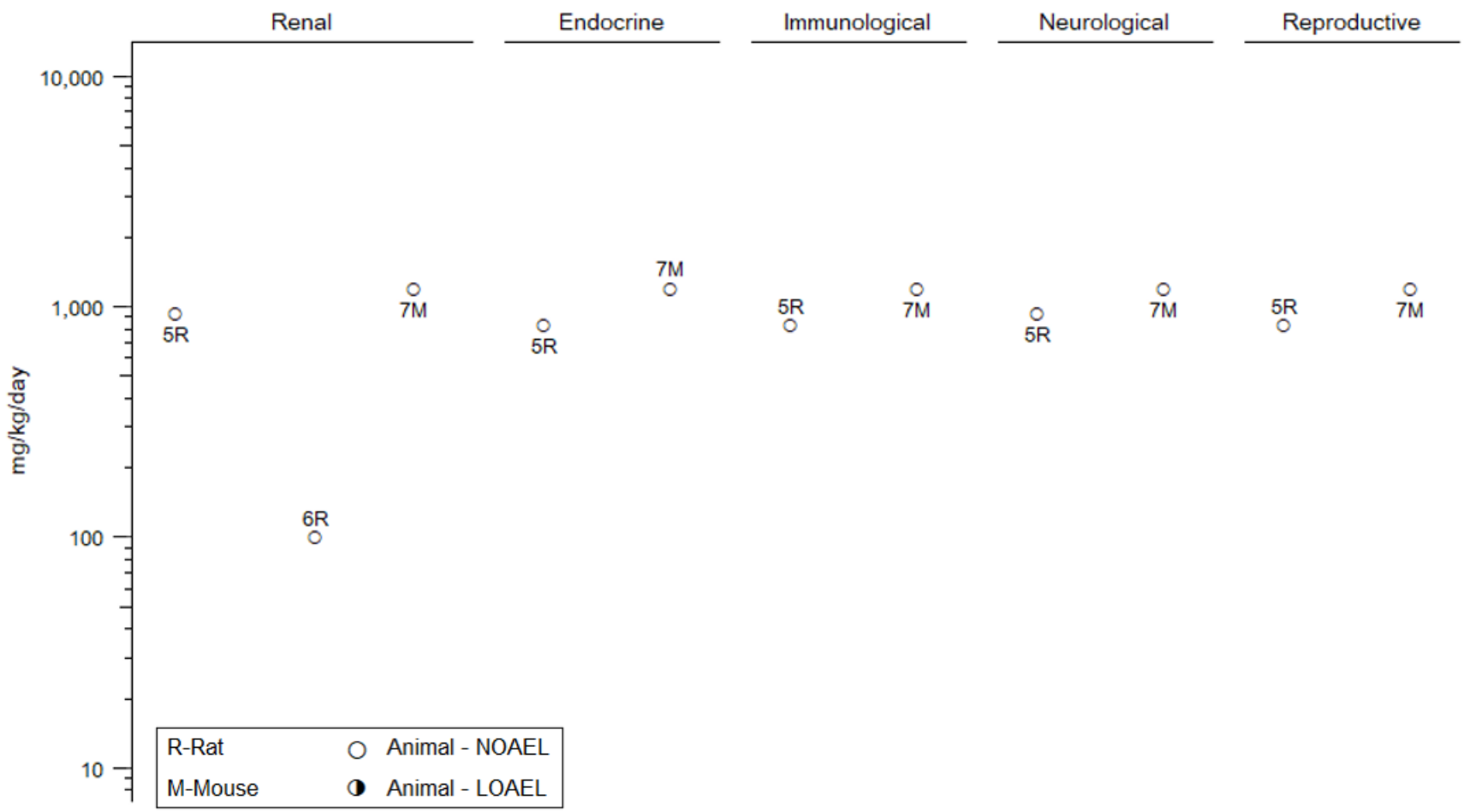


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

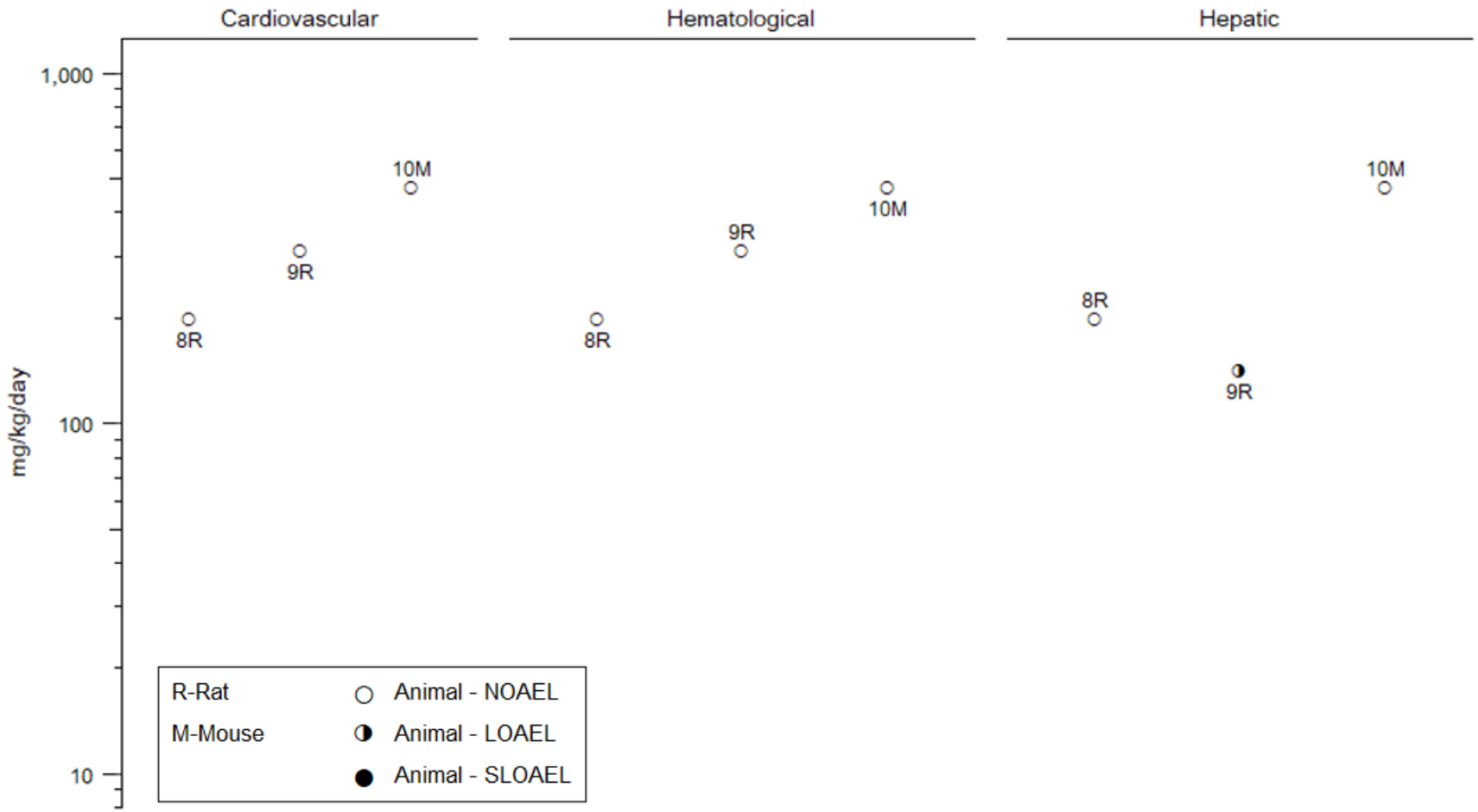


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

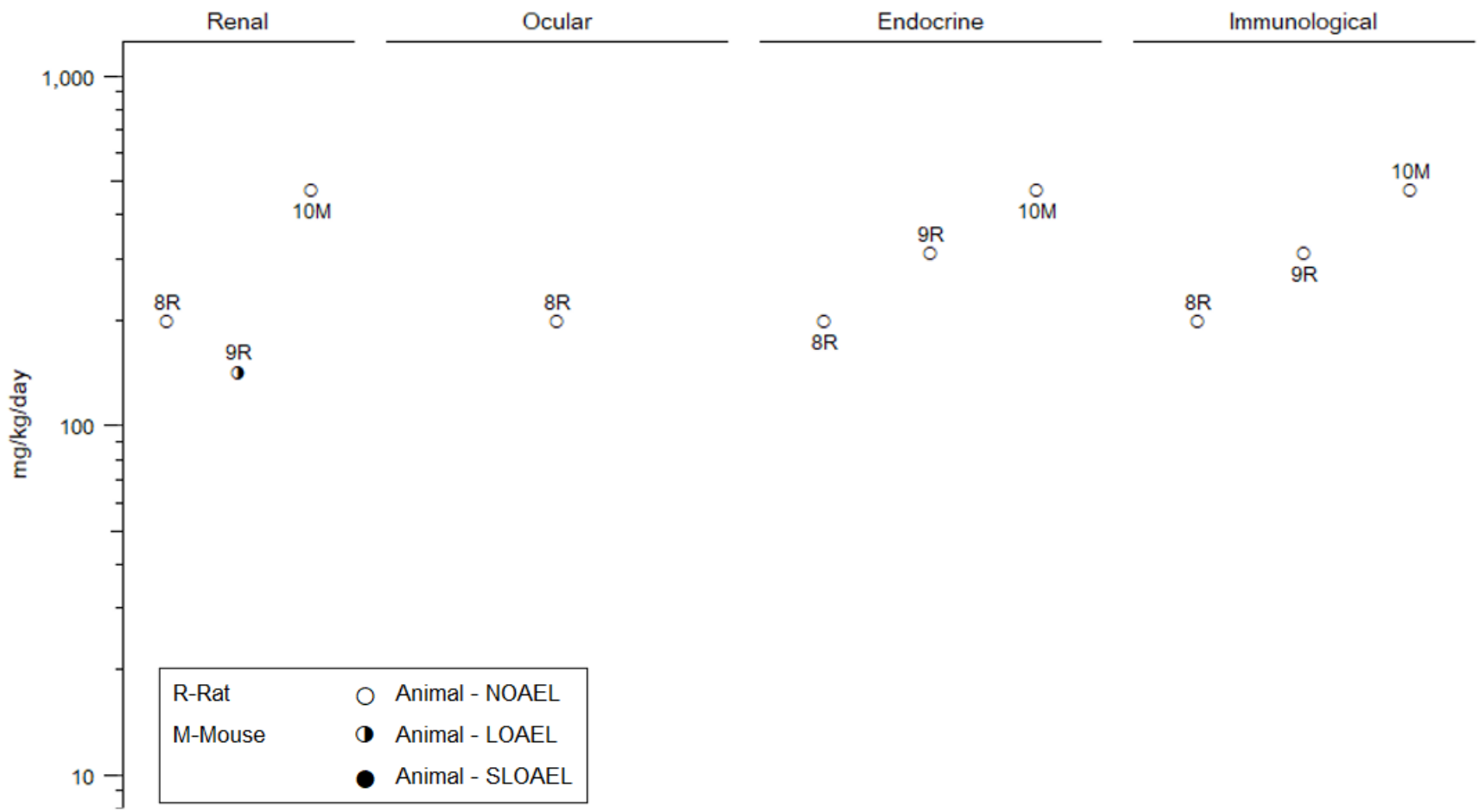


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

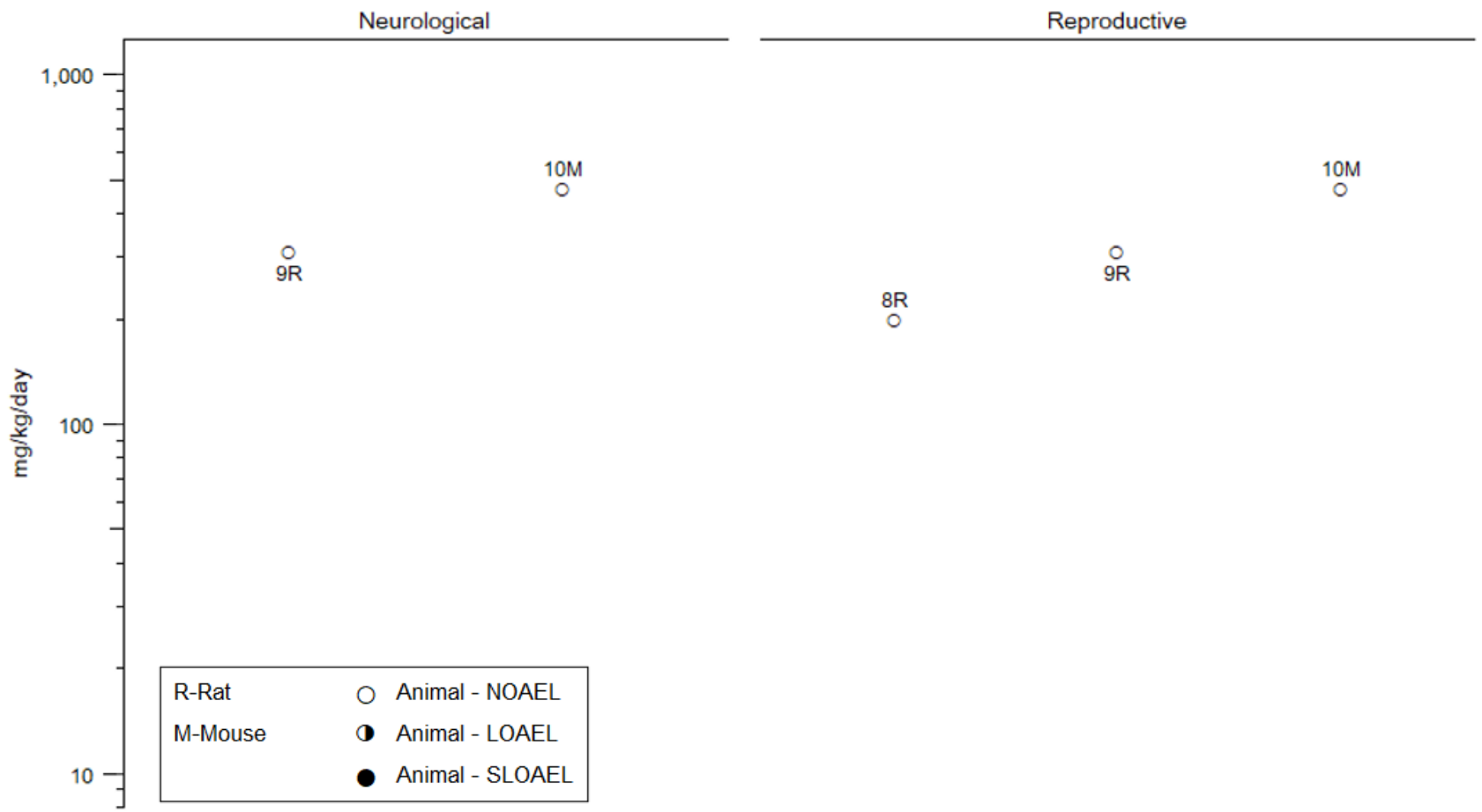


Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
EPA 1995e								
Rat (CD) 3 M, 3 F	14 days, 6 hours/day	0, 3, 10, 300, 1,000, 2,000 mg/kg	CS	Dermal		1,000		Skin irritation (edema and erythema)
P1/P13 creosote								
Zangar et al. 1989								
Rat (Sprague-Dawley) 16–17 F	4 days GDs 11–15 1 time/day	0, 500, 1,500 mg/kg	LE, BW, OW, DX	Bd wt			500	Decreased body weight gain (40%), decreased extragestational body weight gain (45%)
				Hepatic	1,500			
				Renal	1,500			
				Endocr	1,500			
				Immuno	1,500			
				Repro	1,500			
				Develop			500	Increased mid-resorptions, decreased live fetuses/litter, decreased fetal weight, decreased crown-rump length, decreased fetal lung weight
Coal-derived complex organic mixture								
Zangar et al. 1989								
Mouse (CD-1) 7 F	4 days GDs 11–15 1 time/day	0, 500, 1,500 mg/kg	LE, BW, OW, DX	Bd wt			500	Decreased body weight gain (20%)
				Hepatic	1,500			
				Renal	1,500			
				Endocr	1,500			
				Immuno	1,500			
				Repro	1,500			

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
				Develop			500	Increased mid and late resorptions, decreased live fetuses/litter, decreased fetal weight, decreased crown-rump length, decreased fetal lung weight
Coal-derived complex organic mixture								
Emmett 1986								
Rabbit (New Zealand) 6 NS	Single application	0, 0.010 mL	CS, GN	Ocular		0.01		Eye irritation (tearing and mucous discharge)
Coal tar pitch								
EPA 1994								
Rabbit (New Zealand) 5 M, 5 F	24 hours	2,000 mg/kg	LE, CS, BW	Bd wt Neuro	2,000 2,000			
P1/P13 creosote								
EPA 1994								
Rabbit (New Zealand) 3 M, 3 F	Single application	0.1 mL	LE, CS, OP	Ocular		0.1		Conjunctival redness and chemosis
P1/P13 creosote								
EPA 1994								
Rabbit (New Zealand) 2 M, 4 F	4 hours	0.5 mL	CS	Dermal		0.5		Skin irritation (edema and erythema)
P1/P13 creosote								

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1994								
Rabbit (New Zealand) 5 M, 5 F	24 hours	2,000 mg/kg	LE, CS, BW	Bd wt Neuro	2,000 2,000			
P2 creosote								
EPA 1994								
Rabbit (New Zealand) 3 M, 3 F	Single application	0.1 mL	LE, CS, OP	Ocular		0.1		Conjunctival redness and chemosis
P2 creosote								
INTERMEDIATE EXPOSURE								
Boutwell and Bosch 1958								
Mouse (Sutter) 30 F	1 time DMBA (75 µg) 28 weeks 2 times/week	0.025 mL	CS, GN	Cancer			0.03	CEL: Skin tumors (papillomas and carcinomas)
Creosote oil								
Boutwell and Bosch 1958								
Mouse (Sutter) 30 F	4 weeks 2 times/week	0.025 mL	CS, GN	Cancer	0.03			
Creosote oil								
Boutwell and Bosch 1958								
Mouse (Sutter) 30 F	28 weeks 2 times/week	0.025 mL	CS, GN	Cancer			0.03	CEL: Skin tumors (papillomas and carcinomas, 50%)
Creosote oil								

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1995e								
Rat (CD) 10 M, 10 F	13 weeks, 5 days/week, 6 hours/day	0, 4, 40, 400 mg/kg	LE, CS, BW, FI, OP, HE, BC, UR, OW, GN, HP	Bd wt Hemato Dermal Ocular	400 400 400 400			
P1/P13 creosote								
EPA 1997								
Mouse (CD-1) 30 M	5 times/week for 2 weeks, 2-week rest, TPA 2 times/week for 26 weeks	0.5, 25, 56 mg	LE, CS, BW, GN, HP	Bd wt Cancer	56		0.5	CEL: Skin tumors (papillomas and keratoacanthomas)
P1/P13 creosote								
EPA 1997								
Mouse (CD-1) 30 M	1 time DMBA day 11, 2-week rest, creosote 2 times/week for 26 weeks	0.5, 25, 56 mg	LE, CS, BW, GN, HP	Bd wt Cancer	56		25	CEL: Skin tumors (papillomas, keratoacanthomas, and squamous cell carcinomas)
P1/P13 creosote								
EPA 1997								
Mouse (CD-1) 30 M	5 times/week for 2 weeks, 2-week rest, 2 times/week for 26 weeks	56 mg	LE, CS, BW, GN, HP	Bd wt Cancer	56		56	CEL: Skin tumors (papillomas, keratoacanthomas, and squamous cell carcinomas)
P1/P13 creosote								

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mahlum 1983								
Mouse (CD-1) 30 M	1 time DMBA (50 µg) 12 months middle distillate 2 times/week	0.05 mL	GN	Cancer		0.05		Skin non-cancerous tumors (papillomas)
Heavy distillate								
Mahlum 1983								
Mouse (CD-1) 30 M	1 time coal tar 6 months PMA (50 µL) 2 times/week	0.05 mL	GN	Cancer		0.05		Skin non-cancerous tumors (papillomas)
Heavy distillate								
Marston et al. 2001								
Mouse (SENCAR) 10–30 F	1 time coal tar 2 times/week TPA (1 µg) for 25 weeks	0, 1 mg	GN	Cancer		1		Skin non-cancerous tumors (papillomas)
Coal tar								
Phillips and Alldrick 1994								
Mouse (CD-1) 30 F	2 weeks 5 times/week 40 weeks dithranol (50 mg) 3 times/week	1.5%	LE, CS	Cancer		1.5		Skin non-cancerous tumors (papillomas)
Coal tar								
Phillips and Alldrick 1994								
Mouse (CD-1) 4 F	2 weeks 5 times/week	0, 1.5%	LE, CS	Cancer	1.5			
Coal tar								

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Roe et al. 1958								
Mouse (NS) 25 NS	5 months 2 times/week	0, 0.025 mL	GN, CS	Cancer			0.03	CEL: Lung tumors (adenomas), skin tumors
Creosote oil								
Roe et al. 1958								
Mouse (NS) 25 NS	5 months 2 times/week	0, 0.025 mL	GN, CS	Cancer			0.03	CEL: Lung tumors (adenomas), skin tumors
Creosote oil								
Roe et al. 1958								
Mouse (NS) 30 NS	4 weeks 2 times/week	0.025 mL	GN, CS	Cancer			0.03	CEL: Lung tumors (adenomas)
Creosote oil								
Springer et al. 1989								
Mouse (CD-1) 30 F	1 time TPA (5 µg) 2 times/week for 24 weeks	50 µL	GN	Cancer		50		CEL: Skin non-cancerous tumors (papillomas)
Coal derived complex mixture								
CHRONIC EXPOSURE								
Emmett et al. 1981								
Mouse (C3H/HeJ) 50 M	80 weeks 2 times/week (C)	0, 25 mg	CS, GN, HP	Cancer			25	CEL: Skin tumors (papillomas, malignant tumors)
Roofing dust								
Emmett et al. 1981								
Mouse (C3H/HeJ) 50 M	80 weeks 2 times/week (C)	0, 25 mg	CS, GN, HP	Cancer			25	CEL: Skin tumors (papillomas, malignant tumors)
Coal tar pitch								

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Emmett et al. 1981								
Mouse (C3H/HeJ) 50 M	80 weeks 2 times/week (C)	0, 25 mg	CS, GN, HP	Cancer			25	CEL: Skin tumors (papillomas, malignant tumors)
Coal tar bitumen								
Emmett et al. 1981								
Mouse (C3H/HeJ) 50 M	80 weeks 2 times/week (C)	0, 25 mg	CS, GN, HP	Cancer			25	CEL: Skin tumors (papillomas, malignant tumors)
Roofing coal tar bitumen								
Lijinsky et al. 1957								
Mouse (Swiss) 30 F	70 weeks 2 times/week	100%	GN, CS	Cancer			100	CEL: Skin tumors (papillomas and carcinomas)
Creosote oil								
Lijinsky et al. 1957								
Mouse (Swiss) 30 F	1 time DMBA (1%) 70 weeks 2 times/week	2, 10, 100%	GN, CS	Cancer			10	CEL: Skin tumors (papillomas and carcinomas)
Creosote oil								
Niemeier et al. 1988								
Mouse (C3H/HeJ) 50 M	78 weeks 2 times/week	50 µL	LE, CS, GN	Cancer			50	CEL: Skin tumors (papillomas, squamous cell carcinomas)
Coal tar pitch								
Niemeier et al. 1988								
Mouse (Swiss CD-1) 50 M	78 weeks 2 times/week	50 µL	LE, CS, GN	Cancer			50	CEL: Skin tumors (papillomas, squamous cell carcinomas)
Coal tar pitch								

Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Poel and Kammer 1957								
Mouse (C57L) 8–11 B Creosote oil	Lifetime 3 times/week	20, 80%	GN, CS	Cancer		20 F		CEL: Skin non-cancerous tumors (papillomas)
Wallcave et al. 1971								
Mouse (Swiss-albino) 26–29 B Coal tar pitch	82 weeks 2 times/week (C)	1.7 mg	LE, CS, BW, GN, HP	Cancer			1.7	CEL: Skin tumors (papillomas and squamous cell carcinomas)

B = both males and females; BC = blood chemistry; Bd wt or BW = body weight; (C) = capsule; CAS = Chemical Abstracts Service; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DMBA = 7,12-dimethylbenz[α]anthracene; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; GD = gestational day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmology; OW = organ weight; P1/P13 = CAS Registry Number 8001-58-9, coal tar creosote; P2 = CAS Registry Number 65996-92-1, coal tar distillate; PMA = 12-O-tetradecanoylphorbol-13-acetate; Repro = reproductive; Resp = respiratory; SLOAEL = serious LOAEL; TPA = phorbol-12-myristate-13-acetate; UR = urinalysis

2.2 DEATH

Human Studies. Numerous epidemiological studies have evaluated associations between occupational exposure to creosote compounds and mortality, with studies available in creosote workers, coke workers, gas workers, aluminum workers, roofers and pavers, and chimney sweeps. In this section, mortality due to all cancers (combined), all-cause mortality (including cancer), and noncancer causes, including diseases of the respiratory, cardiovascular, renal, and neurological systems are reviewed and discussed; these studies are summarized in Table 2-5. Studies evaluating mortality due to specific cancer types are discussed in Section 2.19. Note that no reports were located of death in humans attributed solely to inhalation exposure to wood creosote or the creosote bush, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles; as such, data are presented by occupation rather than by compound.

Table 2-5. Summary of Studies Evaluating Associations Between Occupational Exposures to Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles and Mortality

		Cause of death					
Worker population	Reference (n)	Resp[a]	CVS[b]	Renal[c]	CNS[d]	All cancer	All-cause mortality
Creosote workers	Wong and Harris 2005[e] (n=2,179)	↔	↔	NR	NR	↔	↔
Coke workers	Bye et al. 1998[f] (n=888)	↔	↔	NR	NR	↔	↔
	Chau et al. 1993 (n=536)	↔	↑ (NS)	NR	NR	↑	↑
	Constantino et al. 1995 (n=5,321)	↔	↔	NR	NR	↑	↑
	Lloyd et al. 1970 (n=2,552)	NR	↔ (W) ↔ (NW)	NR	↔ (W) ↔ (NW)	↔ (W) ↑ (NW)	↔ (W) ↑ (NW)
	Lloyd 1971 (n=2,048)	NR	↔ (W) ↔ (NW)	NR	NR	NR	↔ (W) ↔ (NW)
	Redmond et al. 1972 (n=1,979)	↔ (W) ↔ (NW)	NR	NR	NR	NR	↔ (W) ↔ (NW)
Gas workers	Gustavsson and Reuterwall 1990 (n=295)	↔	↔	NR	↔	↔	↔

Table 2-5. Summary of Studies Evaluating Associations Between Occupational Exposures to Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles and Mortality

Worker population	Reference (n)	Cause of death					
		Resp[a]	CVS[b]	Renal[c]	CNS[d]	All cancer	All-cause mortality
Aluminum workers	Bjor et al. 2008[f] (n=2,264)	↔	↔	NR	↑ (MD)	↔	↔
	Carta et al. 2004[e] (n=1,152)	↔	↔	↔	NR	↔	↓
	Friesen et al. 2009[f] (n=4,316)	↔	↔	NR	NR	NR	NR
	Friesen et al. 2010[e] (n=7,026)	↔	↔	↔	↔	NR	↔
	Gibbs and Sevigny 2007a (n=6,697)[f,g]	↑ (COPD)[h] ↔ (ASTH)	↑ (CVD) ↓ (IHD)	↔	↑ (AD)	↑	↑
	Gibbs et al. 2007[e] (n=5,977)	↑ (COPD) ↔ (ASTH)	↑ (CVD) ↔ (IHD)	NR	↑ (AD)	NR	NR
	Gibbs et al. 2014[e] (n=17,089)	↑ (COPD)[i] ↔ (ASTH)	↑ (CVD) ↔ (IHD)	↔	↔	NR	NR
	Liu et al. 1997[e] (n=6,635)	↔	↑ (CVD)	NR	NR	↑	↔
	Milham 1979[f] (n=400)	↑ (EMP)	↓ (CD)	NR	NR	↔	↓
	Moulin et al. 2000[f] (n=2,133)	↔	↔	NR	↔	↔	↓
	Mur et al. 1987[f] (n=6,455)	NR	↔ (NS)	NR	NR	↔	↔
	Rockette and Arena 1983[f] (n=21,829)	↔	↓ (NS)	↔	NR	↓	↓
	Romundstad et al. 2000c (n=5,611)	↔	↔	↔	NR	↔	↔
	Sim et al. 2009 (n=4,396)	↔	↔	NR	NR	↓	↓
Roofers and pavers	Burstyn et al. 2003[f] (n=58,862)	↑	NR	NR	NR	NR	NR
	Burstyn et al. 2005[e] (n=12,367)	NR	↑	NR	NR	NR	NR
	Stern et al. 2000[f] (n=11,144)	↑ (NS)	↓ (IHD, CVD)	NR	NR	↑	↔
	Swaen and Slangen 1997[f] (n=866)	↔	↔	NR	NR	↔	↔

Table 2-5. Summary of Studies Evaluating Associations Between Occupational Exposures to Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles and Mortality

Worker population	Reference (n)	Cause of death					
		Resp[a]	CVS[b]	Renal[c]	CNS[d]	All cancer	All-cause mortality
Chimney sweeps	Evanoff et al. 1993[e] (n=5,542)	↑ (NS)	↑ (IHD)	NR	NR	↑	↑
	Hansen 1983[f] (n=713)	NR	↑ (IHD)	NR	NR	↔	↔

[a]Respiratory diseases include bronchitis, emphysema, asthma, and COPD.
[b]Cardiovascular diseases include IHD, myocardial infarction, hypertension, and cerebrovascular diseases.
[c]Renal diseases include nephritis and nephrosis.
[d]CNS diseases include mental disorders, multiple sclerosis, Parkinson's disease, motor neuron disease, neurodegenerative diseases, and Alzheimer's disease.
[e]Analyses controlled for smoking.
[f]Analyses controlled for some confounders (e.g., age, race, calendar year, years of exposure), but not for smoking.
[g]Primary cohort broken down into subcohorts; not all subcohorts showed associations.
[h]Significant trend with increasing benzo[a]pyrene exposure.
[i]Positive association in smokers with a significant benzo[a]pyrene exposure-related trend; no association in nonsmokers.

↑ = positive association; ↔ = no association; ↓ = inverse association; AD = Alzheimer's disease; ASTH = asthma; CD = circulatory diseases; CNS = central nervous system; COPD = chronic obstructive pulmonary diseases (may include chronic bronchitis, emphysema, and asthma); CVD = cerebrovascular disease; CVS = cardiovascular diseases; EMP = emphysema; IHD = ischemic heart disease; MD = mental disorder; NR = not reported; NS = not specified; NW = nonwhite workers; Resp = respiratory diseases; W = white workers

Creosote workers. A study of 2,179 creosote workers did not observe associations between creosote exposure and death due to diabetes mellitus, heart, respiratory, hepatic diseases, all cancer, or all-cause mortality compared to U.S. national cause-, gender-, race-, year-, and age-specific mortality rates (Wong and Harris 2005).

Coke workers. Increased cardiovascular disease mortality was observed in 563 retired coke oven workers in France, mostly in those who worked in closest proximity to the ovens (Chau et al. 1993). However, studies examining 888 Norwegian coke workers (Bye et al. 1998) and up to 5,321 coke oven workers in the steel industry in Pennsylvania followed over a 30-year period (Constantino et al. 1995; Lloyd 1971; Lloyd et al. 1970; Redmond et al. 1972) found no associations between exposure and cardiovascular or respiratory disease mortality. Chau et al. (1993) and Constantino et al. (1995) also found increased mortality due to all cancers and all-cause mortality. Lloyd et al. (1970) stratified workers by race (white and non-white) and found increased risk for all cancer mortality and all-cause mortality in non-white workers but not in white workers. Interpretation of these findings is challenging as confounding factors,

such as smoking, were not considered. Lloyd (1971) and Redmond et al. (1972) did not find an increased risk of mortality due to all causes. Note that these studies did not report deaths due to all cancers combined. No increased risk for these mortalities was observed in Norwegian coke workers (Bye et al. 1998).

Gas workers. Gustavsson and Reuterwall (1990) examined mortality and cancer incidence in 295 Swedish gas production workers and found no association between exposure and mortality from respiratory, cardiovascular, nervous system diseases, all cancer, or all-cause mortality.

Aluminum workers. Aluminum workers are the most-studied occupation regarding creosote exposure. Most studies did not identify associations between exposure and increased risks of noncancer mortality, mortality due to all cancer, or all-cause mortality (Carta et al. 2004; Friesen et al. 2009, 2010; Moulin et al. 2000; Mur et al. 1987; Rockette and Arena 1983; Romundstad et al. 2000c; Sim et al. 2009). Gibbs and Sevigny (2007b) and Liu et al. (1997) reported associations between exposure and all cancer deaths, but only Gibbs and Sevigny (2007a) found an increase in all-cause mortality. Other studies found no increased or decreased risk of mortality due to all cancers and all-cause mortality. A few studies have observed increased outcome-specific deaths. Bjor et al. (2008) identified an increase in mental disorder mortality in aluminum workers, with the majority (27 out of 34 deaths) being related to alcohol. Gibbs and Sevigny (2007a) reported an increase in Alzheimer's disease, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) in workers hired after January 1, 1950; however, these associations were only observed in a few of the subcohorts that were evaluated. Similar increases and subcohort differences were observed in follow-up studies by the same group (Gibbs et al. 2007, 2014). Milham (1979) reported increased mortality from emphysema in 2,103 aluminum reduction plant workers; however, no differences were observed for all respiratory disease mortality, and an inverse relationship was observed for all circulatory disease mortality. Liu et al. (1997) identified increased cerebrovascular disease and diseases of the digestive system in the nonsmoking population of a group of aluminum workers in a Shanghai carbon plant (n=6,635; 95,847 person-years).

Roofing and paving workers. An increased risk of death due to all cancers, but not for all-cause mortality, was observed in a study of 11,144 roofers in the United States (Stern et al. 2000). In contrast, no increased risks of death due to all cancers and all-cause mortality were found in 1,773 roofers in The Netherlands (Swaen and Slangen 1997). Increased nonmalignant respiratory and obstructive lung diseases mortality were associated with the estimated cumulative and average exposures to PAHs and coal tar in asphalt workers (Burstyn et al. 2003). Similarly, mortality related to diseases of the circulatory

system and ischemic heart disease (IHD) were reported to be associated with the average exposure to coal tar in asphalt workers (Burstyn et al. 2005). Stern et al. (2000) found an increase in mortality due to pneumoconiosis and other nonmalignant respiratory diseases in asphalt workers compared with U.S. age-, gender-, and race-specific proportional mortality rates, but decreases in mortality due to diabetes and cerebrovascular disease. No exposure-related noncancer associations were identified by Swaen and Slangen (1997) evaluating a group of 907 tar distillery workers and 866 roofers.

Chimney sweeps. Evanoff et al. (1993) evaluated 5,542 chimney sweeps in Sweden between 1951 and 1990 and reported increased mortality from IHD, nonspecific respiratory diseases, all cancer, and all-cause mortality. Similarly, Hansen (1983) reported increased mortality from IHD in 713 male chimney sweeps in Denmark. However, no increased mortality was observed for all cancer or all-cause mortality.

Little information is available regarding mortality following ingestion of creosote compounds. 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. Thus, ingestion of creosote can be fatal to humans, but the dose level required to produce death cannot be accurately estimated from this report.

Animal Studies. Animal studies looking at mortality following exposure to creosote compounds are limited; however, there are some studies available for intermediate- and chronic-duration inhalation exposure to coal tar pitch aerosols, acute-, intermediate-, and chronic-duration oral exposure to coal tar products and wood creosotes, and acute-duration dermal exposure to coal tar creosote.

Coal tar products. No exposure-related deaths were reported in male and female rats exposed to creosote aerosol up to 5,300 mg/m^3 for 4 hours (EPA 1994), or in male rats exposed to high-boiling coal liquid (heavy distillate, HD) at 700 mg/m^3 for 6 weeks (Sasser et al. 1989). Similarly, no deaths were reported in male and female rats or mice exposed to up to 690 mg/m^3 of a coal tar aerosol for up to 13 weeks (Springer et al. 1986b, 1987), or in male and female rats exposed to creosote aerosol up to 102 mg/m^3 for 13 weeks (EPA 1995c, 1995d). Rabbits exposed to 10 mg/m^3 coal tar pitch aerosol in a mixture of benzene, toluene, and xylene (BTX) for 18 months, exhibited higher mortality than the control animals (89 versus 33%), although the authors attributed death to an unrelated chronic respiratory infection (MacEwen et al. 1977).

Several acute oral LD_{50} values are available for coal tar creosote: 2,451 mg/kg for male rats and 1,893 mg/kg for female rats with P1/P13 creosote (EPA 1994), and 2,524 mg/kg for male rats and 1,993 mg/kg for female rats with P2 creosote (EPA 1994). Ten out of 16 female rats died following gavage with 740 mg/kg/day coal tar on gestational days (GDs) 12–16 (Hackett et al. 1984), but no deaths were reported in female rats gavaged with 740 mg/kg/day coal tar on GDs 12–14 (Springer et al. 1986a), or in female rats gavaged with up to 225 mg/kg/day on GDs 6–15 (EPA 1995a, 1995b). No exposure-related deaths were reported in mice after dietary treatment of MGP residue, a form of coal tar, with doses up to 462 mg/kg/day (males) or 344 mg/kg/day (females) for 94 or 185 days (Weyand et al. 1994) or in female mice fed at doses of up to 236 mg/kg/day for 260 days (Weyand et al. 1995). In a set of 2-year feeding studies (Culp et al. 1996, 1998), dietary levels ≥333 mg/kg/day of a composite of coal tar resulted in an increase in early mortality in mice compared with controls, with survival rates ≤21% at the end of the study.

