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).

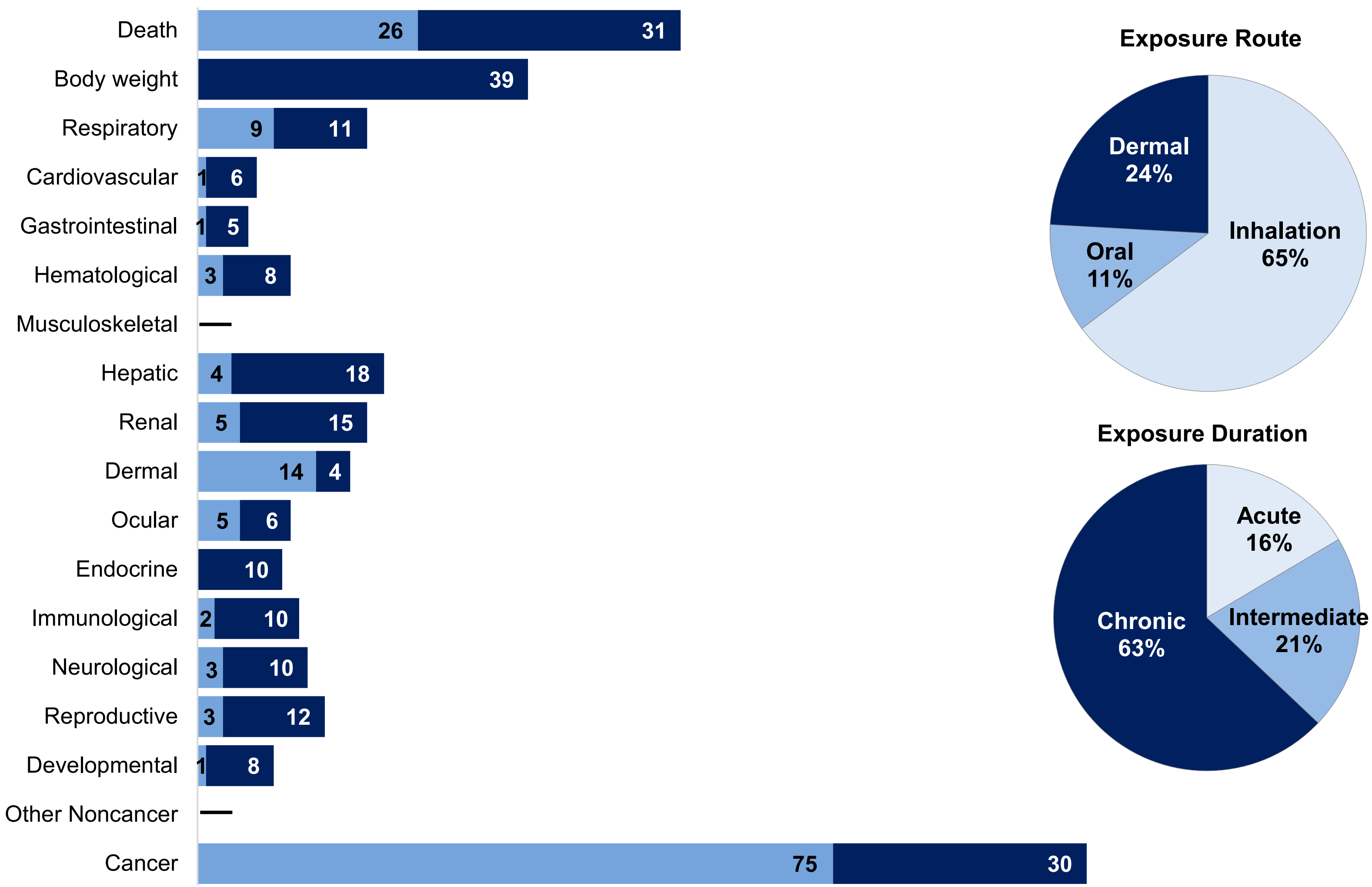
- **Hepatic effects (wood creosotes).** Human case reports of intermediate-duration exposure to wood creosotes have identified the potential of hepatic effects including jaundice and changes in liver enzymes and histopathology. Animal studies have shown mixed results on the hepatic effects of creosote,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

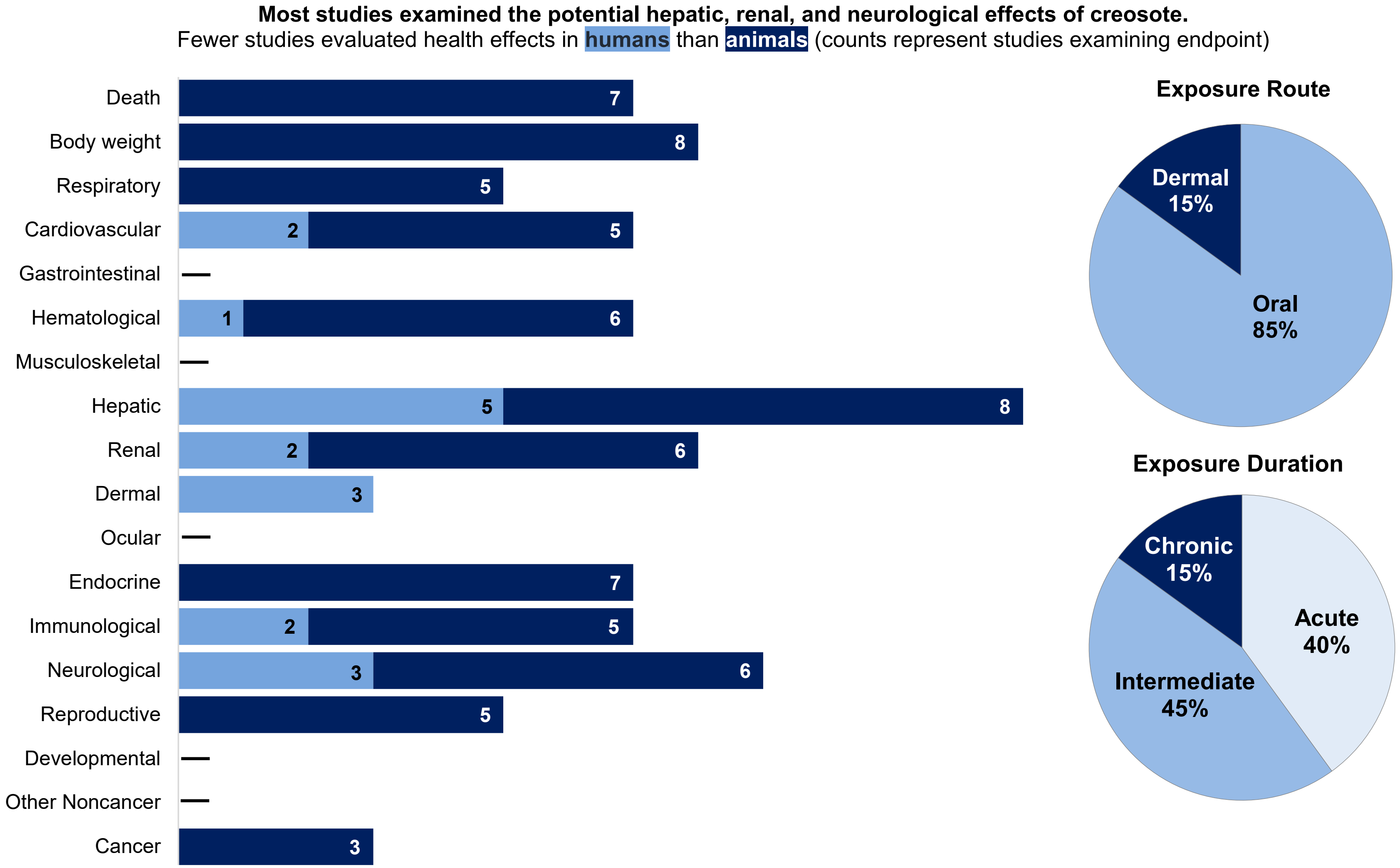
Figure 2-1. Overview of the Number of Studies Examining Creosote (Coal Tar Products) Health Effects*

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*



*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 140 M	 690 M		Increased relative kidney weight, pelvic epithelial hyperplasia
					Endocr	690			
					Immuno	140	690		Decreased relative thymus weight, thymus atrophy
					Neuro	690			
					Repro	140 F 690 M	690 F		Decreased luteal tissue in the ovary
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 30 M	690 F 140 M		Increased relative kidney weight, pelvic epithelial hyperplasia, and pigmentation of cortical tubules

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 M	690 F		Decreased relative weight, decreased luteal tissue in the ovary
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/m³)

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)