No exposure related deaths were observed in male and female rabbits applied dermally with 2,000 mg/kg (EPA 1994) or ocularly instilled with 0.1 mL creosote (EPA 1994), in rats and mice dermally exposed up to 1,500 mg/kg coal tar on GDs 11–15 (Zangar et al. 1989), in male and female rats exposed up to 400 mg/kg for 90 days (EPA 1995e), or in female mice treated topically with 1.5% coal tar ointment 5 times/week for 40 weeks (Phillips and Alldrick 1994).

Wood creosotes. The oral LD_{50} values for a single gavage administration of a 10% aqueous solution of beechwood creosote in rats were 885 mg/kg (males) and 870 mg/kg (females) and in mice were 525 mg/kg (males) and 433 mg/kg (females) (Miyazato et al. 1981). However, no treatment-related deaths were observed when beechwood creosote was added in the feed of rats up to 934 mg/kg/day (males) or 832 mg/kg/day (females) or in mice up to 1,207 mg/kg/day (males) or 1,336 mg/kg/day (females) for 3 months (Miyazato et al. 1981). Increases in mortality were observed in male (30% survival compared to 53% in controls) and female (33% survival compared to 43% in controls) rats administered wood creosote by gavage at 200 mg/kg/day for 40 or 80 weeks, respectively (Kuge et al. 2001), although the study authors suggested that early mortality may have been associated with aspiration of the test material. No treatment-related deaths were observed in female rats (394 mg/kg/day) fed beechwood creosote for 96 weeks or mice (474 mg/kg/day male or 532 mg/kg/day female) for 52 weeks (Miyazato et al. 1984a, 1984b). Male rats fed 313 mg/kg/day for 96 weeks had increased mortality compared to controls (59 versus 43%), although deaths were mostly attributed to bronchopneumonia, which was also prevalent in the control group (Miyazato et al. 1984b)

2.3 BODY WEIGHT

Human Studies. No data were available evaluating body weight changes in humans following exposure to creosote compounds by any exposure route.

Animal Studies. Studies in animals show that exposure to creosote either by inhalation or ingestion may result in decreases in body weight and body weight gain. Studies are available for acute-, intermediate-, and chronic-duration inhalation exposure to coal tar aerosols, and acute-, intermediate-, and chronic-duration oral exposure to coal tar products and wood creosotes. Note that for dietary exposure studies, decreased body weight and body weight gain are frequently accompanied by decreased food consumption. In the absence of information that decreased food consumption is due to a chemical-specific adverse effect rather than due to palatability alone, effects on body weight accompanied by decreased food consumption are not considered to be an adverse effect (e.g., not a LOAEL) of oral exposure to creosote compounds.

Coal tar products. Decreased body weight (11% reduction) was observed in an acute-duration, gestational exposure study in female rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on GDs 12–16, but there was no difference in extragestational body weight (maternal body weight minus the weight of the gravid uterus) compared to controls (Springer et al. 1982). Body weights were decreased in male and female rats exposed to 690 mg/m^3 of a coal tar aerosol for 5 weeks (27 and 14% reduction, respectively) or 13 weeks (39 and 14% reduction, respectively) (Springer et al. 1986b). In contrast, no difference in body weight was observed in mice exposed to up to 690 mg/m^3 coal tar aerosol or in rats exposed up to 106 mg/m^3 for 13 weeks (EPA 1995c, 1995d; Springer et al. 1986b, 1987). Male Fischer 344 rats exposed to HD at 700 mg/m^3 for 6 consecutive weeks showed suppressed growth, with final body weights 17% less than control (Sasser et al. 1989). Female rabbits exhibited a 30% decrease in body weight compared to controls after exposure to 10 mg/m^3 for 9 months (MacEwen et al. 1977). No change in body weight was observed in male or female *Macaca mulatta* monkeys after exposure to 10 mg/m^3 coal tar aerosol for 18 months, although a 11 and 14% decrease in body weight was observed in male and female Sprague-Dawley rats, respectively, exposed under the same conditions (MacEwen et al. 1977).

No difference in body weight gain was observed in male and female rats gavaged with a single dose up to 4,000 mg/kg of P1/P13 or P2 creosote (EPA 1994), in female mice administered 400 mg/kg petroleum creosote by gavage on GDs 5–9 compared to the control group (Iyer et al. 1993), nor in mice gavaged with up to 100 mg/kg creosote in sesame oil once a day for 4 days (Fielden et al. 2000). Decreased body weight gain (43%) was reported in female rats gavaged on GDs 12–16 with ≥180 mg/kg/day coal tar, while decreased extragestational body weight gain (93%) was reported at doses as low as ≥90 mg/kg/day (Hackett et al. 1984). Decreased gestational (19%) and extragestational (40%) body weight gains were also observed in female rats gavaged with 740 mg/kg/day coal tar on GDs 12–14 (Springer et al. 1986a). Decreased body weight gain (16 and 24%) was also observed in in female rats gavaged with 175 and 225 mg/kg/day, respectively, on GDs 6–15 (EPA 1995a, 1995b). No differences in body weights were observed in male rats treated with 50 mg/kg/day coal tar creosote by gavage for 1–5 weeks (Chadwick et al. 1995).

Dietary creosote studies examining body weight often have confounded results due to differences in food consumption by the animals, particularly at the higher coal tar doses. No differences in body weights were observed in mice fed up to 659 mg/kg/day coal tar for 15 days, while mice fed ≥1,871 mg/kg/day showed substantial weight loss due to refusal to eat the higher concentration of coal tar (Weyand et al. 1991). Average body weights were decreased by approximately 16% compared to controls in male mice fed ≥1,693 mg/kg/day coal tar for 28 days, although a dose-related decrease in food consumption was also observed (Culp and Beland 1994). No exposure-related body weight changes were reported for male or female mice fed doses up to 462 and 344 mg/kg/day coal tar, respectively, for 185 days (Weyand et al. 1994), or for female mice fed at doses of up to 236 mg/kg/day to coal tar for 260 days (Weyand et al. 1995). In a set of chronic-duration feeding studies, body weights were decreased approximately 15% in female B6C3F1 mice fed ≥346 mg/kg/day coal tar for 2 years, although food consumption was also decreased by 20–30% in these groups (Culp et al. 1996, 1998).

Dermal studies have shown similar inconsistences in body weight changes. No differences in body weight were observed in male and female rabbits dermally applied with 2,000 mg/kg creosote (EPA 1994), in male and rats dermally exposed with doses up to 400 mg/kg for 90 days (EPA 1995e), or in male mice applied with coal tar pitch (50 µL of a 30–84 mg/mL solution) for 78 weeks (Niemeier et al. 1988). In a developmental study of rats and mice, dermal exposure to ≥500 mg/kg coal tar on GDs 11–15 resulted in a decrease in body weight gain in rats (39% reduction) and mice (20% reduction), while rats also showed a decrease in extragestational body weight (45% reduction) compared with controls (Zangar et al. 1989).

Wood creosotes. Several studies have investigated the effects of oral exposure to wood creosote on body weight, although results are not consistent. No differences in body weights were observed in mice orally administered (method not specified) 5 mg/kg of wood creosote twice a day for 3 days (Takemori et al. 2020) or in male rats exposed daily to Korean beechwood creosote at up to 100 mg/kg/day via syringe for 4 weeks compared to controls (Quynh et al. 2014). Body weight gain was decreased in rats given 163 (males) or 210 (females) mg/kg/day beechwood creosote and in mice given 465 (males) or 134 (females) mg/kg/day beechwood creosote in feed for 3 months; however, as noted earlier in Section 2.3, this is not considered adverse because decreased food consumption, most likely due to palatability, was also observed (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. Body weight reductions were observed in female rats (17% weight reduction) administered wood creosote by gavage at 200 mg/kg/day for 95 weeks (Kuge et al. 2001), and in female rats (10% reduction) fed 394 mg/kg/day for 96 weeks (Miyazato et al. 1984a, 1984b). In contrast, no effects on body weight were observed in male rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks (Kuge et al. 2001), mice fed up to 474 (males) or 532 (females) mg/kg/day for 52 weeks (Miyazato et al. 1984a), or in male rats fed to up to 313 mg/kg/day for 96 weeks (Miyazato et al. 1984a, 1984b).

2.4 RESPIRATORY

Human Studies. Occupational exposure studies evaluating respiratory effects have been conducted in wood processing and wood preservative workers, electrode manufacturing workers, and aluminum industry workers. In addition, respiratory effects have been examined in survey studies of residents living near coal tar creosote wood treatment plants. No studies evaluating respiratory effects specifically to oral exposure of humans to creosote compounds were located.

Environmental exposure to coal tar creosote wood treatment. Long-term residents (n=199) near a wood treatment plant who had low-level environmental exposure (no quantitative estimates) to wood processing waste chemicals had a significant increase in the prevalence of diagnosed bronchitis (17.8 versus 5.8%) and asthma by history (40.5 versus 11%) compared to the matched control group (n=115) (Dahlgren et al. 2004). However, this study has numerous methodological weaknesses, including potential self-selection for study participation in exposed and control groups; lack of defined selection criteria; cases and controls not matched by age, gender, education level, or duration of smoking; and no information on duration of

exposure. Thus, it is difficult to interpret the findings reported by Dahlgren et al. (2004). In a site surveillance program conducted by the Texas Department of Health at a housing development in Texarkana, Texas, 214 residents of an area that had been built on contaminated land formerly occupied by a coal tar creosote wood treatment plant (no quantitative estimates of exposure) showed an increased risk of chronic bronchitis relative to the comparison population (n=212) (ATSDR 1994). These study results are limited by the reliance on self-reporting of health conditions for which diagnosis verification was not always available.

Wood processing and wood preservative workers. An industrial health survey study of employees in four wood preservative plants using coal tar and coal tar creosote exhibited mild-to-moderate pulmonary restrictive and obstructive deficits (exposure not evaluated) (Koppers Company 1979). Reduced lung function (forced vital capacity [FVC]) was observed in 17% (44 of 257) of the employees examined, with most cases (35/44) considered to be mild (reduction in FVC of 66–79%). It should be noted that 34 of the 44 "abnormal" pulmonary function tests were in smokers. Workers in nine coal tar plants had a 33% (150 of 453) incidence of restrictive pulmonary deficits (reduced FVC) compared to controls (Koppers Company 1981). However, the relationship between exposure to coal tar and adverse respiratory effects is uncertain due to potential confounders, including possible co-exposures to other chemicals and cigarette smoke (Koppers Company 1979).

Electrode manufacturing and aluminum workers. Adverse respiratory effects have also been associated with long-term exposure of workers in an electrode manufacturing plant and in the aluminum industry (Gibbs 1985; Petsonk et al. 1988; Rønneberg 1995). A study of 1,615 Australian aluminum smelter workers exposed to the benzene-soluble fraction of coal tar pitch volatiles (BSF), reported increased risk of work-related wheeze and chest tightness with increased exposure (Fritschi et al. 2003). Stratification of exposure by quartiles (Q) showed an increased risk of wheeze in Q2 and Q3 and chest tightness in Q2 and Q3 at cumulative exposures of 0.007–0.017 (Q2) and 0.017–0.11 mg/m^3 years (Q3), respectively. No association was observed in the other two quartiles (Q1: <0.007 mg/m^3 years; Q4: >0.11 mg/m^3 years).

Animal Studies. Most studies evaluating respiratory effects in animals have focused on changes in lung weight, although a few animal studies have shown histopathological changes following creosote exposure, primarily by inhalation. Studies on respiratory effects of creosote compounds include acute-, intermediate-, and chronic-duration inhalation studies on coal tar aerosols, intermediate- and chronic-duration oral studies on wood creosote, and acute-, intermediate-, and chronic-duration oral studies on coal tar products.

Coal tar products. A 19% increase in relative lung weight was reported for female rats exposed to 660 mg/m^3 of a coal tar aerosol on GDs 12–16, but histopathology and pulmonary function were not assessed; therefore, insufficient information is available to determine the toxicological significance of this finding (Springer et al. 1982). 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). Rats showed histiocytosis of the lung tissue when exposed to coal tar concentrations of ≥30 mg/m^3 for 5 weeks (9–10/10 versus 0/10 in controls) or 13 weeks (7–10/10 versus 0/10 in controls) (Springer et al. 1986b). Lesions of the olfactory epithelium were reported for rats (squamous metaplasia 9/20 versus 0/20, suppurative inflammation 10/20 versus 0/20) and mice (epithelial atrophy 19/20 versus 3/20) exposed to 690 mg/m^3 of a coal tar aerosol for 13 weeks, but not for animals exposed to 140 mg/m^3 (Springer et al. 1986b, 1987). Male and female rats exposed to ≥4.7 mg/m^3 of a coal tar aerosol for 13 weeks presented with histological changes in the nasal cavities (chronic inflammation, epithelial hyperplasia, mucoid cysts) and lungs (alveolar macrophages with granular pigmentation) (EPA 1995c, 1995d).

No exposure-related differences in lung weight were observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in dimethyl sulfoxide (DMSO) on GDs 5–9 (Iyer et al. 1993), or in female B6C3F1 mice fed up to 1,300 mg/kg/day of a coal tar mixture from seven coal gasification plant waste sites for 2 years (Culp et al. 1996, 1998). Similarly, no adverse lung lesions (hemorrhage, inflammation, lymphoid filtration, hyperplasia) were observed following dietary exposure to MGP residue at doses up to 462 and 344 mg/kg/day for males and females, respectively, for 94 or 185 days (Weyand et al. 1994).

Wood creosotes. No treatment-related changes in lung weights were observed in Wistar rats and ddY mice fed beechwood creosote up to 934 and 1,336 mg/kg/day, respectively for 3 months, or up to 394 or 532 mg/kg/day, respectively, for 52 weeks (Miyazato et al. 1981, 1984a, 1984b). In a chronic-duration study using Sprague-Dawley rats, reddened lungs were observed in controls and rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks, but only in animals that died prematurely during the study, suggesting that these respiratory effects may have been associated with aspiration of the test material (Kuge et al. 2001). No differences in lung weight were observed in any of the experimental groups.

2.5 CARDIOVASCULAR

Human Studies. Few studies have evaluated cardiovascular effects in humans exposed to creosote compounds, with information limited to an industrial survey study of workers in a wood preservative plant and an experimental study on wood creosote. Available studies do not provide sufficient information to determine with certainty whether exposure of humans to creosote compounds produces sublethal adverse effects to the cardiovascular system due to lack of information, rigorous assessment of cardiovascular function, and appropriate assessment of potential confounding factors (e.g., smoking, co-exposure to other chemicals, family history of cardiovascular disease). Note that increases in mortality due to cardiovascular effects of creosote compounds is discussed in Section 2.2.

Clinical study. In a set of tolerability studies, 30–60 healthy adults were administered one or five oral doses of wood creosote (up to 225 mg), no differences in systolic and diastolic blood pressure, heart rate, or EKG results were observed (Kuge et al. 2003a, 2003b).

Wood processing and wood preservative workers. An industrial health survey of employees in a wood preservative plant in which coal tar creosote, coal tar, and pentachlorophenol were the main treatments used (exposure not evaluated), increased diastolic blood pressure was noted in 21% (24 of 113) of the employees examined, although no additional information was provided (Koppers Company 1979). The ability to relate cardiovascular effects to coal tar exposure was potentially confounded by the possibility that the subjects were also exposed to other chemicals such as pentachlorophenol and cigarette smoke, and there was a lack of medical history (Koppers Company 1979). In addition, blood pressure was measured only once in each study participant, instead of being measured multiple times. This could introduce significant error in the results.

Animal Studies. Most animal studies have found no effects on the cardiovascular system, although a few studies have identified alterations in heart weight, heart rate, and blood pressure. Typically, studies have evaluated heart weight as the only cardiovascular outcome, with few studies evaluating potential histopathological changes and cardiovascular function, limiting the usefulness of these data. The available evidence suggests that the cardiovascular system is not a sensitive target of creosote or creosote products. Studies are available for intermediate-duration inhalation exposure to coal tar aerosol, and intermediate- and chronic-duration oral exposure to coal tar products and wood creosotes.

Coal tar products. No difference in heart weight or histopathological effects of the heart or aorta was found for Fischer rats or CD-1 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). Heart rate and arterial blood pressure were increased by approximately 10 and 20%, respectively, in male rats exposed to HD for 700 mg/m^3 for 6 weeks (Sasser et al. 1989).

A feed study of MGP coal tar in B6C3F1 mice showed no histopathological changes to the aorta after 185-days exposure at doses up to 462 or 344 mg/kg/day in males and females, respectively (Weyand et al. 1994).

Wood creosotes. Several studies have found no effect in heart weight in mice and rats fed beechwood creosote at doses as high as 1,336 mg/kg/day for as long as 96 weeks (Kuge et al. 2001; Miyazato et al. 1981, 1984a, 1984b;). Increased heart weight (14%) was observed in male rats fed ≥143 mg/kg/day beechwood creosote for 96 weeks, but this was not observed in female rats at similar doses and no histopathological changes were observed (Miyazato et al. 1984b).

2.6 GASTROINTESTINAL

Human Studies. Pharmaceutical use of wood creosote derived from the processing of beechwood has been used as a "gastric sedative," a gastrointestinal antiseptic, and an antidiarrheal agent (Kuge et al. 2003a, 2003b, 2004; Ogata et al. 1993). However, no information on potential adverse gastrointestinal effects of this use was identified. Ulceration of the oropharynx and petechial hemorrhages over the gastrointestinal serosal surfaces were noted at autopsy of a 70-year-old man who died following ingestion of an unspecified amount of industrial (presumably coal tar) creosote (Bowman et al. 1984). However, the esophagus and stomach were intact. The authors attributed these effects to acute tissue damage resulting from phenol-induced corrosive effects, since phenol is a component of coal tar creosote.

Animal Studies. Animal studies have examined the antidiarrheal properties of beechwood creosote, while results of studies on coal tar are inconsistent. Studies on gastrointestinal effects of creosote compounds include intermediate-duration inhalation studies on coal tar aerosols, acute-duration oral studies on wood creosote, acute-, intermediate-, and chronic-duration coal tar products, and an acute-duration dermal study on coal tar products.

Coal tar products. No difference in histology of the gastrointestinal tract was reported in female rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 5 weeks or in male or female mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 13 weeks (Springer et al. 1986b, 1987). However, epithelial hyperplasia and chronic inflammation of the cecum was observed in male rats exposed to 690 mg/m^3 coal tar aerosol for 5 weeks (4/10 versus 0/9 in controls) and male (8/10 versus 0/10 in controls) and female (6–7/10 versus 0/10 in controls) rats exposed to 690 mg/m^3 coal tar for 13 weeks (Springer et al. 1986b).

No change in the weight of the small intestines, large intestines, or cecum was noted in male rats treated with 50 mg/kg/day coal tar creosote by gavage for 1–5 weeks (Chadwick et al. 1995). Female mice fed a composite of coal tar from several coal gasification plant waste sites for 4 weeks showed an increase in cell proliferation (measured as the percent of cells in S phase) in the small intestine at ≥346 mg/kg/day and in the forestomach at 1,300 mg/kg/day (Culp et al. (2000). Subsequently, mice treated for 2 years showed dose-related increases in tumor incidence in the small intestine (61% of animals at 739 mg/kg/day) and forestomach (30% of animals at 333 mg/kg/day) (discussed in Section 2.19) (Culp et al. 1998). In another MGP coal tar feed study by Weyand et al. (1994) in mice, no dose-related histopathological lesions of the glandular stomach (after 94-days of exposure) or forestomach (after 185 days of exposure) were observed at doses up to 462 and 344 mg/kg/day in males and females, respectively.

Wood creosotes. The antidiarrheal effect of beechwood creosote has been studied in rats (Ogata et al. 1993) and mice (Ogata et al. 1993; Takemori et al. 2020). Doses in these studies ranged from 10 to 53 mg/kg/day. As these treatments are therapeutic in nature, the gastrointestinal effects of wood creosotes are not considered adverse and therefore are not discussed.

2.7 HEMATOLOGICAL

Human Studies. Basic hematological parameters such as cell counts have been examined in a few human studies, although results have either not shown effects or there may be confounding due to other factors including concurrent and unknown exposures. Case-reports are available describing effects following ingestion of chaparral (creosote bush), while survey studies have looked for associations between occupational or residential exposure and hematological changes.

Case report. A 60-year-old woman hospitalized after taking chaparral for 10 months presented with an increased prothrombin time (15.9–28 seconds versus normal range of 10.9–13.7 seconds) (Gordon et al. 1995).

Environmental exposure to coal tar creosote wood treatment. Compared to the control population (n=115), long-term residents (n=199) near a wood treatment plant who had low-level environmental exposure (no quantitative estimates) to wood processing waste chemicals had decreased lymphocytes (31.4 versus 33.6%), white blood cells (WBCs, 6.36 versus 6.73/1,000 mm^3), and platelets (268 versus 288 $10^5/mm^3$) (Dahlgren et al. 2004). Given the small magnitude of changes, the toxicological significance is uncertain. In addition, interpretation of study findings is very limited due to several methodological inadequacies, as discussed in Section 2.4.

Wood processing and wood preservative workers. In an industrial health survey of employees in four wood preservative plants (exposure not evaluated), hematological effects, including increased number of WBCs (basophils), were noted in 6% (15 of 257) of the employees examined compared to the laboratory's normal range (Koppers Company 1979); this was observed at only one of the four wood preservative plants. The study author concluded that there were no toxicologically significant hematological effects in this worker population. However, it is difficult to determine if effects occurred based on the study design (health survey). Similarly, 8% of the employees in nine coal tar plants surveyed had increased WBCs (eosinophils) (Koppers Company 1981). However, the study authors stated that the distribution and morphology of the WBCs were more characteristic of mild infections and allergies rather than chemical exposure.

Animal Studies. Several studies have examined the hematological effects of creosote exposure in rats and mice, although the results are inconsistent. Studies on hematological effects of creosote compounds include intermediate-duration inhalation studies on coal tar aerosols, and intermediate-duration oral studies on coal tar products and wood creosotes.

Coal tar aerosol. Decreased red blood cell (RBC) counts and hemoglobin (Hgb) concentration and increased reticulocyte (Rt) count have been reported in rodents following inhalation exposure to coal tar aerosols, although mice may be less sensitive to these effects than rats. Male rats exposed to 140 mg/m^3 of a coal tar aerosol for 5 or 13 weeks had decreased RBCs, Hgb, volume of packed red blood cells (VPRC), and eosinophils (Springer et al. 1986b). Female rats also had decreased RBCs, Hgb, and increased reticulocyte (Rt) counts following exposure to 140 mg/m^3 coal tar for 5 weeks and decreased

total WBCs, lymphocytes, eosinophils, and monocytes when exposed to 690 mg/m^3 for 5 or 13 weeks. Decreases in megakaryocytes in the spleen were also observed in male (6/10 versus 0/10 in controls) and female (7/10 versus 0/10 in controls) rats exposed to 690 mg/m^3 coal tar aerosol for 5 weeks and in both male (10/10 versus 2/10 in controls) and female (10/10 versus 0/10 in controls) rats exposed for 13 weeks. Additionally, examination of bone marrow smears showed that rats exposed to 690 mg/m^3 coal tar aerosol for 13 weeks had a marked decrease in the number of megakaryocytes (8/10 in males, 5/10 in females, 0/20 in controls). RBCs, Hgb, and VPRC were also decreased in mice exposed to 690 mg/m^3 of a coal tar aerosol for 13 weeks, but Rt counts were unaffected by exposure (Springer et al. 1987). Decreased RBCs and Hgb and increased Rt counts were observed in male and female rats exposed to creosote aerosol up to 102 mg/m^3 for 13 weeks, but the results were not consistent between the sexes or across similar doses (EPA 1995c, 1995d). Study details are provided in Table 2-6.

In a dietary study of MGP coal tar by Weyand et al. (1994) in mice, no adverse bone marrow histology (granulocytic hyperplasia, erythroid hypoplasia) was reported following exposure for 94 or 185 days at doses up to 344 and 462 mg/kg/day in females and males, respectively. No changes in hematological parameters, including RBCs, WBCs, Hgb, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and platelet counts, were observed in rats dermally exposed with doses up to 400 mg/kg for 90 days (EPA 1995e).

Wood creosotes. No treatment-related differences in hematological parameters including RBCs, WBCs, Hgb, hematocrit (HCT), MCV, MCH, MCHC, or platelet count were observed in male rats orally exposed via syringe to Korean beechwood creosote up to 100 mg/kg/day for 4 weeks (Quynh et al. 2014) or in mice fed beechwood creosote up to 1,207 mg/kg/day (male) or 1,336 mg/kg/day (female) for 3 months (Miyazato et al. 1981). Sporadic alterations in hematology were observed in rats fed beechwood creosote up to 934 mg/kg/day (male) or 832 mg/kg/day (female) for 3 months, but the data did not demonstrate a consistent dose-response relationship, and the study authors did not consider the changes to be toxicologically significant (Miyazato et al. 1981).

Chronic (52 weeks) dietary exposure of mice to up to 474 mg/kg/day (males) or 532 mg/kg/day (females) beechwood creosote resulted in decreased MCV and MCH, and increased lymphocyte and neutrophil counts when compared to the corresponding control values (Miyazato et al. 1984a). However, the study authors stated that the values were within normal physiological ranges. No dose-related differences were observed in male or female rats fed up to 313 or 394 mg/kg/day, respectively, for 96 weeks (Miyazato et al. 1984b).

Table 2-6. Hematological Effects in Rodents Exposed to Inhaled Coal Tar Aerosol

Species	Exposure (duration)	Outcomes measured (percent change)[a]									Reference
		VPRC	Hgb	RBCs	Rts	WBCs	LCs	NPs	EPs	MCs	
Rat	102 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	–	↓ M (8) ↓ F (9)	↔ M ↓ F (11)	↑ M (110) ↑ F (136)	–	–	–	–	–	EPA 1995c
Rat	49 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	–	↓ M (8) ↔ F	↔ M/F	↔ M/F	–	–	–	–	–	EPA 1995d
	106 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	–	↔ M ↓ F (12)	↔ M ↓ F (15)	↔ M ↑ F (169)	–	–	–	–	–	
Rat	30 mg/m^3 (6 hours/day, 5 days/week, 5 weeks)	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↓ M (59) ↔ F	↔ M/F	Springer et al. 1986b
	140 mg/m^3 (6 hours/day, 5 days/week, 5 weeks)	↓ M (9) ↓ F (8)	↓ M (10) ↓ F (9)	↓ M (8) ↓ F (8)	↔ M ↑ F (56)	↔ M/F	↔ M/F	↔ M/F	↓ M (65) ↔ F	↔ M/F	
	690 mg/m^3 (6 hours/day, 5 days/week, 5 weeks)	↓ M (21) ↓ F (7)	↓ M (23) ↓ F (18)	↓ M (21) ↓ F (11)	↑ M (270) ↑ F (153)	↔ M/F	↔ M/F	↑ M (151) ↔ F (88)	↓ M (88) ↓ F (88)	↔ M/F	
Rat	30 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	↓ M (8) ↔ F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↔ M ↓ F (51)	↔ M ↓ F (49)	
	140 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	↓ M (11) ↔ F	↓ M (11) ↓ F (9)	↓ M (7) ↔ F	↔ M/F	↔ M/F	↔ M/F	↔ M/F	↓ M (61) ↓ F (66)	↔ M ↓ F (43)	
	690 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	↓ M (58) ↓ F (39)	↓ M (59) ↓ F (40)	↓ M (63) ↓ F (37)	↔ M ↑ F (227)	↓ M (32) ↓ F (25)	↓ M 34) ↓ F (30)	↔ M/F	↓ M (95) ↓ F (98)	↓ M (88) ↓ F (74)	
Mouse	30 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	↔ M/F	↔ M/F	↔ M/F	↔ M/F	–	–	–	–	–	Springer et al. 1987
	140 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	↔ M/F	↔ M/F	↔ M/F	↔ M/F	–	–	–	–	–	
	690 mg/m^3 (6 hours/day, 5 days/week, 13 weeks)	↓ M (13) ↓ F (10)	↓ M (13) ↓ F (11)	↓ M (14) ↓ F (7)	↔ M/F	–	–	–	–	–	

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.

↑ = increased; ↓ = decreased; ↔ = no change; – = not assessed; EP = eosinophil; F= female(s); Hgb = hemoglobin concentration; LC = lymphocyte; M = male(s); MC = monocyte; NP = neutrophil; RBC = red blood cell; Rt = reticulocyte; VPRC = volume of packed red blood cells; WBC = total white blood cells

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects of creosote compounds in humans or animals.

2.9 HEPATIC

Human Studies. Most information on hepatic effects of creosote in humans comes from therapeutic uses, including case reports of individuals ingesting chaparral and psoriasis patients using topical coal tar mixtures. However, no reliable exposure estimates were reported in these studies. No studies were identified that linked inhalation exposure to creosote to adverse hepatic effects in humans.

Case reports. Acute toxic hepatitis was attributed to continued ingestion of chaparral, which is an herbal nutritional supplement product derived from the leaves of the creosote bush (CDC 1992). Case reports of intermediate-duration ingestion of chaparral have described patients with a variety of hepatic effects including icterus, jaundice, and abdominal pain (Alderman et al. 1994; CDC 1992; Gordon et al. 1995; Katz and Saibil 1990). Elevated levels of bilirubin, gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase have been observed when serum chemistry was evaluated (Alderman et al. 1994; CDC 1992; Gordon et al. 1995). Biopsies have revealed acute inflammation with neutrophil and lymphoplasmacytic infiltration, diffuse hepatocyte disarray and necrosis, focal acute peri-cholangitis, some ductal dilatation, and proliferation of bile ductules in portal-periportal regions (Alderman et al. 1994; Gordon et al. 1995). In one severe case, the patient's liver biopsy showed severe acute hepatitis with areas of lobular collapse and nodular regeneration, mixed portal inflammation, and marked bile ductular proliferation, and the patient underwent orthotopic liver transplantation (Gordon et al. 1995). These case reports often lack information on dose and concurrent exposures, limiting interpretation of potential associations between exposure and hepatic effects. Degeneration and necrosis of hepatocytes were observed at autopsy in the case of a 70-year-old man who ingested industrial creosote (coal tar, amount not specified) (Bowman et al. 1984). No effect on serum alkaline phosphatase, ALT, bilirubin, or total protein was observed by Tham et al. (1994) in 27 psoriasis patients applying 120 g of coal tar to their skin twice daily for 2–6 weeks.

Clinical study. Serum liver enzymes, blood urea nitrogen (BUN), creatinine levels, glucose levels, electrolytes, bilirubin levels, iron levels, ferritin levels, lipid levels, and complete blood count of four

patients prescribed an extract of creosote bush for a span of 1–4 months (insufficient information to calculate dose) were within the normal range and were unchanged throughout the follow up (Heron and Yarnell 2001).

Wood processing and wood preservative workers. In a set of industrial health surveys of workers from either four wood preservative plants (n=257) or nine coal tar plants (n=452), no indications of hepatic disease or liver obstruction were identified (exposure not evaluated) (Koppers Company 1979, 1981).

Animal Studies. Several studies have identified changes in liver weights and histology following exposure to creosote and creosote compounds, while other studies have not observed hepatic effects. Although liver weight was the most frequently examined outcome, effects on hepatic clinical chemistry, gross pathology, and histology were also examined. Studies on hepatic effects of creosote compounds include acute- and intermediate-duration inhalation studies on coal tar aerosols, acute-, intermediate-, and chronic-duration oral studies on coal tar products and wood creosotes, and an acute-duration dermal study on coal tar.

Coal tar products. An acute developmental study using coal tar aerosol did not observe liver weight changes in rats exposed on GDs 12–16 at doses up to 660 mg/m^3 (Springer et al. 1982). Intermediate-duration studies have observed histopathological effects in the liver (increased cytoplasmic basophilia and variability in hepatocellular and nuclear size, the presence of hepatomegalocytes, and loss of cording and lobular pattern) in male and female rats exposed to a coal tar aerosol at 690 mg/m^3 after 5 and 13 weeks (Springer et al. 1986b) and in mice exposed to ≥140 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1987). In addition, these studies reported increased relative liver weights in rats (10% decrease at 30 mg/m^3) and mice (10% decrease at 140 mg/m^3) exposed up to 690 mg/m^3 for as long as 13 weeks.

No exposure-related differences in liver weight were observed in developmental studies using mice and rats gavaged with coal tar up to 400 mg/kg/day between GDs 5–9 and 12–16 (Iyer et al. 1993; Hackett et al. 1984) or in mice gavaged with up to 100 mg/kg creosote once a day for 4 days (data not shown) (Fielden et al. 2000). No differences in liver histopathology were observed in coal tar feeding studies using mice exposed dietarily for 94 or 185 days of exposure to up to 462 mg/kg/day (males) and 344 mg/kg/day (females) (Weyand et al. 1994). Increased liver weight (40%) and associated neoplastic changes (discussed in Section 2.19) were observed in female B6C3F1 mice fed ≥333 mg/kg/day of a coal tar mixture from coal gasification plant waste sites for 2 years (Culp et al. 1998). In a developmental

study of rats and mice, 500 or 1,500 mg/kg coal tar dermally applied on GDs 11–15 resulted in increased maternal liver to extragestational body weight ratios in rats (15 and 30%, respectively) and mice (16 and 35%, respectively) compared with controls, although histopathology was not conducted, making the significance of these changes unclear (Zangar et al. 1989).

Wood creosotes. No differences in serum bile or ALT levels were observed in mice orally administered 5 mg/kg of wood creosote twice a day for 3 days (Takemori et al. 2020). No differences were observed in the blood plasma clinical chemistry, including glucose, cholesterol, albumin, globulin, ALT, and AST in male rats orally exposed to Korean beechwood creosote up to 100 mg/kg/day for 4 weeks compared to controls (Quynh et al. 2014). Increased relative liver weights have been observed in rats and mice fed beechwood creosote at doses ≥150 mg/kg/day and for ≥3 months; however, the toxicological significance of these findings is uncertain in the absence of histopathological assessments, findings, or other measures of hepatic toxicity (Miyazato et al. 1981, 1984a, 1984b). In contrast, a chronic-duration gavage study treating rats at 200 mg/kg/day for 95 weeks found no effect on liver weight (Kuge et al. 2001).

Similarly mixed results have been observed in serum cholesterol. Increased serum cholesterol (10%) was noted in rats following dietary exposure to beechwood creosote in feed up to ≥210 mg/kg/day for 3 months, but not in mice exposed up to 1,336 mg/kg/day for 3 month (Miyazato et al. 1981). Serum cholesterol was also increased in rats exposed to ≥143 mg/kg/day beechwood creosote for 96 weeks (lacked a dose response), and in female mice fed ≥297 mg/kg/day for 52 weeks, but not in male mice fed up to 474 mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b).

2.10 RENAL

Human Studies. Severe renal effects have been reported in humans following continuous ingestion of beechwood creosote-derived chaparral or chronic inhalation of coal tar, while studies examining dermal exposure have not observed adverse renal effects. Several case reports and clinical studies are available, along with a survey study evaluating occupational creosote exposure.

Case reports. A 60-year-old woman hospitalized following chaparral ingestion experienced renal failure requiring dialysis (Gordon et al. 1995). Advanced renal failure (chronic interstitial nephritis) was reported in a 56-year-old woman following chronic coal tar creosote vapor inhalation (Hiemstra et al. 2007). A 70-year-old man who ingested a fatal dose of industrial (coal tar) creosote became acidotic and anuric before he died, consistent with kidney failure (Bowman et al. 1984).

Clinical studies. No impairment of renal function was detected in a study performed by Wright et al. (1992), where 5 or 10 % coal tar 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. No effect on serum creatinine level 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.

Wood processing and wood preservative workers. In an industrial health survey of employees in nine U.S. coal tar plants in which coal tar creosote and coal tar were the main products made (exposure not evaluated), renal effects, including protein and cells in the urine, were noted in the employees examined (Koppers Company 1981). Elevated red and white cell counts in urine were noted in 6 and 8%, respectively, of workers (29 and 34, respectively, of 452) of the employees, although some of these cell count elevations were attributed by the study authors to urinary tract infections (Koppers Company 1981). Additionally, the study authors stated that some of the workers with elevated red and white cell counts in urine had cellular and granular casts and traces of protein, suggesting abnormal renal function. The ability to determine the relationship between exposure and possible renal effects is challenged due to the lack of information on smoking, medical history, and possible exposure to other chemicals in the workplace history in the Koppers Company (1981) report.

Animal Studies. Potential renal effects of creosote exposure have been evaluated based on kidney weights, histology, and clinical chemistry, with kidney weights as the most studied outcome. Conflicting results on renal effects have been observed between studies in rodents exposed to similar exposure conditions. Studies on renal effects of creosote compounds include acute- and intermediate-duration inhalation studies on coal tar aerosols, acute-, intermediate-, and chronic-duration oral studies on coal tar products and wood creosotes, and an acute-duration dermal study on coal tar.