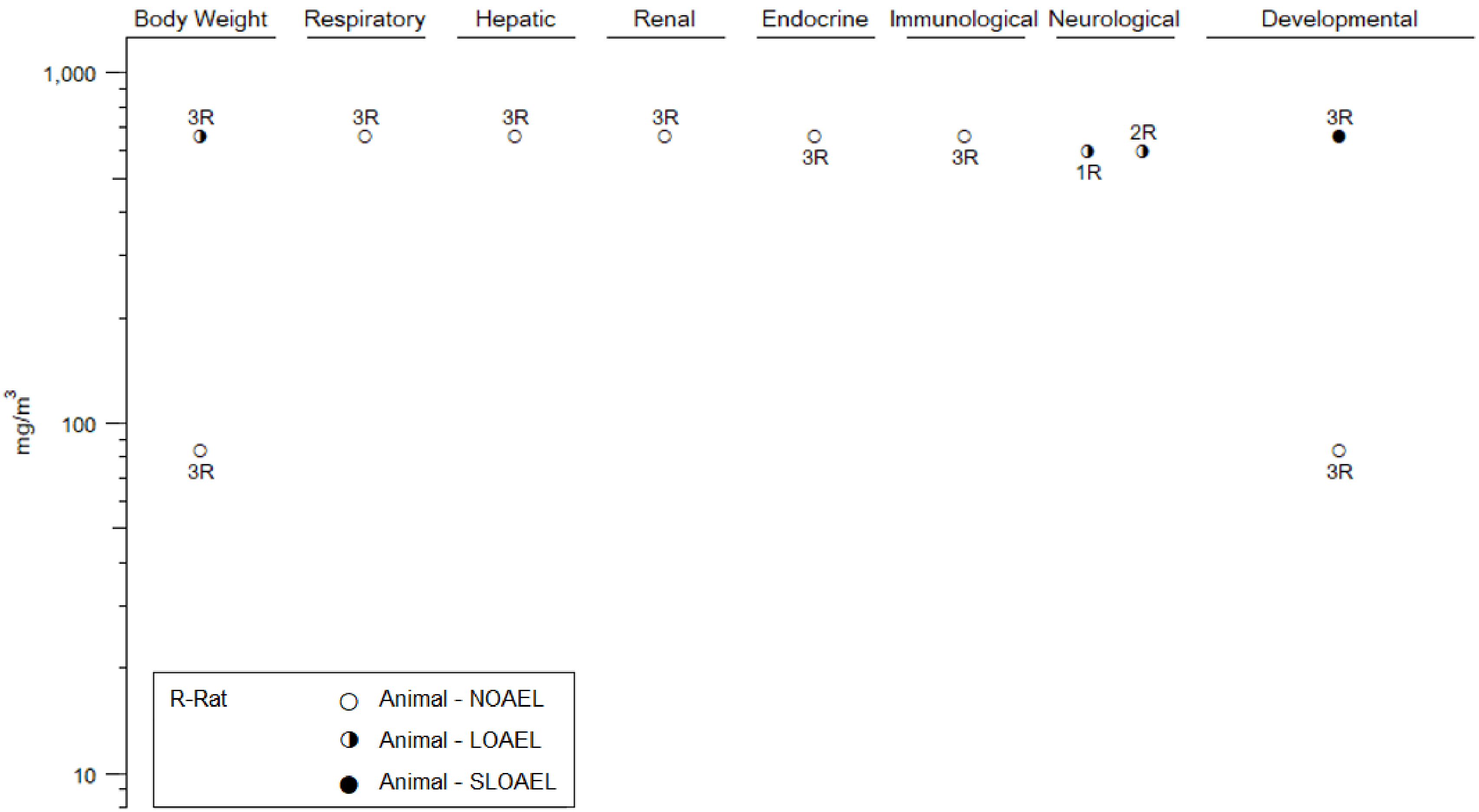


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

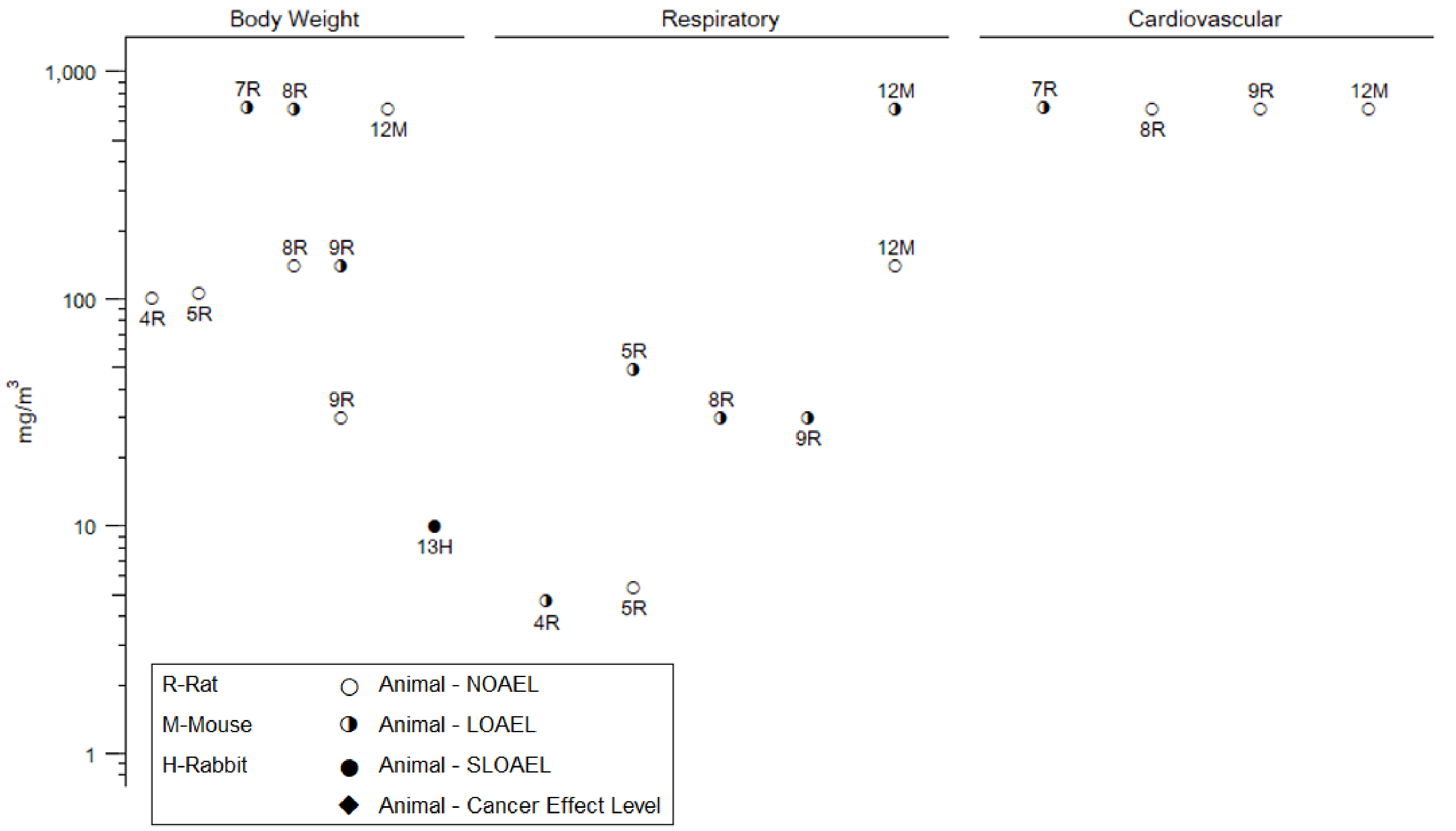


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

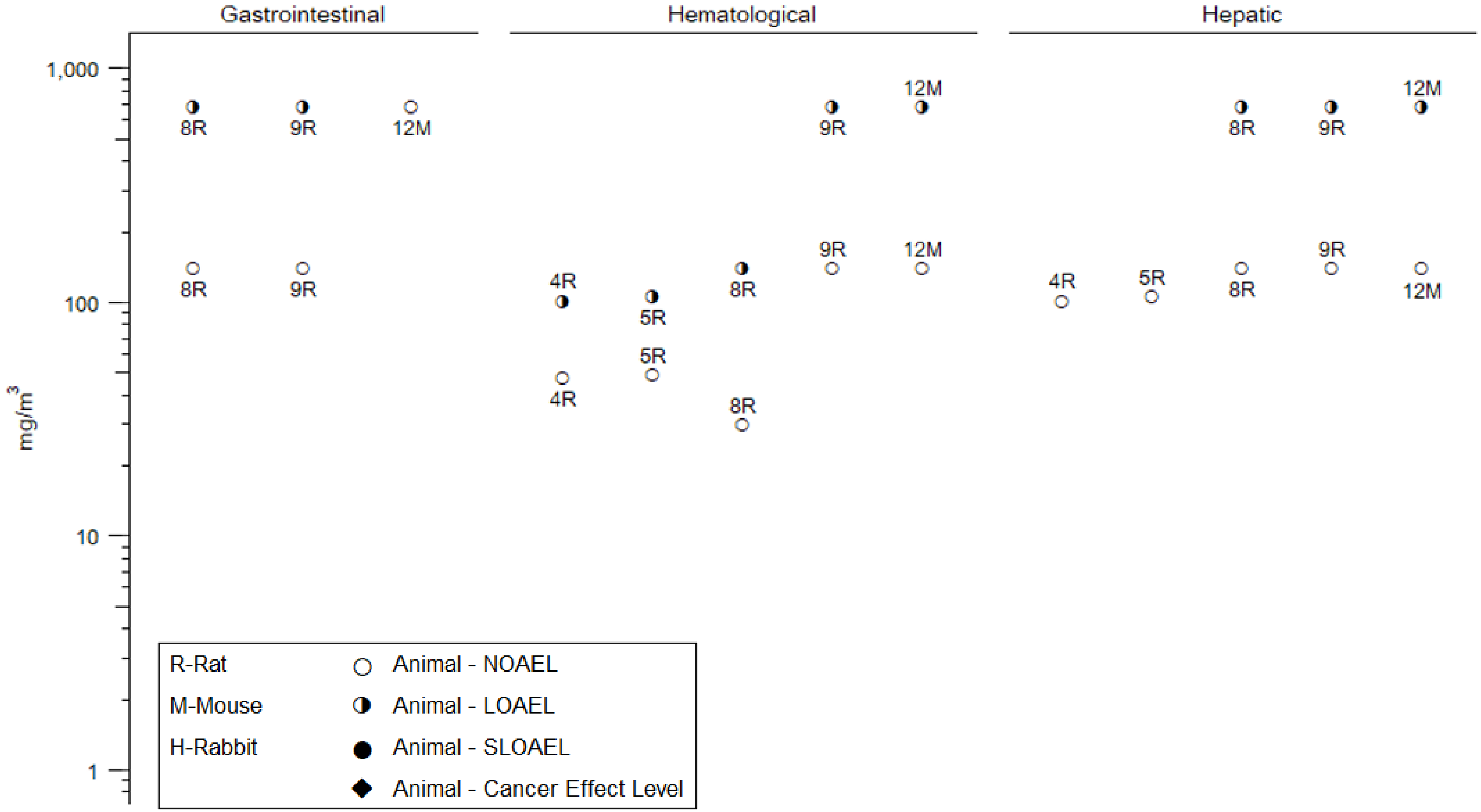


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

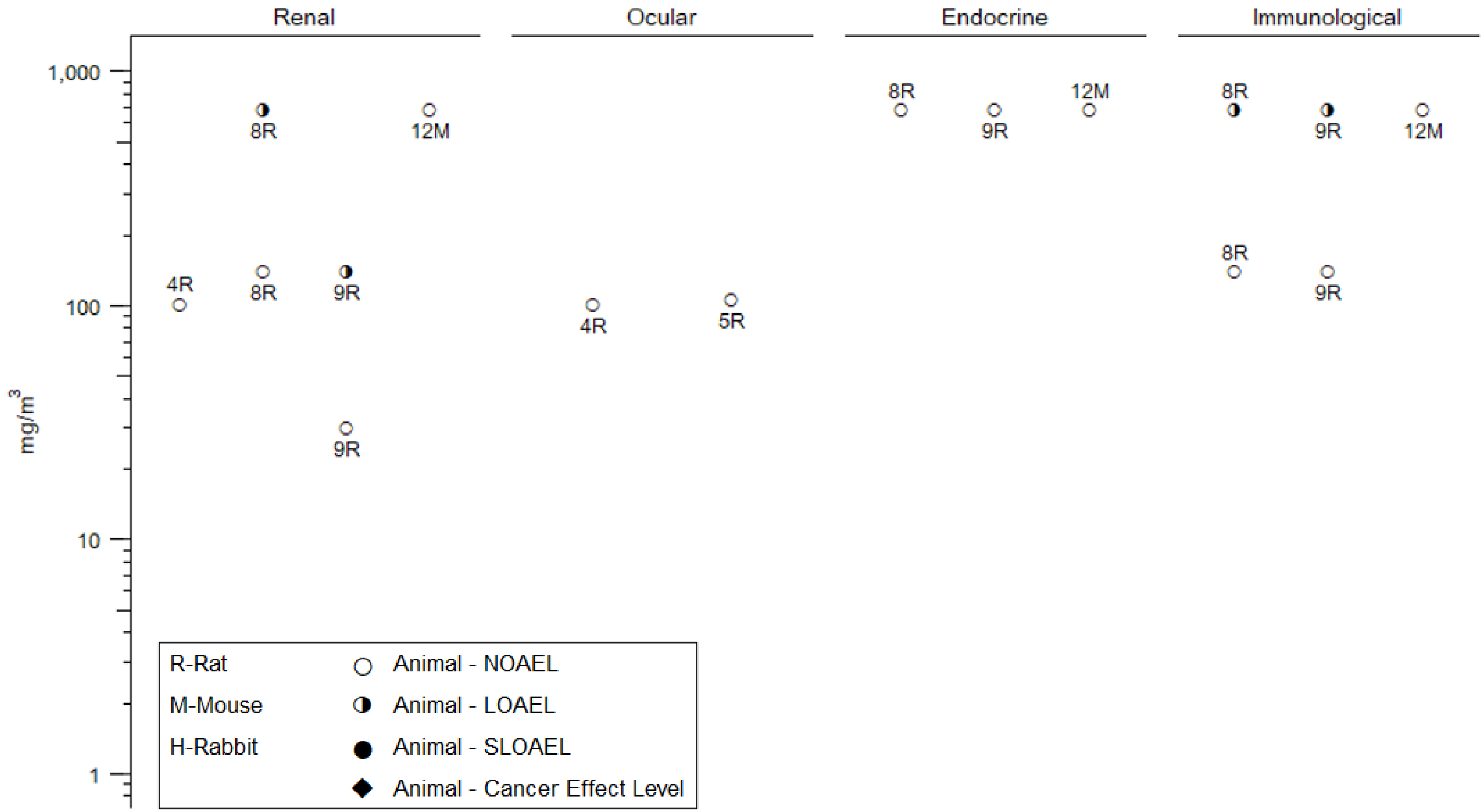