Coal tar products. No difference in kidney weight was reported for female rats exposed to up to 660 mg/m^3 of a coal tar aerosol on GDs 12–16 (Springer et al. 1982) or in mice exposed to 690 mg/m^3 of a coal tar aerosol for 13 weeks (Springer et al. 1987). However, relative kidney weights were increased 27% in rats exposed to 690 mg/m^3 of a coal tar aerosol for 5 weeks, and 30% in rats exposed for 13 weeks (Springer et al. 1986b). Pelvic epithelial hyperplasia and pigmentation of the cortical tubules was observed in male rats exposed to 690 mg/m^3 for 5 weeks and in male and female rats exposed to ≥140 mg/m^3 for 13 weeks (Springer et al. 1986b), but no histopathological findings were reported in the corresponding mouse studies with similar concentrations and durations (Springer et al. 1987).

In an acute oral toxicity study, gross necropsy revealed a dose-related increase in the incidence of distended urinary bladder in male and female rats gavaged with single doses of creosote at 2,500, 3,000, or 4,000 mg/kg (EPA 1994). No exposure-related differences in kidney weight were observed in female mice treated by gavage with 400 mg/kg petroleum creosote on GDs 5–9 (Iyer et al. 1993), in female rats gavaged on GDs 12–16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984), or in female mice fed up to 1,300 mg/kg/day coal tar (Culp et al. 1998). In a feeding study of MGP coal tar by Weyand et al. (1994) in mice, there were no exposure-related histopathological lesions observed in the kidneys or bladder after 94 or 185 days of exposure to up to 462 mg/kg/day (males) and 344 mg/kg/day (females). In a developmental study of rats and mice, coal tar dermally applied on GDs 11–15 resulted in increases in maternal kidney to extragestational body weight ratios in rats at 1,500 mg/kg/day (13%) and in mice at ≥500 mg/kg/day (10%) compared with controls, but a lack of histopathology makes these results questionable (Zangar et al. 1989).

Wood creosotes. Relative kidney weight increases (9%) have been observed in rats exposed to ≥210 mg/kg/day beechwood creosote in the diet for 3 months, but not in mice exposed to higher concentrations (up to 1,336 mg/kg/day) and without observed histopathological changes (Miyazato et al. 1981). Chronic studies have also showed mixed results, with relative kidney weight increases observed in male and female rats fed 143 and 179 mg/kg/day, respectively, beechwood creosote for 96 weeks (Miyazato et al. 1984b), but not in male or female rats gavaged with 200 mg/kg/day for 95 weeks (Kuge et al. 2001), or in mice fed up 532 mg/kg/day for 52 weeks (Miyazato et al. 1984a). In the absence of functional assessments or consistently observed histopathological effects, the toxicological significance of changes in kidney weight remains unclear.

No differences in BUN and total protein were observed in male rats orally exposed to Korean beechwood creosote up to 100 mg/kg/day for 4 weeks compared to controls (Quynh et al. 2014). BUN (93%) and serum inorganic phosphorus (30%) were elevated, and a higher incidence of chronic progressive nephropathy were observed in male rats exposed for 96 weeks, suggesting that long-term exposure to beechwood creosote in feed at a dose of 143 mg/kg/day accelerated the occurrence of chronic progressive nephropathy in male rats (Miyazato et al. 1984b), a unique renal disease that has been shown to be specific to male rats (Hard et al. 2013).

2.11 DERMAL

Human Studies. Dermal effects have been documented in populations occupationally and non-occupationally exposed to coal tar and coal tar products. Burns and irritation of the skin are the most frequent manifestations of coal tar creosote toxicity following dermal exposure. According to a review by EPA (1978), burns from hot pitch are relatively common in occupational settings.

Case reports. Leonforte (1986) reported six confirmed cases of acute allergic dermatitis subsequent to contact with the creosote bush. Smith (1937) described the case of a patient who presented with erythematous and vesicular dermatitis of the face, upper part of the neck, and backs of the hands after collecting creosote bush.

Clinical studies. Contact dermatitis has been reported after short-term contact with coal tar (Cusano et al. 1992). In a study of the efficacy and tolerability of 1% prepared coal tar lotion versus 5% coal tar extract in patients with mild to moderate plaque psoriasis, application site reactions were the most reported adverse events in each group (8% of patients treated with 1% coal tar lotion and 10% of patients treated with conventional 5% coal tar lotion) (Goodfield et al. 2004). In patients medically treated with 5% coal tar, dermal applications induced a photosensitizing effect in all patients within 30 minutes of treatment (Diette et al. 1983). In contrast, no adverse treatment-related dermal effects were reported for 23 patients treated topically with an extract of creosote bush (concentration not stated) in castor oil (Heron and Yarnell 2001).

Environmental exposure to coal tar creosote wood treatment. Residents (n=214) living in or near a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant reported a higher prevalence of skin rashes (27.9%) than the comparison neighborhood (4.9%, n=212) (ATSDR 1994). Long-term residents near a wood treatment plant (n=199) who had low-level environmental exposure (no quantitative estimates) to wood processing waste chemicals had an increased prevalence of self-reported skin rashes following sun exposure than the control population (n=115; 29 versus 5%) (Dahlgren et al. 2004). These studies are limited due to their reliance on self-reported health effects. In addition, no information was provided on the possible co-exposures to other chemicals.

Wood processing and wood preservative workers. An industrial health survey of 251 employees in four wood preservative plants identified 82 instances of dermal effects, including skin irritation, eczema,

folliculitis, and benign growths on the skin (Koppers Company 1979). In another industrial health survey (Koppers Company 1981), workers in nine coal tar plants had a 2% incidence of benign skin growth and a 21% incidence of some other skin condition such as keratosis, eczema, folliculitis, and chloracne. Creosote chemical burns were observed in construction workers who handled wood treated with creosote (presumably coal tar creosote, levels not specified) (Jonas 1943). It was found that 70% of the burn cases were mild and were characterized by erythema of the face, while the remainder of the burn cases (30%) were more severe and were characterized by intense burning, itching, and considerable subsequent pigmentation followed by desquamation. Dermal burning and irritation were reported in five male dock builders which was exacerbated on hot or sunny days (NIOSH 1981). 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. Effects similar to those seen in the NIOSH (1981) study were noted in workers transferring coal tar pitch from a river barge to an ocean barge (NIOSH 1982). Other studies have been published that describe similar effects of coal tar exposure, although exposure levels were 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). 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 several lesions on the hands, forearms, and thighs. One of these lesions was excised and examined and was classified as a benign squamous cell papilloma. Three workers developed erythematous and vesicular eruption above the shoe tops 1–2 weeks after beginning work manufacturing armaments, which were attributed to the creosote that evaporated off the wooden floors (Schwartz 1942).

Electrode manufacturing and aluminum workers. A worker 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 and irritation, described as redness like a sunburn, lasting 2–3 days, with drying and peeling, and photosensitivity, was described by 26 workers transferring coal tar pitch (NIOSH 1982).

Animal Studies. Few studies have examined the noncarcinogenic dermal effects of exposure to creosote products; however, effects consistently show adverse effects, including irritation, erythema, and edema; dermal cancers are discussed in Section 2.19. Studies on noncarcinogenic dermal effects of creosote

compounds include acute-, intermediate-, and chronic-duration dermal studies on coal tar products and wood creosotes.

Coal tar products. Rabbits given single dermal applications of undiluted coal tar creosote exhibited slight to moderate erythema and edema (EPA 1994). Comedones were visible on the ears of male Australian albino rabbits treated with ≥0.1% coal tar 5 days/week for 3 weeks (Kligman and Kligman 1994). Rats dermally exposed with doses ≥1,000 mg/kg creosote for 2 weeks experienced slight to moderate erythema (1–5/6 rats) and slight edema (3–6/6 rats), while dermal irritation was not observed in rats exposed up to 400 mg/kg for 90 days (EPA 1995e). Mice treated with 9% benzene solutions of two coal tar pitches for 80 weeks exhibited hyperplasia of the epidermis frequently accompanied by inflammatory infiltration of the dermis and ulceration with formation of small abscesses (Wallcave et al. 1971). EPA (2015) summarized the intermediate-duration dermal study, which reported dermal inflammation at the application site in rats treated with 400 mg/kg/day creosote (MRID 43616201, DER not available).

Wood creosotes. Beechwood creosote has been found to irritate the periapical tissue (the connective tissue surrounding the apex of the tooth) in dogs 7 days after its application (dose not provided) (Attalla 1968). Localized inflammatory changes and occasional abscess formation were observed in these animals. Application of birch tar to the ears of rabbits for 3 weeks was associated with the formation of comedones on the ear (Kligman and Kligman 1994).

2.12 OCULAR

Human Studies. Direct exposure of the eye to coal tar creosote is irritating to the superficial ocular tissues. Factory and construction workers, roofers, and other workers who handle coal tar, or wood treated with coal tar creosote have experienced conjunctival burns and irritation resulting from accidental exposure (Emmett 1986; Jonas 1943; NIOSH 1980a, 1981). Exposure to the sun exacerbated eye irritation from exposure to creosote or coal tar fumes. It was reported in a review by EPA (1978) that acute episodes involving the eyes usually begin 2–4 hours after initial exposure to pitch fumes or pitch dust. Symptoms may include reddening of the eyelids and conjunctiva. Discontinuation of exposure will not always result in cessation of symptoms, but in mild cases, the symptoms disappear within 3 days. Chronic exposures may lead to damage to the cornea, chronic conjunctivitis, and restriction of the visual field.

Environmental exposure to coal tar creosote wood treatment. Long-term residents near a wood treatment plant (n=199) who had low-level environmental exposure (no quantitative estimates) to wood processing waste chemicals had an increased prevalence of self-reported eye irritation (data not reported) than the control population (n=115) (Dahlgren et al. 2004).

Wood processing and wood preservative workers. Twenty-six transferring workers and five dock construction workers had eye irritation, burning, redness, swelling, tearing, and occasional photophobia for 2 days after exposure to transferring coal tar pitch and dock construction, respectively (NIOSH 1981, 1982). Conjunctivitis was observed in roofers exposed to coal tar pitch volatiles during tear-off operations at levels ≥0.18 mg/m^3, but no cases were observed in workers exposed to levels ≤0.11 mg/m^3; however, reliable incidence data were not reported (Emmett 1986).

Animal Studies. Animal studies examining the ocular effects of creosote and creosote products are extremely limited. A set of intermediate-duration inhalation studies examined the ophthalmological effects of coal tar aerosol, while two studies examined the direct application effects to coal tar creosote in rabbits.

Coal tar products. No treatment-related ophthalmoscopic abnormalities were observed in male and female rats exposed to up to 106 mg/m^3 of a coal tar aerosol for 13 weeks (EPA 1995c, 1995d). Instillation of 0.1 mL undiluted coal tar creosote in the eyes of rabbits produced conjunctival redness and chemosis (EPA 1994). Roofing coal tar pitch volatiles (10 µL) caused tearing and mucous discharge in two of six treated New Zealand rabbits (Emmett 1986).

2.13 ENDOCRINE

Human Studies. No studies evaluating potential endocrine effects of creosote compounds in humans were identified.

Animal Studies. Several studies have identified changes to weights of endocrine organs, but effects are not consistently observed. In addition, due to the lack of functional assessments or observations, and endocrine hormone levels, the toxicological significance of changes to organ weights cannot be determined. Studies on endocrine effects of creosote compounds include acute- and intermediate-duration inhalation studies on coal tar aerosols, acute-, intermediate-, and chronic-duration oral studies on coal tar products and wood creosotes, and an acute-duration dermal study on coal tar.

Coal tar products. No difference in the relative weight of the adrenal glands was reported for female rats exposed to up to 660 mg/m^3 of a coal tar aerosol on GDs 12–16 (Springer et al. 1982). No differences were noted in the histology of the pancreas or the adrenal, parathyroid, pituitary, or thyroid glands in rats exposed to up to 690 mg/m^3 for 5 or 13 weeks or in mice exposed to up to 690 mg/m^3 for 13 weeks (Springer et al. 1986b, 1987).

No adverse effect on adrenal weight was observed in female mice treated by gavage with 400 mg/kg petroleum creosote on GDs 5–9 (Iyer et al. 1993), while adrenal weights were increased 16% in rats gavaged with ≥90 mg/kg/day coal tar on GDs 12–16, although histopathology was not assessed (Hackett et al. 1984). No histological lesions were noted in the pancreas, parathyroid, or adrenal glands in a dietary study using mice treated for 94 or 185 days with up to 462 or 344 mg/kg/day MGP coal tar in males and females, respectively (Weyand et al. 1994). In a developmental study of rats and mice, dermal exposure up to 1,500 mg/kg coal tar on GDs 11–15 produced no change in weight of the adrenal glands of treated animals from both species compared with controls (Zangar et al. 1989).

Wood creosotes. Intermediate- and chronic-duration studies have not observed changes in endocrine-organ weights (Kuge et al. 2001; Miyazato et al. 1981, 1984b). No hypoglycemic effects (i.e., changes in glucose tolerance) were observed in orally administered 5 mg/kg of wood creosote twice a day for 3 days (Takemori et al. 2020).

2.14 IMMUNOLOGICAL

Human Studies. 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 (Leonforte 1986; Smith 1937) and coal tar (Cusano et al. 1992). No additional information on immune function or autoimmune disorders in humans was identified.

Case reports. 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, upper part of the neck, and backs of the hands after collecting creosote bush. Leonforte (1986) reported six cases of acute allergic dermatitis after contact with a creosote bush and confirmed by a patch test. Creosote bush resin differs from creosote extracted from coal and wood tar, but all contain phenolic derivatives.

Clinical study. In a study by Mastrangelo et al. (2003), higher serum IgE levels were observed in 32 patients with psoriatic lesions treated with single application of 3% coal tar, especially in patients under 36 years of age.

Animal Studies. Animal studies have provided evidence of weight and morphological changes in lymphoreticular tissues following exposure to coal tar (Hackett et al. 1984; Zangar et al. 1989), but no information regarding changes in the immune system function, including autoimmune disorders, have been reported. It is uncertain if changes in weights of immune organs without assessments of histopathological or functional changes indicate toxicity. However, results of available studies are suggestive of possible immunotoxic effects. Studies on the immunological effects of creosote compounds include acute- and intermediate-duration inhalation studies on coal tar aerosols, acute-, intermediate-, and chronic-duration oral studies on coal tar products and wood creosotes, and acute- and chronic-duration dermal studies on coal tar.

Coal tar products. A 22% increase in absolute spleen weight and a 58% decrease in absolute thymus weight were reported for female rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on GDs 12–16, but histopathology was not conducted (Springer et al. 1982). Relative thymus weights were decreased in female rats (65%) exposed to 690 mg/m^3 coal tar aerosol 5 weeks and both males (27%) and females (29%) exposed to ≥140 mg/m^3 for 13 weeks (Springer et al. 1986b). The thymus was atrophied (8/8 versus 0/10 in controls) in male rats exposed to 690 mg/m^3 coal tar aerosol for 5 weeks and in both male (6/6 versus 0/10 in controls) and female (8/8 versus 0/10 in controls) 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 (6/10 in males, 4/10 in females, 0/20 in controls). Relative thymus weights were also decreased in male mice (29%) exposed to 690 mg/m^3 or in female mice (31%) exposed to ≥140 mg/m^3 of a coal tar aerosol for 13 weeks, but associated histological changes were not observed (Springer et al. 1987).

Thymus weights were decreased by 34% in female rats gavaged on GDs 12–16 with doses as low as 90 mg/kg/day; histopathology was not conducted and body weight gain was also decreased, making the toxicological significance difficult to determine (Hackett et al. 1984). No change in spleen weight was observed in the same rats at doses up to 370 mg/kg/day coal tar. Mice fed diets containing up to 462 mg/kg/day MGP coal tar (males) and 344 mg/kg/day MGP coal tar (females) exhibited no

histopathological lesions in the spleen, thymus, or bone marrow after treatment for 94 or 185 days (Weyand et al. 1994).

In a developmental study of rats and mice, dermal application of 500 or 1,500 mg/kg coal tar on GDs 11–15 resulted in 67 and 75% decreases, respectively, in maternal thymus to extragestational body weight ratios for treated rats compared with controls, while no change was observed in spleen weight ratios; however, dermal exposure of mice to coal tar produced a 74 and 182% increase in maternal spleen to body weight ratios, while thymus weights were similar in control and treated animals (histopathology not conducted) (Zangar et al. 1989). Amyloidosis of the spleen and inflammatory infiltration of the dermis were observed in mice after topical application of 2.5 mg coal tar pitch in 9% benzene solutions twice weekly for 81–82 weeks (Wallcave et al. 1971).

Wood creosotes. Exposure to beechwood creosote at 934 mg/kg/day in the diet for 3 months resulted in an 11% increase in relative spleen weight of male rats, but not in female rats at doses up to 832 mg/kg/day; histopathology was not conducted (Miyazato et al. 1981). In companion experiments in mice, no treatment-related effect was observed on relative spleen weight at doses up to 1,207 (males) or 1,336 (females) mg/kg/day, in the diet (Miyazato et al. 1981). No differences in spleen or thymus weights were observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, mice exposed to doses of 532 mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b), or male and female rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks (Kuge et al. 2001).

2.15 NEUROLOGICAL

Human Studies. Neurological effects have been reported following inhalation, oral, and dermal exposure to creosote compounds. Case reports of individuals and survey studies suggest that neurotoxicity (e.g., dizziness, altered vision, etc.) may be an early sign of toxic exposure to creosote. However, the available studies do not provide adequate information to determine if there are associations between exposure and neurological effects.

Case reports. Seizure, ataxia, cognitive impairment, and marked generalized cerebral atrophy were reported in a 56-year-old woman following chronic coal tar creosote vapor inhalation (Hiemstra et al. 2007). In another report, a hospitalized 60-year-old woman presented with confusion, anorexia, encephalopathy, and seizures due to toxic hepatitis secondary to chaparral ingestion (Gordon et al. 1995).

Clinical study. In a set of tolerability studies of 30-60 healthy adults dosed with up to 225-mg wood creosote tablets every 2 hours for one to five doses, some adults reported altered taste, somnolence, dizziness, and headaches (Kuge et al. 2003a, 2003b).

Environmental exposure to coal tar creosote wood treatment. Long-term residents near a wood treatment plant (n=199) who had low-level environmental exposure (no quantitative estimates) to wood processing waste chemicals had an increased prevalence of self-reported neurological problems including irritability, light-headedness, and extreme fatigue (incidences not reported) compared to the control population (n=115) (Dahlgren et al. 2004). Exposed adults also had more neurophysiologic abnormalities in reaction time, trail making, visual field defects, and grip strength. However, due to several methodological weaknesses, as described in Section 2.4, data are inadequate to evaluate possible associations between creosote exposure and neurological effects.

Wood processing and wood preservative workers. In a study with workers constructing buildings with coal tar creosote-treated wood, 2.4% of the workers (n=450) reported neurological symptoms including headache, weakness, confusion, vertigo, and nausea (Jonas 1943).

Animal Studies. Similar to some human studies, animal studies suggest that neurotoxicity may be the first sign of toxic creosote exposure. Although brain weight changes were reported in several studies, other studies have reported no changes, suggesting that brain weight changes are not likely related to creosote exposure. Studies on the neurological effects of creosote compounds include intermediate-duration inhalation studies on coal tar aerosols, and acute-, intermediate-, and chronic-duration oral studies on wood creosotes.

Coal tar products. In a series of acute inhalation toxicity studies, male and female rats exposed to creosote aerosol ≥600 mg/m^3 for 4 hours exhibited decreased (based on cage-side observations) activity immediately after exposure and throughout a 2-week follow-up period (EPA 1994). Increased relative brain weights were observed following inhalation of 690 mg/m^3 coal tar aerosol by male rats for 5 weeks (58%) and by male (54%) and female (16%) rats exposed to 690 mg/m^3 for 13 weeks, although no differences in absolute brain weight or histopathological effects were observed; the study authors reported that the animals appeared “listless” prior to termination (Springer et al. 1986b). No exposure-related effects on relative brain weight or histology were observed in mice following inhalation of up to 690 mg/m^3 coal tar aerosol for 13 weeks (Springer et al. 1987).

In a series of oral toxicity studies, male and female rats gavaged with single doses ≥1,500 mg/kg showed ≥90% decreased activity; ≥40% low carriage was noted at doses ≥2,000 mg/kg, and ≥50% prostration was observed at doses ≥2,000 mg/kg (EPA 1994). In a series of acute dermal toxicity studies, application of 2,000 mg/kg creosote did not produce clinical signs of neurotoxicity (based on cage-side observations) in male and female rabbits (EPA 1994).

Wood creosotes. In rats and mice, the first sign of adverse effects following the gavage administration of single high doses of beechwood creosote (≥313 mg/kg in mice, ≥600 mg/kg in rats, specific dose not specified) was muscle twitching followed by convulsions within 1–2 minutes and ultimately asphyxiation, coma, and death (Miyazato et al. 1981). Sporadic changes in relative brain weights have been observed in rats and mice exposed to doses ≥250 mg/kg/day for durations up to 96 weeks, but the results have been inconsistent between the species and sexes, and have lacked a dose-response trend and/or had no associated histopathological findings on microscopic examination (Miyazato et al. 1981, 1984a, 1984b).

2.16 REPRODUCTIVE

Human Studies. Little information was identified on the reproductive effects creosote compounds in humans. Three studies were located on the potential reproductive effects of coal tar creosote, although these studies are limited by reliance on self-reporting and small sample size.

Clinical study. A retrospective survey study was conducted in 56 women between 18 and 35 years old exposed dermally to coal tar for treatment of psoriasis or dermatitis. Results from the questionnaires found slightly increased rates of spontaneous abortion (26% in women who had used coal tar during pregnancy versus 19% with no coal tar use), although limitations of this study include small sample size (Franssen et al. 1999).

Environmental exposure to coal tar creosote wood treatment. No effect on the number of pregnancies was reported for 214 residents at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant. However, interpretation of study results is limited by the study's reliance on self-reporting and small sample size (ATSDR 1994).

Electrode manufacturing and aluminum workers. No adverse effects on sperm characteristics, including sperm count and morphology, were noted in 50 workers exposed to coal tar pitch volatiles in an

aluminum reduction plant (historical exposure levels estimated between 0.5 and 3.42 mg/m^3) compared to 50 controls (Ward 1988).

Animal Studies. Animal studies assessing reproductive organ effects have shown conflicting results. A few studies have shown changes in reproductive organ weights with supporting histopathology, while other studies have shown no changes in organ weight or in histology. These inconsistent results make it difficult to determine if the reproductive system is a target of creosote exposure. Studies on the reproductive effects of creosote compounds include intermediate-duration inhalation studies on coal tar aerosols, acute-, intermediate-, and chronic-duration oral studies on wood creosotes, and an acute-duration dermal study on coal tar.

Coal tar products. Springer et al. (1982) reported that placental weight was decreased 31% in female rats exposed to 660 mg/m^3 of a coal tar aerosol on GDs 12–16 compared to controls. Relative ovary weights were decreased in rats (32%) and mice (29%) exposed to 690 mg/m^3 coal tar aerosol for 13 weeks (Springer et al. 1986b, 1987), while histopathological examination of ovarian sections showed a decrease in the amount of luteal tissue in rats (5/10 versus 0/10 in controls) and mice (3/9 versus 0/9) exposed to 690 mg/m^3 coal tar for up to 13 weeks. Testis weight increased 33% relative to controls in rats exposed to 690 mg/m^3 coal tar for 13 weeks, but similar changes were not observed in mice exposed up to 690 mg/m^3 coal tar for up to 13 weeks; no histopathological effects were observed, and functional assessments were not conducted.

No change in ovary weight was observed in female rats (dams) gavaged on GDs 12–16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984). Placental weights were decreased by 13% in these rats, although body weight gain was also decreased. No differences in uterine weight or vaginal cell cornification were observed in mature or immature ovariectomized (OVX) mice gavaged with up to 100 mg/kg creosote in sesame oil once a day for 4 days (Fielden et al. 2000). Mice fed diets containing up to 462 mg/kg/day (males) and 344 mg/kg/day (females) MGP residue exhibited no exposure-related histopathological lesions on the epididymides, preputial gland, ovaries, uterus, or clitoral gland after treatment for up to 185 days (Weyand et al. 1994). In a developmental study of rats and mice, dermal application of 500 or 1,500 mg/kg coal tar on GDs 11–15 resulted in decreased gravid uterine weight in rats (27%) and in mice (28%) (Zangar et al. 1989). Placental weights were also decreased by 24% in rats exposed to ≥500 mg/kg/day, although no changes were observed in mice.

Wood creosotes. An increase in relative testis weight (14%) was observed in rats administered ≥532 mg/kg/day beechwood creosote in the diet for 3 months, but not in rats receiving ≤207 mg/kg/day or in mice treated with up to 1,207 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 fed up to 832 mg/kg/day beechwood creosote 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). Testis weight was increased 14% in male rats gavaged with 200 mg wood creosote/kg/day for 95 weeks, but there were no histopathological changes observed or exposure-related changes in prostate or epididymis weight (Kuge et al. 2001). Ovary, uterus, and cervix weights were unaffected in female rats administered up to 200 mg wood creosote/kg/day by gavage for 102 weeks.

2.17 DEVELOPMENTAL

Human Studies. Only one study on developmental effects of creosote in humans was identified. 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 creosote wood treatment plant revealed no difference in the number of live births, premature births, spontaneous abortions, stillbirths, low-birth-weight births, or birth defects in 214 residents; interpretation of study results is limited by reliance on self-reporting and small study population size (ATSDR 1994).

Animal Studies. Studies in rats and mice have demonstrated developmental toxicity following exposure to coal tar by all routes of administration (see Table 2-7). Effects include reductions in fetal ossification, crown-rump length, fetal weight, fetal lung weight, and placental weights, cleft palate, and increased early pup mortality. Studies on the developmental effects of creosote compounds include acute-duration inhalation, oral, and dermal studies on coal tar aerosols and coal tar.

Coal tar products. In a study by Springer et al. (1982), there was an increase in the incidence of mid- and late-gestational resorptions in female rats exposed to 660 mg/m^3 of a coal tar aerosol on GDs 12–16 compared to control (0 resorptions). In the pups, decreased crown-rump length and fetal weight were observed, along with an increased incidence of fetuses with reduced ossification and small lungs.

Table 2-7. Summary of Studies Evaluating Developmental Effects in Rodents Exposed to Coal Tar Products

Species	Exposure level	Duration	Developmental outcomes	Reference
Inhalation exposure				
Rat	Heavy distillate (660 mg/m^3)	GDs 12–16 6 hours/day	↑ Mid-gestational resorptions (8 in 6 litters) ↑ Late-gestational resorption (5 in 4 litters) ↓ Crown-rump length (10%) ↓ Fetal body weight (21%) ↑ Reduced ossification (28 in 10 litters) ↑ Small fetal lungs (20 in 8 litters)	Springer et al. 1982
Oral exposure				
Mouse	Petroleum creosote (gavage, 400 mg/kg/day)	GDs 5–9	↔ Resorptions ↔ Number live fetuses ↔ Fetal malformations ↓ Fetal body weight (12%)	Iyer et al. 1993
Rat	Creosote P1/P13 (gavage, 175 mg/kg/day)	GDs 6–15	↑ Resorptions (145%) ↑ Whole litter resorptions (200%) ↓ Number live fetuses (21%) ↑ Fetal malformations (7 in 5 litters)	EPA 1995a
Rat	Creosote P2 (gavage, 225 mg/kg/day)	GDs 6–15	↑ Resorptions (381%) ↑ Whole litter resorptions (433%) ↓ Number live fetuses (38%) ↑ Fetal malformations (1)[a]	EPA 1995b
Rat	Harmarville process solvent (gavage, 740 mg/kg/day)	GDs 12–14	↔ Number live fetuses ↑ Fetal mortality (54%) ↓ Fetal body weight (18%) ↓ Fetal relative thymus weight (17%) ↑ Small fetal lungs (17 in 9 litters)	Springer et al. 1986a
Rat	Heavy distillate (gavage, 90, 140, 180, 370 mg/kg/day)	GDs 12–16	↑ Resorptions (441%, 180 mg/kg/day) ↓ Number live fetuses (11%, 370 mg/kg/day) ↔ Fetal body weight ↓ Fetal relative lung weight (14%, 90 mg/kg/day) ↑ Small fetal lungs (8 in 5 litters, 140 mg/kg/day) ↑ Fetal malformations (12 in 9 litters, 140 mg/kg/day)	Hackett et al. 1984

Table 2-7. Summary of Studies Evaluating Developmental Effects in Rodents Exposed to Coal Tar Products

Species	Exposure level	Duration	Developmental outcomes	Reference
Dermal exposure				
Rat	Coal-derived complex organic mixture (dermal, 500 mg/kg/day)	GDs 11–15	↑ Mid-gestational resorptions (mean 2.53 per litter) ↑ Late-gestational resorption (mean 0.88 per litter) ↓ Number live fetuses (33%) ↓ Fetal body weight (17%) ↓ Crown-rump length (9%) ↓ Fetal relative lung weight (52%) ↑ Small fetal lungs (157 in 17 litters) ↑ Reduced cranial ossification (59 in 15 litters) ↑ Fetal malformations Cleft palate (8 in 4 litters) Edema (17 in 7 litters) Midcranial lesions (23 in 5 litters)	Zangar et al. 1989
Mouse			↓ Number live fetuses (30%) ↑ Fetal malformations Cleft palate (5 in 3 litters) Renal pelvic cavitation (13 in 4 litters) Dilated ureter (12 in 4 litters)	

[a]Half the number of fetuses examined compared to lower dose, 75 mg/kg/day, and three fetal malformations in three litters.

↑ = increased; ↓ = decreased; ↔ = no change; GD = gestational day

Developmental effects have been observed in both rats and mice orally or dermally exposed to coal tar creosote. Increased mid- and late-gestational resorptions were observed in rats gavaged with doses ≥175 mg/kg/day on GDs 6–15 (EPA 1995a, 1995b) or 12–16 (Hackett et al. 1984), or dermally exposed to 500 mg/kg/day (Zangar et al. 1989), but not in mice gavaged with 400 mg/kg/day on GDs 5–9 (Iyer et al. 1993) or dermally exposed to 500 mg/kg/day (Zangar et al. 1989). Decreased number of live fetuses born (EPA 1995a, 1995b; Hackett et al. 1984; Zangar et al. 1989) and increased early fetal mortality (Hackett et al. 1984; Springer et al. 1986a) have been observed in both rats and mice gavaged or dermally exposed to ≥175 mg/kg/day, but not in mice gavaged with 400 mg/kg/day on GDs 5–9 (Iyer et al. 1993). EPA (2015) summarized a two-generation reproduction study where fetal body weights were decreased in the F0 generation following maternal gavage at 25 mg/kg/day for 17 weeks, while fetal weights in the F1 generation were only decreased at the highest dose (150 mg/kg/day) (MRID 42893201, DER not available). EPA (2015) noted that rabbits gavaged with 75 mg/kg/day on GDs 6–18 showed increased abortions, decreased live fetuses, and decreased implantation sites (MRID 44839802, DER not available).

Decreased fetal body weight is commonly observed following oral or dermal exposure to coal tar (EPA 1995b; Hackett et al. 1984; Iyer et al. 1993; Springer et al. 1986a; Zangar et al. 1989), while no differences in fetal weights were reported in rats gavaged with up to 175 mg/kg/day on GDs 6–15 (EPA 1995a); rats gavaged up to 370 mg/kg/day on GDs 12–16 (Hackett et al. 1984); or mice dermally exposed up to 1,500 mg/kg/day (Zangar et al. 1989). As seen with coal tar aerosols, fetal lung size/weight appears to be a sensitive target in rats for both oral and dermal exposure (Hackett et al. 1984; Springer et al. 1986a; Zangar et al. 1989), although mice dermally exposed did not show a similar sensitivity (Zangar et al. 1989). Increased incidences of fetal malformations are also a commonly reported effect following oral (EPA 1995a, 1995b; Hackett et al. 1984) or dermal (Zangar et al. 1989) exposure, but these effects may have a sensitive window of exposure as they were not observed in mice gavaged with 400 mg/kg/day on GDs 5–9 (Iyer et al. 1993). Common fetal malformations include cleft palate, syndactyly/ectrodactyly, and reduced ossification.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals after inhalation, oral, or dermal exposure to creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles.

2.19 CANCER

Cancer Classifications. HHS (NTP 2021) has classified the potential for creosote compounds to cause cancer in humans as follows.

- *Coal tars and coal-tar pitches* are known to be human carcinogens based on sufficient evidence of carcinogenicity from studies in humans.
- *Coke-oven emissions* are known to be human carcinogens based on sufficient evidence of carcinogenicity from studies in humans.

EPA's Integrated Risk Information System (IRIS) concluded the following regarding the carcinogenicity of creosote compounds:

- *Creosote* is classified as a probable human carcinogen (Group B1) based on limited evidence in humans and sufficient evidence in animals (IRIS 1988).
- *Coke over emissions (coal tar pitch volatiles)* are classified as a human carcinogen (Group A) based on sufficient evidence in humans and animals (IRIS 1989).

IARC (2010) classified *creosotes* as probably carcinogenic to humans (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. In addition, IARC (2012a) classified the carcinogenicity of creosote compounds for specific occupational settings and cancer types.

- *Coke production* is carcinogenic to humans (Group 1) based on:
  - sufficient evidence in humans for the carcinogenicity of coke production (cancer of the lung), and
  - sufficient evidence in experimental animals for the carcinogenicity of samples of tar taken from coke ovens.
- *Coal gasification* is carcinogenic to humans (Group 1) based on:
  - sufficient evidence in humans for the carcinogenicity of coal gasification (cancer of the lung), and
  - sufficient evidence in experimental animals for the carcinogenicity of coal-tars from gasworks and MGP residues.
- Occupational exposure during *aluminum production* is carcinogenic to humans (Group 1) based on:
  - sufficient evidence in humans for the carcinogenicity of occupational exposures during aluminum production (cancers of bladder and lung), and
  - sufficient evidence in experimental animals for the carcinogenicity of airborne particulate polynuclear organic matter from aluminum-production plants.

- Occupational exposures during *coal-tar distillation* are carcinogenic to humans (Group 1) based on:
  - sufficient evidence in humans for the carcinogenicity of occupational exposures during coal-tar distillation (cancer of the skin), and
  - sufficient evidence in experimental animals for the carcinogenicity of coal tars.
- Exposure to *coal tar pitch in roofers and pavers* is carcinogenic to humans (Group 1) based on:
  - sufficient evidence in humans for the carcinogenicity of coal-tar pitch as encountered in paving and roofing (cancers of the lung and bladder), and
  - sufficient evidence in experimental animals for the carcinogenicity of coal-tar pitch.

Human Studies. The epidemiological database of studies examining associations between occupational exposure to creosote compounds and cancer is extensive; therefore, it is not feasible to present in this toxicological profile a comprehensive review of all studies. Furthermore, the carcinogenicity of creosote has been extensively reviewed in assessments conducted by HHS (NTP 2021), IRIS (1988, 1989), and IARC (2010, 2012a); these reviews provide evidence of associations between occupational exposures to creosote compounds and cancer. Therefore, the presentation of the cancer epidemiology data that follows includes a tabular summary of the important studies identified by IARC (2010, 2012a) and a discussion of newer studies.

Although, collectively, epidemiological studies provide strong evidence of carcinogenicity of creosote chemicals, studies have not uniformly found associations with exposures to creosote. Several factors may have contributed to these apparent discrepancies, including differences in study designs and cohort sizes, exposures (levels and durations), co-exposures to other carcinogens, and extent to which association metrics were adjusted for potential biases (e.g., smoking, age).

Studies of occupational populations have evaluated cancers of the following organs/systems: lung and respiratory system; kidney and bladder; lymphatic-hematopoietic; oral cavity, esophagus, and stomach; pancreas; prostate; and skin. The most extensively studied are lung, bladder, and lymphatic-hematopoietic cancers (Table 2-8). The studies reviewed in Table 2-8 are those emphasized by IARC (2010, 2012a) and provide a balanced overview of studies finding associations and no associations between occupational exposures to creosote compounds and cancer outcomes. However, occupational exposure to coal dust inhalation has been reported to cause fibrosis, silicosis, and asbestosis, as well as lung and liver cancer (Howarth et al. 2011; IARC 1997; Jenkins et al. 2013). Populations studied included workers in creosote processing and application (e.g., creosote impregnating), coke processing,

coal gasification, coal tar distillation, roofing and paving, and aluminum processing. These populations are likely to have been exposed to many different chemicals, including components of creosote, which may have contributed to the observed cancer outcomes.

Table 2-8. Summary of Studies Evaluating Associations Between Occupational Exposures to Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles and Cancer

		Cancer type		
Population	Reference (n)	Lung	Bladder	Lymphatic-hematopoietic
Creosote workers	Eriksson and Karlsson 1992 (n=275 cases and 275 controls)[a]	NR	NR	↔ (MM)
Workers exposed to creosote compounds in other occupations (e.g., impregnators, power station workers, miscellaneous exposures)	Alicandro et al. 2016[b] (n=3,101)	NR	NR	↔ (LEU, NHL)
	Karlehagen et al. 1992 (n=922)	↔	↔	↑ (HL, LEU, NHL)
	Poynter et al. 2017 (n=2,073)	NR	NR	↑ (LEU)
	Siemiatycki et al. 1994[c] (n=2,896)	NR	↔	NR
	Steineck et al. 1989[c,d] (n=1,905,660)	NR	↑	NR
	Tornqvist et al. 1986 (n=10,061)	↔	↔	↔ (LEU)
	Wong and Harris 2005[a] (n=2,179)	↔	↔	↔
Coke workers	Alicandro et al. 2016[b] (n=15,550)	NR	NR	↔
	UK HSE 2002[b] (meta-analysis of 10 studies)	↑	↔	NR
	Armstrong et al. 2004[b] (meta-analysis of 10 studies)	↑	NR	NR
	Bertrand et al. 1987[a] (n=1,299)	↑	NR	NR
	Bosetti et al. 2007 (meta-analysis of 10 studies)	↑	↔	NR
	Bye et al. 1998 (n=888)	↔	↔	↔
	Chau et al. 1993[a] (n=536)	↑[e]	↔	NR
	Constantino et al. 1995 (n=5,321)	↑[f]	↔	↔
	Franco et al. 1993 (n=538)	↑	NR	NR
	Redmond et al. 1976 (n=3,567)[g]	↑	↔	↔
	Wu 1988 (n=3,107)	↑	NR	NR
	Wu-Williams et al. 1993[a] (n=1,924)	↔	NR	NR
Coal gasification workers	UK HSE 2002[b] (meta-analysis of four studies)	↑	↔	NR
	Armstrong et al. 2004[b] (meta-analysis of five studies)	↑	NR	NR
	Berger and Manz 1992[c] (n=789)	↑	NR	NR
	Bosetti et al. 2007[b] (meta-analysis of five studies)	↑	↑	NR

Table 2-8. Summary of Studies Evaluating Associations Between Occupational Exposures to Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles and Cancer

		Cancer type		
Population	Reference (n)	Lung	Bladder	Lymphatic-hematopoietic
	Gustavsson and Reuterwall 1990 (n=295)	↔	↔	↔
	Hansen et al. 1986 (n=46)[g]	↑	NR	NR
	Kawai et al. 1967 (n=504)[g]	↑	NR	NR
	Martin et al. 2000 (n=1,535)	↑	NR	NR
Aluminum workers	Alicandro et al. 2016[b] (n=78,058)	NR	NR	↔ (HL, NHL, MM, LEU)
	Armstrong and Gibbs 2009[a] (n=16,431)	↑	NR	NR
	UK HSE 2002[b] (meta-analysis of eight studies)	↑	↑	NR
	Armstrong et al. 2004[b] (meta-analysis of eight studies)	↑	NR	NR
	Bjor et al. 2008 (n=2,264)	↑[h]	↔	↔ (NHL)
	Bosetti et al. 2007[b] (meta-analysis of 15 studies)	↔	↑	NR
	Carta et al. 2004[a] (n=1,152)	↔	↔	↑
	Friesen et al. 2009[a] (n=4,316)	↔	↔	↔
	Gibbs 1985 (n=5,891)	↑	↑	NR
	Gibbs and Sevigny 2007a, 2007b[a] (n=10,454)	↑	↑	↔
	Gibbs et al. 2007[a] (n=5,977)	↑[i]	↑[i]	↔ (NHL)
	Gibbs et al. 2014[a] (n=17,089)	↑[j]	↑[j]	↑[i]
	Milham 1979 (n=2,103)	↔	↔	↑
	CDC 1983 (n=1,238)	↔	↔	NR
	Moulin et al. 2000[c] (n=2,133)	↔	↔	↔
	Mur et al. 1987[c] (n=6,455)	↔	↔	↔
	Rockette and Arena 1983[c] (n=21,829)	↔	↔	↑
	Romundstad et al. 2000a[a] (n=1,790)	↔	↔	↔
	Romundstad et al. 2000b[c] (n=11,103)	↔	↑[k]	↔
	Romundstad et al. 2000c[a] (n=5,627)	↔	↑[l]	↔
	Rønneberg et al. 1999 (n=2,888)	↔	↔	↔
	Scarnato and Morelli 2012 (n=618)	NR	NR	↔
	Selden et al. 1997[c] (n=6,454)	↑[m]	↔	↔
	Sim et al. 2009[c] (n=4,396)	↔	↔	↔
	Spinelli et al. 1991[a] (n=4,213)	↔	↑	↑[m] (NHL)
	Spinelli et al. 2006[a] (n=6,423)	↑[n]	↑[n]	↑[n] (NHL)
	Thériault et al. 1981[a] (n=182)	NR	↑	NR
	Thériault et al. 1984[a] (n=340)	NR	↑	NR

Table 2-8. Summary of Studies Evaluating Associations Between Occupational Exposures to Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles and Cancer

Population	Reference (n)	Cancer type		
		Lung	Bladder	Lymphatic-hematopoietic
	Tremblay et al. 1995[a] (n=552)	NR	↑	NR
	Wigle 1977 (n=163,350)	↑	↑	NR
Coal tar distillation workers	Alicandro et al. 2016[b] (n=2,873)	NR	NR	↔ (LEU)
	Armstrong et al. 2004[b] (meta-analysis of three studies)	↔	NR	NR
	Moulin et al. 1988 (n=963)	↔		↔
	Swaen and Slangen 1997 (n=1,773)[o]	↔	↔	↔
Roofers, pavers, highway workers	Alicandro et al. 2016[b] (n=36,625)	NR	NR	↔ (LEU, HL MM, NH)
	Bender et al. 1989 (n=4.849)[c]	↔	↔	↔ (LEU, HL MM)
	Blair et al. 1993[a] (n=1,867)	NR	NR	↔ (NHL)
	Boffetta et al. 2003[c] (n=29,820)	↑	↔	↔
	Olsson et al. 2010[a] (n=1,686)	↔	NR	NR
	Pukkala 1995 (n=NR)[p]	↑	NR	NR
	Stern et al. 2000[c] (n=11,144)	↑	↑	↔
	Swaen and Slangen 1997 (n=1,773)[o]	↔	↔	↔

[a]Analyses controlled for smoking.
[b]Meta-analysis.
[c]Analyses controlled for some confounders (e.g., age, race, calendar year, years of exposure, other chemical exposures), but not for smoking.
[d]Exposures were self-reported and intensity of exposure was not assessed; 56 cases of bladder cancer were reported.
[e]Association between exposure and lung cancer in smokers, but no association in nonsmokers.
[f]Positive trends for lung cancer and years of exposure and weighted exposure index to coal tar pitch volatiles.
[g]Not adjusted for smoking.
[h]Positive association for workers employed for >10 years, but no association for workers employed for ≤10 years.
[i]Positive trend based on benzo[a]pyrene exposure.
[j]Positive associations between benzo[a]pyrene exposure level for smokers and nonsmokers; however, in smokers, positive associations were observed at lower benzo[a]pyrene exposures.
[k]Positive trend based on PAH exposure.
[l]Positive association at the highest cumulative PAH exposure with a lag time of 30 years.
[m]Positive association in men (n=6,454) working <1 year but not 1–>20 years; the study authors proposed that the finding in short-term workers was related to smoking (although study did not provide data on smoking). No association for women (n=629).
[n]Positive associations for the two highest cumulative exposure categories (measured by benzene soluble material).
[o]Combined coal tar distillery workers and roofers.
[p]The number of roofers and pavers evaluated in this study was not reported.

HL = Hodgkin's lymphoma; LEU = leukemia; LH = lymphatic-hematopoietic; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NR = not reported; PAH = polycyclic aromatic hydrocarbon

As noted above, IARC (2012a) cancer classifications based on occupation indicate that exposures are associated with cancers of the lung and/or bladder, except for exposure for coal-tar distillation workers, which is associated with skin cancer. This assessment, as discussed in IARC (2010), indicates that two surveillance studies form the basis of this classification: Letzel and Drexler (1998), and Henry (1946). Letzel and Drexler (1998), a study of 606 German refinery workers, shows associations between exposures and squamous cell and basal cell carcinomas. The study authors noted that exposure to sunlight is a "cofactor" in the development of skin cancer. However, since some skin cancers occurred in areas typically covered by clothing, co-exposure to sunlight does not appear to be required for the development of skin cancer. Henry (1946) reported 767 of epitheliomatous ulcerations or cancers of the skin in coal tar distillers in England and Wales during the period 1920–1943. Ulcerations and cancers were located on the head, neck, arms, hands, and scrotum.

After IARC (2010, 2012a), a meta-analysis examined incidence and mortality from lymphatic and hematopoietic cancers reported in 41 studies of occupational exposures to PAH (Alicandro et al. 2016). Populations included workers in the iron and steel foundries, aluminum processing, coke processing, carbon electrode manufacturing, asphalt paving and roofing, and coal tar distilling. Meta risk estimates (relative risk) were calculated based on standard mortality ratios (SMR), standard incidence ratios (SIR), or risk ratios (RR); estimates were also weighted for variance and evaluated for heterogeneity between studies. Outcomes evaluated included Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia or multiple myeloma. Although some individual studies found associations between exposure to PAH and cancer, meta-RR estimates were not elevated for any category of cancers in any of the industry categories (95% confidence interval [CI] included 1). The highest meta-RR was estimated for non-Hodgkin's lymphoma in creosote workers (2.01; 95% CI: 0.96, 4.22).

A case-control study examined 420 cases of acute myeloid leukemia and 265 myelodysplastic syndromes reported in the Minnesota Cancer Surveillance System, along with 1,388 general population controls (Poynter et al. 2017). Exposure to creosote was associated with increased risk of acute myeloid leukemia (odds ratio [OR]: 2.83; 95% CI: 1.46, 5.47) but not myelodysplastic syndromes (OR: 1.31 95% CI: 0.56, 3.05). ORs were adjusted for age, sex, household income, smoking, exposure to radiation, and residence on a farm or in a rural area >1 year.

A cohort study of 13,200 psoriasis and eczema patients examined associations between treatments with dermal applications of coal tar and cancer risk (Roelofzen et al. 2010). The study estimated cancer hazard ratios (HR) for dermal coal tar treatment compared to dermal corticosteroid treatment. Dermal coal tar

treatment was not associated with increased risk of non-skin cancers (HR 0.92; 95% CI: 0.78, 1.09) or skin cancer (HR: 1.09; 95% CI: 0.69, 1.72). A case-control study examined 1,387 bladder cancer cases reported in the Department of Registry and Research of the Comprehensive Cancer Centre (Nijmegen, the Netherlands), along with 5,182 controls (Roelofzen et al. 2015). Self-reported history of dermal coal tar treatment for skin diseases was not associated with bladder cancer (OR: 1.37, 95% CI: 0.93, 2.01). ORs were adjusted for age, gender, and tobacco smoking.

Animal Evidence. Carcinogenicity has been assessed in rodents following inhalation, oral, and dermal chronic-duration exposure to creosote compounds. Studies have shown that dermal or inhalation exposure to coal tar products has resulted in skin and lung cancer in animals, while oral studies have shown that animals fed diets containing coal tar developed cancer of the lungs, liver, and stomach. Data from these studies are summarized in Table 2-9.

Coal tar products. Lung tumors are the most common carcinogenic response following chronic-duration exposure to coal tar aerosols in rats. Female rats exposed to 1.1 and 2.6 mg/m^3 coal tar pitch aerosol for 10 months developed mostly squamous cell carcinomas of the lung (Heinrich et al. 1994a, 1994b). Similar results were also observed in female rats exposed to the same regime for 20 months (Heinrich et al. 1994a, 1994b), and in male and female rats exposed to 10 mg/m^3 coal tar aerosol for 18 months (MacEwen et al. 1977).

A series of studies in mice have shown skin tumors following chronic-duration exposure to coal tar aerosols. Skin tumors (type not specified) developed in tumor-susceptible ICR CF-1 mice exposed continuously for 90 days to 2 and 10 mg/m^3, while a lower incidence was observed in tumor-resistant CAF1-JAX mice (MacEwen et al. 1977). Exposure to 10 mg/m^3 coal tar aerosol-BTX mixture intermittently (6 hours/day, 5 days/week) for 18 months showed lower incidences of skin tumors, 7 and 4% in ICR CF-1 and CAF1-JAX mice, respectively (MacEwen et al. 1977). Calculation of total exposure indicated the amount of coal tar reaching the skin of the animals was the same in the 90-day continuous and the 18-month intermittent studies. However, during intermittent exposure, animal self-grooming was allowed, leading to an oral component to exposure.

Table 2-9. Summary of Studies Evaluating Tumor Response in Rodents Exposed to Creosote Compounds by Inhalation, Oral, and Dermal Routes

Species (sex, n)	Exposure level	Duration	Tumor outcomes	Reference
Inhalation/aerosol exposure—coal tar aerosols				
Wistar rat (F, 72/group)	Coal tar pitch (1.1, 2.6 mg/m^3)	17 hours/day, 5 days/week, 10 months	Squamous cell carcinomas (lung)[a] 1/72 at 1.1 mg/m^3 28/72 at 2.6 mg/m^3 Bronchiolo-alveolar adenocarcinoma 2/72 at 1.1 mg/m^3 Bronchiolo-alveolar adenosquamous carcinoma 1/72 at 2.6 mg/m^3	Heinrich et al. 1994a, 1994b
		17 hours/day, 5 days/week, 20 months	Squamous cell carcinomas (lung)[a] 20/72 at 1.1 mg/m^3 68/72 at 2.6 mg/m^3 Bronchiolo-alveolar adenocarcinoma 1/72 at 2.6 mg/m^3	
SD rat (M/F, 40/group)	Coal tar (10 mg/m^3)	6 hours/day, 5 days/week, 18 months	Squamous cell carcinomas (lung)[a] 31/38 (F) and 38/38 (M)	MacEwen et al. 1977
ICR CF-1 mouse (F, tumor-susceptible)	Coal tar-BTX (0.2, 2, 10 mg/m^3)	90 days continuously	Skin tumors (NS)[a] 14/75 (19%) at 2 mg/m^3 44/55 (80%) at 10 mg/m^3	
	Coal tar-BTX (10 mg/m^3)	6 hours/day, 5 days/week, 18 months	Skin tumors (NS)[a] 5/75	
CAF1-JAX mouse (F, tumor-resistant)	Coal tar-BTX (0.2, 2, 10 mg/m^3)	90 days continuously	Skin tumors (NS)[a] 3/65 (5%) at 2 mg/m^3 18/43 (42%) at 10 mg/m^3	
	Coal tar-BTX (10 mg/m^3)	6 hours/day, 5 days/week, 18 months	Skin tumors (NS)[a] 2/50	
Oral exposure—coal tar products				
A/J mouse (F, 30/group)	Coal tar (diet, 100, 236 mg/kg/day)	260 days	Pulmonary adenomas 100% at 236 mg/kg/day, 12.17/mouse 70% at 100 mg/kg/day, 1.19/mouse	Weyand et al. 1995

Table 2-9. Summary of Studies Evaluating Tumor Response in Rodents Exposed to Creosote Compounds by Inhalation, Oral, and Dermal Routes

Species (sex, n)	Exposure level	Duration	Tumor outcomes	Reference
B6C3F1 mouse (F, 48/group)	Coal tar Mixture 1 (diet, 12, 33, 117, 333, 739, 1,300 mg/kg/day tar)	2 years	333 mg/kg/day coal tar[b] Hepatocellular adenomas/carcinomas (liver, 14/45) Alveolar/bronchiolar adenomas and carcinomas (lung, 27/47) Papillomas/carcinomas (forestomach, 14/46) Hemangiosarcomas (11/48) 739 mg/kg/day coal tar[b] Adenocarcinomas (small intestine, 22/36)	Culp et al. 1996, 1998
	Coal tar Mixture 2 (diet, 40, 120, 346 mg/kg/day tar)	2 years	120 mg/kg/day coal tar[b] Alveolar/bronchiolar adenomas/ carcinomas (lung, 10/48) 346 mg/kg/day coal tar[b] Hepatocellular adenomas/carcinomas (liver, 10/45) Forestomach papillomas/carcinomas (13/44) Hemangiosarcomas[c] (17/48) Histiocytic sarcomas[d] (11/48)	
Oral exposure—wood creosotes				
SD rat (M/F, 60/group)	Wood creosote (gavage, 20, 50, 200 mg/kg/day)	102 weeks	No dose-related effects	Kuge et al. 2001
ddY mouse (M/F, 57/group)	Beechwood creosote (diet, M: 0, 247, 474 mg/kg/day, F: 0, 297, 532 mg/kg/day)	52 weeks	No dose-related effects	Miyazato et al. 1984a
Wistar rat (M/F, 51/group)	Beechwood creosote (diet, M: 0, 143, 313 mg/kg/day, F: 0, 179, 394 mg/kg/day)	96 weeks	No dose-related effects	Miyazato et al. 1984b

Table 2-9. Summary of Studies Evaluating Tumor Response in Rodents Exposed to Creosote Compounds by Inhalation, Oral, and Dermal Routes

Species (sex, n)	Exposure level	Duration	Tumor outcomes	Reference
Dermal exposure—coal tar products				
Mouse (strain, sex NS) (25/group, reared in stainless steel cages)	Coal tar creosote (25 µL)	2 times/week, 5 months (stainless-steel cages)	Lung adenomas, average 5.8/mouse[a] "High incidence" of skin tumors	Roe et al. 1958
Mouse (strain, sex NS) (29/group, reared in creosote-treated wood cages)		2 times/week, 5 months (creosote-treated wood cages)	Lung adenomas, average 10.8/mouse[a] "High incidence" of skin tumors	
Albino mouse (strain, sex NS) (30/group, reared in stainless steel cages)		2 times/week, 4 weeks (stainless-steel cages)	Lung adenomas, average 1.6/mouse[a]	
C57L mouse (M/F, 8–11/group)	"Light" creosote (50%, 1 drop)	3 times/week for lifespan or until papilloma development	11/11 skin papillomas over 22–41 weeks[a]	Poel and Kammer 1957
	"Blended" creosote (20–80%, 1 drop)		8/8 skin papillomas over 22–43 weeks (20%) or 19–34 weeks (80%); 7/8 malignant[a]	
Sutter mouse (F, 30/group)	Creosote oil (25 µL) (initiating)	2 times/week, 4 weeks	No effect	Boutwell and Bosch 1958
		2 times/week, 28 weeks	Skin papillomas (50% at 20 weeks)[a] Skin carcinomas (50% at 26 weeks)	
	DMBA (75µg) Creosote oil (25 µL) (promoting)	1 time DMBA 2 times/week creosote oil, 28 weeks	Skin papillomas (50% at 16 weeks)[a] Skin carcinomas (50% at 23 weeks)	
Swiss albino mouse (M/F, 26–58/group)	Coal tar (25 µL; 1.7 mg)	2 times/week, 82 weeks	Skin papillomas (53/58)[a] Skin carcinomas (31/58)	Wallcave et al. 1971
CD-1 mouse (F, 30/group)	Coal tar ointment (1.5%)	5 times/week, 2 weeks	No effect	Phillips and Alldrick 1994
	Coal tar ointment (1.5%) Dithranol (0.1%) (promotor)	5 times/week, 2 weeks, 40 weeks dithranol	Skin papillomas (4/27)[a] Enlarged lymph nodes (12/27)	

Table 2-9. Summary of Studies Evaluating Tumor Response in Rodents Exposed to Creosote Compounds by Inhalation, Oral, and Dermal Routes

Species (sex, n)	Exposure level	Duration	Tumor outcomes	Reference
C3H/HeJ mouse (M, 20–50/group)	Coal-tar pitch (25 mg)	2 times/week, 80 weeks	Malignant skin tumors (45/49)[e] Average time to papillomas 18 weeks	Emmett et al. 1981
	Coal-tar bitumen (25 mg)		Malignant skin tumors (39/48)[e] Average time to papillomas 21.5 weeks	
	Coal-tar bitumen from roofing operation (25 mg)		Malignant skin tumors (38/45)[e] Average time to papillomas 10.5 weeks	
	Roofing dust (25 mg)		Malignant skin tumors (10/14)[e] Average time to papillomas 16.5 weeks	
Swiss CD-1 mouse (M, 50/group)	Coal tar pitch fume condensate (50 µL)	2 times/week, 78 weeks	Approximately 7% malignant skin tumors[a] Average latency period 48–65 weeks	Niemeier et al. 1988
C3H/HeJ mouse (M, 50/group)			Approximately 68% malignant skin tumors Average latency period 40–49 weeks	
Crl:CD-1(ICR)BR mouse (M, 30/group)	Creosote P1/P13 (0.5, 25, 56 mg/mouse) TPA (initiation)	Creosote 5 times/week for 2 weeks, 2-week rest, TPA 2 times/week for 26 weeks	0.5 mg/mouse—skin tumors 27/30 papillomas 4/30 keratoacanthomas 25 mg/mouse—skin tumors 24/30 papillomas 7/30 keratoacanthomas 2/30 squamous cell carcinomas 56 mg/mouse—skin tumors 26/30 papillomas 7/30 keratoacanthomas 2/30 squamous cell carcinomas	EPA 1997
	DMBA creosote P1/P13 (0.5, 25, 56 mg/mouse) (promotion)	DMBA 1 time on day 11, 2-week rest, creosote 2 times/week, 26 weeks	0.5 mg/mouse—skin tumors 2/30 papillomas 25 mg/mouse—skin tumors 23/30 papillomas 14/30 keratoacanthomas 21/30 squamous cell carcinomas 1/30 basal cell carcinoma 56 mg/mouse—skin tumors 25/30 papillomas	

Table 2-9. Summary of Studies Evaluating Tumor Response in Rodents Exposed to Creosote Compounds by Inhalation, Oral, and Dermal Routes

Species (sex, n)	Exposure level	Duration	Tumor outcomes	Reference
			11/30 keratoacanthomas 29/30 squamous cell carcinomas 3/30 basal cell carcinoma	
	Creosote P1/P13 (56 mg/mouse)	Creosote 5 times/week, 2 weeks, 2-week rest, creosote 2 times/week, 26 weeks	Skin tumors 16/30 papillomas 4/30 keratoacanthomas 28/30 squamous cell carcinomas 2/30 basal cell carcinoma 2/30 lymphomas 4/30 lung nodules	
CD-1 mouse (F, 30/group)	Crude coal tar fractions (5 mg), TPA (5 µg)	1 time coal tar fraction, 2 weeks later TPA 2 times/week, 24 weeks	0.3–4.52 skin papillomas/mouse[a]	Springer et al. 1989
CD-1 mouse (F, 30/group)	Coal distillates (50 µL), PMA (50 µL)	1 time distillate fraction, 2 times/week PMA	15–95% incidence of skin papillomas at 6 months[a]	Mahlum 1983
	50 µg DMBA, middle distillate (50 µL)	1 time DMBA, 2 times/week distillate	17% incidence of skin papillomas at 6 months[a]	
Swiss mouse (F, 30/group)	Coal tar creosote (undiluted)	2 times/week, 70 weeks	23 skin tumors (NS, 16 malignant) 13/26 mice, latency period 50 weeks[a]	Lijinsky et al. 1957
	1% DMBA, coal tar creosote (undiluted)	1 time DMBA, 2 times/week, 70 weeks creosote	32 skin tumors (NS, 26 malignant) 17/23 mice, latency period 39 weeks[a]	
	1% DMBA, creosote (10% in acetone)		15 skin tumors (NS, 8 malignant) 11/29 mice, latency period 43 weeks[a]	
	1% DMBA, basic fraction coal tar creosote (2% in acetone)		No effects	

Table 2-9. Summary of Studies Evaluating Tumor Response in Rodents Exposed to Creosote Compounds by Inhalation, Oral, and Dermal Routes

Species (sex, n)	Exposure level	Duration	Tumor outcomes	Reference
SENCAR mouse (F, 10–35/group)	Medium crude coke oven coal tar (1 mg per 125 µL toluene), TPA (1 µg/200 µL acetone)	1 time coal tar, 2 times/week TPA (1 µg), 25 weeks	4.1–5.3 skin papillomas/tumor-bearing animal[a]	Marston et al. 2001

[a]Statistical analysis not conducted.
[b]p<0.05 for dose compared to control group, p<0.01 for dose-response related trend.
[c]Organs involved include skin, mesentery, mesenteric lymph nodes, heart, spleen, urinary bladder, liver, uterus, thoracic cavity, ovary, and skeletal muscle.
[d]Organs involved include mesentery, forestomach, skin, and kidney.
[e]95% confidence level compared to positive control.

DMBA = 7,12-dimethylbenz[α]anthracene; F = female(s); M = male(s); PMA = phorbol-12-myristate-13-acetate NS = not specified;
TPA = 12-O-tetradecanoylphorbol-13-acetate

Oral exposure to coal tar products has been shown to induce several tumor types in mice, including neoplastic changes in the lung and liver. Female mice fed diets containing 100 or 236 mg/kg/day for 260 days had a significant increase in the incidence of lung tumors, mostly pulmonary adenomas, compared to controls (Weyand et al. (1995). In a series of 2-year feeding studies using two mixtures of MGP coal tar samples, female mice developed tumors of the liver, lung, and forestomach. Both mixtures showed increasing positive dose-related trends for hepatocellular adenomas/carcinomas (22 and 31 versus 0% in controls), alveolar/bronchiolar adenomas/carcinomas, and forestomach papillomas/carcinomas at doses ≥333 mg/kg/day (Culp et al. 1996, 1998).

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). 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. The study authors concluded that, 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.

A large body of evidence exists to show that coal tar 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 (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 skin and lung tumors may result from dermal exposure to coal tar products.

Lung adenomas were observed in a series of studies by Roe et al. (1958), where dermally applied coal tar creosote (25 µL undiluted for 5 months) induced a higher number of lung adenomas in mice reared in creosote-treated wooden cages than in mice reared in stainless steel cages (10.8/mouse versus 5.8/mouse), with both groups showing a “high incidence” of skin tumors. Lung nodules were also observed in a study that treated mice with 50 mg creosote for 30 weeks (EPA 1997), while dermal application of blended coal tar creosote for 26 weeks resulted in 7/16 mice with tumors that metastasized to the lungs or regional lymph nodes (Poel and Kammer 1957), suggesting that dermal exposure may result in carcinogenic effects far from the application site.

Skin papillomas and carcinomas have been observed in multiple chronic-duration studies in mice and rabbits following dermal application of creosote oil, coal tar, and coal tar creosote (Boutwell and Bosch 1958; Emmett et al. 1981; Kligman and Kligman 1994; Lijinsky et al. 1957; Mahlum 1983; Marston et al. 2001; Niemeier et al. 1988; Poel and Kammer 1957; Roe et al. 1958; Wallcave et al. 1971; Springer et al. 1989). A few studies have also found no tumor response (Boutwell and Bosch 1958; Lijinsky et al. 1957; Phillips and Alldrick 1994) but these studies used lower doses and/or shorter durations, making the comparison challenging. Most tumors present as benign in the form of squamous cell papillomas and keratoacanthomas, while some tumors progress into squamous cell carcinomas and may metastasize to other regions.

While creosote compounds alone have been shown to cause skin tumors (Boutwell and Bosch 1958; EPA 1997; Emmett et al. 1981; Kligman and Kligman 1994; Lijinsky et al. 1957; Niemeier et al. 1988; Poel and Kammer 1957; Wallcave et al. 1971), several studies have also evaluated the initiating and promoting activity of coal tar and coal tar creosote (Boutwell and Bosch 1958; EPA 1997; Lijinsky et al. 1957; Mahlum 1983; Marston et al. 2001; Phillips and Alldrick 1994; Siddens et al. 2015; Springer et al. 1989). Initiating activity has been observed with coal tar creosote, coal tar ointment, and crude coal tar in combination with croton oil, dithranol, or 12-O-tetradecanoylphorbol-13-acetate (TPA), while the promoting activity has been observed with creosote oil, coal distillates, and crude coal tar in combination with 7,12-dimethylbenz(a)anthracene (DMBA).

Wood creosote. No exposure-related neoplastic changes were observed in Sprague-Dawley rats administered up to 200 mg/kg/day wood creosote by gavage for up to 102 weeks (Kuge et al. 2001), rats fed doses up to 394 mg/kg/day for 96 weeks (Miyazato et al. 1984b), or mice fed doses of 532 mg/kg/day for 52 weeks (Miyazato et al. 1984a). Sporadic tumors were observed in all three studies, but the increases did not appear to be dose-related, and there was a high incidence of neoplastic changes in the control groups, limiting the evidence that ingested beechwood creosote is carcinogenic to mice or rats.

2.20 GENOTOXICITY

Coal Tar Products. The genotoxicity of coal tar creosote, coal tar, and coal tar volatiles have been studied using *in vitro* assays in prokaryotic organisms and mammalian cells and following *in vivo* exposures of humans and laboratory animals. Results of *in vitro* studies provide consistent evidence of mutagenicity. In addition, deoxyribonucleic acid (DNA) adducts, sister chromatic exchange (SCE), and

micronuclei formation have also been reported, although these endpoints have not been extensively studied. Results of *in vitro* studies are summarized in Table 2-10.

Table 2-10. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro*

Species (test system)	Endpoint	Result		Reference
		With activation	Without activation	
Coal tar creosote				
Prokaryotic organisms:				
Salmonella typhimurium (vapor exposure)	Gene mutation	+	–	Bos et al. 1983, 1985
S. typhimurium	Gene mutation	+	–	Zeiger et al. 1992
Coal tar				
S. typhimurium (vapor exposure)	Gene mutation	+	–	Bos et al. 1985
S. typhimurium	Gene mutation	+	–	Mayura et al. 1999
Calf thymus DNA	DNA adducts	+	No data	Koganti et al. 2000
Coal tar pitch volatiles				
Prokaryotic organisms:				
S. typhimurium	Gene mutation	+	–	Donnelly et al. 1996
Mammalian cells:				
Mouse lymphoma cells	Gene mutation	+	–	EPA 1978b
V79	Gene mutation	–	–	DOE 1994
V79	SCE	+	+	DOE 1994
V79	Micronucleus	+	+	DOE 1994

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; SCE = sister chromatid exchange; V79 = Chinese hamster lung cell line

In vivo studies on genotoxicity have been conducted in workers, psoriasis patients, and laboratory animals. Results are summarized in Table 2-11. Studies in coal tar and coke oven workers show DNA strand breaks, chromosomal aberrations, and micronuclei formation in WBCs and buccal cells. In psoriasis patients, dermal application of coal tar has been consistently shown to induce DNA adduct formation in skin cells and leukocytes. Results of *in vivo* genotoxicity tests in laboratory animals provide strong evidence of gene mutation, DNA damage, and DNA adduct formation.

Table 2-11. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo*

Species (cell type)	Route	Endpoint	Results	Reference
Coal tar				
Mouse/skin	Dermal	Gene mutation	+	Vogel et al. 2001
Mouse/skin	Dermal	DNA synthesis	+	Walter et al. 1978
Human/lymphocytes	Occupational (coal tar workers)	DNA strand breaks	+	Giri et al. 2011, 2012
Human/lymphocytes	Occupational (coal tar workers)	Chromosomal aberrations/SCE	+	Yadav and Seth 1998
Human/lymphocytes	Occupational (coal tar workers)	Chromosomal aberrations	+	Kumar et al. 2011
Human/ buccal cells	Occupational (coal tar workers)	Micronuclei	+	Kumar et al. 2011
Human/buccal cells	Occupational (coal tar workers)	Micronuclei	+	Giri et al. 2012
Human/lymphocytes	Dermal (psoriatic patients)	DNA adducts	–	Pavanello and Levis 1992
Human/lymphocytes	Dermal (psoriatic patients)	DNA adducts	+/–	Pavanello and Levis 1994
Human/leukocytes	Dermal (psoriatic patient-GT)	DNA adducts	+	Santella et al. 1995
Human/leukocytes, skin	Dermal (eczema patients)	DNA adducts	+	Godschalk et al. 1998
Human/skin	Dermal (psoriatic patients)	DNA adducts	+	Schoket et al. 1990
Human/skin	Dermal (psoriatic patients)	DNA adducts	+	Zhang et al. 1990
Human/skin	Dermal (atopic eczema patients)	DNA adducts	+	Rojas et al. 2001
Human/skin	Dermal (atopic eczema patients)	DNA adducts	+	Godschalk et al. 2001
Human/skin	Dermal (healthy and psoriatic patients)	DNA adducts	+	Roelofzen et al. 2012
Human/lymphocytes	Dermal (psoriatic patients)	Chromosomal aberrations/SCE	+	Sarto et al. 1989
Human/lymphocytes	Dermal (psoriatic patients- GT)	Chromosomal aberrations	+	Borska et al. 2006
Mouse/liver	Dermal	DNA strand breaks	–	Thein et al. 2000
Mouse/skin	Dermal	DNA strand breaks/DNA adducts	+	Thein et al. 2000
Mouse/skin	Dermal	DNA adducts	+	Hughes et al. 1993
Mouse/skin	Dermal	DNA adducts	+	Phillips and Alldrick 1994
Mouse/skin, lung	Dermal	DNA adducts	+	Schoket et al. 1990

Table 2-11. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo*

Species (cell type)	Route	Endpoint	Results	Reference
Mouse/liver	Dermal	DNA adducts	+	Thein et al. 2000
Mouse/liver, lung, forestomach	Oral	DNA adducts	+	Culp and Beland 1994
Mouse/forestomach, small intestine	Oral	DNA adducts	+	Culp et al. 1996
Mouse/lung	Oral	DNA adducts	+	Koganti et al. 2000, 2001
Coal tar pitch				
Human/lymphocytes	Occupational	SCE	+	Wu 1988
Coal tar pitch volatiles				
Human/WBC	Occupational (coke oven workers)	Chromosomal aberrations/SCE	+	Bender et al. 1988
Human/lymphocytes	Occupational (aluminum reduction plant)	Chromosomal aberrations	–	Heussner et al. 1985
Human/WBC	Occupational (coke oven workers)	DNA adducts	+	Lewtas et al. 1997
Rat/lung	Inhalation	DNA adducts	+	Lewtas et al. 1997

+ = positive results; – = negative results; (+/–) = mixed results; DNA = deoxyribonucleic acid; SCE = sister chromatid exchange; WBC = white blood cell

Few studies investigating the genotoxicity of coal tar creosote were identified; studies are limited to *in vitro* studies only (Table 2-10). Vapors released from heating coal tar creosote were mutagenic to *S. typhimurium* in the presence of metabolic activators (Bos et al. 1983, 1985; Zeiger et al. 1992).

Numerous studies provide consistent evidence that exposure to coal tar is genotoxic. Results of *in vitro* studies demonstrate that coal tar produced gene mutation in prokaryotic cells with metabolic activation (Bos et al. 1985; Mayura et al. 1999) and DNA adducts in calf thymus DNA (Koganti et al. 2000); results are summarized in Table 2-10. *In vivo* studies provide consistent evidence of genotoxicity in humans and laboratory animals, including DNA damage, chromosomal aberrations, and micronuclei formation (Table 2-11). In coal tar workers, DNA strand breaks (Giri et al. 2011, 2012) and chromosomal aberrations were observed in lymphocytes (Kumar et al. 2011; Yadav and Seth 1998) and increased micronuclei formation was observed in buccal cells (Giri et al. 2012; Kumar et al. 2012). Several studies have evaluated genotoxicity in psoriasis or eczema patients treated with topical coal tar preparations containing 1.5–10% coal tar. These studies provide evidence that dermal exposure to coal tar produces DNA adducts in epidermal cells, lymphocytes, and leukocytes, and chromosomal aberrations in lymphocytes. Several studies in mice provide consistent evidence of genotoxicity following oral and

dermal exposure to coal tar. Following oral exposure, DNA adducts were observed in cells of the forestomach, small intestine, and lung (Culp and Beland 1994; Culp et al. 1996; Koganti et al. 2000, 2001). In epidermal cells of mice exposed to dermal coal tar, gene mutations (Vogel et al. 2001), increased DNA synthesis (Walter et al. 1978), DNA strand breaks (Thein et al. 2000), and DNA adducts (Hughes et al. 1993; Phillips and Alldrick 1994; Schoket et al. 1990; Thein et al. 2000) were observed. DNA adducts also were observed in hepatocytes following dermal exposure of mice to coal tar (Schoket et al. 1990; Thein et al. 2000).

Genotoxicity of coal tar pitch and coal tar pitch volatiles has been investigated in *in vitro* studies and *in vivo* studies. *In vitro* studies on coal tar pitch volatiles have found gene mutations in *S. typhimurium* (Donnelly et al. 1996), although no mutations were observed in the Chinese hamster lung cell line V79 (DOE 1994). Increased SCE and increased micronuclei formation also were observed in V79 cells (DOE 1994). In coke oven and coal tar workers, studies have found DNA adducts in leukocytes (Lewtas et al. 1997) and increased SCE in lymphocytes (Bender et al. 1988; Wu 1988). In contrast, no chromosomal aberrations were observed in lymphocytes of aluminum reduction workers exposed to coal tar pitch volatiles (Heussner et al. 1985). In rats exposed to an aerosol coal-tar pitch for 10 months, there was a dose-related increase in total DNA adduct formation in the lung (Lewtas et al. 1997).

Several studies have examined additional DNA effects following exposure to coal tar products, including alterations in DNA methylation, changes in telomere length, and chromosomal instability (Alhamdow et al. 2018, 2020; Feng et al. 2015; Li et al. 2020; Zhang et al. 2017). Decreased methylation of several cancer-related genes was observed in chimney sweeps and creosote-exposed workers (workers made wooden railroad ties), but telomere lengths did not differ compared to controls (Alhamdow et al. 2018, 2020). Decreased telomere length, increased telomere activity, chromosomal instability, and alterations in gene expression have been reported in *in vitro* studies following exposure to coal tar pitch extract in the human bronchial epithelial cell line, BEAS-2B (Feng et al. 2015; Li et al. 2020; Zhang et al. 2017). Additionally, BEAS-2B cells treated with coal tar pitch extract showed decreased DNA methylation and induced tumors when injected in the flanks in nude mice (Duan et al. 2021). Due to the complex chemical nature of coal dusts, it is difficult to classify specific genotoxicity events; however, associations between epigenetic alterations and shortening of telomere length in occupational workers exposed to coal dust were reported (de Souza et al. 2018; Shoeb et al. 2021).