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Intermediate (15–364 days)

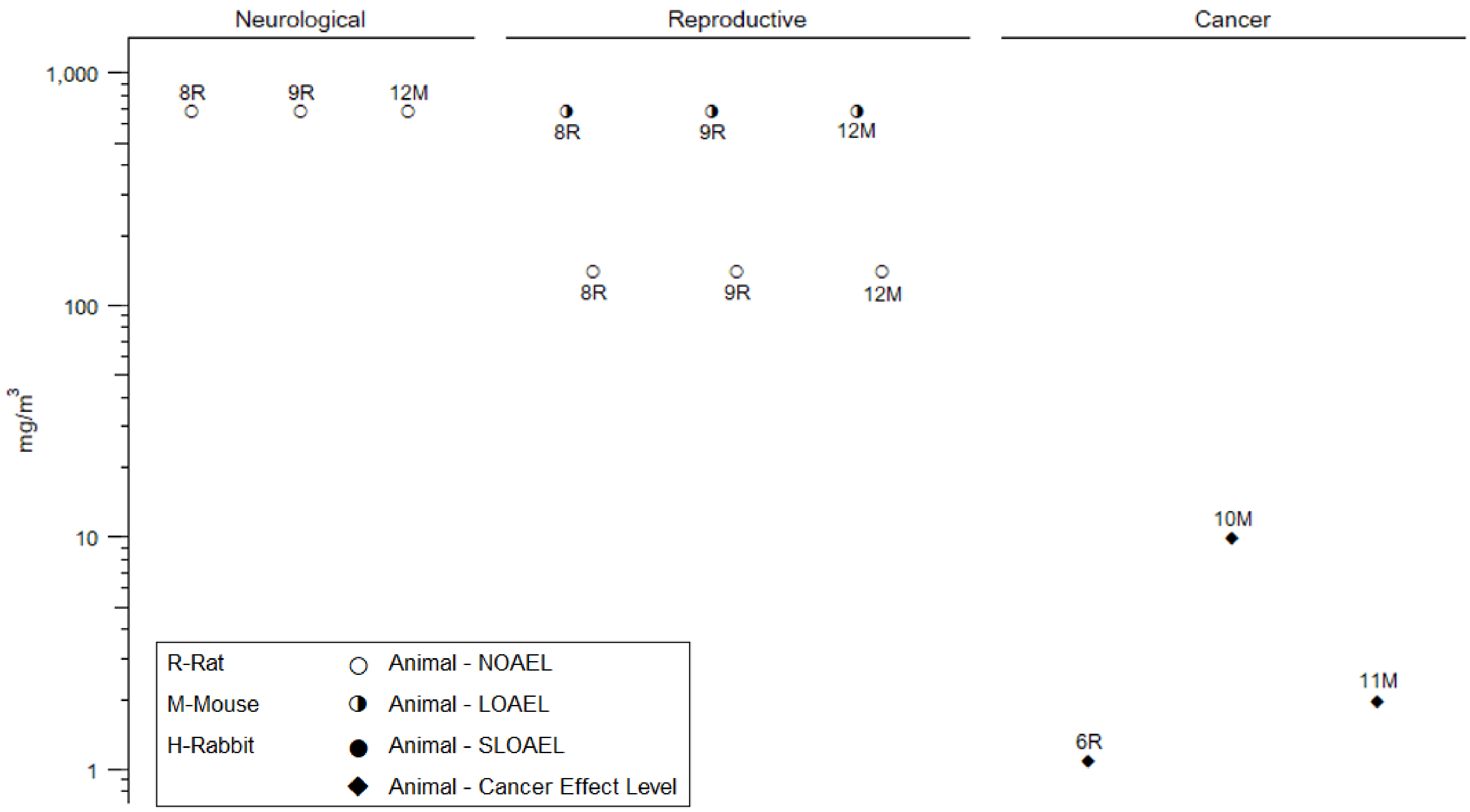


Figure 2-3. Levels of Significant Exposure to Coal Tar Products – Inhalation
Chronic (≥365 days)

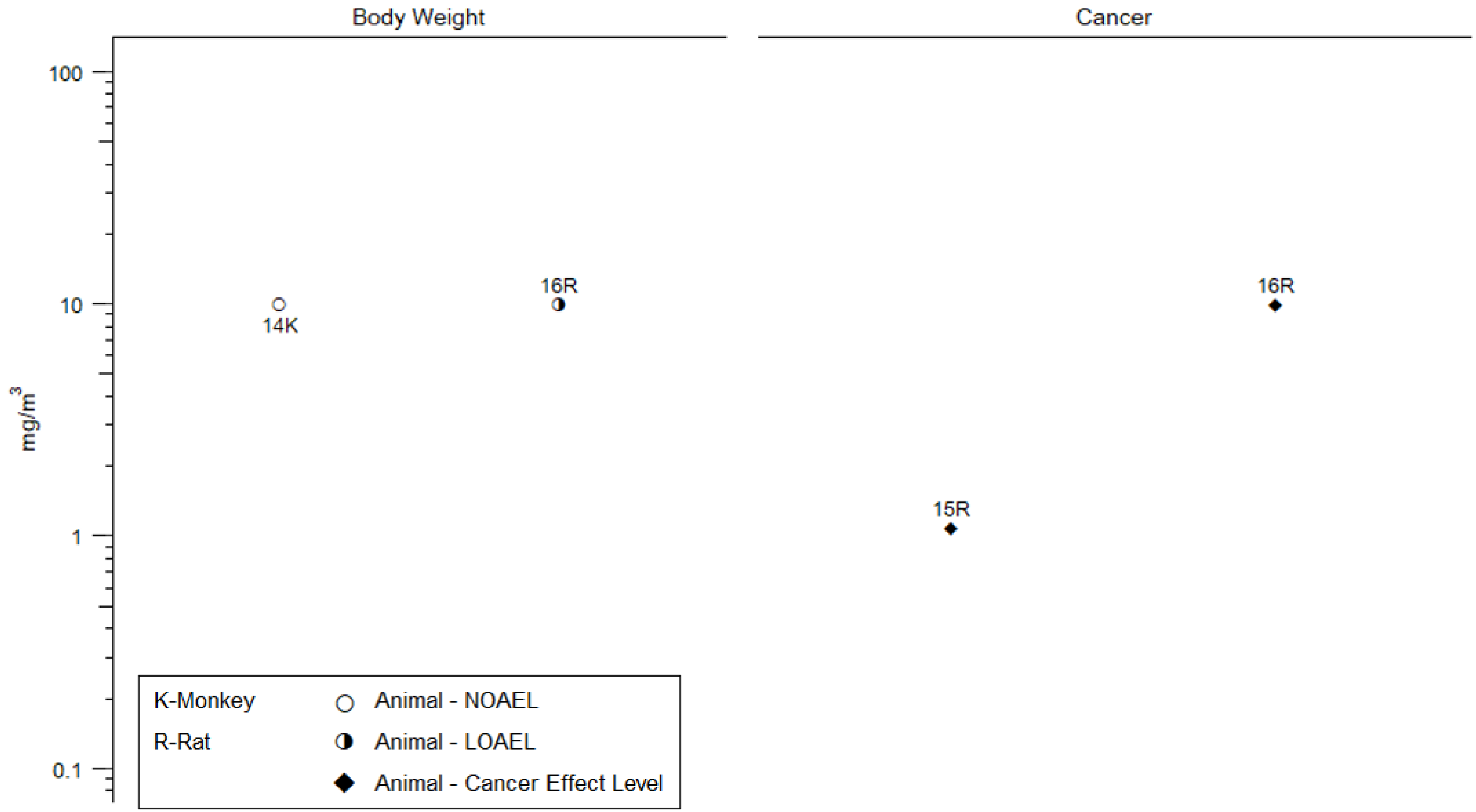


Table 2-2. Levels of Significant Exposure to Creosote (Coal Tar Products) – Oral (mg/kg/day)

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)