Wood Creosotes. Results of one *in vitro* study found beechwood creosote not mutagenic both with and without metabolic activation in *S. typhimurium*. No *in vivo* studies on beechwood creosote were identified.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 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. No method is currently available to measure the parent creosote mixture in human tissues or fluids. Toxicokinetics of the major constituents of creosote can be predicted from studies of the individual constituents and structural analogs; however, due to the variable composition of creosote compounds, the predictive value of studies conducted using these individual constituents is limited and should therefore be used with caution when drawing any conclusions. This information is provided in various ATSDR toxicological profiles, including cresols (ATSDR 2008a), naphthalene (ATSDR 2005), PAHs (ATSDR 1995), phenol (ATSDR 2008b), and xylene (ATSDR 2007a).

3.1.1 Absorption

Inhalation Exposure. Many of the substances in wood creosote, coal tar creosote, and coal tar are semi-volatile and often exist in the breathing zone in occupational settings where these products are used (e.g., wood treatment facilities using coal tar creosote). No studies in humans or animals were located regarding the direct analysis of the extent or rate of absorption of wood creosote following inhalation exposure.

Coal tar products. 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.

No studies in humans or animals 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 inhalation exposure. However, there is evidence to suggest that inhalation absorption of coal tar products may occur. 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 pyrene, a creosote component, 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 six 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. Particulate PAHs were collected using a filter during the whole shift (from 6:00 am to 2:00 pm) and analyzed within 7 weeks (total of 30 samples). All workers wore leather protective gloves and cotton overalls. Two employees worked overtime on Monday, which was an exception to the regular 8-hour schedule, reducing their 64-hour work-free period. 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 concentrations were 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) chiseling 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 (Heikkilä 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 chiseler 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 chiseling) 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 for the chiseler was 1.2 mmol/shift. Excretion of urinary 1-hydroxypyrene was detected for all participants.

Four rotation shift crews (working hours rotated between 12:00 am–8:00 am, 8:00 am–4:00 pm, and 4:00 pm–12:00 am) of about 29 workers and one day crew (working hours 8:00 am–4:30 pm) of 22 workers worked in a 5-day shift, 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators that 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, which would have detected only volatile and semi-volatile constituents, 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 to 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 (CDC 1980). Similar exposure may result from coal tar creosote-treated logs (CDC 1982).

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX 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 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 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.

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

Oral Exposure. No studies were located regarding the direct analysis of the extent or rate of coal tar creosote, coal tar pitch, or coal tar pitch volatile absorption following oral intake in humans or animals.

Wood creosote. Constituents of wood creosote have been detected in plasma and urine following oral dosing with wood creosote (Kuge et al. 2003a; Ogata et al. 1995). Eight healthy male volunteers were orally administered a single dose of a 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. Absorption appeared to be substantial based on the high percentage of the dose of creosote phenols recovered in urine over a 24-hour period following dosing (group mean): 103% for p-cresol, 75% for phenol, 74% for cresol, and 45% for guaiacol. Kuge et al. (2003a, 2003b) administered single oral doses of wood creosote (45–225 mg) to 30 adults and followed the kinetics of appearance and elimination of creosol, o-cresol, 4-ethyguaiacol, and guaiacol from plasma. The time for maximum plasma levels ranged from 0.46 to 1.08 hours and did not appear to be affected by the creosote dose level.

Coal tar products. 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 that 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.

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.

Male rats fed diets amended with coal tar residue from an MGP showed increases in PAH-DNA adducts in liver and lung (measured by ^{32}P-post-labeling), indicating absorption of PAH from the amended diets (Bordelon et al. 2000). In the same study, increased adduct levels were also observed in rats fed diets amended with soil that had been spiked with coal tar residue. When standardized to the total ingested dose of PAHs, rats fed diets amended with coal tar spiked soil had lower adduct levels than rats fed diets amended directly with coal tar, suggesting that interactions with soil may decrease the bioavailability of coal tar-derived PAHs.

Male B6C3F1 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-post-labeling. 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 B6C3F1 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 of MGP components.

Dermal Exposure. No studies in humans or animals were located regarding the direct analysis of the extent or rate of absorption of wood creosote following dermal exposure.

Coal tar products. 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 (Van Rooij 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 and <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 underestimate the absorption of other components.

No studies in humans or animals were located regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, or coal tar pitch absorption following 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; 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 in PAH absorption between individuals 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 study indicating that coal tar components are absorbed trans-dermally was reported by Paleologo et al. (1992). These investigators evaluated the occurrence of benzo[a]pyrene diolepoxide (B[a]PDE)-DNA adducts in WBCs 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 showed that the mean adduct level during the treatment period was 0.26±0.16 fmole benzo[a]pyrene/g DNA (7.7±4.9 adducts/10^8 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 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 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 that 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 1–6 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 gas chromatography/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. However, without additional information, no statements can be made regarding the dermal absorption of other coal tar components or whether acridine was preferentially absorbed 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 first 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).

Studies conducted in animals have shown that chemicals in coal tar creosote can be absorbed across the skin. Dermal absorption of chemicals in coal tar creosote was quantified in rats (EPA 2007a). In this

study, coal tar creosote spiked with radiolabeled (^{14}C) benzo[a]pyrene, 2-methylnapththalene, fluoranthene, anthracene, naphthalene-benzene, phenanthrene, biphenyl, and pyrene were applied to an occluded area of the shaved backs of adult rats for 8 hours. The total systemically absorbed dose was estimated based on recovery of radiolabel in tissues and excreta (including expired air). Following the 8-hour exposure, the total absorbed dose was estimated to be 6.3% of the applied dose; this increased to 34% at 496 hours following cessation of dosing. In a follow-up study, the total absorbed dose 496 hours following cessation of dosing was estimated to have been 8.9%.

A study of *in vitro* preparations of rat and human skin found that the rate of penetration of radiolabeled constituents of coal tar creosote was approximately 4 times higher in rat skin comparted to human skin (EPA 2009a). In this study, coal tar creosote spiked with radiolabeled (^{14}C) benzo[a]pyrene, 2-methylnaphthalene, fluoranthene, anthracene, naphthalene-benzene, phenanthrene, biphenyl, and pyrene were applied to the epidermal side of the skin specimens mounted in the static diffusion cell and the rate of transfer radiolabel across the skin was measured for a period of 8 hours. The rate of transfer was approximately linear with time, with the mean rate estimated to be 85.3 μg equivalents/cm^2 hour in rat skin and 19.7 μg equivalents/cm^2 hour in human skin.

The kinetics of uptake of a coal tar mixture with Carbopol (an emulsifier) was estimated in an *in vitro* preparation of rat skin (Sharma et al. 2020). Aggregate coal tar constituents were measured by fluorescent spectroscopy of the washed skin after application to the epidermal side of the skin preparations contained in a Franz diffusion cell. Levels of coal tar fluorescence in skin increased at a rate of 0.348 $hour^{-1}$, peaked after 5 hours of exposure, and then declined at a rate of 0.085 $hour^{-1}$.

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 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 a >10-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.

3.1.2 Distribution

Inhalation Exposure. No studies in humans were located regarding the distribution of wood creosote following inhalation exposure.

Coal tar products. No studies in humans were located regarding the distribution of coal tar creosote, 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 (ATSDR 1995). PAHs and their metabolites are known to cross the placenta (ATSDR 1995). PAHs have also been detected in human breast milk (Madhavan and Naidu 1995). Individuals concerned with the potential exposure of breastfeeding infants to PAHs should consult their doctor. Coal tar creosote is also likely to distribute to the liver as evidenced by the presence of metabolites in the urine, indicating microsomal enzyme induction.

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 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 was 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 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 following administration. 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 GDs 18 and 19 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.

Oral Exposure. No studies in humans or animals were located 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 the 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.

Wood creosote. 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 high-performance liquid chromatography (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 post dose serum detected low concentrations of guaiacol and *p*-cresol.

Coal tar products. Culp and Beland (1994) fed male B6C3F1 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-post-labeling. 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 (≈10- to 30-fold greater in the liver and forestomach, and >90-fold greater in the lungs at the lower doses).

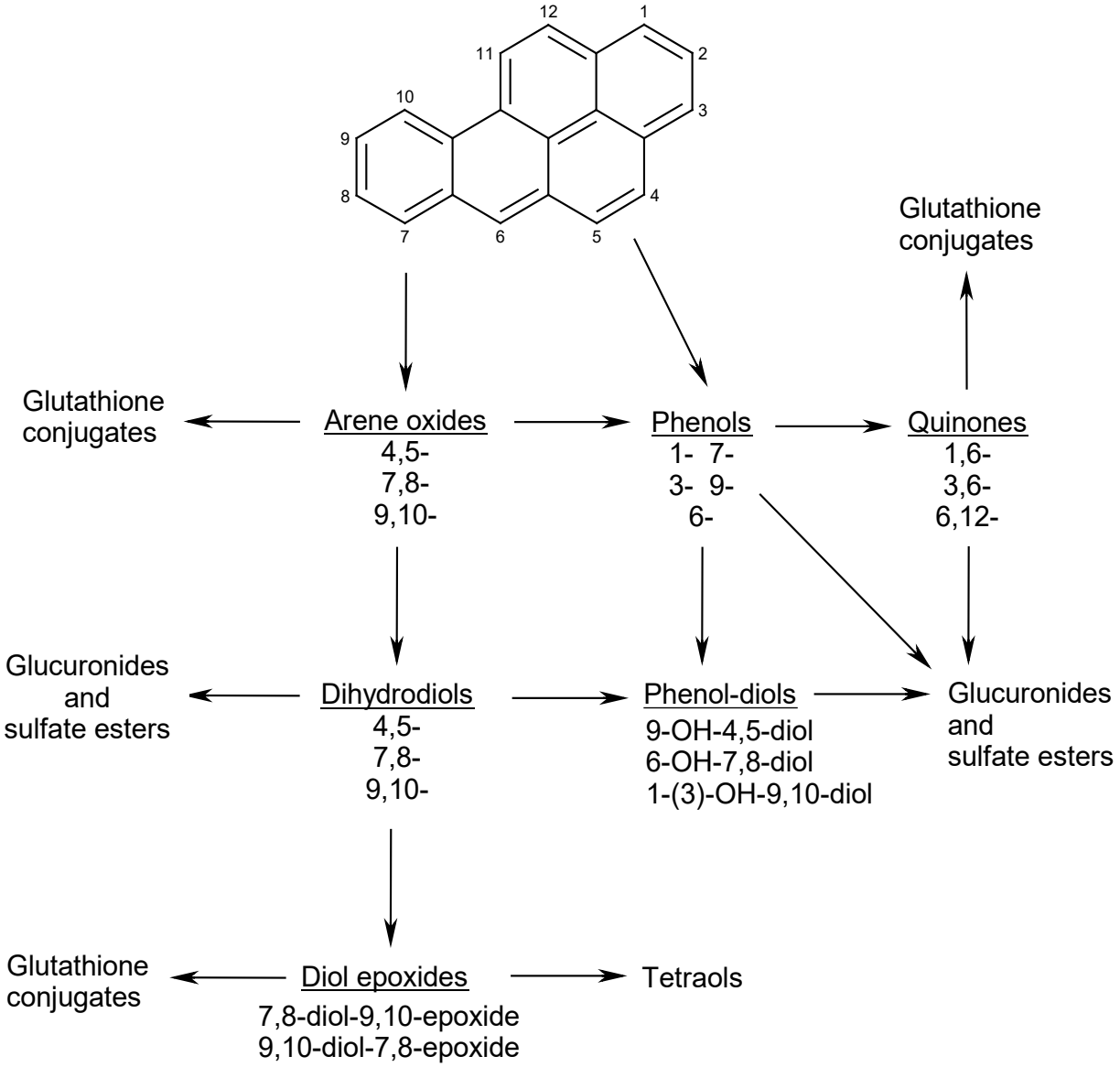
Dermal Exposure. No studies in humans or animals were located regarding the distribution of wood creosote, coal tar creosote, coal tar, or coal tar pitch following dermal exposure. Distribution of creosotes or coal tar products in humans following dermal exposure is expected to be qualitatively similar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

3.1.3 Metabolism

Metabolism of major constituents of creosote can be predicted from studies of the individual constituents and structural analogs. This information is provided in various ATSDR toxicological profiles, including cresols (ATSDR 2008a), naphthalene (ATSDR 2005), PAHs (ATSDR 1995), phenol (ATSDR 2008b), and xylene (ATSDR 2007a). Generally, the PAH components of wood creosote, 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 major reaction pathways. Hence, the metabolites are structurally very similar. The proposed metabolic scheme for a representative PAH, benzo[a]pyrene, is presented in Figure 3-1. The principal products include phenols, phenol diols (including catechols), 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 wood or coal tar 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; Heikkilä 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, some 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), Luukkanen et al. (1997), Genevois et al. (1998), and Fielden et al. (2000) assessed metabolic induction and activity of AHH, glucuronosyltransferase, and cytochrome P450 in response to coal tar.

Figure 3-1. Proposed Metabolic Scheme for Benzo[a]pyrene



Coal tar products induce AHH and a variety of metabolic enzymes. Application of coal tar to skin of human adults induced activities of the following enzymes in skin at the site of application: CYP1A1, CYP1A2, CYP1B1, CYP2C18, quinone reductase, glutathione S-transferase (GSTP1), glutamyl cysteine synthetase, glutathione peroxidase-1, cyclooxygenase-2 and heme oxygenase-1 (Smith et al. 2003, 2006). 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). In this same study, incubation of human skin with coal tar solution *in vitro* also caused induction of AHH, which reached a maximum after 24 hours; and application of coal tar to the skin of rats produced significant induction of AHH both in skin (10-fold) and in liver (>20-fold). Dermal treatment

of healthy volunteers with 10% coal tar for 4 days produced an 18-fold induction of CYP1A1 messenger ribonucleic acid (mRNA) levels in coal-tar-treated skin (Li et al. 1995). Pretreatment of mice with gavage doses resulted in induction of hepatic glucuronidation of 1-hydroxypyrene (18-fold) and *p*-nitrophenol (2–3-fold) (Luukkanen et al. 1997). Nordihydroguaiaretic acid, a constituent of wood creosote, was shown to inhibit CYP1A2, CYP3A, CYP2B, and CYP2C11 in *in vitro* preparations of rat liver microsomes (Billinsky et al. 2012).

Numerous studies of have identified metabolites of PAHs in human urine following exposures to coal tar products (Bowman et al. 1997; Grimmer et al. 1997; Jongeneelen et al. 1985, 1988; Malkin et al. 1996; Santella et al. 1994; Weston et al. 1994). Observations made on subjects who experienced repeated exposures to creosote and coal tars would be expected to reflect the changes in metabolism that resulted from enzyme induction.

Inhalation Exposure

Coal tar products. Workers in a coal tar creosote wood-impregnating plant were exposed to coal tar creosote by inhalation during 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-hydroxy-pyrene 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 naphthalene) in six workers from a creosote impregnation plant and five male smokers not occupationally exposed to creosote (Heikkilä 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 in the concentrations of 1- and 2-naphthols between the urine of exposed and unexposed workers ($p<0.05$). The correlation between the concentrations of naphthols in urine and naphthalene in air were statistically significant ($p<0.001$).

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 4 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 4 days analyzed. However, in urine obtained from three workers (high/low exposure not specified), there was a significant difference between individuals for the absolute amounts of metabolites excreted and 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 over the duration of the experiment, but there was a significant difference between individuals for both the absolute amounts of metabolites excreted and the ratio of metabolites produced.

Oral Exposure

Wood creosote. 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, 0.91±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 values 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.

Coal tar products. 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. In addition, 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).

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 (Luukkanen et al. 1997). Microsome preparations from the livers of these rats were used to assay the activities of 1-hydroxypyrene uridine 5'-diphospho-glucuronosyltransferase (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 by 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, six control and six treated rats were administered 75 mg/kg 2,6-DNT in dimethyl sulfoxide (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 dinitrotoluene (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.

Induction of CYP1A1 and CYP2B10 in liver microsomes from ovariectomized mature and immature DBA/2 mice and ICR mice that received gavage doses of 10, 50, or 100 mg/kg creosote in sesame oil once a day for 4 days was compared with that in microsomes derived from control animals that received

only sesame oil (Fielden et al. 2000). CYP1A1 and CYP2B10 activities were assessed based on ethoxyresorufin-O-deethylase (EROD) and pentoxyresorufin-O-dependentylase (PROD) activities, respectively. Creosote treatment significantly increased the activity of CYP1A1 and CYP2B10 in both immature and mature mice, but the CYP1A1 increase was age-dependent, with immature mice showing a 5.9-fold increase in EROD activity after treatment with 100 mg/kg/day creosote while mature mice treated similarly had an 11.4-fold increase in liver EROD activity. No age-dependent difference was seen in induction of CYP2B10 since PROD activity was increased by creosote treatment 1.6–2.2-fold in both mature and immature mice.

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.

Dermal Exposure

Coal tar products. Several 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-10-tetrahydroxy-7,8,9,10-tetrahydro-benzo[a]pyrene (Bowman et al. 1997). The metabolite, r-7,t-8,t-9,c-10-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 creatinine and that for controls 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,c10-tetrahydroxy-7,8,9,10-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,c10-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 from 36 to 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-enzyme-linked immunosorbent assay (ELISA) were elevated in patients (mean 730±1,370 mmol) as compared to untreated volunteers (110±90 mmol equivalents of benzo[a]pyrene/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 National Institute for Occupational Safety and Health (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. Pre- and post-shift 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. Pre-shift 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 post-shift levels ranged from 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 pre-shift 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 P4501A1 (CYP1A1) expression was increased in healthy volunteers treated dermally with 10% coal tar for 4 days producing an 18-fold induction of CYP1A1 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 receptor (AHR) demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYP1A 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 CYP1A 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 CYP1A1.

3.1.4 Excretion

Few studies are available that provide quantitative estimates of the excretory fate of creosote constituents following systemic absorption from exposures to creosote (e.g., percent of external or absorbed dose).

However, the excretory fate of major constituents of creosote can be predicted from studies of the individual constituents and structural analogs. This information is provided in various ATSDR toxicological profiles, including cresols (ATSDR 2008a), naphthalene (ATSDR 2005), PAHs (ATSDR 1995), phenol (ATSDR 2008b), and xylene (ATSDR 2007a). In general, urinary excretion is expected to be the dominant excretory pathway for lower molecular weight constituents such as phenols, cresols, guaiacol, xylenols, and their metabolites. Biliary-fecal excretion may also contribute to clearance of glucuronide conjugates of these substances and would be expected to play a larger role in the clearance of the larger molecular weight creosol constituents, such as PAHs (Sanders et al. 1986; Weyand and Bevan 1987). The reader is referred to the pertinent ATSDR toxicological profiles for more information on these pathways. This section is focused on studies that provide quantitative estimates of the excretory fate of creosote constituents following exposures to creosote. Numerous studies have analyzed urine for the presence of creosote constituents, such as PAHs, following exposure to creosote. Typically, these studies do not report estimates of actual exposures to the constituents and, therefore, do not provide quantitative estimates of the percent of the external or absorbed dose excreted, or of the kinetics of excretion. Pertinent studies of this type are noted in the Section 3.3.1 (Biomarkers of Exposure).

Wood creosote. Urinary excretion of phenols was measured following a single oral dose of wood creosote (113 mg) administered in a capsule to eight adult subjects after a light breakfast (Ogata et al. 1995). The wood creosote contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). The 24-hour cumulative urinary excretion (mean±standard deviation [SD], eight adults), expressed as percent of dose, was as follows: phenol, 75±35; guaiacol, 45±36; 103±51 p-cresol; and 74±36% cresol.

Coal tar products. Elevated urinary levels of PAHs were observed in workers in a creosote impregnation plant (Elovaara et al. 1995). The geometric mean (range) workplace 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. Urinary PAH levels were higher 6–9 hours following the work shift and lower following absence from work for 64 hours. Urinary levels of PAH were measured in assemblers who handled creosote-impregnated wood or who chiseled coal tar pitch insulation (Heikkilä et al. 1995). The total air concentrations of PAHs and of 4–6 aromatic ring-containing PAHs when chiseling was 440 mg/m^3 (50-fold higher than assemblers) and 290 mg/m^3 (200-fold higher than assemblers), respectively. Excretion of urinary 1-hydroxypyrene was higher in chiselers compared to assemblers. Workers in potrooms had elevated levels of 1-hydroxypyrene in urine (Ny et al. 1993). Those who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging

from 10 to 2,710 mg/m^3. Urinary 1-hydroxypyrene levels were correlated with PAH exposure. Urinary levels of 1-hydroxypyrene were higher in creosote workers (silicon carbide production, wood treatment, PAH decontamination) compared to a nonoccupational exposure group (Viau et al. 1995).

Weyand et al. (1991) fed male mice 0.25% MGP residue, a form of 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. In another study by Weyand et al. (1994), five groups of B6C3F1 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 byproduct of coal gasification, for a period of 185 days. The total amount of 1-hydroxypyrene excreted reached a maximum of 5–6 mg within 34 days of diet administration.

Numerous studies conducted in humans have demonstrated that, following dermal exposures, metabolites of constituents of coal tar creosote (e.g., PAHs) are excreted in urine (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).

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 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. 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.

Clonfero et al. (1989) measured urinary PAHs in four male nonsmoking psoriatic patients undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar-based ointment, followed by exposure to UV irradiation). 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. A control group consisted of 52 nonsmokers who exhibited values of 1.3 mg/g creatinine. Levels of 1-hydroxypyrene were 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 a study of 57 patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, patients' 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/tar/day. Urinary PAH metabolites were approximately 7 times higher in patients compared to controls. Urinary levels of 1-hydroxypyrene were also elevated in patients compared with controls.

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

Maternal-fetal-infant transfer. Information of maternal-fetal and maternal infant transfer of major constituents of creosote can be predicted from studies of the individual constituents and structural analogs. This information is provided in various ATSDR toxicological profiles, including cresols (ATSDR 2008a), naphthalene (ATSDR 2005), PAHs (ATSDR 1995), phenol (ATSDR 2008b), and xylene (ATSDR 2007a). Direct skin-skin, or skin-mouth contact between mother and infant can also result in absorption of creosote constituents in infants (Scheepers et al. 2009).

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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart

2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

The pharmacokinetics of wood creosote, coal tar creosote, 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.

3.1.6 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 that treated more than one species of animal with the same sample of creosote (Miyazato et al. 1981), 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.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to creosote are discussed in Section 5.7, Populations with Potentially High Exposures.

The effects of creosote as a mixture have not been thoroughly studied in children, although information may be available on some of the individual components (see Section 3.1). 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. The pharmacokinetics of wood creosote, coal tar creosote, 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. 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 1–3 years of age (Leeder and Kearns 1997).

Age. No information was located pertaining to adverse health effects in children or young animals from wood creosote or coal tar products. Only one study was located that examined effects of exposure to coal tar creosote in children (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.

No reports of adverse developmental effects on humans after exposure to wood creosote or coal tar products 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). Coal tar exposure produces developmental toxicity in rats and mice (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). However, the developmental risk to humans of exposure to coal tar is less clear. The doses that 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.

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 Chapter 2 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 Chapter 2 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 than individuals exposed as adults. Mutagenic compounds may have greater impacts on early life stages due to differences in growth rates and cell replication, but this has not been evaluated in children following exposure to creosote.

Pre-existing Conditions, Diseases, and Exposure to Other Substances. Data indicate that 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; Poel and Kammer 1957; Roe et al. 1958)

indicate that prolonged dermal exposure to coal tar creosote may increase the risk of developing skin cancer. 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 (Koppers Company 1979, 1981; Lenson 1956; Lijinsky et al. 1957; Sall and Shear 1940). There is 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 cardiovascular, respiratory, kidney, skin, 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).

Genetic Polymorphisms. 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. Genetically expressed AHH inducibility may be 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-dependent expression and susceptibility may therefore vary with the age of the individual. However, no studies were located that addressed differential susceptibility of children to the effects of creosote. Theoretically, combinations of polymorphisms many enhance or reduce susceptibility to creosote.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

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 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to creosote are discussed in Section 3.3.1.

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 2006). 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 effect caused by creosote are discussed in Section 3.3.2.

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 (e.g., increased dermal absorption due to skin diseases that compromise skin integrity), a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Coal Tar Products. 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; Preuss et al. 2005). PAH components of the creosote mixture and their metabolites can also be measured in the urine of exposed individuals (Bickers and Kappas 1978; Borak et al. 2002; 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; Hecht et al. 2010; Heikkilä et al. 1995; Jongeneelen et al. 1985, 1988; Malkin et al. 1996; McClean et al. 2007; Ny et al. 1993; Persoons et al. 2020; Raulf-Heimsoth et al. 2008; 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 pyrene (which is a constituent of coal tar creosote), 1-hydroxypyrene, in concentrations of 1–40 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 specific to creosote could be detected following exposure to low levels of creosote. However, in another study, workers exposed to coal tar while 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. Urinary 1-hydroxypyrene was also detected in study of 21 coal tar sealant workers (McCormick et al. 2022). 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.

Wood Creosotes. 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.

3.3.2 Biomarkers of Effect

Coal Tar Products. 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 benzo[a]pyrene 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 effect caused by creosote, nor is it possible to determine whether the genotoxic effects result from either acute- or chronic-duration 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-duration 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.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Coal Tar Products. 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, potentiators, or inhibitors of carcinogenesis (Haverkos et al. 2017). 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. 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. The increase in urinary excretion of mutagenic metabolites was significantly greater than in rats that received only DNT at weeks 1 and 3, but not at week 5 (Chadwick et al. 1995).

As discussed in Section 2.19, 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 benzo[a]pyrene. 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 act synergistically with coal tar creosote or coal tar to produce photosensitivity.

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. In addition, PAHs undergo a weathering process in soils and sediment (EPA 2006). No specific information was identified to define how weathering affects interactions with other chemicals.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity, chemical synonyms, and identification numbers for wood creosote, coal tar creosote, and coal tar is provided in Tables 4-1 through 4-3. 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. The partitioning behavior of PAHs and other semi-volatile substances between the vapor and particulate phase in air is well understood (Eisenreich et al. 1981; Xie et al. 2014). In general, several of the low molecular weight constituents are semi-volatile and exist in air in the vapor-phase, while larger PAHs are less volatile and tend to exist in the particulate phase; this affects atmospheric transport, degradation, and deposition into the lungs (Volckens and Leith 2003).

Table 4-1. Chemical Identity of Wood Creosote

Characteristic	Information	Reference
Chemical mixture name	Wood creosote	Budavari 1989
Synonym(s) and registered trade name(s)	Beechwood creosote; creosote; creasote	Budavari 1989
Chemical formula[a]	Not applicable	
SMILES	Not applicable	
Chemical structure[a]	Not applicable	
CAS Registry Number	8021-39-4	Budavari 1989
TSCA definition	A complex combination of phenols obtained as a distillate from wood tar.	EPA 2022a

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

CAS = Chemical Abstracts Service; TSCA = Toxic Substances Control Act

Table 4-2. Chemical Identity of Coal Tar Creosote

Characteristic	Information	Reference
Chemical mixture name	Coal tar creosote	AWPA 1988
Synonym(s) and registered trade name(s)	Creosote; standard creosote oil; creosote, coal tar; creosotum; naphthalene oil; heavy oil; brick oil; wash oil; cresylic creosote; coal tar oil; liquid patch oil; petroleum creosote, creosote P1; sakresote 100; Emulsified Refined Coal-Tar (Ready to Use, Commercial Grade; Road Tar (RT-1, RT-2, RT-3, RT-4, RT-5, RT-6, RT-7, RT-8, RT-9, RT-10, RT-11, RT-12, RT.C.B.-5, and RT.C.B.-6)	ASTM 2016, 2017; NLM 2022a
Chemical formula[a]	Not applicable	
SMILES	Not applicable	
Chemical structure[a]	Not applicable	
CAS Registry Number	8001-58-9	Budavari 1989; Weiss 1986; NLM 2022a
TSCA definition	The distillate of coal tar produced by the high temperature carbonization of bituminous coal. It consists primarily of aromatic hydrocarbons, tar acids, and tar bases.	EPA 2022a

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

CAS = Chemical Abstracts Service; TSCA = Toxic Substances Control Act

Table 4-3. Chemical Identity of Coal Tar

Characteristic	Information	Reference
Chemical mixture name	Coal tar	Budavari 1989
Synonym(s) and registered trade name(s)	Crude coal tar; pixalbol; tar; Psorigel; Clinitar; coal tar extract	Budavari 1989; NLM 2022b
Chemical formula[a]	Not applicable	
SMILES	Not applicable	
Chemical structure[a]	Not applicable	
CAS Registry Number	8007-45-2	NLM 2022b

Table 4-3. Chemical Identity of Coal Tar

Characteristic	Information	Reference
TSCA definition	The byproduct from the destructive distillation of coal. Almost black semisolid. A complex combination of aromatic hydrocarbons, phenolic compounds, nitrogen bases, and thiophene.	EPA 2022a

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

CAS = Chemical Abstracts Service; TSCA = Toxic Substances Control Act

4.2 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.

Wood Creosote. Wood creosotes are derived from either beechwood (referred to herein as beechwood creosote) or 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 stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States. Beechwood creosote is obtained from fractional distillation (200–220°C at atmospheric pressure) of beechwood or related plants. The mixture has been characterized by Ogata and Baba (1989). Phenol, *p*-cresol, and guaiacols (guaiacol and 4-methylguaiacol) comprise the bulk of beechwood creosote. Xylenols, other methylated guaiacols, and trimethylphenols account for virtually all the remaining phenolics in the material. Since beechwood creosote is obtained from different sources using no standardized 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 (see Table 4-4) were represented by just four components (phenol, p-cresol, guaiacol, and 4-methylguaiacol). Information regarding selected chemical and physical properties of wood creosote are shown in Table 4-5.

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

Compound	Relative peak area (percentage identified in mixture)
Phenol	14.5%
Methylhydroxycyclopentenone	0.23%
o-Cresol	3.22%
Dimethylhydroxycyclopentanone	0.50%
p-Cresol	13.6%
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 4-5. Physical and Chemical Properties of Wood Creosote[a]

Property	Information	Reference
Molecular weight	Not applicable	
Color	Yellowish to colorless	Budavari 1989
Physical state	Liquid	Weiss 1986
Melting point	No data	
Boiling point	203°C	Budavari 1989
Density at 20°C	Not applicable	
Odor	Characteristic smokey odor	Budavari 1989
Odor threshold:		
Water	No data	
Air	No data	

Table 4-5. Physical and Chemical Properties of Wood Creosote[a]

Solubility:		
Water	150–200 parts water	Budavari 1989
Organic solvents	Miscible with alcohol, ether, fixed or volatile oils	Budavari 1989
Partition coefficients:		
Log K_{ow}	Not applicable	
Log K_{oc}	Not applicable	
Vapor pressure at 20°C	Not applicable	
Henry's law constant at 25°C	Not applicable	
Autoignition temperature	No data	
Flashpoint	74°C (closed cup)	Clayton and Clayton 1981
Flammability limits	No data	
Conversion factors	Not applicable	
Explosive limits	No data	

[a]Physical-chemical properties will vary by sample as the constituents of the complex mixture are not constant. Not applicable has been used for several properties since a wide range of values are expected based upon chemical composition of the mixture.

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.

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 (CAS) Registry Numbers 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 byproducts 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 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 (AWPA 1988). Coal tar creosote is defined by the latter organization as:

> 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°C (AWPA 1988).

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). The substance is a complex mixture typically composed of approximately 85% PAHs and 2–17% phenolics (Bedient et al. 1984). The composition of the creosote mixture is dependent on the sources and preparation parameters of the coal tar, 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 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.

The International Programme on Chemical Safety (IPCS) Concise International Chemical Assessment Document (CICAD) for coal tar creosote lists some common constituents of some coal tar creosotes that were analyzed for their chemical identity (IPCS 2004). These are summarized in Table 4-6.

Table 4-6. Some Constituents and Weight Percentage of Eight Coal Tar Creosote Mixtures

	Weight percentage[a]							
Coal tar creosote mixture A		B	C	D	E	F	G	H
Aromatic hydrocarbons								
Indene					0.6	0.43	0.87	
Biphenyl	0.8/1.6	2.1	1–4	0.8	1.3	1.45	4.1	
PAHs								
Naphthalene	1.3/3.0*	11	13–18	7.6	12.9	12.32	11.4	
1-Methylnaphthalene	0.9*/1.7		12–17	0.9	2.2	3.29	8.87	

Table 4-6. Some Constituents and Weight Percentage of Eight Coal Tar Creosote Mixtures

	Weight percentage[a]							
Coal tar creosote mixture	A	B	C	D	E	F	G	H
2-Methylnaphthalene	1.2*/2.8	3.0	12.0	2.1	4.5	7.51	11.5	
Dimethylnaphthalenes	2.0*/2.3	5.6			1.6	3.42	5.16	
Acenaphthylene					0.2	0.15	0.1	
Acenaphthene	9.0*/14.7	3.1	9.0	8.3	5.8	12.51	5.86	
Fluorene	7.3/10.0*	3.1	7–9	5.2	4.6	5.03	6.33	
Methylfluorenes	2.3/3.0*				3.1			
Phenanthrene	21*	12.2	12–16	16.9	11.2	10.21	6.7	1–3.3
Methylphenanthrenes	3.0*				3.1	0.45	0.54	
Anthracene	2.0*		2–7	8.2	1.7	0.9	0.8	0.4–1.2
Methylanthracenes	4.0*	5.9						
Fluoranthene	7.6/10.0*	3.4	2–3	7.5	4.6	4.41	2.27	0.2–2.2
Pyrene	7.0/8.5*	2.2	1–5	5.3	3.7	2.0	1.13	0.1–1.5
Benzofluorenes	1.0/2.0*	3.4			2.2			
Benz[a]anthracene					0.5	0.26	0.17	
Benzo[k]fluoranthene					0.22			0.16–0.3
Chrysene	2.6/3.0*	2.2	1		0.5–1.0	0.21	<0.05	
Benzo[a]pyrene				0.43	0.2	<0.1	<0.05	0.02–0.16
Benzo[e]pyrene					0.2			
Perylene					0.1			
Tar acids/phenolics								
Phenol					0.24	0.56	0.24	
o-Cresol					0.10		0.2	
m-, *p*-Cresol					0.24	2.31	0.6	
2,4-Dimethylphenol					0.12	0.59	0.48	
Naphthols					0.12			
Tar bases/nitrogen-containing heterocycles								
Indole				2				
Quinoline			1	2.0	0.59	0.58	0.89	
Isoquinoline				0.7	0.18	0.30	0.59	
Benzoquinoline				4	0.29	0.05	0.5	
Methylbenzoquinoline				0.3				
Carbazole		2.4		3.9	0.7	0.53	0.22	
Methylcarbazoles				2				
Benzocarbazoles				2.8	0.1			
Dibenzocarbazoles				3.1				
Acridine				2	0.2	1.5	0.12	
Aromatic amines								
Aniline				0.05	0.21			

Table 4-6. Some Constituents and Weight Percentage of Eight Coal Tar Creosote Mixtures

	Weight percentage[a]							
Coal tar creosote mixture	A	B	C	D	E	F	G	H
Sulfur heterocycles								
Benzothiophene				0.3	0.4	0.3	0.5	
Dibenzothiophene					1.0	0.78	0.73	
Oxygen-containing heterocycles/furans								
Benzofuran						<0.1	<0.1	
Dibenzofuran	5.0*/7.5	1.1	4–6	3.9	3.7	6.14	5.59	
Other not specified components								
Unidentified component					23.1			

[a]An asterisk indicates that data were obtained from a literature survey; measurements without an asterisk indicate main components in an AWPA standard creosote.

AWPA = American Wood-Preservers' Association; PAH = polycyclic aromatic hydrocarbon

Source: IPCS 2004

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 1.18–1.23 (66/60°F). Soluble in ether, benzene, carbon disulfide, chloroform; partially soluble in alcohol, acetone, methanol, and benzene; only slightly soluble in water.

The composition of the mixture will vary across lots and across manufacturers. Gallacher et al. (2017a, 2017b) performed an analysis of 16 coal tar samples obtained from five different production processes. They identified a total of 2,369 unique compounds. This included 948 aromatics, 196 aliphatics, 380 sulfur-containing compounds, 209 oxygen-containing compounds, 262 nitrogen-containing compounds, and 865 heterocyclic compounds (15 mixed heterocycles); of all the PAHs, 359 were hydroxylated. The contents of both heterocyclic and hydroxylated PAHs varied greatly with the production process used. Of the 2,369 compounds identified, 173 were found to be present in all samples (the majority of these were PAHs). A full list of these compounds can be obtained (Gallacher et al. (2017c). Properties of coal tar creosote are shown in Table 4-7.

Table 4-7. Physical and Chemical Properties of Coal Tar Creosote[a]

Property	Information	Reference
Molecular weight	Not applicable[b]	
Color	Translucent brown to black; oily liquid; yellowish to dark green-brown	Budavari 1989
Physical state	Liquid	Weiss 1986
Melting point	No data	
Boiling point	194–400°C	Clayton and Clayton 1981
Density at 20°C	Not applicable	
Odor	Aromatic smokey smell; characteristic smokey odor	Budavari 1989; DOT 1985
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water	Slightly soluble	Clayton and Clayton 1981
Organic solvents	Miscible with alcohol, ether, fixed or volatile oils	Clayton and Clayton 1981
Partition coefficients:		
Log K_{ow}	Not applicable	
Log K_{oc}	Not applicable	
Vapor pressure at 20°C	Not applicable	
Henry's law constant at 25°C	Not applicable	
Autoignition temperature	335°C	Budavari 1989
Flashpoint	74°C (closed cup)	Budavari 1989
Flammability limits	No data	
Conversion factors	Not applicable	
Explosive limits	No data	

[a]Physical-chemical properties will vary by sample as the constituents of the complex mixture are not constant.
[b]Not applicable has been used for several properties since a wide range of values are expected based upon chemical composition of the mixture.