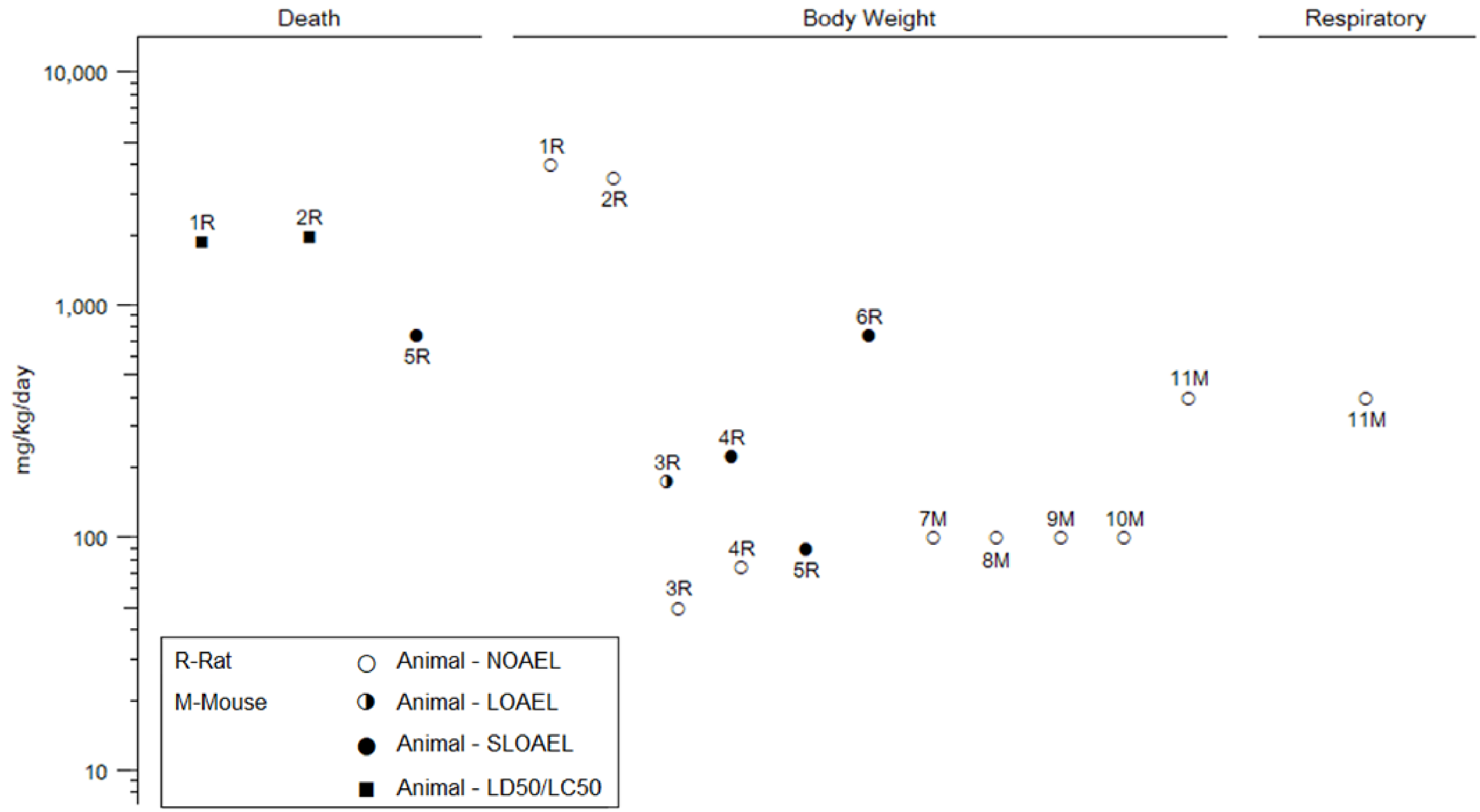


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Acute (≤14 days)

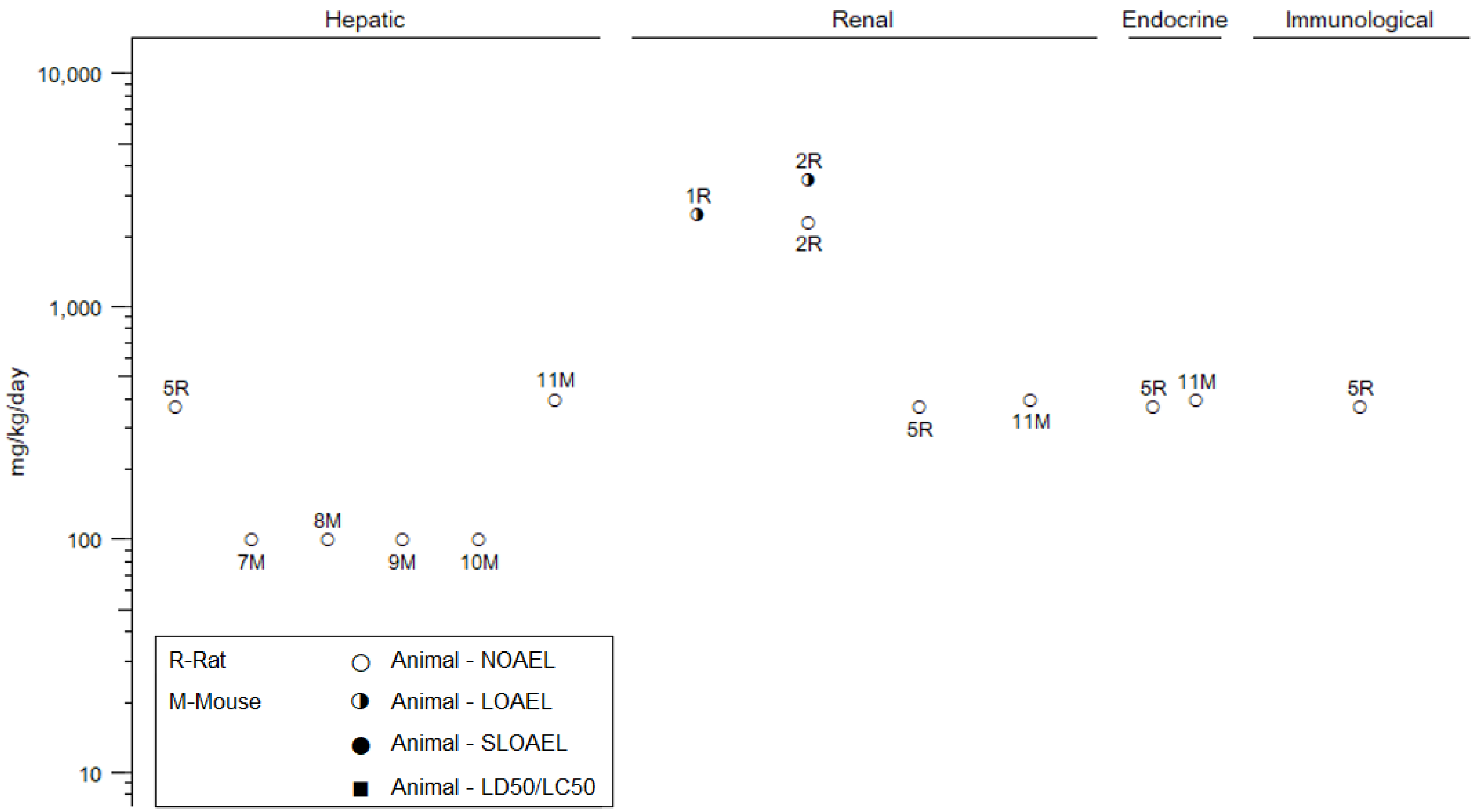


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Acute (≤14 days)

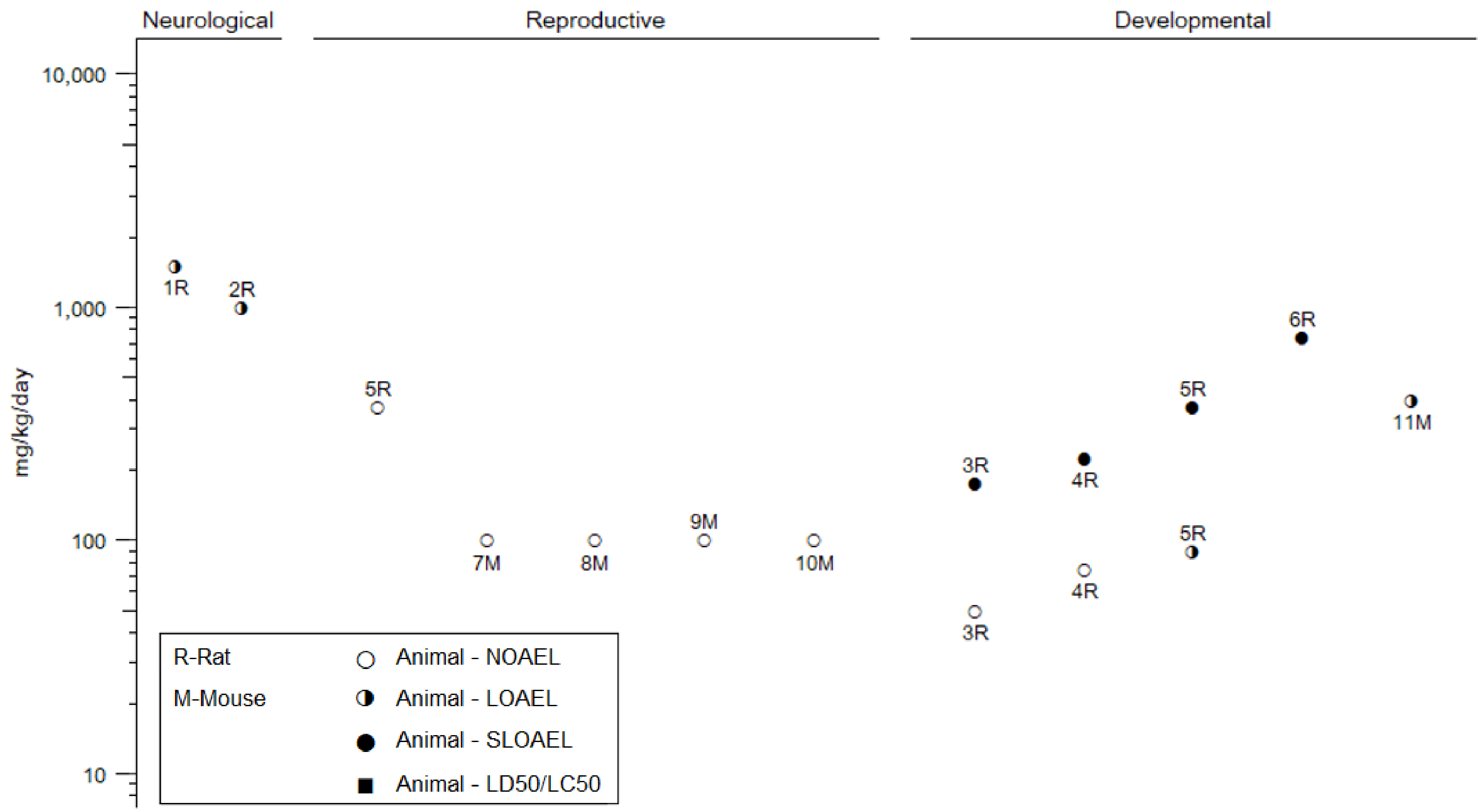


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Intermediate (15–364 days)