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 (EPA 2015). A list of the components comprising the PAH fraction of coal tar pitch is shown in Table 4-8. Table 4-9 summarizes physical/chemical data for coal tar. Properties for this substance are similar or identical to those shown in Table 4-7 for coal tar creosote. Because these substances are all complex mixtures, physical-chemical properties such as log K_{ow} and

Henry's Law constants cannot be represented by a single value. Ranges of values for several physical-chemical properties for the chemical classes of coal tar creosote have been published (IPCS 2004). Because of the variability in feedstock and manufacturing processes, presentation of exact values for various properties presented in Tables 4-7 and 4-9 is not possible.

Table 4-8. Identity of PAH Components of Coal Tar Pitch[a]

Peak No.	Compound[b]	Peak No.	Compound[b]
1	Naphthalene	101	Methylbenz[a]anthracene or isomer
2	Benzo[b]thiophene	102	Dimethylbenz[a]anthracene or isomer
3	Quinoline	103	11H-Benz[bc]aceanthrylene or isomer
4	2-Methylnaphthalene	104	Methylbenz[a]anthracene or isomer
5	1-Methylnaphthalene	105	4H-Cyclopenta[def]chrysene or isomer
6	Biphenyl	106	Methylbenz[a]anthracene or isomer
7	2-Ethylnaphthalene	107	Binaphthalene or isomer
8	Dimethylnaphthalene	108	4H-Cyclopenta[def]triphenylene or isomer
9	Dimethylnaphthalene	109	Dimethylbenz[a]anthracene or isomer
10	Dimethylnaphthalene	110	Methylbenz[a]anthracene or isomer
11	Methylbiphenyl	111	Binaphthalene or isomer
12	Acenaphthene	112	Dimethylbenz[a]anthracene or isomer
13	Naphthonitrile or azaacenaphthylene	113	Methylbenz[a]anthracene or isomer
14	Dibenzofuran	114	Binaphthalene or isomer
15	Fluorene	115	Phenylphenanthrene or isomer
16	Methylacenaphthene	116	Dihydrobenzofluoranthene or isomer
17	Methylacenaphthene	117	Dimethylchrysene or isomer
18	Methylacenaphthene	118	Dibenzophenanthridine or isomer
19	Methyldibenzofuran	119	Biquinoline
20	Methyldibenzofuran	120	Biquinoline
21	9,10-Dihydroanthracene	121	Benzo[j]fluoranthene
22	9,10-Dihydrophenanthrene	122	Dihydrobenzofluoranthene or isomer
23	Methylfluorene	123	Benzo[b]fluoranthene
24	Methylfluorene	124	Dihydrobenzofluoranthene or isomer
25	Methylfluorene	125	Benzo[k]fluoranthene
26	Methylfluorene	126	Dibenzonaphthofuran or isomer
27	1,2,3,4-Tetrahydroanthracene	127	Dihydrobenzofluoranthene or isomer
28	Dibenzo[bd]thiophene	128	Dimethylchrysene or isomer
29	Phenanthrene	129	Azabenzopyrene or isomer
30	Anthracene	130	Dibenzonaphthofuran or isomer
31	Acridine	131	Benzophenanthrothiophene
32	Phenanthridine	132	Azabenzopyrene or isomer
33	Carbazole	133	Benzo[e]pyrene
34	Methylphenanthrene, -anthracene	134	Dibenzonaphthofuran or isomer
35	Methylphenanthrene, -anthracene	135	Benzo[a]pyrene

Table 4-8. Identity of PAH Components of Coal Tar Pitch[a]

Peak No.	Compound[b]	Peak No.	Compound[b]
36	Methylphenanthrene, -anthracene	136	Dibenzonaphthofuran or isomer
37	4H-Cyclopenta[def]phenanthrene	137	Perylene
38	Methylphenanthrene, -anthracene	138	Dibenzonaphthofuran or isomer
39	Methylphenanthrene, -anthracene	139	Methylbenzofluoranthene or isomer
40	Methylcarbazole	140	Methylbenzofluoranthene or isomer
41	Methylcarbazole	141	Azabenzopyrene or isomer
42	2-Phenylnaphthalene	142	4H-Naphtho[1,2,3,4-def]carbazole or isomer
43	Dihydropyrene or isomer	143	Methylbenzofluoranthene or isomer
44	Fluoranthene	144	Dibenzofluorene or isomer
45	Azafluoranthene, -pyrene	145	Dihydroindenopyrene or isomer
46	Phenanthro[4,5-bcd]thiophene	146	Dibenzofluorene or isomer
47	Azafluoranthene, -pyrene	147	Dibenzofluorene or isomer
48	Pyrene	148	Methylbenzopyrene or isomer
49	Benzonaphthofuran	149	Dibenzo[cg]phenanthrene or isomer
50	Benzacenaphthene or isomer	150	Dimethyldibenzonaphthofuran or isomer
51	Benzacenaphthene or isomer	151	Methylbenzopyrene or isomer
52	Benzonaphthofuran	152	Methylbenzopyrene or isomer
53	Benzonaphthofuran	153	11H-Cyclopenta[ghi]perylene or isomer
54	Benzo[lmn]phenanthridine	154	Methylbenzopyrene or isomer
55	Benzo[kl]xanthene	155	Dimethylbenzopyrene or isomer
56	Methylfluoranthene, -pyrene	156	Methylbenzopyrene or isomer
57	4H-Benzo[def]carbazole	157	Methylbenzopyrene or isomer
58	Azafluoranthene, -pyrene	158	Dimethylbenzopyrene or isomer
59	Benzo[a]fluorene	159	11H-Indeno[2,1,7-cde]pyrene or isomer
60	Methylfluoranthene, -pyrene	160	Dimethylbenzopyrene or isomer
61	Benzo[a]fluorene	161	Dinaphthothiophene
62	Benzo[c]fluorene or isomer	162	Dimethylbenzopyrene or isomer
63	Methylbenzacenaphthene or isomer	163	Dibenzophenanthridine or isomer
64	Methylbenzonaphthofuran or isomer	164	Dibenzonaphthothiophene
65	Methylpyrene or isomer	165	Dimethylbenzopyrene or isomer
66	Methylpyrene or isomer	166	Dibenzocarbazole
67	Methylbenzonaphthofuran or isomer	167	Dimethylbenzopyrene or isomer
68	Methylbenzonaphthofuran or isomer	168	Dibenzo[bg]phenanthrene or isomer
69	Methylazapyrene or isomer	169	Benzo[g]chrysene or isomer
70	Methylbenzonaphthofuran or isomer	170	Dinaphthothiophene
71	Methylbenzofluorene	171	Dimethylbenzofluoranthene or isomer
72	Dihydrochrysene or isomer	172	Dibenzoacridine or isomer
73	Dimethylfluoranthene, -pyrene	173	Dinaphthothiophene
74	Trimethylfluoranthene, -pyrene	174	Dinaphthothiophene
75	Dimethylfluoranthene, -pyrene	175	Benzo[c]chrysene or isomer

Table 4-8. Identity of PAH Components of Coal Tar Pitch[a]

Peak No.	Compound[b]	Peak No.	Compound[b]
76	Benzo[b]naphtho(2,1-d)thiophene	176	Dibenzocarbazole
77	Benzo[c]phenanthrene	177	Dimethylbenzofluoranthene or isomer
78	Benzo[ghi]fluoranthene	178	Dibenz[aj]anthracene
79	Dimethylbenzonaphthofuran	179	Indenopyrene or isomer
80	Benzo[b]naphtho[1,2-d]thiophene	180	Dimethyldibenzonaphthofuran
81	Dibenzoquinoline or isomer	181	Methyldibenzophenanthrene, anthracene
82	Tetrahydrochrysene or isomer	182	Indenopyrene or isomer
83	Benzo[a]naphtho[2,3-d]thiophene	183	Methylbenzophenanthrothiophene
84	Benz[a]anthracene	184	Dibenz[ac]anthracene
85	Chrysene	185	Methyldibenzophenanthrene, anthracene
86	11H-Benzo[a]carbazole	186	Dimethylbenzofluoranthene or isomer
87	Naphthacene	187	Dibenz[ah]anthracene
88	Methylbenzonaphthothiophene	188	Trimethylbenzofluoranthene or isomer
89	Methylbenz[a]anthracene or isomer	189	Dimethyldibenzophenanthrene, anthracene
90	Tetramethylfluoranthene or isomer	190	Benzo[b]chrysene
91	7H-benzo[c]carbazole	191	Dimethyldibenzonaphthofuran
92	Methylbenz[a]anthracene or isomer	192	Picene
93	Tetramethylfluoranthene or isomer	193	Dimethylbenzopyrene or isomer
94	5H-benzo[b]carbazole	194	Dimethyldibenzonaphthofuran
95	Methylbenzophenanthridine or isomer	195	Benzo[ghi]perylene
96	Dimethylbenzo[cdf]carbazole	196	Benzo[a]naphthacene or pentacene
97	Methylchrysene or isomer	197	Dimethyldibenzonaphthofuran
98	Methylchrysene or isomer	198	Anthanthrene
99	Methylbenz[a]anthracene or isomer	199	Methyl indenopyrene or isomer
100	Dimethylbenz[a]anthracene or isomer		

[a]The amount and specific PAHs in coal tar pitch will vary as the constituents of the complex mixture are not constant.
[b]PAHs identified in GC-MS elution peaks from a coal tar sample. Some PAHs will elute in multiple peaks.

GC-MS = gas chromatography-mass spectrometry; PAH = polycyclic aromatic hydrocarbon

Source: Guillén et al. 1992

Table 4-9. Physical and Chemical Properties of Coal Tar[a]

Property	Information	Reference
Molecular weight	Not applicable[b]	
Color	Almost black, thick liquid, or semisolid	Budavari 1989
Physical state	Semisolid	Weiss 1986
Melting point	No data	

Table 4-9. Physical and Chemical Properties of Coal Tar[a]

Boiling point	No data	
Density at 20°C	Not applicable	
Odor	Naphthalene-like	Osol 1980
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water	Slightly soluble	Budavari 1989
Organic solvents	Mostly dissolves in benzene; partially dissolves in alcohol, ether, chloroform, acetone, and petroleum ether	Budavari 1989
Partition coefficients:		
Log K_{ow}	Not applicable	
Log K_{oc}	Not applicable	
Vapor pressure at 20°C	No data	
Henry's law constant at 25°C	Not applicable	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	Not applicable	
Explosive limits	No data	

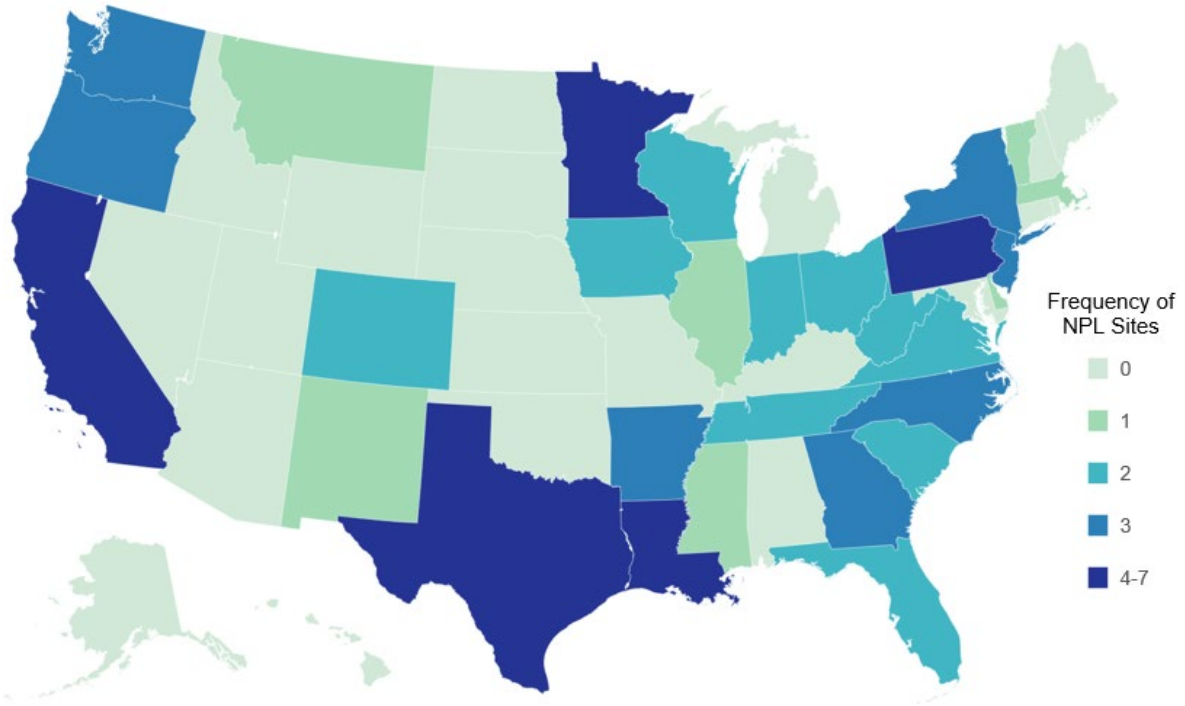
[a]Physical-chemical properties will vary by sample as the constituents of the complex mixture are not constant.
[b]Not applicable has been used for several properties since a wide range of values are expected based upon chemical composition of the mixture.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Coal tar creosote, coal tars, and coal tar pitch have been identified in at least 72 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which coal tar creosote, coal tars, and coal tar pitch has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Wood creosotes have not been evaluated at NPL sites (ATSDR 2022).

Figure 5-1. Number of NPL Sites with Coal Tar Creosote, Coal Tars, and Coal Tar Pitch Contamination



Source: ATSDR 2002

- Persons employed in industries that use coal tar creosote such as wood treatment facilities or production facilities that manufacture coal tar may be exposed to the constituents of these complex mixtures through dermal and inhalation routes. Persons using coal tar-based asphalt sealants may also be exposed to the constituents of these mixtures through dermal and inhalation pathways, and there is evidence that coal tar-based sealants may lead to increased levels of PAHs in settled indoor house dust. Family members of workers in industries using these products could be potentially exposed from contaminated work clothing or footwear.

- Dilute solutions of coal tar are used as a treatment for a variety of skin conditions, so dermal exposure from these shampoos or lotions can occur for persons using them. Wood creosote was

formerly used for medicinal purposes as an expectorant, anti-septic, astringent, anesthetic, and laxative; however, today, these uses seem rare in the United States.

- Coal tar creosote is a restricted use pesticide, so it is not available to the public for wood treatment uses. In locations where accidental spills occurred or creosote was released in effluents, nearby populations may be exposed to the constituents of coal tar creosote from contaminated environmental media such as air, soil, or water. Several of the constituents of coal tar and coal tar creosote bioconcentrate in fish and aquatic organisms; therefore, ingestion of fish near contaminated sites may result in exposure to populations consuming fish in these areas.

- The fate and transport of the components of these complex mixtures will be reflective of their individual properties. In general, high molecular weight PAHs are relatively nonvolatile and are slow to biodegrade in the environment, particularly under anaerobic conditions.

- If released to water, adsorption to suspended solids will attenuate volatilization for most of the components of these mixtures, and sediment is considered an environmental sink.

- The lower molecular weight constituents are volatile and undergo oxidation in air by vapor-phase reaction with atmospheric oxidants with half-lives of a few hours to a few days.

Coal tar creosote is a complex commercial mixture of thousands of organic constituents. The most common forms are derived from coal tar distillation, yielding coal tar creosote in temperature ranges between 210 and 280°C. Coal tar and coal tar pitch share many of the PAH 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 (Brown et al. 2006; Gallacher et al. 2017a, 2017b). For example, Brown et al. (2006) studied 10 coal tars obtained from MGPs in the eastern United States and while there were similarities in chemical distributions of PAHs, they also noted a very wide range of bulk and chemical properties, which reflects the variability in the full chemical composition of these mixtures. Coal tar, coal tar creosote, and coal tar pitch consist primarily of PAHs and, therefore, the fate of many of the components of the mixture is similar to that of PAHs; however, the variability in final composition of these complex mixtures will impact the overall fate and transport.

Coal tar creosote has been widely used as a wood-treatment pesticide since the turn of the 20th 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. In addition to PAHs, workers in coal tar and creosote industries may also be exposed to many other potentially hazardous compounds such as asbestos, silica, sulfur-substituted hydrocarbons, solvents, aliphatic amines, and aldehydes, making for a complex risk characterization (IARC 2012a). The public is unlikely to experience any significant exposure to liquid creosote through the direct use of wood preservative products because EPA canceled all non-wood uses of the material and restricted use of coal tar creosote products to certified applicators in January 1986 (EPA 1986a).

Children are exposed to the components of creosote via the same routes that adults are, but 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. In addition, creosote residues are found in coal tar sealants for driveways, which are commonly used in the United States. 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. 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-cyclopenten-1-ones. Wood creosote has been used as an expectorant, a gastric sedative, a gastrointestinal antiseptic, and particularly as an antidiarrheal agent (Ogata et al. 1993). Its current use in the United States is likely to be low or nonexistent; however, there appear to be web-based suppliers of wood creosote.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 summarizes information on companies that reported the production, import, or use of coal tar creosote for the Toxics Release Inventory (TRI) in 2022 (TRI22 2024). TRI data should be used with

caution since only certain types of industrial facilities are required to report. This is not an exhaustive list. Facilities report 16 EPA criteria PAHs thought to be contained in creosote in their threshold calculations and this is what the TRI data reflect.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	5	10,000	9,999,999	8
AR	4	10,000	9,999,999	8, 9, 12
CA	1	1,000	9,999	12
CT	1	100,000	999,999	8
DE	1	10,000	99,999	12
IL	2	1,000,000	49,999,999	1, 4, 8
IN	1	100,000	999,999	8
KY	3	100,000	9,999,999	8, 12
LA	4	100,000	9,999,999	8, 12
MO	1	100,000	999,999	8
MS	2	100,000	999,999	8
NC	1	10,000	99,999	7, 8
ND	1	100,000	999,999	12
NE	1	10,000	99,999	9, 12
NV	1	10,000	99,999	12
OH	3	100	99,999	12
OK	1	100,000	999,999	12
OR	1	1,000,000	9,999,999	8
PA	3	100,000	9,999,999	8
SC	2	1,000	49,999,999	8, 12
TN	2	100,000	9,999,999	1, 4, 8, 9
TX	7	1,000	9,999,999	7, 8, 12
UT	1	10,000	99,999	9, 12
VA	2	100,000	49,999,999	8

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WI	2	1,000,000	9,999,999	8
WV	2	100,000	999,999	8

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

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

Source: TRI22 2024 (Data are from 2022)

The EPA is conducting a review of the Registration Eligibility Decision (RED) for creosote and issued a Preliminary Work Plan in March of 2015 (EPA 2015) and Registration Review Draft Risk Assessment in 2019 (EPA 2019). An Interim Registration Review Decision was released by the EPA in December 2020 (EPA 2020a). The last completed RED for creosote occurred in 2008. The EPA conducts reviews of registered pesticides every 15 years to determine under what conditions and uses they may continue to be used. In the Interim RED, the EPA reported that as of February 2020, there were 15 actively registered products containing coal tar creosote. According to the National Pesticide Information Retrieval System (NPIRS), there are five corporations that produce 16 different restricted use coal tar creosote products. Table 5-2 summarizes these data and lists currently registered products.

Table 5-2. Manufacturers of EPA Restricted Use Coal Tar Creosote Products

Company	Product Name	EPA Registration Number	Percent active ingredient
Arbor Preservative Systems, LLC 1421 Channel Avenue Memphis, Tennessee	Creosote	97080-6	98.5
	Creosote solution	97080-7	97.0
	Creosote for pressure application	97080-8	55.0
Coopers Creek Chemical Corporation 884 River Road West Conshohocken, Pennsylvania	The C-4 brand black creosote coal tar solution	363-14	95.0
	The C-4 brand coopersote creosote oil	363-15	98.5
	P-2 creosote-petroleum solution	363-48	75.0

Table 5-2. Manufacturers of EPA Restricted Use Coal Tar Creosote Products

Company	Product Name	EPA Registration Number	Percent active ingredient
Koppers Inc. 436 Seventh Avenue, K-1900 Pittsburgh, Pennsylvania	Coal tar creosote	61468-1	98.0
	60/40 creosote-coal tar solution	61468-3	95.0
	Creosote manufacturing use	61468-6	98.5
	Creosote petroleum solution	61468-9	75.0
Lone Star Specialty Products PO Box 247 Lone Star, Texas	Creosote solution	82024-1	97.5
	Creosote oil	82024-2	98.5
	P3 creosote petroleum solution	82024-3	75.0
Rain CII Carbon LLC 1330 Greengate Drove Suite 300 Covington, Louisiana	Coal tar creosote	61470-1	98.0
	Coal tar creosote P2	61470-3	98.0
	P3 creosote-petroleum solution	61470-4	75.0

Source: NPIRS 2022

In 2004, U.S. consumption of coal tar creosote was estimated at 785 million pounds (EPA 2008, 2015). A study conducted by the Treated Wood Council (TWC) estimated that approximately 82.9 million gallons (760 million pounds) of coal tar creosote were used in the United States in 2007 to treat 101 million cubic feet of wood (Bolin and Smith 2013). Data from the EPA Chemical Data Reporting (CDR) database showed a production volume of 6,190,222 pounds of coal tar creosote in 2019; however, the data only contained information from Lone Star Specialty Products (EPA 2022b). There were no reported production volumes for wood creosote (CAS Registry Number 8021-39-4).

5.2.2 Import/Export

The EPA CDR showed import volumes of coal tar creosote as 4,345,214 pounds in 2019 and no export volumes (EPA 2022b). The U.S. International Trade Commission (USITC) reported that 89,280,999 liters of creosote oils (HTS 27079100) were imported into the United States for consumption in 2021 with no domestic export data available (USITC 2022).

5.2.3 Use

Coal tar creosote has been used as a wood preservative pesticide in the United States for over 100 years. It is a fungicide, insecticide, and sporicide used as a wood preservative for above- and below-ground wood protection treatments as well as for treating wood in marine environments and each of the currently

registered products in Table 5-2 are restricted use pesticides meaning that they are not available for purchase by the general public in the United States and may only be used by certified pesticide applicators (EPA 2008, 2015). Coal tar creosote products are registered for use in the pressure treatment of terrestrial and aquatic non-food wood and wood structures. According to EPA, there are two major types of coal tar creosote for use as a pesticide (EPA 2008, 2015). The P1/P13 fraction is used in the pressure treatment of utility poles and pilings. The P2 fraction is used in the pressure treatment of railroad ties/crossties and is more viscous than the P1/P13 blend. Potential end uses include utility poles/crossarms, railroad ties, switch ties, bridge timbers, fence and guardrail posts, foundation timbers, marine and foundation round piles, sawn lumber and timber products, and exterior structural composite glue laminated wood and plywood products. There are no registered residential uses of coal tar creosote or creosote-treated wood (EPA 2020a). Coal tar is used in the production of coal-tar products, such as coal tar creosote and coal-tar pitch, and refined chemicals. Low concentrations of coal tar have long been used to treat various skin conditions, such as eczema, psoriasis, and dandruff (NCI 2018; Veenhuis et al. 2002). The 2020 CDR contains many different entries of coal tar distillates all with unique CAS Registry Numbers that are products derived from coal tar under different distilling conditions. The major use of coal tar pitch is as the binder for aluminum smelting electrodes. Pitch is also used in roofing, surface coatings, and pitch coke production. Pipe-coating enamels made from pitch are used to protect buried oil, gas, and water pipes from corrosion (IARC 1985). Carbon black is also produced from the combustion of coal tar.

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

5.2.4 Disposal

According to the TRI, 44,835 pounds of coal tar creosote were transferred off-site from facilities that use or process coal tar creosote, presumably for treatment and disposal (TRI22 2024). 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]):

- Waste waters, process residuals, preservative drippage, 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
- Wastewater 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 1990). 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 1988a]). Industrially used creosote-treated wood can be burned in an industrial incinerator or boiler (EPA 1986a). Treated wood used in the home or farm should be buried or disposed with household garbage; it should not be incinerated (AWPA 1988). The potential for many types of hazardous pollutants to be included with creosote wastes seriously diminishes the potential for recycling or re-use.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022c). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022c).

There are no known natural sources of creosote mixture (IARC 1973). However, several of the PAH constituents of creosote mixtures are known to have natural sources; the reader is referred to the ATSDR toxicological profile for PAHs (ATSDR 1995) and cresols (ATSDR 2008a) for additional information on natural sources, releases, and levels of PAHs and cresols associated with creosote production, use, and disposal.

PAH levels in environmental media are typically used as a metric for coal tar creosote releases from nearby point sources such as wood treatment facilities. However, levels in these media are confounded by the many sources of PAHs in the environment including vehicle emissions, coke-oven emissions, and coal, oil, and wood combustion that result in atmospheric deposition of PAHs to water, soil, sediment, and vegetation. PAH levels near a known source (e.g., wood treatment facility using coal tar creosote) are most reflective of releases from that source.

Spills from wood treatment facilities or wastewater effluents are a major source of creosote released to the environment (IPCS 2004). Emissions may also occur during the transfer of creosote from an incoming tanker or rail car to plant storage facilities (EPA 1998). Transfer of the product, whether from rail car or tanker, is typically performed using a closed piping system. The greatest chance for fugitive emissions is at the origin, where creosote is leaving the tanker or rail car, and at the end of the transfer, where creosote is entering the storage vessel. Coal tar creosote components may also be slowly released from the surface of treated wood products by oil exudation, leaching by rainwater, or volatilization. Losses of creosote from impregnated wood are dependent on temperature, salinity, water flow, density of the wood, and length of time since treatment of the wood (CSCC 2010). Kang et al. (2005) studied the leaching behavior of creosote treated wood in flowing fresh water by monitoring PAH levels over time at varying flow rates. Seven of 16 monitored compounds were detected in the water, and all detected PAHs increased immediately after immersion, then decreased sharply, and reached a steady state after 1 week. Higher molecular weight PAHs, including anthracene, chrysene, benzo[b]fluoranthene, benzo[f]fluoranthene, benzo[a]pyrene, indenopyrene, benzo[e]perylene, and dibenzo[a,h]anthracene, were not detected at any point in the test. The results suggest that PAH concentrations from creosote-treated wood appear to decline rapidly to ng/mL levels after initial exposure.

Treatment of wastewaters from wood-preserving processes that use creosote and/or pentachlorophenol produces bottom sediment sludge. EPA defines these as K001 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 K001 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 byproduct of the production of so-called town gas, an illuminating gas made from

coal (Arvin and Flyvbjerg 1992; EPA 1988b; 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 1988b). From 1816 to 1947, more than 11 billion gallons of coal tar were 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 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 1988b; Flyvbjerg et al. 1993).

No major sources of wood creosote releases to the environment have been reported.

5.3.1 Air

Estimated releases of 145,457 pounds (~66 metric tons) of creosote to the atmosphere from 55 facilities reporting to TRI domestic manufacturing and processing facilities in 2022, accounted for about 36% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Creosote[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	5	9,210	46	0	0	0	9,256	0	9,256
AR	4	28,236	0	0	0	0	28,236	0	28,236
CA	1	3	0	0	160,506	0	160,509	0	160,509
CT	1	454	0	0	0	0	454	0	454
DE	1	15	0	0	2,529	0	99	2,445	2,544
IL	2	6,500	0	0	0	0	6,500	0	6,500

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Creosote[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
IN	1	5,528	0	0	0	0	5,528	0	5,528
KY	3	5,486	0	0	13,249	0	10,246	8,489	18,735
LA	4	33,659	24	0	10,950	0	44,361	272	44,633
MS	2	2,885	43	0	0	0	2,928	0	2,928
MO	1	5,532	0	0	0	3,568	5,532	3,568	9,100
NE	1	4	0	0	0	0	4	0	4
NV	1	0	0	0	30,267	0	30,267	0	30,267
NC	1	0	0	0	0	5,880	0	5,880	5,880
ND	1	0	0	0	0	0	0	0	0
OH	3	1	0	0	0	0	1	0	1
OK	1	40	0	0	0	0	40	0	40
OR	1	604	0	0	0	0	604	0	604
PA	3	6,911	18	0	4,335	0	6,929	4,335	11,264
SC	2	2,328	0	0	66	0	2,328	66	2,393
TN	2	4,106	0	0	397	0	4,106	397	4,503
TX	7	13,322	22	0	21,683	0	17,767	17,261	35,028
UT	1	0	0	0	0	0	0	0	0
VA	3	10,373	13	0	0	0	10,386	0	10,386
WV	1	2,623	0	0	0	2,122	2,623	2,122	4,745
WI	2	7,637	13	0	8	0	7,658	0	7,658
Total	55	145,457	179	0	243,990	11,570	356,361	44,835	401,196

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

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 (EPA 1986b). 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 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.

Gallego et al. (2008) examined the emissions of volatile organic compounds (VOCs) and PAHs from wood recently treated with creosote. The primary components of the vapors released from the creosote-treated wood were identified as naphthalene, toluene, *m*-/*p*-xylene, ethylbenzene, *o*-xylene, isopropylbenzene, benzene, and 2-methylnaphthalene. VOC emission concentrations ranged from 35 mg/m^3 of air on the day of treatment to 5 mg/m^3 8 days later. PAHs emission concentrations were 28 $\mu g/m^3$ of air on the day of treatment and 4 $\mu g/m^3$ 8 days later. Volatilization is likely to 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°C than at 4°C.

Volatilization from coal tar-based pavement sealants has been identified as a source of VOCs and PAHs into the atmosphere. Van Metre et al. (2012) measured PAH levels above parking lots sealed with coal tar-based sealants and compared them to levels of unsealed or asphalt lots. The geometric mean concentration of the sum of eight frequently detected PAHs 0.03 m above the lots using coal tar-based sealants was 1,320 ng/m^3. This was approximately 20 times greater than the total PAH levels in the unsealed lots (66.5 ng/m^3).

Coal tar is listed as a pollutant in the National Emissions Inventory (EPA 2017a). EPA's NEI database contains data regarding sources that emit criteria air pollutants and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The 2017 NEI report lists coal tar as a HAP, with air emissions ranging from 0.2 pounds

(waste disposal) to 4,407 pounds. The industrial sectors and emissions for 2017 reporting are shown in Table 5-4.

Table 5-4. Reported Emissions from the 2017 NEI for Coal Tar

Sector	Pollutant type	Emissions (pounds)
Industrial processes; storage and transfer	HAP	4,407.2
Industrial processes; chemical manufacture	HAP	4,301
Solvent; industrial surface coating and solvent use	HAP	2,048.2
Industrial processes; not elsewhere categorized	HAP	1,384.6
Solvent; graphic arts	HAP	192
Industrial processes; petroleum refineries	HAP	102
Bulk gasoline terminals	HAP	73.6
Waste disposal	HAP	0.2
Industrial processes; non-ferrous metals	HAP	0

HAP = hazardous air pollutant

Source: EPA 2017a

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.

5.3.2 Water

Estimated releases of 179 pounds (<1 metric tons) of creosote to surface water from 55 domestic manufacturing and processing facilities in 2022, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI22 2024). These releases are summarized in Table 5-3.

A source of coal tar creosote released into surface waters and ground water is wastewater effluents from wood-preserving facilities or accidental spills (IPCS 2004). In previous years, wastewater generated from wood treatment facilities was often discharged to unlined evaporation/settling lagoons where a sludge was formed. Water-soluble coal tar 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 coal tar creosote waste waters and sludge stored in unlined surface water impoundments occurred at a wood treatment facility in Pensacola, Florida (Baedecker et al. 1988; Elder and Dresler 1988; Goerlitz et al. 1985). Similar contamination problems have occurred in Conroe, Texas (Borden 1986), and St. Louis Park, Minnesota (Hickok et al. 1982). An additional source of coal tar creosote released to waters is due to leaching from coal tar creosote-treated wood pilings (CSCC 2010). Leaching rates of contaminants from coal tar creosote-treated wood are variable and greatest during the first few years after placement, but also continues for many years. Leaching from coal tar creosote treated wood pilings is a function of salinity, temperature, flow, density of the wood, length of time since treatment of the wood, whether leaching occurs from the end grain or the face, and the surface area-to-volume ratio. In an investigation of the release of coal tar 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°C; slower migration occurred from aged than from freshly treated pilings. In a microcosm study of the leaching of PAHs from coal tar creosote-impregnated pilings into aquatic environments, the aqueous concentration of PAHs increased with the number of pilings used (Bestari et al. 1998). The study authors calculated a rate loss of coal tar creosote from the wood pilings into the water of approximately 50 μg/cm^2/day (273 mg/piling/day). Coal tar 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.

Given the very viscous nature of coal tar creosote or coal tar 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 ground water (Goerlitz et al. 1985). In most instances, the main concern over coal tar 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 ground water from disposal sites, coal tar creosote has often been introduced to receiving waters as the result of spills from wood treatment facilities or during the

transportation of 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 coal tar creosote (Gunster et al. 1993).

Runoff from coal tar-based driveway and parking lot sealants has been identified as a source of PAHs in nearby waters (Mahler et al. 2012). An estimated 85 million gallons (321 million liters) of coal-tar-based sealcoat are used annually in the United States.

5.3.3 Soil

Estimated releases of 243,990 pounds (~111 metric tons) of coal tar creosote to soil from 55 domestic manufacturing and processing facilities in 2022, accounted for about 61% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-3.

In addition to accidental spills, coal tar creosote may be released to soils at wood treatment facilities because of bleeding of the product from treated timber in stockyard and storage areas. Rainwater 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 1988b). Coal tar creosote-treated wood pilings also may release constituents to sediment in a marine environment.

Dust and runoff from coal tar sealed driveways and parking lots is also a source of PAH contamination to urban waterways and sediments in locations where these products are used, although quantifying the direct contributions from sealants versus atmospheric deposition from other sources is subject to uncertainty (O'Reilly et al. 2011). Analysis of parking lot dust samples from six central and eastern U.S. cities where coal tar sealants are frequently used were shown to be much greater than dust samples in three western cities, which predominantly used asphalt-based sealants (Van Metre et al. 2009). The study authors found that bottom sediments of lakes of central and eastern U.S. cities contained greater PAH levels than the lakes of the western cities sampled and concluded that coal tar-based sealants were a source for these higher levels (Van Metre et al. 2009). A second study analyzed PAH levels in sediments from 40 urban lakes in areas in eastern and central U.S. versus levels from western lakes (Van Metre and

Mahler 2010). The study authors employed a chemical mass balance model to estimate the source apportionment of PAHs into the lake sediments and concluded that approximately 57% of the PAHs in bottom sediments in eastern and central U.S. lakes studied could be attributed to coal tar treated pavement, 11–20% arose from vehicle emissions, 18–26% from coal/oil combustion, and 5% from wood combustion.

5.4 ENVIRONMENTAL FATE

As with other chemical mixtures, the fate and transport processes affecting coal tar creosote can be extremely complex. The components of this mixture 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 coal tar creosote will show limited ability to move off-site. Johnston et al. (1993) studied the PAH composition of coal-tar-containing samples collected at several 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. As with releases to water, the migration of newly sealed and weathered driveway and parking lots that use coal tar-based driveway sealant may be a source to nearby soils (Mahler et al. 2012).

Newly produced coal tar 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 coal tar 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 coal tar creosote contamination. A large percentage reduction by total weight does not always translate into a

corresponding reduction in toxicity (Brooks et al. 1998; Hyötyläinen and Oikari 1999; Mueller et al. 1991).

5.4.1 Transport and Partitioning

Air. The environmental fate and transport of wood creosote, coal tar creosote, coal tar, and coal tar pitch are reflective of the individual components of these complex mixtures. Some identifiable components of these mixtures were presented in tables in Chapter 4. Phenols, which are representative of the components of wood creosote, generally have moderate to high vapor pressures and would be expected to exist primarily in the vapor phase in the ambient atmosphere. For example, phenol has a vapor pressure of approximately 0.35 mmHg at 25°C (EPA 2012). These compounds typically have relatively short atmospheric half-lives so would not be subject to long range transport in air. Coal tar creosote, coal tar, and coal tar pitch are more complex chemical mixtures; however, the lower molecular weight substances are also semi-volatile and tend to exist in the vapor phase in the ambient atmosphere. According to the International Programme on Chemical Safety chemical assessment of coal tar creosote, there are six major classes of compounds present in most mixtures: aromatic hydrocarbons, including PAHs and alkylated PAHs (which can constitute up to 90% of coal tar creosote); tar acids/phenolics; tar bases/nitrogen-containing heterocycles; aromatic amines; sulfur-containing heterocycles; and oxygen-containing heterocycles, including dibenzofurans (IPCS 2004). In general, phenolic compounds, low molecular weight PAHs, and some heterocycles tend to exist predominantly in the gaseous phase; however, the higher molecular weight PAHs will likely be present predominantly in the particulate phase. Substances in the particulate phase generally have longer atmospheric half-lives than vapor-phase substances and are removed from the atmosphere by wet and dry deposition.

Water. 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 coal tar creosote, generally tend to sorb strongly to soil and sediment particulates, and often have low aqueous solubilities and mobility (Hickok et al. 1982; IPCS 2004). Many components in the PAH fraction, particularly the higher molecular weight PAHs, will remain in a virtually stationary tar-like mass at the place where they were deposited (dense nonaqueous phase layer [DNAPL]). Nitrogenous bases present in coal tar creosote wastewater (e.g., aniline, toluidines, and xylidines) are relatively soluble, mobile, and persistent in groundwater (Pereira et al. 1983). Volatilization from water surfaces is likely only an important environmental fate process for phenols and low molecular weight PAHs. Behavior at a given site is also dependent on site-specific characteristics.

For example, PAHs, phenol, and heterocyclic components of coal tar 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).

Similar to other environmental fate and transport properties, the potential to bioconcentrate and bioaccumulate in aquatic organisms is highly dependent upon the properties of the individual constituents of the complex mixtures. Jonsson et al. (2004) studied the bioconcentration potential of eight different PAHs representative of coal tar creosote mixtures in fish (sheepshead minnows) at two different exposure levels using a flow through aquarium. Bioconcentration factor (BCF) values in the fish ranged from 145 (pyrene) to 23,859 (2-isopropylnaphthalene) in the low-exposure (7.57 µg/L) group and from 97 to 46,536 in the high-exposure (72.31 µg/L) group.

Sediment and Soil. Sediment and soil tend to act as an environmental sink for most constituents of coal tar creosote, coal tar, and coal tar pitch, particularly the high molecular weight PAH components. The rate of vertical or horizontal migration of these components in soil is dependent upon the physical-chemical properties of the individual components of the mixture as well as the soil properties and environmental conditions (IPCS 2004). Laboratory model and field experiments (simulating coal tar creosote spills) showed a high retardation of transport of high molecular weight compounds coupled with a fast downward migration of lower molecular weight compounds. 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).

In a study of the extent of coal tar creosote contamination at four wood-preservative plants with process water surface impoundments, unspecified coal tar 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 an investigation of the volatilization of PAHs from coal tar creosote-treated wood, desorption of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene was directly related to concentration and was greater at 30°C than at 4°C (Gevao and Jones 1998). The study authors reported desorption half-

lives of 0.7–31 years at 4°C and 0.3–1 year at 30°C 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 constants ranging from 0.11 to $8.65x10^{-8}$ atm m^3/mole and vapor pressures of 95 to $1.2x10^{-8}$ mmHg (Swann et al. 1983), indicating that some newly leached compounds may volatilize from both moist and dry soil surfaces.

In a terrestrial microcosm study that examined the transport of coal tar creosote containing substances impregnated in wood posts, 2.7% of radiolabeled phenanthrene and 4.3% of radiolabeled acenaphthene were found in soil samples taken in a 10-cm zone around coal tar 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 coal-tar contaminated surface sediments, PAHs were observed to have moved 400 m 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 coal tar creosote components may be released over time. In a laboratory study of coal tar creosote-contaminated sediment and natural lake water, Hyötyläinen and Oikari (1999) found that coal tar creosote-derived 4–6-ring PAHs released from the sediment during incubation were toxic to water fleas (*Daphnia magna*) and to the photoluminescent bacteria *Vibrio fischeri*.

Other Media. Atmospheric deposition of VOCs and PAHs contained in coal tar creosote is a possible source of contamination of leafy parts of plants and vegetable; however, uptake from roots is also possible. Moret et al. (2007) studied levels of light molecular weight PAHs (fluorene, phenanthrene, anthracene, fluoranthene, pyrene) and heavy molecular weight PAHs (benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene, indeno[1,2,3-cd]pyrene) in olives grown in locations that stored old railroad ties that were treated with coal tar creosote. Levels of the light-weight PAHs were approximately 5,679 and 6,359.9 µg/kg in olive oil extracted from trees grown 1 and 2 m away from the railroad ties, respectively but oil extracted from trees 50 m away had total PAH levels of only 41.1 µg/kg. The study authors also indicated that very little of the heavy PAH components were found in olive oil extracts. The total concentration of heavy PAHs in olive oil from trees 1 m away was 6.2 µg/kg and decreased to 2.8 µg/kg at a distance of 50 m.

Animals such as voles, crickets, snails, pill bugs, and worms have exhibited the capacity to assimilate radiolabeled coal tar creosote components in terrestrial microcosm studies. Coal tar creosote components were found to accumulate to the greatest extent in the vole, with 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 coal tar creosote-treated pilings have been found to contain significantly more benzo[a]pyrene, a coal tar creosote constituent, than those growing elsewhere (Dunn and Stich 1976). Accumulation of coal tar creosote-derived PAHs has occurred 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. The total PAH levels of mussels grown in cages near creosote treated wood pilings in Sooke Basin, British Columbia increased within 14 days of exposure from background levels of about ~16 to 68 ng/g, but then returned to baseline levels after 184 days (Brooks 2011a). No adverse effects on the survival of mussels suspended from the pilings were observed during the 2-year study period.

5.4.2 Transformation and Degradation

Air. Volatile constituents of these complex mixtures 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 for representative coal tar creosote containing substances in the range of $1.12–103x10^{12}$ cm/molecules-second at 25°C and using an average atmospheric hydroxyl radical concentration of $5x10^5$ molecules/cm^3 (Atkinson 1989; Meylan and Howard 1993). Rates for constituents in the atmosphere with low vapor pressures may be slowed because they will exist in the particulate phase and, therefore, undergo atmospheric oxidation and direct photolysis at slower rates as compared to substances that exist primarily in the vapor phase (Eisenreich et al. 1981). Additionally, some components may undergo nighttime reactions with nitrate radicals (Atkinson et al. 1987). Based on an experimental rate constant of $3.8x10^{-12}$ 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).

Water. Many of the constituents of these complex mixtures 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 constituents which may undergo aqueous photolysis are acenaphthalene, anthracene, benzene, quinoline, phenol, cresol. In a microcosm study, PAHs leached from coal tar 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).

Coal tar creosote components are degraded in aquatic environments mainly by microfauna metabolism (Borthwick and Patrick 1982; Ingram et al. 1982). Microorganisms may act on the coal tar creosote-treated wood itself or on coal tar creosote components that have leached from the treated wood. Quinoline, the major tar base in coal tar creosote, may be degraded in surface water and ground water by bacteria of the genus *Pseudomonas* (Bennett et al. 1985). Biotransformation of the phenolic components of coal tar creosote apparently also occurs under anaerobic conditions in contaminated ground water (Ehrlich et al. 1983; Goerlitz et al. 1985). Adaptation of soil microorganisms to PAH contaminants in ground water originating from coal tar creosote treatment plant wastes has also been reported (Wilson et al. 1985).

Work on NPL sites has helped identify numerous bacteria and fungi that can biodegrade coal tar 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 ground water is not completely anoxic, numerous soil microorganisms can degrade coal tar creosote materials. Work at NPL sites suggests that up to 90% of the coal tar creosote degradation is associated with biologically mediated processes. Although this can lead to an appreciable reduction in the quantity of the coal tar creosote materials, it is the phenolic and lower molecular weight PAHs that are degraded while the higher molecular weight PAHs that have been shown to resist biological attack may persist. In a study of biodegradation of coal tar creosote-contaminated ground water 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 higher molecular weight PAHs that remained after 14 days of incubation. The higher levels of biodegradation observed for the lower molecular weight PAHs was attributed to their greater aqueous solubility and consequent greater bioavailability.

Work on town-gas sites in Europe has demonstrated that where nitrate levels are high, or where nitrate is supplied to ground water, 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 for most constituents of coal tar creosote. Even when supplied

with ample quantities of such electron acceptors as nitrates, half-lives >20 days were observed in laboratory microcosms for the anoxic biodegradation of dimethylphenol components in coal tar creosote, and cresol components showed little indication of significant disappearance unless the experiments were continued in excess of 90 days (Arvin and Flyvbjerg 1992).

Coal tar creosote components have been detected in surface water samples taken near a wood-treatment facility that ceased operation 30 years earlier (Black 1982). The coal tar 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 coal tar 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.

Sediment and Soil. Smułek et al. (2020) studied the biodegradation of PAHs in soils contaminated by creosote oil of a railway sleeper treatment plant in Koźmin Wielkopolski in central Poland. A total of 10 soil samples were collected from three different boreholes across the polluted area and used for laboratory studies to identify potentially useful creosote degrading bacterial strains that could be isolated from these soil samples. The authors identified *Pseudomonas mendocina* and *Brevundimonas olei* as the most effective strains that were capable of degrading more than 60% of the total content of PAHs during a 28-day incubation period.

A remediation method combining biodegradation and electroosmosis showed enhanced degradation of PAHs from coal tar creosote-polluted soils (Niqui-Arroyo and Ortega-Calvo 2007). A predominantly clay and a loamy soil were studied that contained a mixture of PAHs typically present in coal tar creosote and amended with a surfactant and soil bacterium capable of degrading PAHs. In the loamy soil, 50% degradation of benzo[a]pyrene was observed after only 7 days, which was significantly greater than the degradation observed using electrokinetical flushing and bioremediation alone.

In a study of PAH-contaminated soil from the Reilly Tar Superfund Site in St. Louis Park, Minnesota, total EPA priority pollutant PAH concentrations were decreased 48–74% following treatment with one of four bioremediation technologies (Brooks et al. 1998). The remediation methods included bioslurry, biopile, compost, and land treatment. None of the four techniques tested was successful at removing the 5- and 6-ring higher molecular weight PAHs; however, it was suggested that compost and land treatment processes were the most effective treatment techniques.

PAHs from soil contaminated with coal tar creosote can also be removed by biodegradation, using fungi. A field study at a wood treatment facility located in Mississippi investigated the effects of solid-phase bioremediation using the white rot fungus, *Phanerochaete sordida* (Davis et al. 1993). This fungus has been shown to also biodegrade PCP, which has often become mixed with the wastes found at coal tar creosote production or disposal sites. The study authors observed 85–95% degradation of 3-membered PAHs and 24–72% loss of 4-membered PAHs following a 56-day treatment period; however, PAHs containing 5 or more rings were persistent. Byss et al. (2008) observed the white rot fungus, *Pleurotus ostreatus*, to be a more efficient coal tar creosote-degrading organism than *Irpex lacteus* in a laboratory-scale study.

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. FWS (1987) found that many aquatic organisms are able to rapidly metabolize and eliminate PAHs, the major constituents of the commercial mixture.

5.5 LEVELS 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. Concentrations of creosote in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on creosote levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. Current air sampling methods for semi-volatile substances employ two-stage sampling media, which includes a filter to collect particles and a sorbent material to collect vapors. Data collected historically using only a filter or a sorbent material most likely underestimated actual atmospheric levels and subsequent inhalation exposures. Due to the lipophilic nature of many of the components of this mixture, care should be given to storage and handling of samples to avoid adsorption to a storage vehicle, which could lead to inaccurate measurements.

Table 5-5 shows the typical limit of detections that are achieved by analytical analysis in environmental media for some important PAHs or VOCs expected to be present in creosote mixtures. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-6. PAHs are expected to be found in all environmental media from a variety of sources; therefore, only levels that were found around known sources of coal tar, coal tar creosote, or coal tar pitch sources are discussed.

Often, total PAHs will be provided in monitoring data. This typically refers to the sum total of 16 substances designated High Priority Pollutants by the EPA; they include: naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benzo[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[g,h,i]perylene, indeno[1,2,3-c,d]pyrene, and dibenz[a,h]anthracene (Hussar et al. 2012).

Table 5-5. Lowest Limit of Detection for PAHs and VOCs in Creosote Mixtures Based on Standards[a]

Media	Detection limit	Reference
Air	0.0054−4.4006 ng/m^3	EPA 2020b
Drinking water	0.033–0.66 ng/L	Aygun and Bagcevan 2019
Surface water and groundwater	0.06–5,7 µg/L (pore water) 0.013–0.64 µg/L (groundwater/waste)	EPA 2007b Method 8272 EPA 1986c Method 8310
Soil	0.020 µg/g	USDA 2004
Sediment	0.020 µg/g	USDA 2004
Whole blood	20 ng/mL ~2 ng/mL	Ramesh et al. 2015 Anderson et al. 2015

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

PAH = polycyclic aromatic hydrocarbon; VOC = volatile organic compound

Table 5-6. Summary of Environmental Levels of Creosote

Media	Low	High	For more information
Outdoor air (ng/m^3)	1.6	90	Section 5.5.1
Indoor air (workplace air) (µg/m^3)	<LOD	1,211	Section 5.6
Surface water	<LOD	>100,000 µg/L	Section 5.5.2
Groundwater	<LOD	>100,000 µg/L	Section 5.5.2
Sediment	0.074 mg/kg	15,000 mg/kg	Section 5.5.3
Food/fish	0.11 mg/kg	60.1 mg/kg	Section 5.5.4
Soil	0.39 mg/kg	657 mg/kg	Section 5.5.3

LOD = limit of detection

Detections of coal tar creosote in air, water, and soil at NPL sites are summarized in Table 5-7.

Table 5-7. Coal Tar Creosote Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	13,400	6,570	160	4	4
Soil (ppb)	21,000	20,500	190	4	4
Air (ppbv)	No data				

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Information regarding creosote constituents in ambient air are confounded by the fact that PAHs will arise from other sources such as automobile emissions or industrial processes (Brooks 2011b). A maximum concentration of 90 ng/m^3 has been reported for naphthalene at 2,000 m from a creosote using facility, with levels decreasing with distance from the plant (IPCS 2004). For example, the concentration of fluoranthene decreased from 64 ng/m^3 at 500 m to 1.6 ng/m^3 at 5,000 m away from the facility. Chen et al. (2002) performed air monitoring studies at a cleanup site of a gasification plant in Kingston, Ontario that contained large underground tanks of coal tar. The study authors measured concentrations of naphthalene, typically the most abundant PAH in coal tars, over a 3-week monitoring period. A total of 168 half-hour concentrations were determined at several different locations upwind and downwind of the site. The highest half hour average level of naphthalene measured was 250 µg/m^3, and in 45% of the samples collected, the level of naphthalene exceeded the Ontario Ministry of the Environment guideline of 36 µg/m^3. Air sampling was performed in Globeville, Colorado, a residential area located near the Koppers wood treating facility and two asphalt plants, after residents complained of an odor described as tar or asphalt became noticeable (Morgan et al. 2015). Several VOCs and PAHs were detected during these odor events but were not often detected in background samples or the suspected industrial sources. Naphthalene, dibenz[a,h]anthracene, benzo[g,h,i]perylene, and indeno[1,2,3-cd]pyrene were detected in the air at levels of 25.00, 2.70, 1.70, and 2.10, ppbv (131.06, 30.73, 19.21, and 23.73 µg/m^3), respectively, during one of these odor events. For example, naphthalene has a geometric mean odor detection threshold in air of 0.038 ppm (NLM 2023). ATSDR has been petitioned to evaluate exposures associated with many creosote facilities with odors being a common complaint (ATSDR 2004, 2007b, 2009). As a result, the agency developed a website to assist communities with their environmental odors (https://www.atsdr.cdc.gov/odors/).

Construction materials containing coal tar and coal tar creosote products may be a source of PAHs in indoor air. Kozicki and Niesłochowski (2020) published the results of indoor air measurements of 11 PAHs in 14 buildings including residential buildings, office buildings, and public buildings such as schools, hotels, and museums that used coal tar products to treat wood structures or other construction materials such as coal tar containing bituminous mixtures or coal tar containing adhesives. Indoor air levels tended to be greatest for naphthalene and methylnaphthalenes, with maximum levels of 42±6 and 34±5 μg/m^3, respectively, measured in public buildings. Six PAHs (naphthalene, methylnaphthalenes, dimethylnaphthalenes, biphenyl, acenaphthene, and dibenzofuran) were detected in residential, office, and public structures. Fluorene, phenanthrene, anthracene, fluoranthene, and pyrene were not detected in any of the five office buildings, or five public buildings studied; however, they were detected in residential buildings, with maximum levels of 3±1 μg/m^3 (fluoranthene) to 11±2 μg/m^3 (anthracene). Piñeiro et al. (2021) discussed PAH levels in the indoor air of a residential structure in Madrid, Spain constructed using waterproof coal tar membrane roofing materials. PAHs such as naphthalene, methylnaphthalenes, acenaphthene, acenaphthylene, phenanthrene, and fluorine were detected at levels that exceeded recommended indoor air guidelines. Total PAH levels of the 16 High Priority Pollutants were 1,167 μg/m^3 in the living room, and naphthalene levels extracted from the inter-joist pan form were as high as 6,152 μg/m^3.

ATSDR's guidance for evaluating the vapor intrusion pathway identifies coal tars and creosote as a potential source of volatile and semi-volatile contaminants, including naphthalene, benzene, toluene, ethylbenzene, and xylene (ATSDR 2016a). The contaminants may off gas from creosote and coal tar contamination in groundwater and soil gas and migrate up into the indoor air of buildings by a process called vapor intrusion. DNAPL may serve as an ongoing source of contamination into groundwater as contaminants dissolve into the aqueous phase.

Coal tar-based driveway and parking lot sealants have been associated with high levels of PAHs in indoor dust samples (Mahler et al. 2010). A study that examined PAH levels in the indoor dust from 23 apartments found that the median concentration of total PAHs in dust from coal tar sealed parking lots was 4,760 μg/g (n=11). The median indoor dust level from 12 residencies that had pavement surfaces not sealed with coal tar-based products was 9 μg/g.

Workplace air concentration data are discussed in Section 5.6. Data on ambient atmospheric concentrations of PAHs derived from other sources can be found in the ATSDR toxicological profile for PAHs (ATSDR 1995).

5.5.2 Water

Levels of PAHs in the ppb to ppm range have been found for some individual PAHs in surface water at creosote contaminated sites (IPCS 2004).

Following a fire at a wood treatment facility and subsequent creosote spill in Louisiana, PAHs were detected in surface water in Bayou Bonfouca. Levels of selected PAHs were: 400–39,700 µg/L anthracene; not detected–5,500 µg/L benzofluoranthenes; 300–6,600 µg/L benzo[a]pyrene; 1,200–110,000 µg/L fluoranthene; 600–12,300 µg/L fluorene; 700–14,100 µg/L naphthalene; 2,300–155,000 µg/L phenanthrene; and 2,100–85,000 µg/L pyrene (Catallo and Gambrell 1987). Sixteen PAHs were monitored in surface water from five railway ditches flowing to salmon streams in British Columbia, Canada (Wan 1991). At sites where PAHs were detected in ditch water, the average total PAH concentration was 606.9 µg/L, with a range of 1–3,515.9 µg/L.

The IPCS (2004) summarized groundwater levels of monocyclic aromatic and phenolic compounds detected at creosote-contaminated sites from eight different studies conducted in the United States, Canada, and Denmark. The highest level detected was for *m*-cresol (25,170 µg/L) at an abandoned wood treatment facility in the United States. This publication also summarized PAH levels at creosote contaminated sites in the United States, Canada, and Denmark from studies performed in the 1980s to the 1990s. The highest levels were observed in groundwater near the Escambia Wood Treating Company in Pensacola, Florida that manufactured treated utility poles, foundation pilings, and lumber with creosote and PCP from 1942 until 1982. Levels exceeded 100,000 µg/L for several PAHs including pyrene, phenanthrene, fluorene, and fluoranthene. This facility was abandoned in 1991 and remediation began shortly thereafter. EPA released the fourth 5-year review report and groundwater monitoring data conducted from 2013 to 2016 (EPA 2017b). Levels of most PAHs were significantly lower than previous measurements. For example, concentrations of phenanthrene in groundwater wells were below detection limits in wells sampled in 11 out of 12 sampling periods with a maximum concentration of 58 µg/L from sampling conducted in 2014. Fluorene was also not detected during most sampling periods and had a maximum concentration of 92 µg/L in sampling conducted in November 2014.

At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed from 1903 to 1961, creosote-derived naphthalene, acenaphthene, fluorene, pyrene, and phenanthrene were measured in surface water and groundwater at levels up to 100,000 µg/L (ATSDR 1994). Remediation began in 1993 and the EPA 5-year review of this remediated site showed no surface water detections for 16 EPA criteria PAHs in sampling conducted from 2011 to 2014 (EPA 2016).

A public health assessment was conducted by ATSDR and the North Carolina Department of Health and Human Services Division of Public Health on the Holcomb Creosote Company that operated as a coal-tar creosote wood-treating facility from 1951 to 2009. EPA began remediation and removal actions to address contamination of environmental media at this site in 2011. Surface water samples collected after 2011 had onsite levels of total PAHs ranging from 7.14 to 31.8 µg/L (NC DHHS 2020).

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).

5.5.3 Sediment and Soil

PAHs undergo a weathering process in soils and sediment (EPA 2006). This results in the lighter fractions (i.e., shorter chain molecules) being removed more readily than heavier PAHs. This occurs mainly by volatilization, but some proportion of the material moves through the soil vadose zone and into the groundwater. Heavier fractions tend to adsorb more readily to the soil organic matter and remain behind in the topsoil horizons. Weathering occurs in sediments as well, but much more slowly.

Soil samples were studied for PAH levels from the Des Plaines River wetlands in Will County, Illinois near a Commonwealth Edison railroad line (USDA 2004). PAHs were observed above detection limits in five of six baseline wetland soil samples. Total PAH concentrations ranged from 0.183 to 0.893 µg/g (183–893 µg/kg) dry soil with a mean and 95% confidence interval of 0.430±0.183 µg/g.

On- and offsite sampling was conducted at the Holcomb Creosote Company, North Carolina, which operated as a coal-tar creosote wood-treating facility from 1951 to 2009 (NC DHHS 2020). PAHs were

detected in 18 of 23 onsite soil samples collected prior to 2011, with a range (total PAHs) of 0.39–290 mg/kg. Onsite sediment samples had detectable levels of PAHs in six out of seven samples, with summed total levels ranging from 7.05 to 657 mg/kg. Offsite sediment samples collected prior to 2011 had total PAH levels of 2.33–6.92 mg/kg (three out of seven positive samples).

Soil samples were studied at locations that stored old railway ties treated with coal tar creosote in Italy (Moret et al. 2007). High levels of PAHs were detected in soil samples very close to the railroad ties (0–1 m) with total concentrations of 2,157 µg/kg for light molecular weight PAHs (fluorene, phenanthrene, anthracene, fluoranthene, pyrene) and 3,121.8 µg/kg for heavy molecular weight PAHs (benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene, indeno[1,2,3-cd]pyrene). The total PAH load was shown to decrease rapidly with the distance from the railway ties. For example, at a distance of 20 m, the level of the total light PAHs decreased to 15.2 µg/kg and the concentration of the total heavy PAHs was 25 µg/kg.

Baldwin et al. (2020) studied PAH contaminants in surficial streambed sediments at 71 locations across 26 Great Lakes Basin watersheds. Although there are numerous sources of PAHs to these watersheds, coal tar-sealed pavement dust was the most likely source of PAHs to most of the locations sampled. The total (summed) concentration of 16 EPA priority pollutant PAHs was 7.4–196,000 µg/kg (0.0074–196 mg/kg) and the median value was 2,600 µg/kg (2.6 mg/kg).

High levels of PAHs have been observed in the Elizabeth River near the Chesapeake Bay due to spills that occurred from the Atlantic Wood Industries facility (Di Giulio and Clark 2015). PAH levels in sediment samples remain high near wood treatment facilities years to decades after cessation of plant operations. A maximum total PAH concentration of 15,000 mg/kg was observed in sediments of the Elizabeth River adjacent to a wood treatment facility.

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.

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 0.7–1.8-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 1 to 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 m 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).

5.5.4 Other Media

Fish and aquatic organisms exposed to coal tar creosote in waters have been shown to accumulate PAHs. Largemouth bass collected at Dobbins Pond (2012–2014) at the Holcomb Creosote Company, North Carolina had total PAH levels ranging from 0.11 to 60.1 mg/kg and white catfish had levels ranging from 0.057 to 0.07 mg/kg (NC DHHS 2020). Total PAH levels in largemouth bass from a reference pond not on the site had PAH levels of 0.121–0.221 mg/kg, and PAHs were not detected in any channel catfish samples off site. West et al. (2019) studied the potential accumulation of PAHs in Pacific herring (*Clupea pallasii*) embryos near creosote-treated pilings in the Puget Sound. Total PAH levels in embryo samples placed close to the creosote treated pilings were approximately 90 times greater than levels observed in reference embryo samples.

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). Clams introduced to an area near a major creosote spill showed tissue concentrations of benzopyrenes up to 600 ppb after 4 weeks of exposure, compared to a background level of 87 ppb. Marsh clams are a major food item for crustaceans, such as the blue crab, that are part of commercial fisheries in the Lake Pontchartrain area.

Olives grown near sites that stored old creosote treated railroad ties were shown to have PAHs levels which decreased with distance from the source and were different based upon the molecular weights of the PAHs studied (Moret et al. 2007). Levels of light weight PAHs (fluorene, phenanthrene, anthracene, fluoranthene, pyrene) were reported as 5,679 and 6359.9 µg/kg in olive oil extracted from trees grown 1 and 2 m away from the railroad ties, respectively, but oil extracted from trees 50 m away had total PAH levels of only 41.1 µg/kg, suggesting that the railroad ties were likely the source of PAHs in the olives. Levels of heavy PAHs (benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene,

benzo[a]pyrene, dibenz[a,h]anthracene, benzo[g,h,i]perylene, indeno[1,2,3-cd]pyrene) components were much lower in olive oil extracts. The total concentration of heavy PAHs in olive oil from trees 1 m away was 6.2 µg/kg and decreased to 2.8 µg/kg at 50 m.

5.6 GENERAL POPULATION EXPOSURE

Since coal tar creosote is now a restricted use pesticide, the general population exposure to the PAHs associated with this use is limited to inhalation and dermal contact with potentially finished products. For persons residing near known sources exposures may be greater. Chemical contaminants from wood processing waste were reported in residents and residential homes adjacent to a wood treatment plant that used creosote and PCP to treat wood for over 70 years (Dahlgren et al. 2003, 2007). For a period of time, the plant also burned treated wood products. Analysis of blood samples from 10 residents showed elevated octachlorodibenzo-*p*-dioxin and heptachlorodibenzo-*p*-dioxin, consistent with PCP as the source. Soil sediment and dust samples had higher than background levels of carcinogenic PAHs. The estimated air levels for benzo[a]pyrene and tetrachlorodibenzodioxin were also elevated.

Potential sources of non-occupational human exposure to creosote include contact with creosote-treated wood products (e.g., railroad ties or poles), incineration of creosote-treated scrap lumber, and contact with contaminated environmental media at hazardous waste sites (e.g., ingestion of contaminated ground water). 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). There is also potential for family members of workers from industries manufacturing or using coal tar or creosote products to be unintentionally exposed to the constituents of these mixtures from contaminated items such as worker clothing or footwear.

Risk of exposure to creosote constituents through contact with contaminated ground water 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 the 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 1-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 effect 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. Patients with atopic dermatitis and treated with topical coal tar preparations had increased urinary 1-hydroxypyrene excretion rates (Veenhuis et al. 2002). The urinary 1-hydroxypyrene excretion rate was dependent on the amount of coal tar applied to the skin and the total body area treated, and less on the severity of the atopic dermatitis. 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 Vyskocil 1995). Viau and Vyskocil 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. The general public may also be exposed via dermal or inhalation routes to PAHs or from accidental ingestion of

contaminated dust particles from the use of coal tar-based driveway sealants (Van Metre and Mahler 2010; Van Metre et al. 2012; Williams et al. 2012, 2013).

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. The IPCS CICAD on coal tar creosote summarized levels of components of coal tar creosote in the workplace air of several wood treatment facilities located in the United States, Netherlands, Finland, Sweden, and Germany (IPCS 2004). Potential exposure to coal tar creosote in these plants is minimized by using 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 using highly mechanized processes.

ATSDR performed public health assessment and health consultation activities at four creosote wood treatment sites (ATSDR 2006, 2013, 2016b, 2020). The evaluations identified no public health hazards from exposure to creosote-related contamination in environmental media at the four sites.

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 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°C than at 4°C (Gevao and Jones 1998).

No data from the National Health and Nutrition Examination Survey (NHANES) on blood and urine levels of the entire creosote mixture are available. NHANES does provide data on blood and urine levels

of some components of creosote mixtures, including several naphthalene and other polycyclic hydrocarbons (CDC 2024).

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. Williams et al. (2012) noted that non-dietary intake of PAHs might be considerably higher for children who live in homes that use coal tar-based driveway sealants since young children often put their hands and objects into their mouths, which could include dust containing PAHs from these products.

Occupational exposure to PAHs from coal tar, coal tar creosote, and coal tar pitch are expected to be higher than for the general population. Assennato et al. (2004) reported that PAH concentrations in breathing zone air of coke-oven workers employed at a plant in Taranto, Italy ranged from 20.40 to 76.68 mg/m^3, with a median of 30.00 mg/m^3. The urinary levels of 1-hydroxypyrene samples ranged from 0.01 to 1.32 μmol/mol, with a median of 0.33 μmol/mol in the pre-shift, and from 0.01 to 31.04 μmol/mol, with a median of value of 2.41 μmol/mol, in post-shift. For workers exposed to creosote by chiseling a coal tar pitch layer by hand (one worker) or by handling creosote-impregnated wood (four workers), exposure to total PAHs and 4–6-ring PAHs was 50 times higher for the one 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 4–6-ring PAHs were measured at 440 and 290 μg/m^3, respectively, in the work area of the chiseler. Urinary concentrations of 1-hydroxypyrene were 2–4 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 4–6-ring PAHs were measured for the urinary biomarker 1-naphthol (Heikkilä et al. 1997). The mean post-shift urinary concentration was 20.5 μmol/L; urinary concentrations in occupationally nonexposed male smokers were below the detection limit of 0.07 μmol/L. The study 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.

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. This was done 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 1-hydroxypyrene/mol creatinine was equated with the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) 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. However, 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).

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 pre-shift mean of 1.00 μmol/mol creatinine to a post-shift level of 1.7 μmol/mol creatinine. 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 post-shift urinary excretion levels of 1-hydroxypyrene for coke oven workers were 0.89 and 2.47 μmol/mol creatinine; for asphalt pavers, respective levels were 1.35 and 1.76 μmol/mol creatinine.

Analysis of 319 breathing zone air samples and 31 general air samples indicated that exposures to coal tar pitch volatiles of workers at all jobs in 10 coke facilities surveyed in 1966 exceeded the threshold limit of 0.2 mg/m^3 time-weighted average (TWA) (Fannick et al. 1972).

Exposure to coal tar pitch volatiles (CTPV) has also been reported in aluminum smelter workers in Quebec (Lavoué et al. 2007). Exposures to CTPV were assessed by use of a job-exposure matrix (JEM) and estimated benzene-soluble material and benzo[a]pyrene levels. The JEM incorporated job and time period, including 28,910 jobs, from seven facilities from 1916 to 1999. Estimated exposures were 0.01–

68.08 μg/m^3 benzo[a]pyrene and 0.01–3.64 mg/m^3 benzene-soluble material. The exposures were lowest before 1940 and after 1980.

Air samples and urinary 1-hydroxypyrene in post-shift urine samples and next-day urine samples were analyzed for 36 creosote-exposed wood treatment plant workers (Borak et al. 2002). The results indicate that creosote is absorbed from both inhalation and dermal exposure, but that dermal absorption may be the predominant pathway. Compared to workers who showered following their shift, urinary 1-hydroxypyrene continued to increase in unshowered workers. Determination of volatized PAHs in the breathing zone was more useful than the traditional analysis of benzene soluble fraction of air samples for assessing creosote exposure.

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 coveralls had total pyrene skin contamination of 47–1,510 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 breathing-zone air was measured at 0.3–3.0 μg/m^3. The study 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).

Note that susceptibility of children and other sensitive populations is discussed in Section 3.2.

CHAPTER 6. 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 NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of creosote.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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.

6.1 INFORMATION ON HEALTH EFFECTS

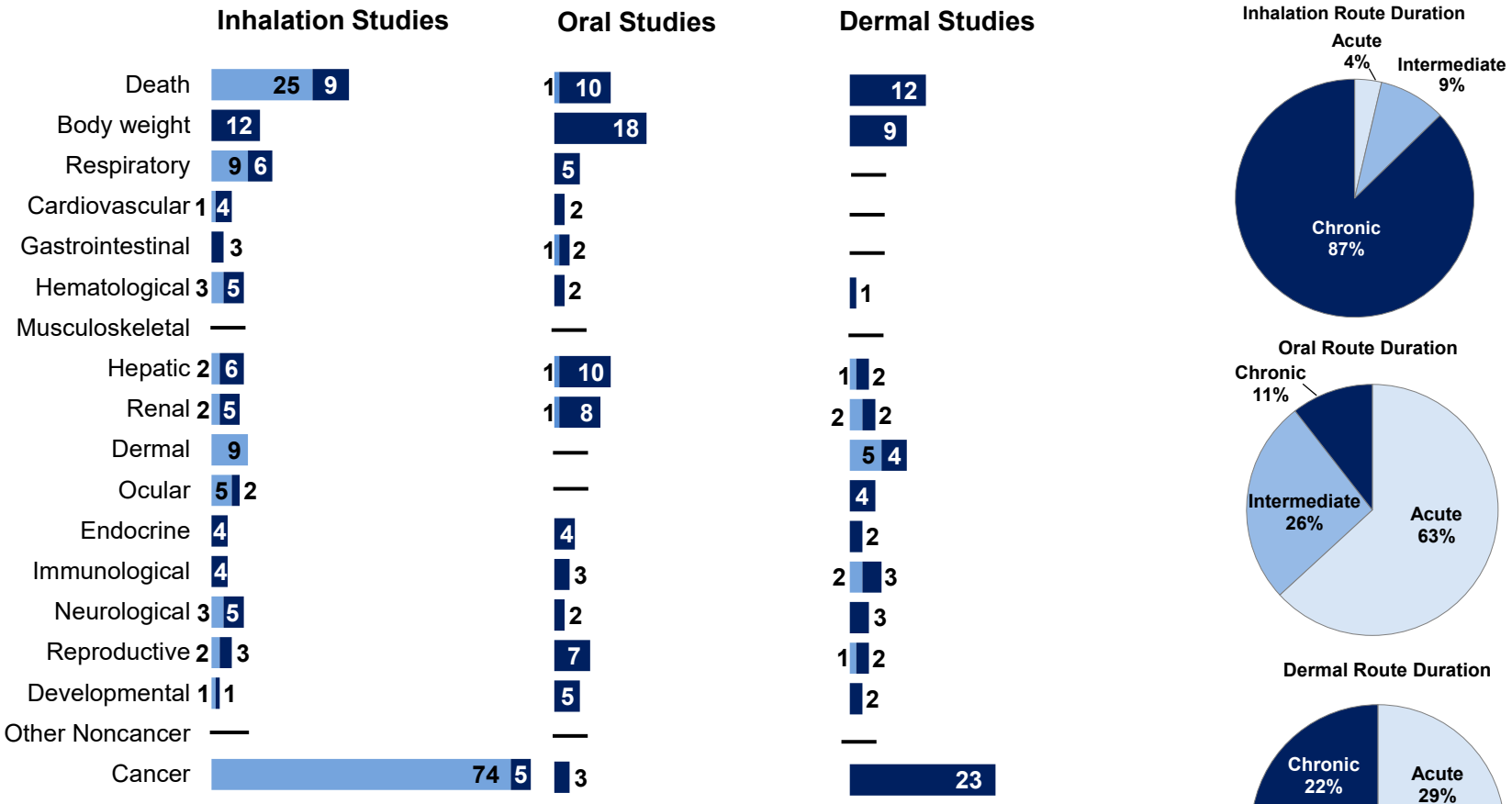
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to coal tar products and wood creosotes that are discussed in Chapter 2 are summarized in Figures 6-1 and 6-2, respectively. The purpose of these figures is to illustrate the information concerning the health effects of creosote. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1 and 6-2 should not 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 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature. The toxic effects that have been found for chemicals within the complex creosote mixtures should be used to direct further research for the complex mixtures. With the variability of creosote mixtures, the relevant receptor mechanisms are multiple.