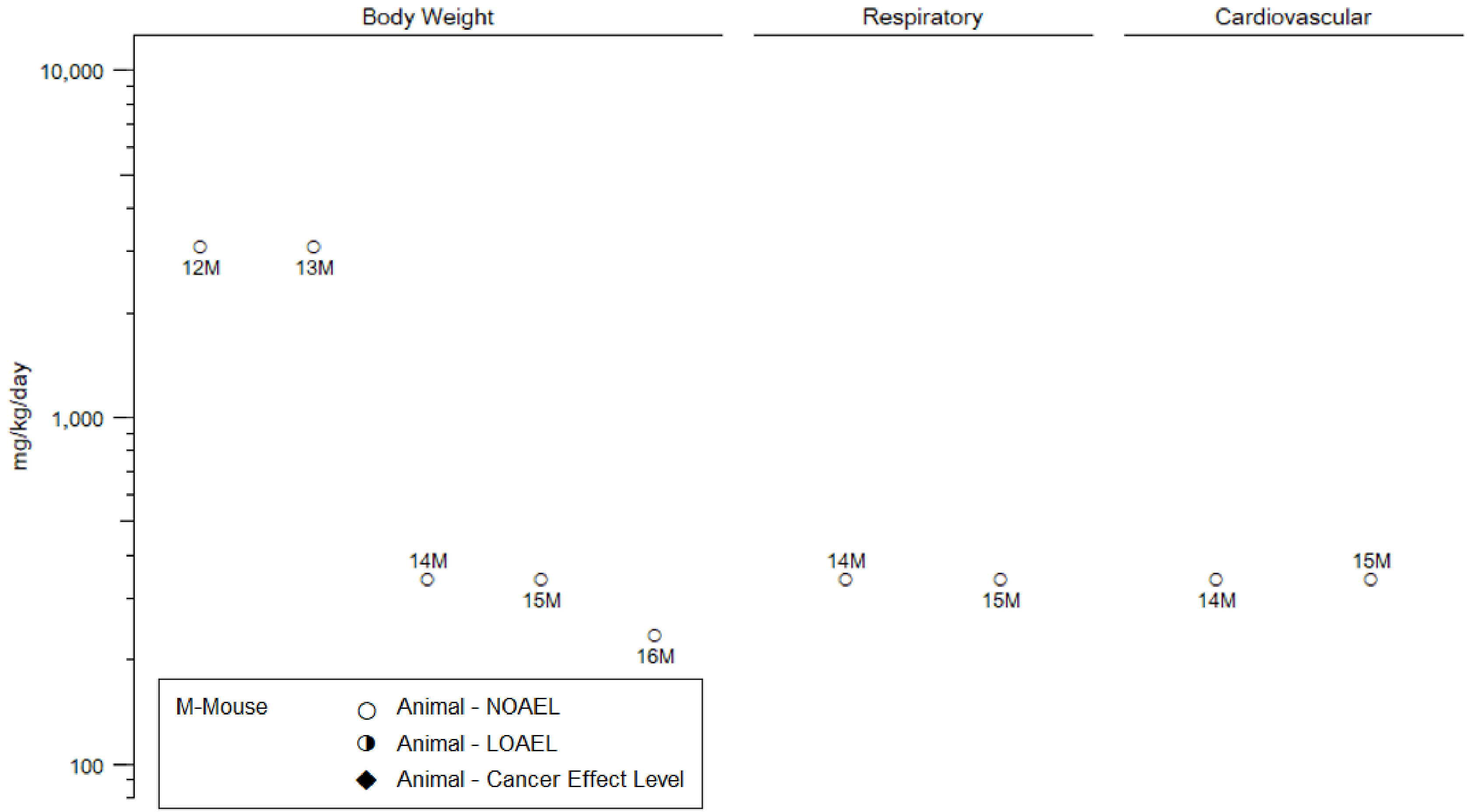


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Intermediate (15–364 days)

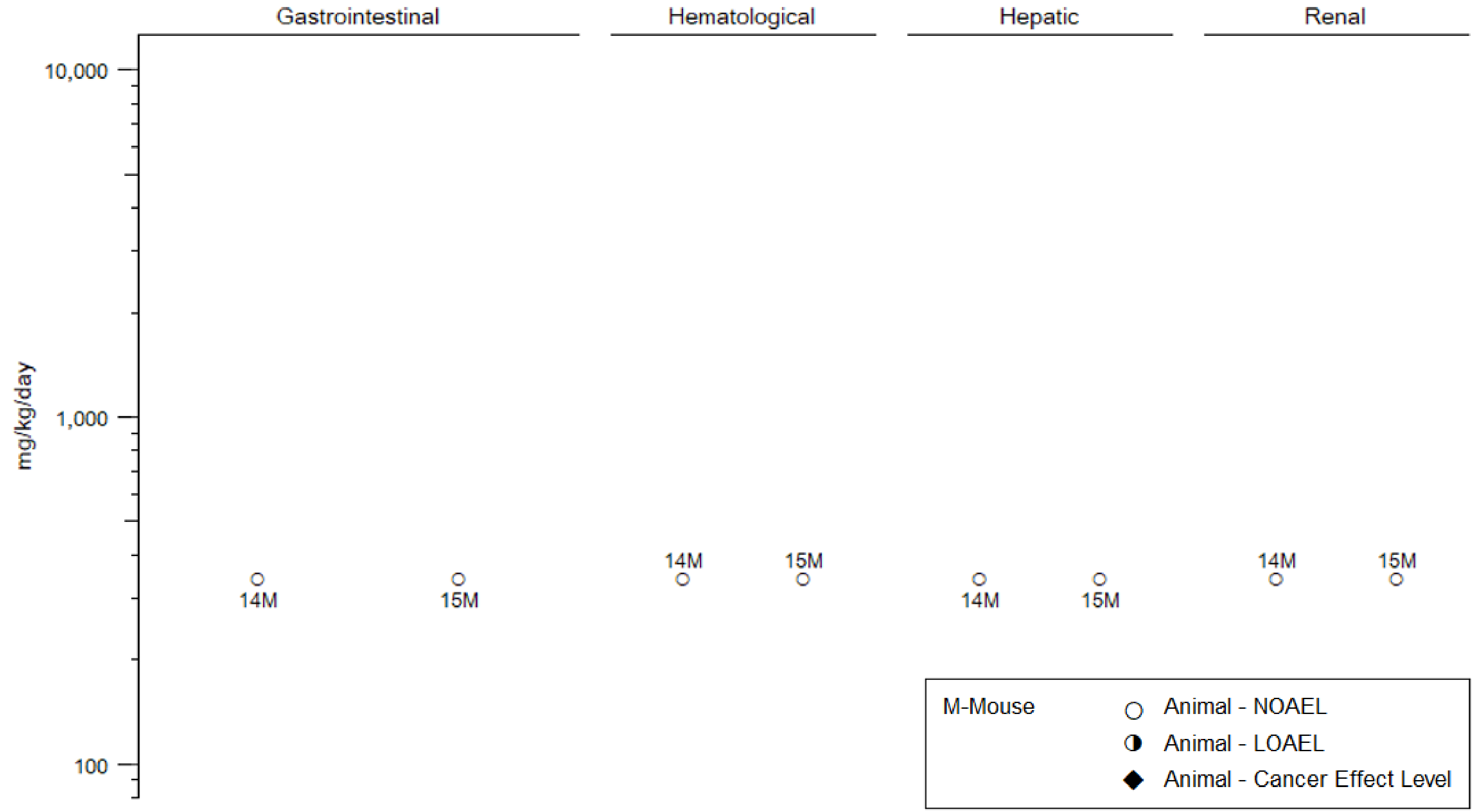


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Intermediate (15–364 days)

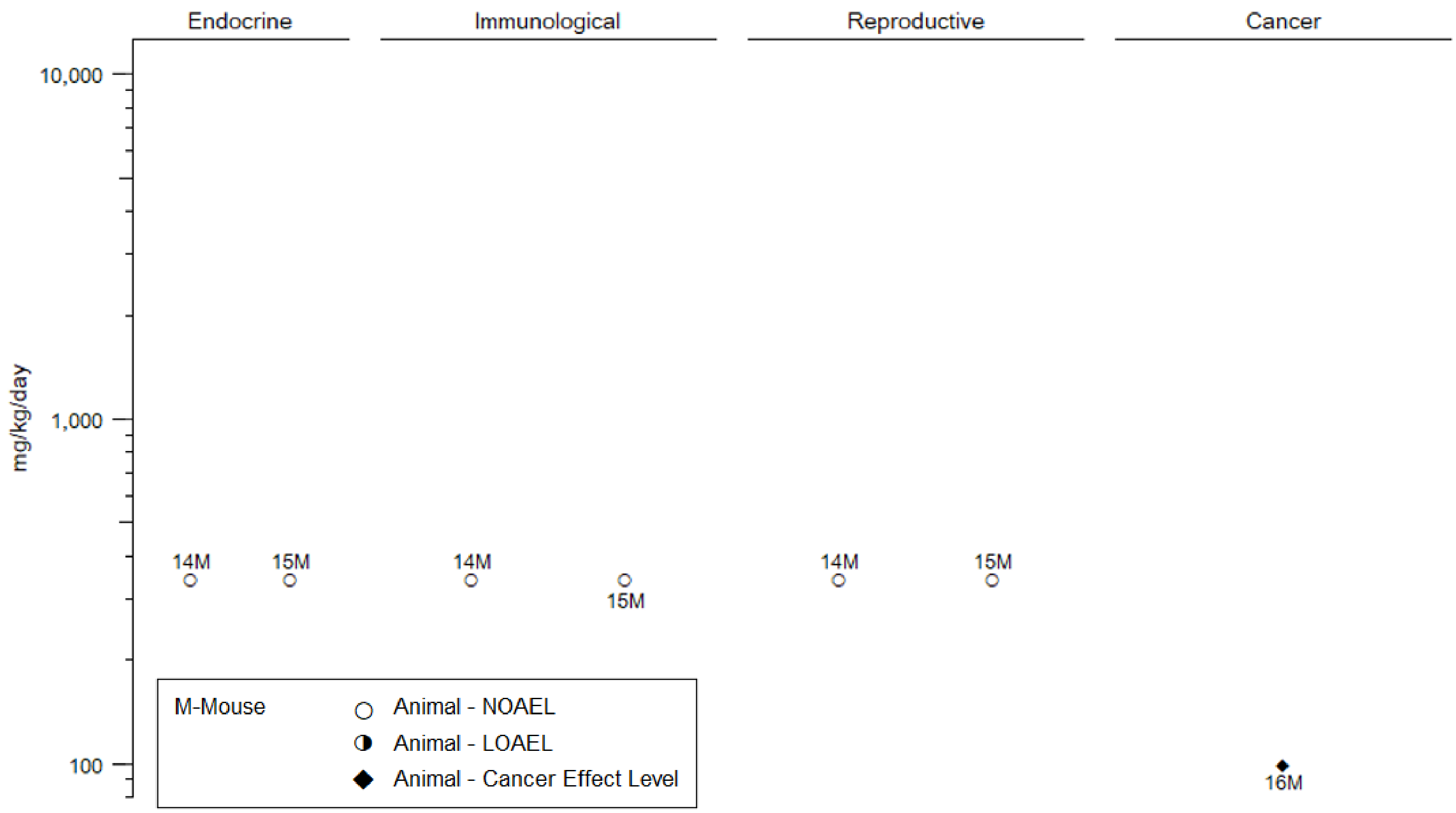


Figure 2-4. Levels of Significant Exposure to Coal Tar Products – Oral
Chronic (≥365 days)