Figure 6-1. Summary of Existing Health Effects Studies on Creosote (Coal Tar Products) by Route and Endpoint*

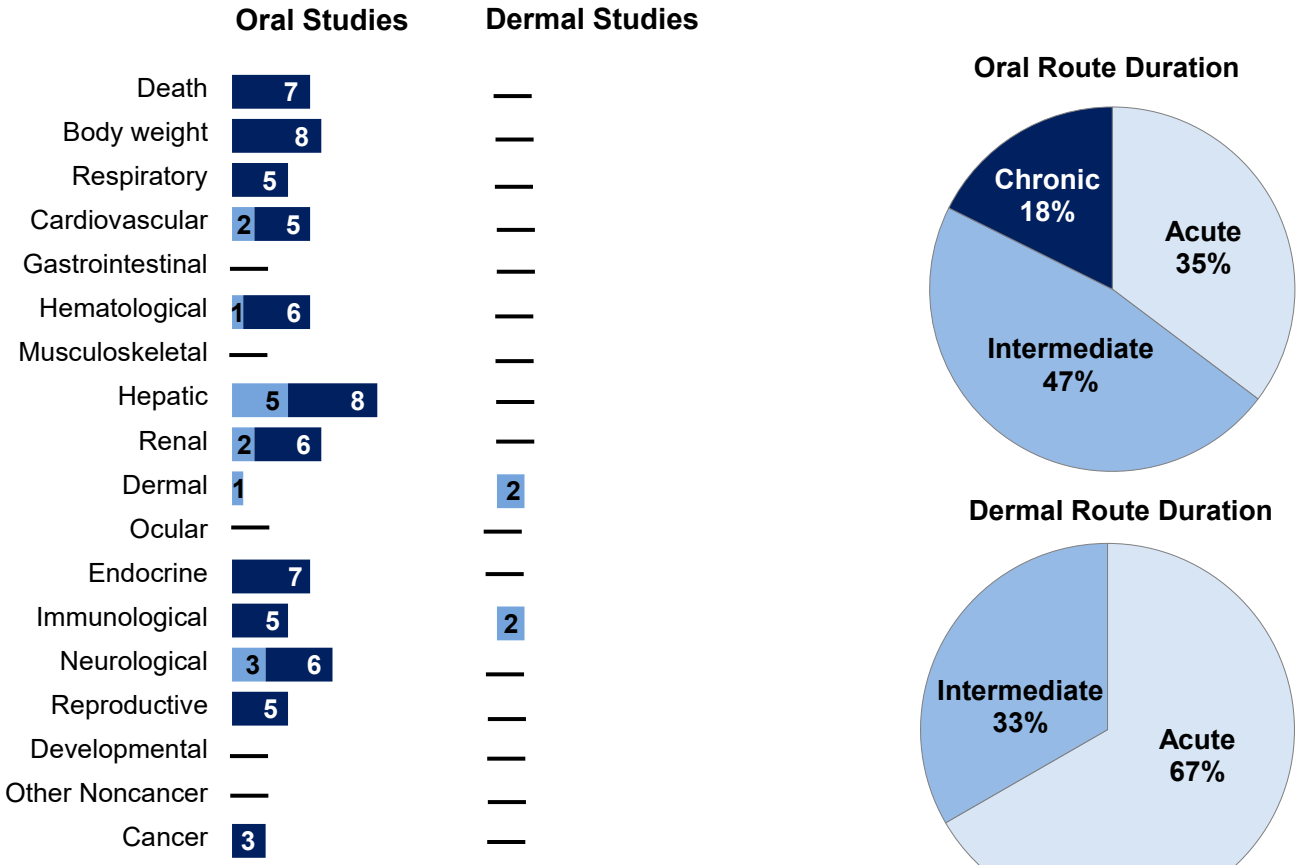
Potential cancer, death, and body weight were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints.

Figure 6-2. Summary of Existing Health Effects Studies on Creosote (Wood Creosotes) by Route and Endpoint*

Potential hepatic, renal, and neurological effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.
Most studies examined multiple endpoints.

MRLs. MRLs for coal tar products and wood creosotes have not been derived for any route or duration of exposure. Coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles and wood creosotes are extremely complex mixtures containing numerous compounds; however, the compositions of the mixtures are not consistent. Even within a class of creosote compounds, the chemical mixtures vary such that adverse effect profiles and potency may vary within a class of creosote compounds. This is demonstrated by inconsistent results observed in studies evaluating the same class of compounds. Therefore, derivation of an MRL based on a single study or group of studies may not be protective for other exposures.

Health Effects.

Reproductive. 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 (ATSDR 1994) and another indicated no increased risk of spontaneous abortion from the use of coal tar as a dermal treatment for psoriasis during pregnancy (Franssen et al. 1999). However, animal studies have shown that exposure to coal tar causes decreased ovary weights (with a loss of luteal tissue) and increased testis weights in mice and rats (Hackett et al. 1984; Springer et al. 1982, 1986b, 1987). An increase in relative testis weight was also observed in rats administered beechwood creosote in the diet for 3 months (Miyazato et al. 1981). No accompanying gross or histopathological lesions of the testes in these animals were observed; therefore, 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. Information on the developmental effects of creosote in humans was not found. Studies in animals have demonstrated serious developmental toxicity for rats and mice exposed to coal tar by all routes, including increases in resorptions and reductions in fetal ossification, crown-rump length, fetal weight, fetal lung weight, and placental weights (Springer et al. 1982), a significant increase in the incidence of cleft palate (Hackett et al. 1984), increased early mortality in pups of treated dams (Springer et al. 1986a), and significant increases in

prenatal mortality in exposed rat and mouse fetuses (Zangar et al. 1989). In many of these studies, it is not possible to exclude the potential role of maternal toxicity in the development of adverse fetal effects. Additional studies on developmental effects, including neurodevelopmental effects, of inhalation, oral, and dermal exposure to coal tar creosote would be important to fully evaluate the developmental toxicity of coal tar creosote. Concerns regarding the contribution of maternal toxicity to developmental effects could be addressed by employing a cross-foster study design. 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.

Immunological. 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 (Leonforte 1986; Smith 1937) and coal tar (Cusano et al. 1992). Animal studies have provided evidence of weight and morphological changes in lymphoreticular tissues following exposure to coal tar (Hackett et al. 1984; Zangar et al. 1989), but no information regarding associated changes in the immune system was identified. The relevance of these findings to human exposure to creosotes is not known. However, these data are suggestive of possible immunotoxic effects. Immunotoxicity studies of coal tar creosote, coal tar, and coal tar pitch by inhalation and dermal routes and studies of wood creosote by inhalation, oral, and dermal routes would fill the data needs for these mixtures.

Neurological. The available information about the possible neurotoxic effects of creosote is very limited, but some signs of neurological involvement in humans and animals following exposure to beechwood creosote and creosote bush (Gordon et al. 1995; Miyazato et al. 1981) and coal tar (Hanlon 1938; NIOSH 1980b) 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 on 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- 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 better characterizing potential neurological effects of coal tar creosote.

Epidemiology and Human Dosimetry Studies. Few controlled epidemiological studies have been conducted in humans on the effects of exposure to coal tar creosote. Epidemiological studies of workers in creosote treatment plants accompanied by accurate occupational exposure data would be useful to 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 occupational studies in the wood-preserving and construction industries (Karlehagen et al. 1992; Kerr et al. 2000; Persson et al. 1989; Stern et al. 2000). Limitations inherent in these studies include unknown 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. Only one epidemiological study of people living near a coal tar creosote-contaminated area was found in the literature (ATSDR 1994). Additional well-controlled epidemiological studies of people with documented exposure to creosote, living near areas where coal tar creosote has been detected in surface water 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. Health effects that should be examined in future studies include cancer, developmental, reproductive, immunotoxic, and neurotoxic effects as well as adverse noncancer dermal effects.

Biomarkers of Exposure and Effect. No method is currently available to measure the parent creosote mixture in human tissues or fluids. However, 1-hydroxypyrene, the metabolite of pyrene, a component of the creosote mixture, can be measured in the urine of exposed individuals following relatively high-level exposures of acute- and chronic-duration (Bos and Jongeneelen 1988; Jongeneelen et al. 1985, 1988). The identification of PAH metabolites in urine could potentially 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 cannot always be attributed to creosote exposure alone. 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.

The formation of benzo[a]pyrene-DNA adducts has been demonstrated (Pavanello and Levis 1992; Zhang et al. 1990) 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 unique to 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 creosote components, the PAHs. For more information on the toxicokinetics of PAHs, please refer to the ATSDR toxicological profile for polycyclic aromatic hydrocarbons (ATSDR 1995).

Absorption of creosote occurs following all routes of exposure. The presence of creosote components in tissues and the presence of metabolites in urine are 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. Specific kinetic aspects of individual components of coal tar products have been described. 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.

PBPK Models. 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.

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 that compare the effects of creosote exposure on animals of different ages would provide information on the comparative susceptibility of young and adult individuals.

Physical and Chemical Properties. Limited physical property data, such as boiling point and density (see Table 4-2), 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 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 type of 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.

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. There is a data need to capture airborne levels of individual constituents of these mixtures and report the levels in both the vapor and particulate phases. 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 higher molecular weight 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 lower molecular weight 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. 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 (ATSDR 1995; Gile et al. 1982), whereas bioconcentration in aquatic organisms from contaminated surface waters has been demonstrated (Jonsson et al. 2004). 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 high molecular weight 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 can rapidly metabolize and eliminate PAHs, the major constituents of the commercial mixture (FWS 1987). However, the marsh clam, *Rungia cuneata*, which is a major food item for crustaceans such as the blue crab 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 a 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. Monitoring data typically consist of levels of well-known PAHs in air, water, soil, and sediment near coal tar or coal tar creosote sources. Limited information is available regarding ambient concentrations of creosote-derived PAHs in air (Chen et al. 2002; IPCS 2004). Monitoring data at facilities that use coal tar creosote have shown high levels of PAHs in soil, sediment, groundwater, and surface water (Davis et al. 1993; DeLeon et al. 1988; EPA 1988b, 2017a; IPCS 2004).

Monitoring data for the levels of creosote in contaminated media at hazardous waste sites should be continued.

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 and/or near railroad ties. 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, bridges, 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.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding creosote in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. Note that no MRLs have been derived for creosote (see Section 1.3 and Appendix A for detailed information).

Table 7-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, Coal Tar Pitch Volatiles, and Wood Creosote

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not assessed	IRIS 1988
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009b
	RfD	Not assessed	IRIS 1988
WHO	Drinking water quality guidelines	Not listed[a]	WHO 2022
FDA	Food and drugs regulations		
	Beechwood creosote	Allowed under synthetic flavoring substances and adjuvants regulation	FDA 2023a
	Coal tar 0.5–5%	Allowed as active ingredient for the control of dandruff, seborrheic dermatitis, and psoriasis	FDA 2023d
	Any over-the-counter drug product introduced after the dates specified that is labeled, represented, or promoted for the uses specified is regarded as a new drug for which an approved new drug application is required for marketing		FDA 2023b
	Beechwood creosote (1990)	Expectorant drug products	
	Beechwood creosote and creosote (1993)	Poison ivy, oak, and sumac drug products	
	Beechwood creosote,	Nasal decongestant drug	

Table 7-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, Coal Tar Pitch Volatiles, and Wood Creosote

Agency	Description	Information	Reference
	oral (1991) and topical (1995)	products	
	Coal tar (1991)	Topical acne drug products and diaper rash drug products	
	Drugs, recommended warning and caution statements		FDA 2023c
	Creosote in preparations for external use	Caution: do not apply to large areas of the body	
	Creosote in douche preparations	The use of solutions stronger than those recommended may result in severe local irritation, burns, or serious poisoning. Do not use more often than twice weekly unless directed by physician	
	Cancer		
HHS	Carcinogenicity classification		NTP 2021
	Coal tars and coal-tar pitches	Known to be human carcinogens	
EPA	Carcinogenicity classification		IRIS 1988
	Creosote	B1[b]	
IARC	Carcinogenicity classification		
	Creosotes	Group 2A[c]	IARC 2010
	Occupational exposures during coal tar distillation	Group 1[d]	IARC 2012a
	Coal tar pitch	Group 1[d]	IARC 2012b
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		OSHA 2021a, 2021b, 2021c
	Coal-tar pitch volatiles (benzene-soluble fraction)	0.2 mg/m^3	
NIOSH	REL (up to 10-hour TWA)		
	Coal-tar pitch volatiles (cyclohexane-extractable fraction)	0.1 mg/m^3 [e]	NIOSH 1977, 2018
	IDLH	80 mg/m^3 [e]	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2018a
	Creosote (coal tar)		
	PAC-1[f]	0.6 mg/m^3	
	PAC-2[f]	120 mg/m^3	
	PAC-3[f]	700 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, Coal Tar Pitch Volatiles, and Wood Creosote

Agency	Description	Information	Reference
	Coal tar pitch volatiles		
	PAC-1[f]	0.6 mg/m^3	
	PAC-2[f]	120 mg/m^3	
	PAC-3[f]	700 mg/m^3	
	Coal tar, aerosol		
	PAC-1[f]	2.8 mg/m^3	
	PAC-2[f]	31 mg/m^3	
	PAC-3[f]	190 mg/m^3	

[a]In relation to benzo[a]pyrene drinking-water contamination, it is recommended that coal tar-based pipe linings and coatings on storage tanks be discontinued.
[b]B1: probable human carcinogen (limited evidence of carcinogenicity from epidemiological studies) based on EPA's 1986 cancer guidelines.
[c]Group 2A: probably carcinogenic to humans.
[d]Group 1: carcinogenic to humans.
[e]Potential occupational carcinogen.
[f]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs for creosote, including wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, cannot be determined because available data are insufficient for exposures of all durations (acute, intermediate, chronic) via any route (inhalation, oral, dermal). 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 could be as many as 10,000 other chemicals present in the mixture. Creosote derived from plants is composed of various organic compounds including phenols, cresols, and guaiacol. Additionally, wood creosote and coal tar product mixtures have highly variable compositions and the individual components do not always share the same mode of action. The mixtures' composition is dependent on the sources and preparation parameters of coal tar 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, is most likely inadequate for extrapolation to other creosote samples, unless their compositions are similar.

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

This profile addresses the toxicological database for several creosote mixtures: wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. These mixtures are composed of many individual compounds of varying physical and chemical characteristics and differ from each other with respect to their composition.

Coal tars are byproducts of the carbonization of coal to produce coke or natural gas. They are complex combinations of PAHs, phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. Coal tar creosotes are distillation products of coal tar. 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 contains PAHs and their methyl and polymethyl derivatives, as well as heteronuclear compounds (AWPA 1988). 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; Rønneberg 1995; Rønneberg and Anderson 1995). Coal tar

creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants (EPA 1981a, 1984).

Wood creosotes are derived from beechwood (Fagus, referred as beechwood creosote) and the resin from leaves of the creosote bush (Larrea, referred as creosote bush resin). Wood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol. Creosote bush resin consists of phenolic (e.g., flavonoids and nordihydroguaiaretic acid), neutral (e.g., waxes), basic (e.g., alkaloids), and acidic (e.g., phenolic acids) compounds. 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).

Although wood creosote and coal tar creosote have some components in common, such as phenols, the differences in composition are pronounced enough to assume with reasonable certainty that they will have different toxicological properties. For the purposes of this profile, the creosote mixtures have been grouped into coal tar products (coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles) and wood creosotes (creosote bush and beechwood creosote).

Rationale for Not Deriving an MRL: When evaluating health effect data for creosote, it is important to consider that the composition of a particular creosote mixture, although referred to by specific name (e.g., wood creosote or coal tar creosote), is not consistent because 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. 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 could be as many as 10,000 other chemicals present in the mixture. Creosote derived from plants is composed of various organic compounds including phenols, cresols, and guaiacol. Additionally, wood creosote and coal tar product mixtures have highly variable compositions and the individual components do not always share the same mode of action. The mixtures' composition is dependent on the sources and preparation parameters of coal tar creosote and, as a result, the creosote components are rarely consistent in their type and concentration. Thus, comparisons across studies are problematic, as toxicological evaluations of one creosote sample, for instance, is most likely inadequate for extrapolation to other creosote samples, unless their compositions are similar. This is demonstrated by inconsistent results observed in studies evaluating the same class of compounds; a single LOAEL value may not be representative for a class of compounds. Thus, derivation of an MRL based on single study or group of studies may not be protective for other exposures. Therefore, ATSDR elected not to derive MRLs for creosote, including wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CREOSOTE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to creosote.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for creosote. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of creosote have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of creosote are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for Creosote released for public comment in 2023; thus, the literature search was restricted to studies published between November 2020 and November 2023. The following main databases were searched in November 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for creosote. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to creosote were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
11/2023	(("Creosote"[mh] OR "Coal Tar"[mh] OR 8021-39-4[rn] OR 8007-45-2[rn] OR 8001-58-9[rn] OR 65996-93-2[rn]) AND 2020/11/01:3000[mhda]) OR (("alquitran, hulla"[tw] OR "AquaTar"[tw] OR "Brick oil"[tw] OR "Carbo-cort"[tw] OR "Coal tar"[tw] OR "Coal tars"[tw] OR "Coke-oven tar"[tw] OR "Coking tar"[tw] OR "Creosote"[tw] OR "Creosotes"[tw] OR "Creosotum"[tw] OR "Fototar"[tw] OR "Impervotar"[tw] OR "Ionil-T"[tw] OR "KC 261"[tw] OR "KOHLENTEER"[tw] OR "Lavatar"[tw] OR "Liquid pitch oil"[tw] OR "Naphthalene oil"[tw] OR "Oil pitch"[tw] OR "Particulate polycyclic aromatic hydrocarbons"[tw] OR "Picis carbonis"[tw] OR "Pitch, coal tar"[tw] OR "Pixalbol"[tw] OR "Polytar bath"[tw] OR "Preserv-O-sote"[tw] OR "Sakresote 100"[tw] OR "STEINKOHLENTEER"[tw] OR "TAR LIQUID"[tw] OR "Tar, coal"[tw] OR "Tar, coking"[tw] OR "Tarcron 180"[tw] OR "Tarcron 180L"[tw] OR "Tarcron 230"[tw] OR "Teer, Kohlen-"[tw] OR "Vanseb-T"[tw] OR "Wash oil"[tw] OR "Zetar"[tw] OR ("PPAH"[tw] AND (particl* OR particul* OR hydrocarbon*)) OR "tar distillates"[tw] OR "Tar oil"[tw] OR "Tar oils"[tw] OR "Wood tar"[tw]) AND (2020/11/01:3000[edat] OR 2020/11/01:3000[crdat]))
NTRL	
11/2023	Date Published 2020 to 2023 Searched in Title or Keyword "alquitran, hulla" OR "AquaTar" OR "Brick oil" OR "Carbo-cort" OR "Coal tar" OR "Coal tars" OR "Coke-oven tar" OR "Coking tar" OR "Creosote" OR "Creosotes" OR "Creosotum" OR "Fototar" OR "Impervotar" OR "Ionil-T" OR "KC 261" OR "KOHLENTEER" OR "Lavatar" OR "Liquid pitch oil" OR "Naphthalene oil" OR "Oil pitch" OR "Particulate polycyclic aromatic hydrocarbons" OR "Picis carbonis" OR "Pitch, coal tar" OR "Pixalbol" OR "Polytar bath" OR "Preserv-O-sote" OR "Sakresote 100" OR "STEINKOHLENTEER" OR "TAR LIQUID" OR "Tar, coal" OR "Tar, coking" OR "Tarcron 180" OR "Tarcron 180L" OR "Tarcron 230" OR "Teer, Kohlen-" OR "Vanseb-T" OR "Wash oil" OR "Zetar" OR "PPAH" OR "tar distillates" OR "Tar oil" OR "Tar oils" OR "Wood tar"
Toxcenter	
11/2023	FILE 'TOXCENTER' ENTERED AT 13:52:12 ON 17 NOV 2023 CHARGED TO COST=EH038.09.02.LB.05 L1 1340 SEA FILE=TOXCENTER 8021-39-4 OR 8007-45-2 OR 8001-58-9 OR 65996-93-2 L2 8855 SEA FILE=TOXCENTER "ALQUITRAN, HULLA" OR "AQUATAR" OR "BRICK OIL" OR "CARBO-CORT" OR "COAL TAR" OR "COAL TARS" OR "COKE-OVEN

Table B-2. Database Query Strings

Database search date	Query string
	TAR" OR "COKING TAR" OR "CREOSOTE" OR "CREOSOTES" OR "CREOSOTU M" OR "FOTOTAR" OR "IMPERVOTAR" OR "IONIL-T" OR "KC 261" OR "KOHLENTEER" OR "LAVATAR" L3 325 SEA FILE=TOXCENTER "LIQUID PITCH OIL" OR "NAPHTHALENE OIL" OR "OIL PITCH" OR "PARTICULATE POLYCYCLIC AROMATIC HYDROCARBONS" OR "PICIS CARBONIS" OR "PITCH, COAL TAR" OR "PIXALBOL" OR "POLYTAR BATH" OR "PRESERV-O-SOTE" OR "SAKRESOTE 100" OR "STEINKOHLENTEER" L4 237 SEA FILE=TOXCENTER "TAR LIQUID" OR "TAR, COAL" OR "TAR, COKING" OR "TARCRON 180" OR "TARCRON 180L" OR "TARCRON 230" OR "TEER, KOHLEN-" OR "VANSEB-T" OR "WASH OIL" OR "ZETAR" L5 81 SEA FILE=TOXCENTER PPAH AND (PARTICL? OR PARTICUL? OR HYDROCARB ON?) L6 1069 SEA FILE=TOXCENTER "TAR OIL" OR "TAR OILS" OR "WOOD TAR" OR "TAR DISTILLATES" L7 10202 SEA FILE=TOXCENTER L1 OR L2 OR L3 OR L4 OR L5 OR L6 L8 8288 SEA FILE=TOXCENTER L7 NOT PATENT/DT L9 411 SEA FILE=TOXCENTER L8 AND ED>20201031 ACTIVATE TOXQUERY/Q --------- L10 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L11 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L12 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L13 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L14 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L15 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L16 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L17 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L18 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L19 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L20 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L21 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L22 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L23 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L24 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L25 QUE (ENDOCRIN? AND DISRUPT?)
	L26 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L27 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L28 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L29 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L30 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L31 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L32 QUE (NEPHROTOX? OR HEPATOTOX?)
	L33 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L34 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L35 QUE L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34
	L36 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L37 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L38 QUE L35 OR L36 OR L37
	L39 QUE (NONHUMAN MAMMALS)/ORGN
	L40 QUE L38 OR L39
	L41 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L42 QUE L40 OR L41

	L43 234 SEA FILE=TOXCENTER L9 AND L42
	L44 70 SEA FILE=TOXCENTER L43 AND MEDLINE/FS
	L45 164 SEA FILE=TOXCENTER L43 NOT MEDLINE/FS
	L46 184 DUP REM L44 L45 (50 DUPLICATES REMOVED)
	L*** DEL 70 S L43 AND MEDLINE/FS
	L*** DEL 70 S L43 AND MEDLINE/FS
	L47 70 SEA FILE=TOXCENTER L46
	L*** DEL 164 S L43 NOT MEDLINE/FS
	L*** DEL 164 S L43 NOT MEDLINE/FS
	L48 114 SEA FILE=TOXCENTER L46
	L49 114 SEA FILE=TOXCENTER (L47 OR L48) NOT MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	D SCAN L49

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2023	Compounds searched: 8021-39-4; 8007-45-2; 8001-58-9; 65996-93-2
NTP	
11/2023	Limited to 2020-present or ROC/Testing Status/CEBS "Creosote" "Creosotes" "Coal tar" "Coal tars" "8021-39-4" "8007-45-2" "8001-58-9" "65996-93-2" "alquitran, hulla" "AquaTar" "AWPA 1" "Brick oil" "Carbo-cort" "Coke-oven tar" "Coking tar" "Creosotum" "Fototar" "Impervotar" "Ionil-T" "KC 261" "KOHLENTEER" "Lavatar" "Liquid pitch oil" "Naphthalene oil" "Oil pitch" "Particulate polycyclic aromatic hydrocarbons" "Picis carbonis" "Pitch, coal tar" "Pixalbol" "Polytar bath" "Preserv-O-sote" "Sakresote 100" "STEINKOHLENTEER" "TAR LIQUID" "Tar, coal" "Tar, coking" "Tarcron 180" "Tarcron 180L" "Tarcron 230" "Teer, Kohlen-" "Vanseb-T" "Wash oil" "Zetar" "PPAH" "Tar oil" "Tar oils" "Wood tar" "tar distillates"
Regulations.gov	
11/2023	Limited to posted date 11/1/2020-present; Dockets/Notices "8021-39-4" "8007-45-2" "8001-58-9" "65996-93-2" creosote "coal tar"
NPIRS	
11/2023	Limited to submission date 01/01/2020-11/17/2023 Active Ingredient: Creosote, wood (CAS #: 8021-39-4) (PC Code: 25002), Coal tar (CAS #: 8007-45-2) (PC Code: 22003), Coal tar creosote (CAS #: 8001-58-9) (PC Code: 25004), Coal Tar Pitch >351 deg.C (AWPI) (CAS #: 65996-93-2) (PC Code: 128939)
NIH RePORTER	
02/2024	Search Criteria: Fiscal Year: Active Projects; Text Search: "alquitran, hulla" OR "AquaTar" OR "Brick oil" OR "Carbo-cort" OR "Coal tar" OR "Coal tars" OR "Coke-oven tar" OR "Coking tar" OR "Creosote" OR "Creosotes" OR "Creosotum" OR "Fototar" OR "Impervotar" OR "Ionil-T" OR "KC 261" OR "KOHLENTEER" OR "Lavatar" OR "Liquid pitch oil" OR "Naphthalene oil" OR "Oil pitch" OR "Particulate polycyclic aromatic hydrocarbons" OR "Picis carbonis" OR "Pitch, coal tar" OR "Pixalbol" OR "Polytar bath" OR "Preserv-O-sote" OR "Sakresote 100" OR "STEINKOHLENTEER" OR "TAR LIQUID" OR "Tar, coal" OR "Tar, coking" OR "Tarcron 180" OR "Tarcron 180L" OR "Tarcron 230" OR "Teer, Kohlen-" OR "Vanseb-T"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	OR "Wash oil" OR "Zetar" OR "PPAH" OR "tar distillates" OR "Tar oil" OR "Tar oils" OR "Wood tar" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 339
- Number of records identified from other strategies: 38
- Total number of records to undergo literature screening: 377

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on creosote:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

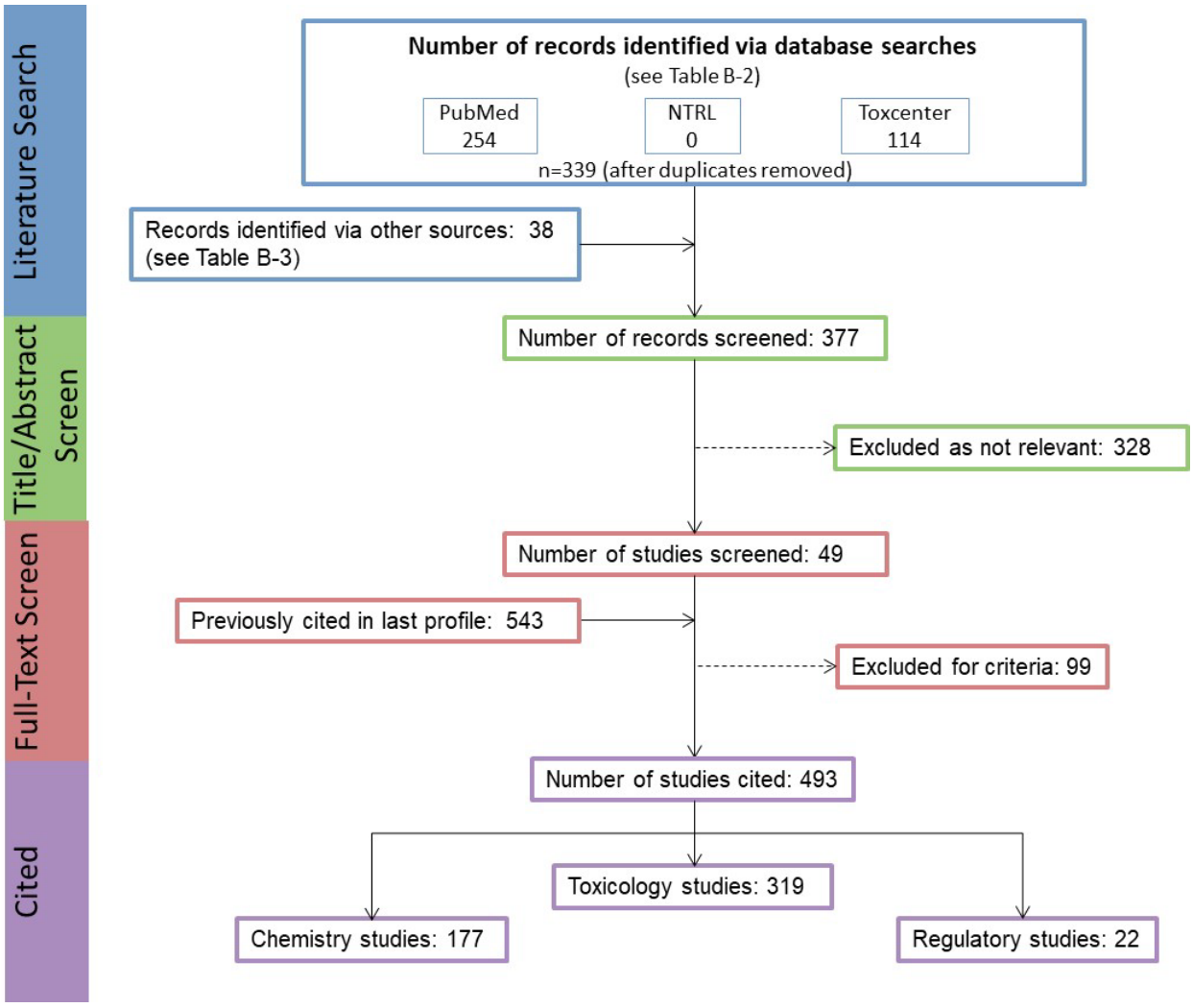
- Number of titles and abstracts screened: 377
- Number of studies considered relevant and moved to the next step: 49

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 49
- Number of studies cited in the pre-public draft of the toxicological profile: 543
- Total number of studies cited in the profile: 493

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. November 2023 Literature Search Results and Screen for Creosote



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR CREOSOTE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to creosote, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to creosote:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to creosote. The inclusion criteria used to identify relevant studies examining the health effects of creosote are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

As noted in Appendix B, the current literature search was intended to update the Draft Toxicological Profile for Creosote released for public comment in 2023; thus, the literature search was restricted to studies published between November 2000 and November 2023. See Appendix B for the databases searched and the search strategy.

A total of 377 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.1 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of creosote.

Title and Abstract Screen. In the Title and Abstract Screen step, 377 records were reviewed; there were no new documents that were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 155 health effect documents (documents cited in older versions of the profile) was performed. From those 155 documents, 193 studies were considered for inclusion in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted from Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Creosote and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, 2-3, and 2-4, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for coal tar products and wood creosotes identified in human and animal studies are presented in Tables C-3, C-4, C-5, and C-6 respectively. The available human studies are focused mainly on mortality and cancer following occupational exposure. Additional studies have reported respiratory, dermal, and hepatic effects. Animal studies have examined a number of endpoints following inhalation, oral, or dermal exposure, including cancer, and have reported body weight, respiratory, hematological, hepatic, reproductive, and developmental effects.

Studies were not carried through the systematic review process due to the complicated nature of creosote products. Coal tars products are complex mixtures of PAHs, phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. Wood creosotes are derived from beechwood and the resin from leaves of the creosote bush. Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol, while creosote bush resin consists of phenolic (e.g., flavonoids and nordihydroguaiaretic acid), neutral (e.g., waxes), basic (e.g., alkaloids), and acidic (e.g., phenolic acids) compounds.

When evaluating health effect data for creosote, it is important to consider the composition of a particular creosote mixture. Wood creosote and coal tar product mixtures have highly variable compositions and

the individual components do not always share the same mode of action. The mixtures' composition is dependent on the sources and preparation parameters of coal tar creosote and, as a result, the creosote components are rarely consistent in their type and concentration. Thus, comparisons across studies are problematic, as toxicological evaluations of one creosote sample, for instance, is most likely inadequate for extrapolation to other creosote samples, unless their compositions are similar. This is demonstrated by inconsistent results observed in studies evaluating the same class of compounds; a single LOAEL value may not be representative for a class of compounds.

Therefore, ATSDR elected not to take the identified studies through the systematic review process for creosote, including wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Creosote (Coal Tar Products) Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		2							2	3							61
		2							2	3							41
Case control																	8
																	4
Population																	2
																	2
Case series		1						1	3	1			2				
		1						1	3	1			2				
Cross sectional		5	1		3		2	1	4	1			1	2	1		3
		5	1		3		0	1	4	1			1	0	0		2
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series				1			1	1									
				1			1	1									
Dermal studies																	
Cohort														1			
														0			
Case control																	
Population																	
Case series									3			1					
									3			1					
Clinical trial							1	1	2			1					
							0	0	2			1					
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

APPENDIX C

Table C-4. Overview of the Health Outcomes for Creosote (Coal Tar Products) Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	3	1					1	1			1	1	2		1		
	1	0					0	0			0	0	2		1		
Intermediate-duration	7	5	4	3	5		5	4		2	3	3	3	3			3
	4	5	1	2	5		4	2		0	0	2	0	3			3
Chronic-duration	2																2
	1																2
Oral studies																	
Acute-duration	11	1					6	4			2	1	2	5	5		
	4	0					0	2			0	0	2	0	5		
Intermediate-duration	5	2	2	4	2		2	2			2	2		2			1
	0	0	0	2	0		0	0			0	0		0			1
Chronic-duration	2	2					2	2									2
	0	0					2	0									2
Dermal studies																	
Acute-duration	4						2	2	2	3	2	2	3	2	2		
	2						0	0	2	3	0	0	0	0	2		
Intermediate-duration	4				1				1	1							15
	0				0				0	0							13
Chronic-duration	1								1			1					7
	0								1			1					7

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

APPENDIX C

Table C-5. Overview of the Health Outcomes for Creosote (Wood Creosotes) Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series					1 1		4 4	2 1	1 1				1 1				
Clinical trial			2 0				1 0						2 2				
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series									2 2			2 2					
Clinical trial								1 0	1 0								

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

APPENDIX C

Table C-6. Overview of the Health Outcomes for Creosote (Wood Creosotes) Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	2 0						2 0				2 0		2 2				
Intermediate-duration	3 0	2 0	2 0		3 0		3 1	3 0			2 0	2 0	2 0	2 0			
Chronic-duration	3 2	3 1	3 1		3 0		3 1	3 1			3 0	3 0	2 0	3 0			3 0
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives 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.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive 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 no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a more

complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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 chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints 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) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

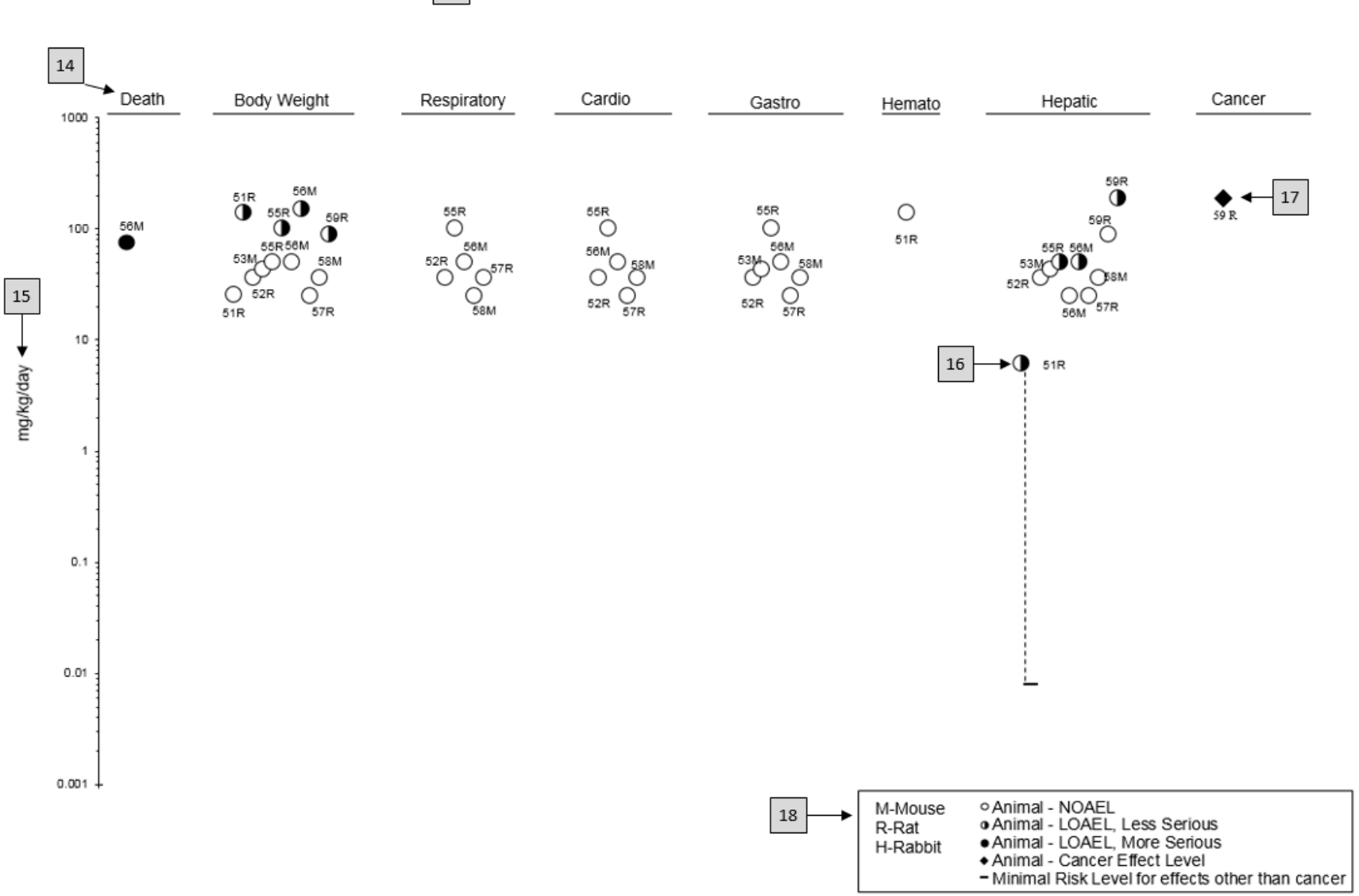
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

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

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. 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 may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/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 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to 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, 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 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) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

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, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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 response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—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.

Excretion—The process by which metabolic waste products are removed from the body.

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.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that 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.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the 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, which are changes 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 hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level 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. Although effects may be produced at this exposure level, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. 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—A type of physiologically based dose-response model that is 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, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air 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 a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is 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 oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound 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 hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result