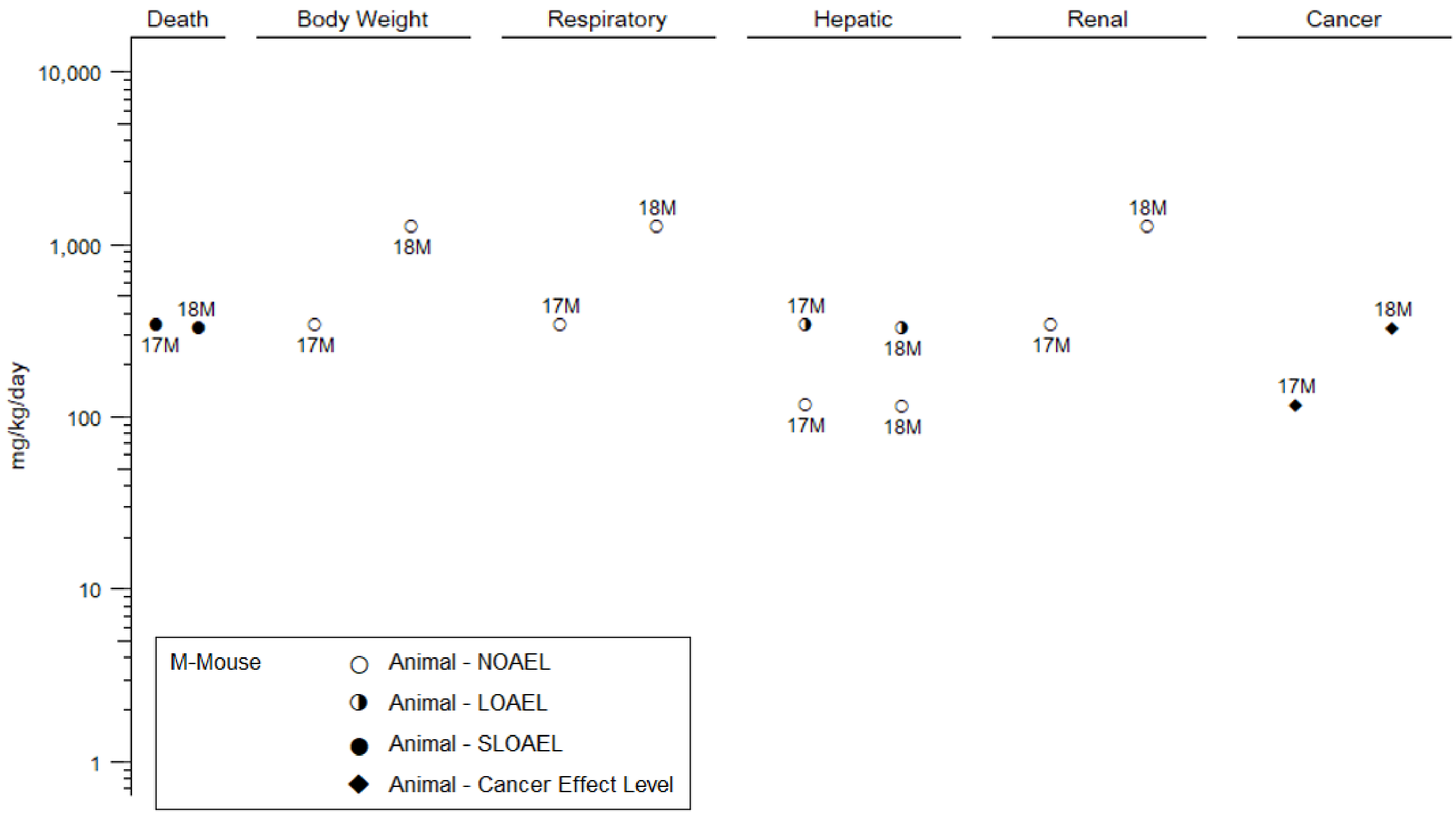


Table 2-3. Levels of Significant Exposure to Creosote (Wood Creosotes) – Oral (mg/kg/day)

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	10			
					Hepatic	10			
					Endocr	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	10			
					Hepatic	10			
					Endocr	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 M	200 F		Decreased terminal body weight (14%)
					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 313 M	394 F		Decreased body weight (10%)
					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)

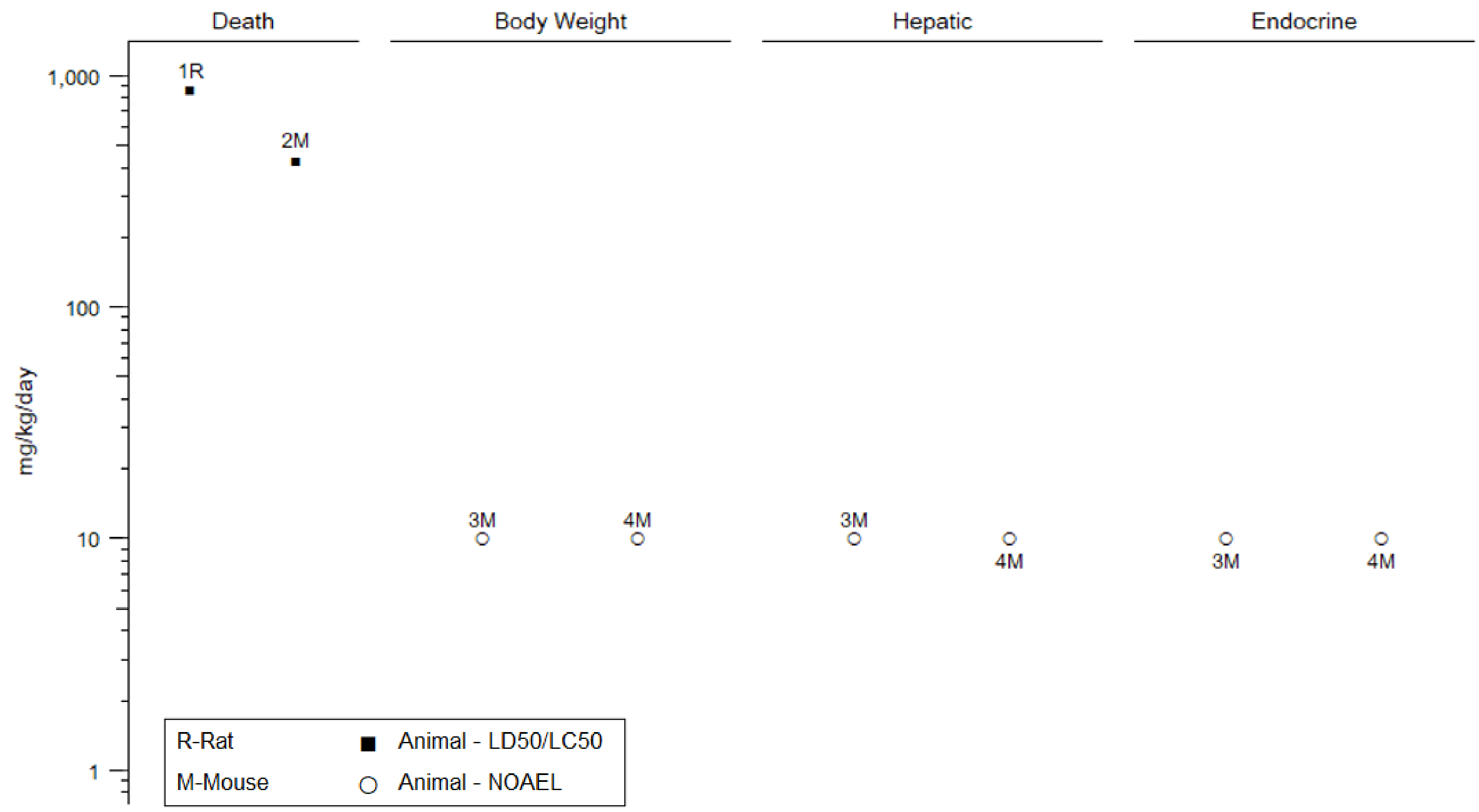


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Intermediate (15–364 days)

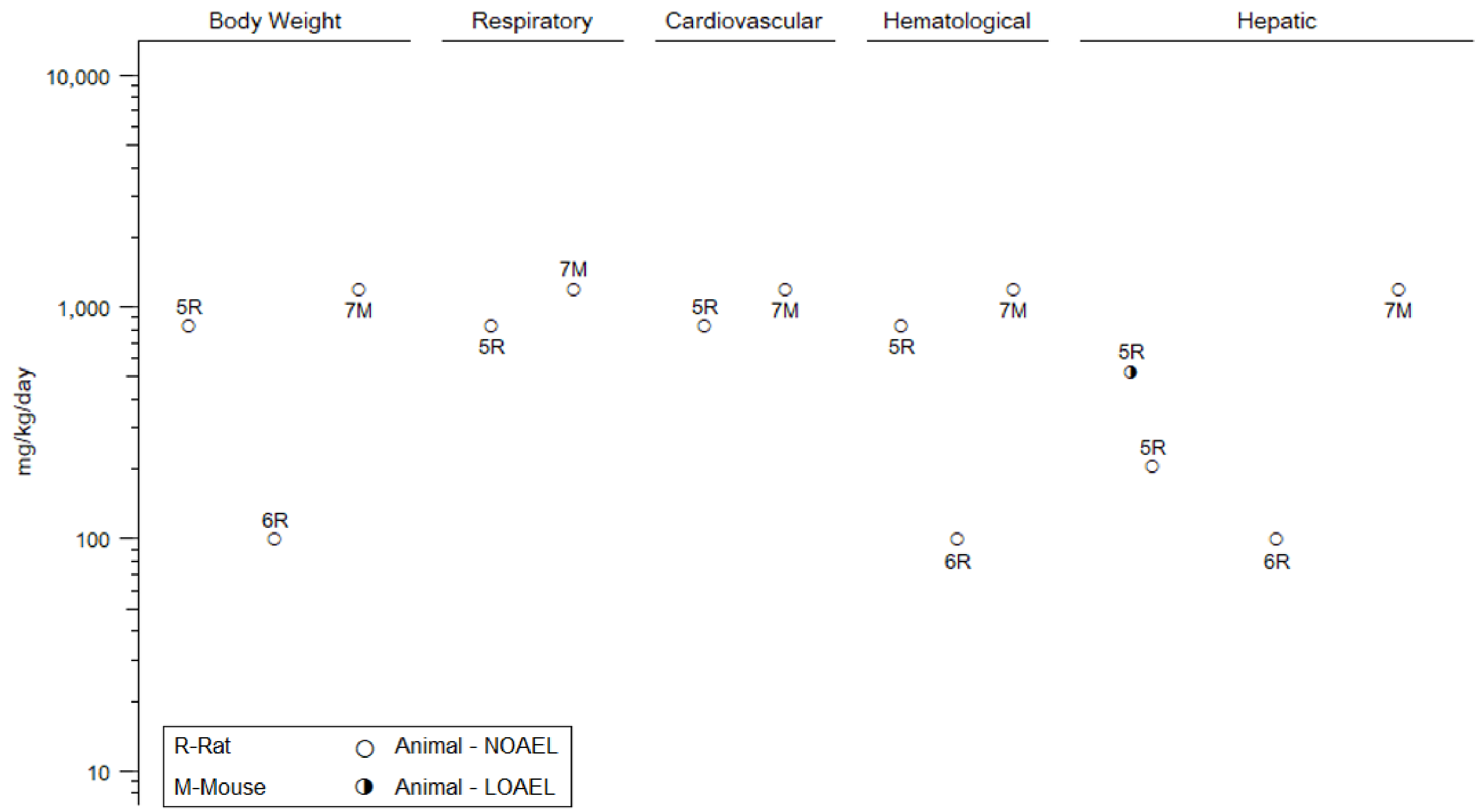


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Intermediate (15–364 days)

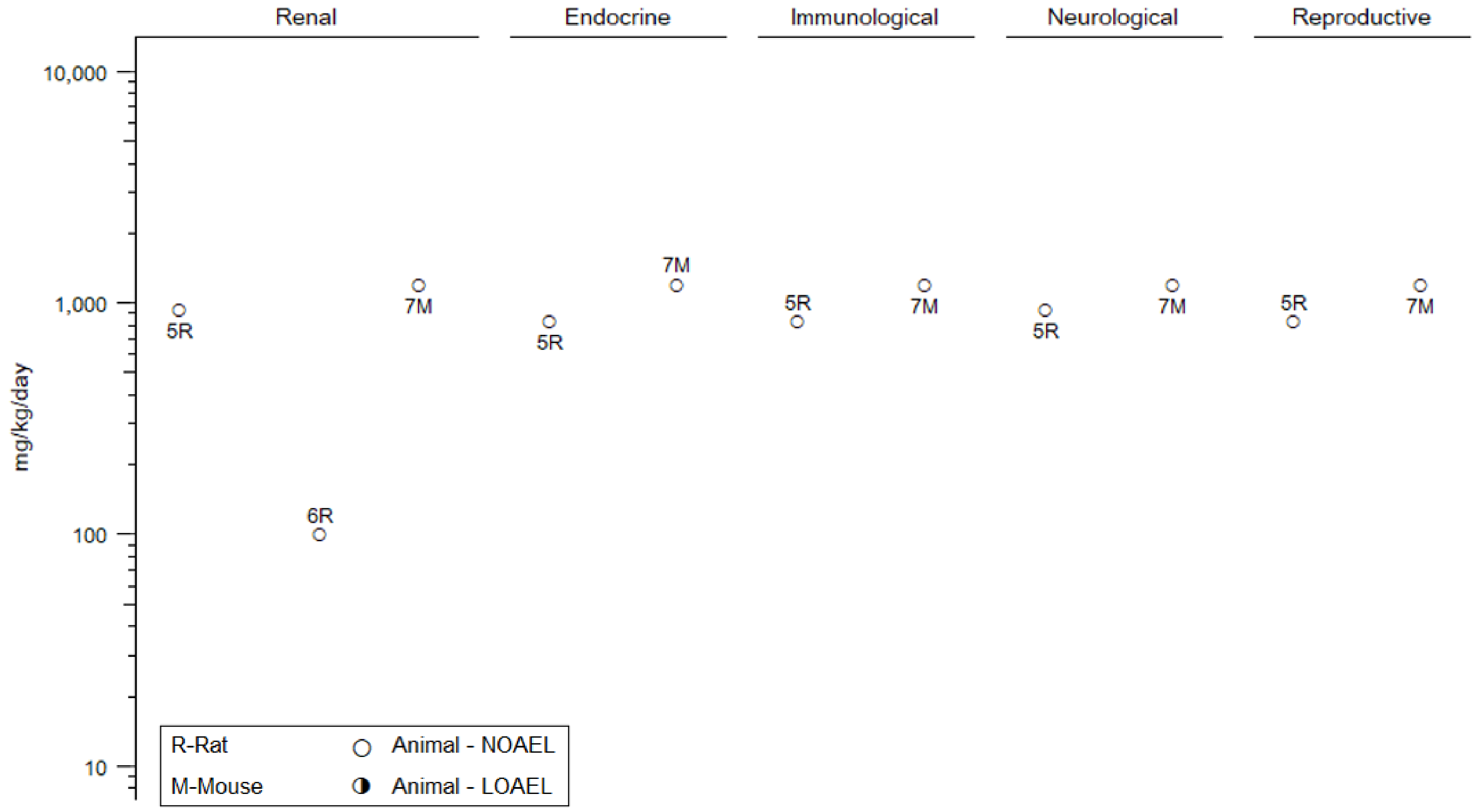


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

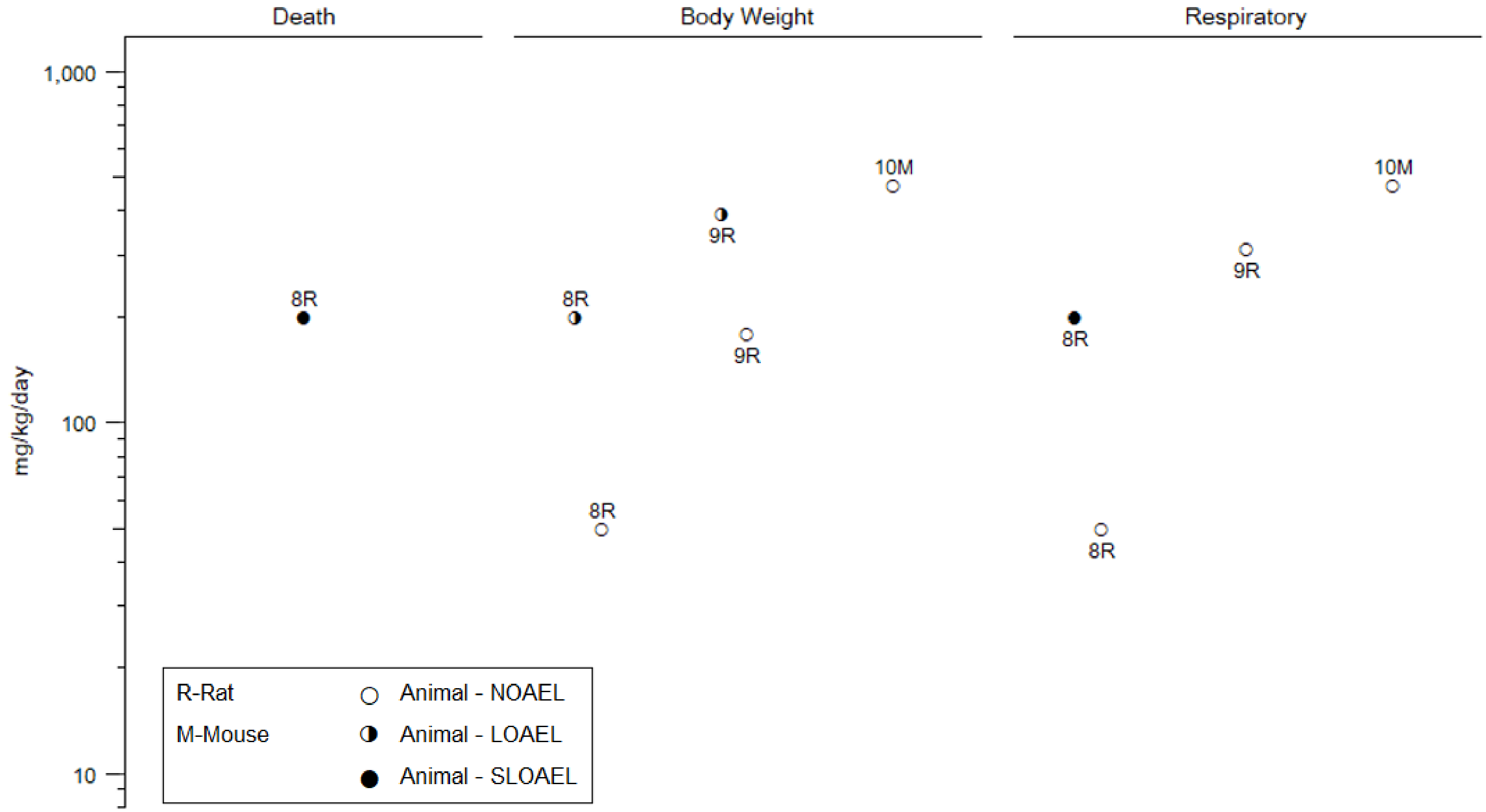


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

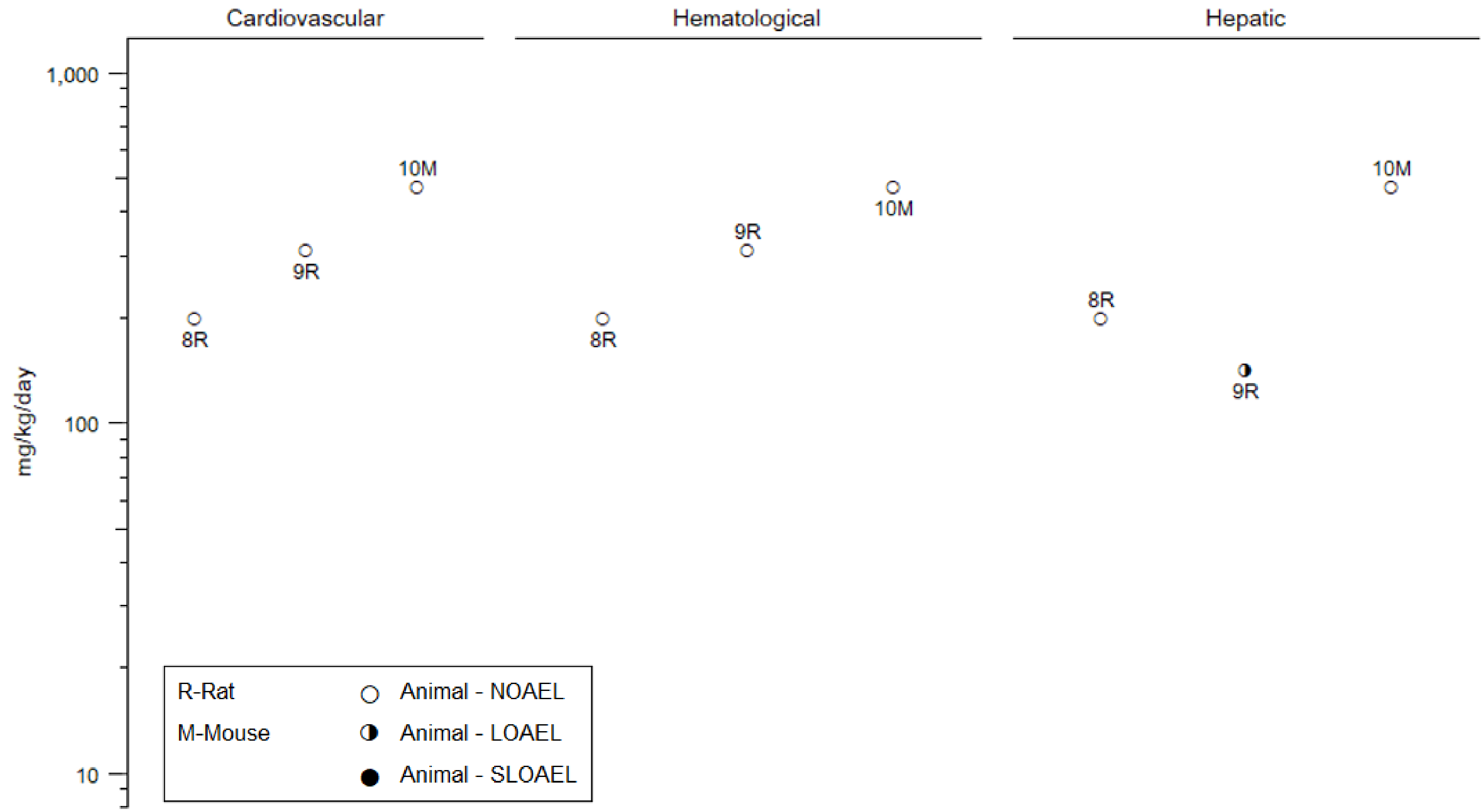


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

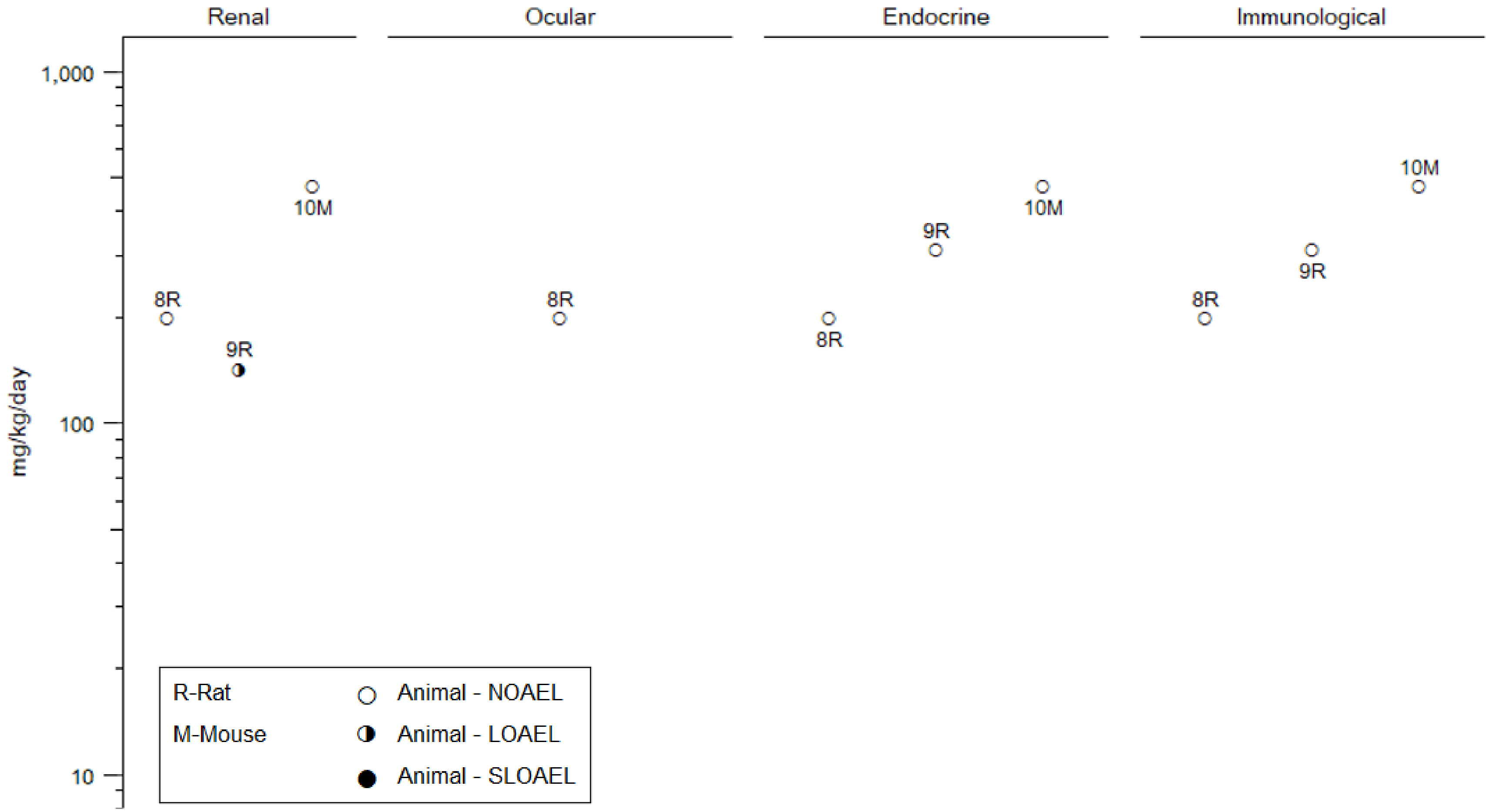


Figure 2-5. Levels of Significant Exposure to Wood Creosotes – Oral
Chronic (≥365 days)

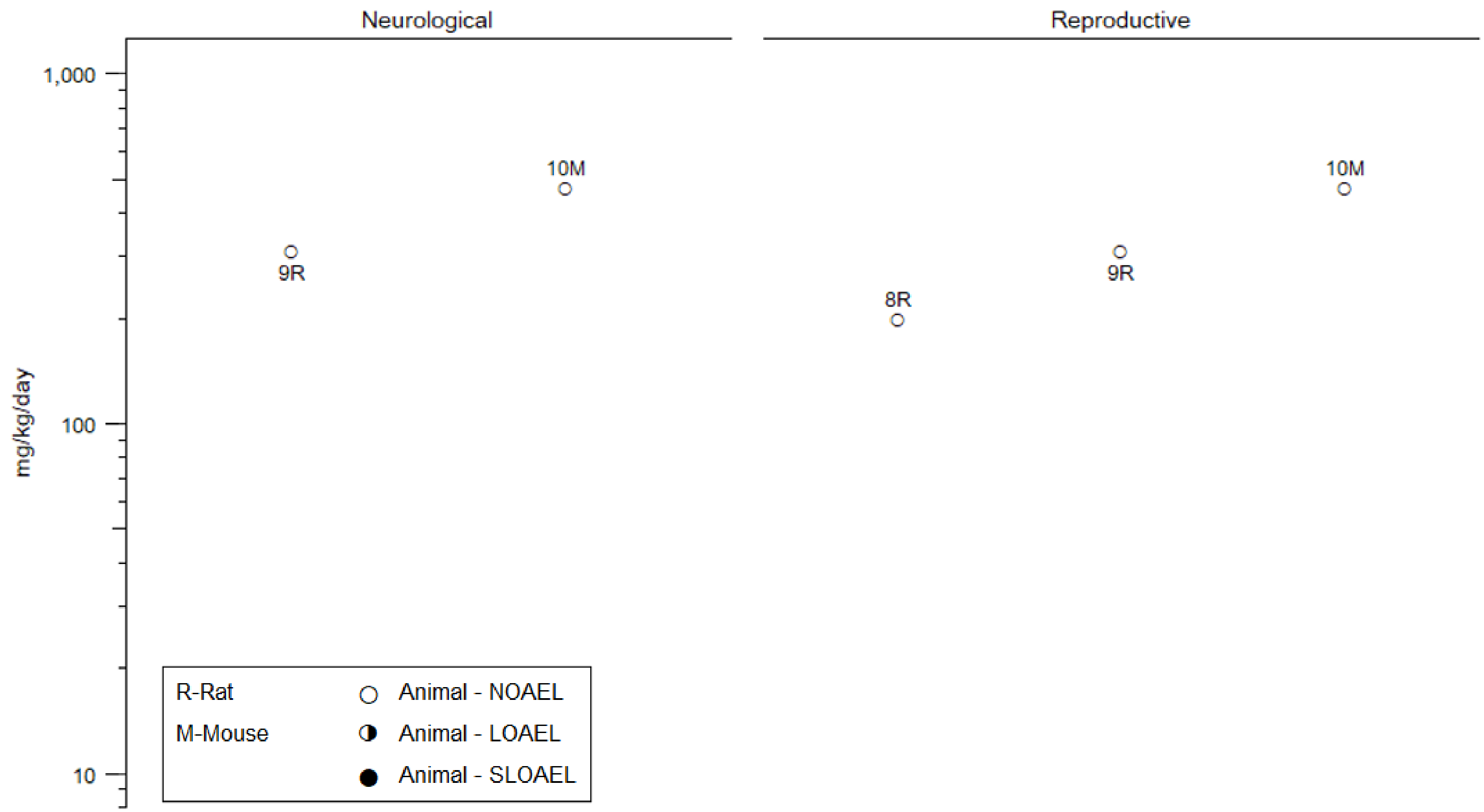


Table 2-4. Levels of Significant Exposure to Creosote (Coal Tar Products) – Dermal

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	2,000			
				Neuro	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 P2 creosote	24 hours	2,000 mg/kg	LE, CS, BW	Bd wt	2,000			
				Neuro	2,000			
EPA 1994								
Rabbit (New Zealand) 3 M, 3 F P2 creosote	Single application	0.1 mL	LE, CS, OP	Ocular		0.1		Conjunctival redness and chemosis
INTERMEDIATE EXPOSURE								
Boutwell and Bosch 1958								
Mouse (Sutter) 30 F Creosote oil	1 time DMBA (75 μg) 28 weeks 2 times/week	0.025 mL	CS, GN	Cancer			0.03	CEL: Skin tumors (papillomas and carcinomas)
Boutwell and Bosch 1958								
Mouse (Sutter) 30 F Creosote oil	4 weeks 2 times/week	0.025 mL	CS, GN	Cancer	0.03			
Boutwell and Bosch 1958								
Mouse (Sutter) 30 F Creosote oil	28 weeks 2 times/week	0.025 mL	CS, GN	Cancer			0.03	CEL: Skin tumors (papillomas and carcinomas, 50%)

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	400			
				Hemato	400			
				Dermal	400			
				Ocular	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	56			
				Cancer			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	56			
				Cancer			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	56			
				Cancer			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

		Cause of death					
Worker population	Reference (n)	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

		Cause of death					
Worker population	Reference (n)	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

		Outcomes measured (percent change)[a]									
Species	Exposure (duration)	VPRC	Hgb	RBCs	Rts	WBCs	LCs	NPs	EPs	MCs	Reference
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

		Cancer type		
Population	Reference (n)	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: With activation	Result: Without activation	Reference
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.